EPIDEMIOLOGY OF HEALTHCARE-ASSOCIATED INFECTIONS IN THE NETHERLANDS

Surveillance and research data for action

Tjallie van der Kooi

Epidemiology of healthcare-associated infections in the Netherlands: surveillance and research data for action

Tjally Ida Irene van der Kooi

ISBN: 978-94-6506-222-8

Financial support for printing of this thesis was kindly provided by the National Institute for Public Health and the Environment.

Cover: Tjallie van der Kooi
Printing/layout: Ridderprint, www.ridderprint.nl

Over de achterkant: de torenvalk herken je makkelijk door zijn kenmerkende 'bidden': klapwiekend tegen de wind in kan deze valk stilstaan in de lucht om, met zijn scherpe ogen, zijn jachtgebied te overzien. Daarom is de torenvalk als symbool gekozen voor de PREZIES surveillance.

university of groningen

Epidemiology of healthcare-associated infections in the Netherlands: surveillance and research data for action

PhD thesis

to obtain the degree of PhD at the
University of Groningen
on the authority of the
Rector Magnificus Prof. J.M.A. Scherpen
and in accordance with
the decision by the College of Deans.

This thesis will be defended in public on

Wednesday 2 October 2024 at 16.15 hours

by

Tjally Ida Irene van der Kooi

born on 2 January 1968

Supervisors
Prof. A. Voss
Prof. H. Grundmann

Co-supervisor
Dr. S.C. de Greeff

Assessment Committee
Prof. B.N.M Sinha
Prof. J.A.J.W. Kluytmans
Prof. M.C. Vos

Table of contents

Chapter 1

Introduction

Healthcare is meant to cure and care for patients, but unfortunately invasive devices and procedures also form a risk for patients to acquire infections. This type of infection is termed nosocomial or healthcare-associated infections (HAI) and they increase morbidity and mortality. In this thesis, HAI will usually refer more specifically to hospital-associated infections. Time spent in a hospital can itself be a risk factor for HAI, as certain pathogens are more concentrated than in the community and may have evolved resistance to antibiotics due to antibiotic selection pressure. The aim of this thesis is to describe achievements in HAI prevention over the last two decades, as measured through surveillance, and the role of the promotion of best practices. In the latter the emphasis is on central venous catheter-related bloodstream infection (CRBSI) – prevention bundles, and hand hygiene.

1.1 Prevention of hospital infections in historical perspective

During millennia of human history, in times of conflict or peace, people have suffered injuries and diseases that needed medical attention. In medieval Europe, treatment in infirmaries and sick-houses was often a death sentence, with gastroenteritis and louse-borne typhus ("hospital fever") infesting the crowded wards, where beds were usually shared. Neither surgical tools nor hands or gowns were cleaned or changed, and postsurgical mortality rates of 60-80% were common, mostly due to infectious gangrene [1]. The second half of the 19th century was, however, an era of many scientific achievements. Even before the exact nature of infections was understood or accepted, the importance of hygiene ("cleanliness") became increasingly acknowledged and led to improvements [2, 3]. The discovery of the role of micro-organisms laid the foundations of "germ-theory", which led to sterilisation of surgical tools and bandages and, consequently, decreasing rates of infection and mortality [1, 3]. Semmelweis, Pasteur, Koch, Lister and Nightingale were the well-known pioneers in the field of infection prevention. Other advances in health technology that ensured safer healthcare and surgery were the introduction of X-ray units in hospitals, intravenous fluid therapy and clinical thermometry [1], and anaesthesia in surgery (although initially it increased risk as it allowed surgery to last longer) [6].

While infection prevention improved, infection treatment did not progress until the first half of the last century, when penicillin, discovered in 1928, was introduced in patient care and other antibiotics followed [4]. Despite the hope of some that this would spell the end for infectious diseases, antimicrobial resistance evolved almost instantaneously. Hospital outbreaks and indeed a pandemic of a single lineage of penicillin-resistant *Staphylococcus aureus* followed within a single decade after the widespread introduction of penicillin. This set the stage for professional hospital

infection control programmes, which were first initiated in the 1950s in the UK and the USA [1, 5]. In the Netherlands, the Dutch government asked the Health Council for advice on this matter and, starting with the Council's report in 1966, infection prevention and control in hospitals acquired a legal basis through several laws and guidelines [6]. In the 1960s the Centers for Disease Control (CDC) in the USA recommended hospitals to perform surveillance of HAI, to inform the development of control measures. Since 1970 the CDC has coordinated surveillance of HAI in a group of voluntarily cooperating hospitals known as the National Nosocomial Infections Surveillance (NNIS) system [7]. In the 1970s, the CDC-initiated study on the efficacy of nosocomial infection control (SENIC) concluded that organised surveillance and control activities in a multimodal infection prevention and control programme could reduce HAI rates by one third [5]; since then, surveillance of healthcare-associated infections is considered a cornerstone of prevention and control [8].

The monitoring of HAI rates has increased awareness and improved insight into patients at increased risk, enabling targeted interventions. Subsequently, interventions could also be evaluated for their effectiveness. To this day, continuous surveillance initiatives facilitate feedback and have improved institutionalised healthcare (Plan-Do-Check-Act). Moreover, sufficiently standardised surveillance programmes allow for the benchmarking of institutions as an incentive and a means of quality assessment.

1.2 HAI: current incidence and etiology

At present, the most frequently diagnosed HAI in the Netherlands are surgical site infections (SSI), lower respiratory tract infections including pneumonia, bacteraemia, and urinary tract infections (UTI). *Clostridioides difficile* infection (CDI) is the dominant type of gastrointestinal HAI and can severely affect hospitalised patients [9, 10]. In point prevalence surveys during 2017-2019, the three years preceding the COVID-19 pandemic, the prevalence of SSI was 1.7% (95% confidence interval (CI) 1.6-1.8), of pneumonia 1.1% (1.0-1.2), of bacteraemia 0.9% (0.8-1.0) and of symptomatic UTI 0.8% (0.7-0.9). *C. difficile* was the responsible micro-organism in 37% of the hospital-associated gastrointestinal infections [11].

The acquisition of HAI is influenced by endogenous and exogenous risk factors. Advanced age, acute or chronic illness, impairment of organ functions, or metabolic disturbances, as well as disruption of individual microbiomes or reduced immunity are endogenous factors that additionally increase exposure to exogenous risk factors. The latter includes frequent hospital admissions, diagnostic and/or therapeutic interventions and repeated antibiotic therapy. Institutional factors such as - but not limited to - infection prevention practices and behaviour of healthcare workers (HCW) add

confounding causes for HAI. Direct and conditional causes involve surgery, whereby wounds can become infected, resulting in SSI. Venous catheters, especially central venous catheters (CVC), form a port d'entrée too, allowing bacteria and other pathogens to enter the body and/or adhere to the vascular device and possibly develop into a bloodstream infection (BSI). Approximately half of BSIs are secondary to other infections, either community-acquired or hospital-acquired. Impaired mobility is a risk factor for developing hospital-acquired pneumonia, and the risk is accentuated when invasive ventilation is required. Infections such as (ventilator-associated) pneumonia and bacteraemia typically develop in seriously ill patients in whom such endogenous and exogenous factors coincide. Healthcare-associated infections in these patients may be more challenging to prevent.

Urinary catheters increase the risk of UTI, which, although less serious than SSI, BSI or pneumonia, is a frequent nosocomial infection and can result in secondary bloodstream infection. Antibiotic use can cause a severe imbalance in the human microbiome, increasing the risk of infections with opportunistic pathogens that thrive under selective pressure. The risk of acquiring a nosocomial infection is further enhanced by the frequent contact with HCWs and with other patients (through HCWs, fomites or the environment). Moreover, nosocomially transmitted pathogens are sometimes antibiotic-resistant organisms that thrive in hospitals where antibiotics are more frequently prescribed than in the community. An infection with a resistant micro-organism may result in a delay of adequate treatment[12]. Almost all HAI cause delayed or inadequate recovery, additional pain and/or anxiety, and sometimes result in secondary bloodstream infection, sepsis and even permanent disability or death [10, 13-20].

Cassini et al. estimated that in 2011-2012, the burden of the five major HAI (SSI, BSI, pneumonia, UTI and CDI) together with healthcare-associated neonatal sepsis in the European Union was 501 (95% CI 429-582) disability-adjusted life-years (DALYs) per 100,000 inhabitants of the general population [10]; the burden of antibiotic-resistant infections, mostly hospital-acquired, was 131 (113-149) infections per 100,000, with an attributable mortality of 6.4 (5.5-7.5) per 100,000 (2015 data). The burden is lowest (<50/100,000) in the Netherlands, Scandinavian countries and a few others [15]. Although the recent focus has been very much on antibiotic resistance, these figures show that HAI with non-resistant micro-organisms likewise result in morbidity and mortality.

HAI can be expressed as an incidence (e.g. events per 100 or 1,000 patients or hospital admissions) or an incidence density (e.g. events per 1,000 patient-days or device-days) when exposure time is taken into account. Incidence-based surveillance is

suited to monitor specific types of HAI and the associated risk factors in appropriate patient categories, e.g. surgery patients at risk for SSI, ventilated patients at risk for ventilator-associated pneumonia (VAP), and patients with a CVC at risk for CRBSI. Incidence-based surveillance of all hospital patients would be very time-consuming and not very effective, as patients not included in SSI, VAP or CRBSI surveillance are generally at low risk to develop a HAI. An alternative is the point prevalence survey (PPS) in which a cross-section of the hospital population is observed for one or more types of HAI at one time-point only. These surveys are more suitable to assess all patients in the hospital than incidence-based surveillance, as they do not include patient follow-up. They can identify possible patient populations at increased risk and opportunities for intervention, but are less suitable to assess new risk factors.

1.3 HAI in the early 2000s: expansion of surveillance programmes (Part I)

Following the SENIC study many industrialised countries have initiated regional or national HAI monitoring programmes , [5]. To allow interhospital comparisons and trend monitoring surveillance requires standardized criteria to define HAI. The US CDC were the first to establish such criteria [21], which form the basis for most other surveillance programmes [22]. In 1996 the Dutch Institute for Public Health and the Environment (RIVM) and the former Dutch Institute for Healthcare Improvement joined to form one national surveillance programme: Prevention of Hospital infections by Interventions and Surveillance (PREventie van ZIEkenhuisinfecties door Surveillance, PREZIES) (https://www.rivm.nl/prezies). To this day PREZIES, in which hospitals and the RIVM participate, enables hospitals to monitor HAI according to a standardised protocol, including a limited set of relevant literature-based risk factors; it also provides feedback and benchmarks.

The first national surveillance initiative in the Netherlands targeted SSI, complemented in 1998 by a surveillance programme focussed on the intensive care unit (ICU), where patients are more at risk of acquiring HAI than in most other hospital wards. Lasting four years, this program monitored ICU-acquired infections, including (device-associated) pneumonia, BSI and UTI, and patient mortality. **Chapter 2** describes the incidence of these device-associated infections, but the data were also used to quantify the recorded risk factors, including device use, for both infection and mortality. Evaluation of the ICU-programme led to the development of two more targeted programmes, one aimed at VAP and one at CRBSI, with more detailed patient and device-specific data to improve case mix correction, increase insight and provide more specific leads for interventions. Both outcome and time at risk (device-use days) were recorded to calculate incidence densities. The first results of these two programmes are presented

in Chapter 3 (CRBSI) and 4 (VAP). In **chapter 3,** the incidence of and independent risk factors for CRBSI are described. These results were also used to evaluate the data requirements of the protocol. In **chapter 4**, incidence of and independent risk factors for VAP are described.

Meanwhile, awareness increased that national prevalence surveys of a wider range of HAI could be worthwhile for hospitals, while providing RIVM and the national government with better understanding of the disease burden imposed by the full range of HAI. Point prevalence surveys (PPS) were therefore introduced in 2007. The results of the first two years are presented in **chapter 5** and describe the range of HAI prevalence, use of medical devices, and use of antibiotics among hospitals.

Apart from HAI themselves, related outcomes can be monitored in surveillance programmes. HAI can lead to longer hospital admissions, repeated surgeries, readmissions, and increased mortality. These measures illustrate the impact of HAI on patients and the healthcare system. Attributing them to nosocomial infection is, however, often not straightforward and requires adjusting for the patient's condition by using statistical approaches or relying on clinicians' opinion. The inter-rater reliability of a clinician-based measure for the contribution of HAI to mortality was evaluated in a multicentre study commissioned by the European Centre for Disease Prevention and Control (ECDC). The results are presented **in chapter 6.**

1.4 Prevention of HAI: improving compliance to best practices (Part II)

Although surveillance is known to increase awareness and can lead to improvement, in this case lower HAI rates [5, 23-26], certain requirements must be met. HCWs must have knowledge of best practices and perceive them to be important and feasible; materials must be available and care processes optimally organised. The prevention of HAI is one aspect of 'patient safety'. This concept within healthcare quality and the notion that it should be embedded and fostered throughout the entire healthcare system was developed in the USA [27]. Following the seminal studies from Berenholtz and Pronovost et al. [28, 29], the Institute for Healthcare Improvement (IHI) in the USA, in its 100,000 Lives Campaign to improve patient safety and outcomes in 2004, recommended as one of six interventions the "central line bundle" [30]. Central line bundles to prevent CRBSI or central-line associated BSI (CLABSI) have been implemented in many hospitals and national surveillance programmes since [30-32]. The bundle approach emphasises compliance to a coherent set of best practices instead of an uncoordinated introduction and monitoring of individual best practices. Included in these bundles is hand hygiene during the CVC insertion, as hand hygiene is a corner stone of infection prevention in general. Improving hand hygiene has proven to be challenging [33]. Whether a CRBSI

prevention bundle, a World Health Organisation (WHO)-based intervention addressing hand hygiene, or both in combination would be effective in CRBSI prevention was evaluated in a wide range of European hospitals by the PROHIBIT (Prevention of hospital infections by intervention and training) study. As discussed in **chapter 7**, both process parameters - the CVC insertion score and hand hygiene compliance - were measured, and facilitating factors and barriers were evaluated in-depth in a related study of six hospitals [34].

The individual HCW's response to a hand hygiene intervention remains terra incognita in most studies. In **chapter 8** additional analyses of individual hand hygiene in seven PROHIBIT hospitals are presented. More insight into personal uptake of a hand hygiene intervention enables the design of more effective interventions in the future.

To ensure that a large number of hospitals adopt a multifaceted intervention without too much delay, the key is a national or otherwise large-scale movement, such as the IHI or, based on this initiative, the Dutch Hospital Patient Safety Programme (DHPSP), starting in 2009. The DHPSP encouraged Dutch hospitals to introduce a CRBSI prevention bundle and 62% of them acted upon this, with a concurrent reduction in CRBSI rates. In **chapter 9** the association between bundle compliance and CRBSI risk is evaluated.

Finally, **chapter 10** presents a discussion and reviews the merits and limitations of the surveillance and study methods. It will briefly consider the consequences of the current HAI incidence and achieved reductions for the relevance of and future set-up of HAI surveillance, particularly with regard to CRBSI in the Netherlands. The relevance of hand hygiene and the current compliance in Dutch hospitals are additionally discussed.

REFERENCES

1. Smith PW, Watkins K, Hewlett A. Infection control through the ages. Am J Infect Control. 2012;40(1):35-42 https://doi.org/10.1016/j.ajic.2011.02.019.
2. Kernahan PJ. Causation and cleanliness: George Callender, wounds, and the debates over Listerism. J Hist Med Allied Sci. 2009;64(1):1-37 https://doi.org/10.1093/jhmas/jrn043.
3. Vogel MJ. The invention of the modern hospital, Boston 1870-1930. Chicago: Chicago: University of Chicago Press; 1980.
4. Durand GA, Raoult D, Dubourg G. Antibiotic discovery: history, methods and perspectives. Int J Antimicrob Agents. 2019;53(4):371-82 https://doi.org/10.1016/j.ijantimicag.2018.11.010.
5. Haley RW, Culver DH, White JW, Morgan WM, Emori TG, Munn VP, et al. The efficacy of infection surveillance and control programs in preventing nosocomial infections in US hospitals. Am J Epidemiol. 1985;121(2):182-205 https://doi.org/10.1093/oxfordjournals.aje.a113990.
6. Koeleman JGM, Verbrugh HA. Preventie en bestrijding van ziekenhuisinfecties: wetten, richtlijnen en organisatie. Nederlands Tijdschrift voor Medische Microbiologie. 1999;7(4):115-21.
7. Emori TG, Culver DH, Horan TC, Jarvis WR, White JW, Olson DR, et al. National nosocomial infections surveillance system (NNIS): description of surveillance methods. Am J Infect Control. 1991;19(1):19-35 https://doi.org/10.1016/0196-6553(91)90157-8.
8. PREZIES (Dutch national surveillance network for healthcare associated infections). History of PREZIES [Available from: https://www.rivm.nl/prezies/over-prezies/historie-prezies.
9. Hopmans TEM, Smid EA, Wille JC, van der Kooi TII, Koek MBG, Vos MC, et al. Trends in prevalence of healthcare-associated infections and antimicrobial use in hospitals in the Netherlands: 10 years of national point-prevalence surveys. J Hosp Infect. 2019 https://doi.org/10.1016/j.jhin.2019.10.005.
10. Cassini A, Plachouras D, Eckmanns T, Abu Sin M, Blank HP, Ducomble T, et al. Burden of Six Healthcare-Associated Infections on European Population Health: Estimating Incidence-Based Disability-Adjusted Life Years through a Population Prevalence-Based Modelling Study. PLoS Med. 2016;13(10):e1002150 https://doi.org/10.1371/journal.pmed.1002150.
11. PREZIES (Dutch national surveillance network for healthcare associated infections). Reference figures 2017 - 2021: HAI prevalence surveys Bilthoven: National Institute for Public Health and the Environment (RIVM); 2023 [Available from: https://www.rivm.nl/documenten/referentiecijfers-prezies-prevalentieonderzoek-2021.
12. Kadri SS, Lai YL, Warner S, Strich JR, Babiker A, Ricotta EE, et al. Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant in-vitro susceptibilities: a retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals. The Lancet infectious diseases. 2021;21(2):241-51 https://doi.org/10.1016/S1473-3099(20)30477-1.
13. Bergmans DCJJ, Bonten, M.J.M.,. Nosocomial pneumonia. In: Mayhall CG, editor. Hospital epidemiology and infection control. Philadelphia: Lippincott, Williams and Wilkins; 2004.
14. Melsen WG, Rovers MM, Groenwold RH, Bergmans DC, Camus C, Bauer TT, et al. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. The Lancet infectious diseases. 2013;13(8):665-71 https://doi.org/10.1016/S1473-3099(13)70081-1.
15. Rupp ME. Nosocomial bloodstream infections. In: Mayhall CG, editor. Hospital epidemiology and infection control. Philadelphia: Lippincott Williams & Wilkins; 2004.

16. Brady M, Oza A, Cunney R, Burns K. Attributable mortality of hospital-acquired bloodstream infections in Ireland. J Hosp Infect. 2017;96(1):35-41 https://doi.org/10.1016/j.jhin.2017.02.006.
17. Burke JPY, T.W. Nosocomial urinary tract infections. In: Mayhall CG, editor. Hospital epidemiology and infection control. Philadelphia: Lippincott Williams and Wilkins; 2004.
18. Khanafer N, Barbut F, Eckert C, Perraud M, Demont C, Luxemburger C, et al. Factors predictive of severe Clostridium difficile infection depend on the definition used. Anaerobe. 2016;37:43-8 https://doi.org/10.1016/j.anaerobe.2015.08.002.
19. Johnson SG, D.N.;. *Clostridium difficile*. In: Mayhall CG, editor. Hospital epidemiology and infection control. Philadelphia: Lippincott Williams and Wilkins; 2004.
20. Ressler A, Wang J, Rao K. Defining the black box: a narrative review of factors associated with adverse outcomes from severe Clostridioides difficile infection. Therap Adv Gastroenterol. 2021;14:17562848211048127 https://doi.org/10.1177/17562848211048127.
21. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control. 1988;16(3):128-40 https://doi.org/10.1016/0196-6553(88)90053-3.
22. Gastmeier P. European perspective on surveillance. J Hosp Infect. 2007;65 Suppl 2:159-64 https://doi.org/10.1016/S0195-6701(07)60036-X.
23. Schröder C, Schwab F, Behnke M, Breier AC, Maechler F, Piening B, et al. Epidemiology of healthcare associated infections in Germany: Nearly 20 years of surveillance. Int J Med Microbiol. 2015;305(7):799-806 https://doi.org/10.1016/j.ijmm.2015.08.034.
24. Geubbels EL, Nagelkerke NJ, Mintjes-De Groot AJ, Vandenbroucke-Grauls CM, Grobbee DE, De Boer AS. Reduced risk of surgical site infections through surveillance in a network. Int J Qual Health Care. 2006;18(2):127-33 https://doi.org/10.1093/intqhc/mzi103.
25. Badia-Cebada L, Penafiel J, Saliba P, Andres M, Camara J, Domenech D, et al. Trends in the epidemiology of catheter-related bloodstream infections; towards a paradigm shift, Spain, 2007 to 2019. Euro Surveill. 2022;27(19) https://doi.org/10.2807/1560-7917.ES.2022.27.19.2100610.
26. Centers for Disease Control and Prevention (CDC). Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central Line Associated Bloodstream Infection) Atlanta, USA: Centers for Disease Control and Prevention; 2023 [Available from: https://www.cdc.gov/nhsn/psc/bsi/.
27. Gross PA. Dramatic improvements in healthcare quality: you can do it too. In: Mayhall CG, editor. Hospital Epidemiology and Infection Prevention: Lippincott Williams & Wilkins; 2004.
28. Berenholtz SM, Pronovost PJ, Lipsett PA, Hobson D, Earsing K, Farley JE, et al. Eliminating catheter-related bloodstream infections in the intensive care unit. Crit Care Med. 2004;32(10):2014-20 https://doi.org/10.1097/01.ccm.0000142399.70913.2f.
29. Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med. 2006;355(26):2725-32 https://doi.org/10.1056/NEJMoa061115.
30. Berwick DM, Calkins DR, McCannon CJ, Hackbarth AD. The 100,000 lives campaign: setting a goal and a deadline for improving health care quality. JAMA. 2006;295(3):324-7 https://doi.org/10.1001/jama.295.3.324.
31. Ista E, van der Hoven B, Kornelisse RF, van der Starre C, Vos MC, Boersma E, et al. Effectiveness of insertion and maintenance bundles to prevent central-line-associated

bloodstream infections in critically ill patients of all ages: a systematic review and meta-analysis. The Lancet infectious diseases. 2016;16(6):724-34 https://doi.org/10.1016/S1473-3099(15)00409-0.

32. Centers for Disease Control and Prevention. Central Line Insertion Practices (CLIP) Adherence [Available from: https://www.cdc.gov/nhsn/psc/clip/index.html.

33. Gould DJ, Chudleigh JH, Moralejo D, Drey N. Interventions to improve hand hygiene compliance in patient care. Cochrane Database Syst Rev. 2007(2):CD005186 https://doi.org/10.1002/14651858.CD005186.pub2.

34. Clack L, Zingg W, Saint S, Casillas A, Touveneau S, da Liberdade Jantarada F, et al. Implementing infection prevention practices across European hospitals: an in-depth qualitative assessment. BMJ Qual Saf. 2018;27(10):771-80 https://doi.org/10.1136/bmjqs-2017-007675.

Part I

HAI in the early 2000s: expansion of surveillance programmes

Chapter 2

Incidence and risk factors of device-associated infections and associated mortality at the intensive care in the Dutch surveillance system

Tjallie I.I. van der Kooi, Annette S. de Boer, Judith Manniën,
Jan Wille, Mariëlle T. Beaumont, Ben W. Mooi, Susan van den Hof

---

Intensive Care Medicine 2007(33): 271-278

ABSTRACT

Objective: To examine the incidence of and risk factors for device-associated infections and associated mortality.

Design and setting: Prospective surveillance-based study in ICUs of 19 hospitals in The Netherlands.

Patients: The study included 2,644 patients without infection at admission during 1997-2000, staying at the ICU for at least 48 h.

Measurements and results: The occurrence of ventilator-associated pneumonia (VAP), central venous catheter (CVC)-related bloodstream infection (CR-BSI), urinary catheter-associated urinary tract infection (CA-UTI) and risk factors was monitored. Of the ventilated patients 19% developed pneumonia (25/1,000 ventilator days); of the patients with a central line 3% developed CR-BSI (4/1,000 CVC days) and of the catheterized patients 8% developed CA-UTI (9/1,000 catheter days). Longer device use increased the risk for all infections, especially for CR-BSI. Independent risk factors were sex, immunity, acute/elective admission, selective decontamination of the digestive tract, and systemic antibiotics at admission, dependent upon the infection type. Crude mortality significantly differed in patients with and without CR-BSI (31% vs. 20%) and CA-UTI (27% vs. 17%) but not for VAP (26% vs. 23%). Acquiring a device-associated infection was not an independent risk factor for mortality. Being in need of ventilation or a central line, and the duration of this, contributed significantly to mortality, after adjusting for other risk factors.

Conclusions: Device use was the major risk factor for acquiring VAP, CR-BSI and CA-UTI. Acquiring a device-associated infection was not an independent risk factor for mortality, but device-use in itself was.

INTRODUCTION

Information on the incidence of different intensive care unit (ICU) acquired infections and their risk factors can help clinicians, other healthcare workers and hospital policy makers to try to reduce the burden of ICU-acquired infections in patients. This will not only lead to less suffering, but may also be cost saving. In a European prevalence survey in which 78 ICUs in the Netherlands participated 16% of the Dutch patients had an ICU-acquired infection [1]. In the Netherlands PREZIES, a national network, started a surveillance of nosocomial infections at the ICU in 1997 which continued until the end of 2000. As in most European surveillance systems, the definitions used were based on those of the Centers for Disease Control (CDC)/National Nosocomial Infections Surveillance (NNIS) system. However, unlike the surveillance in the United States [2] and Germany [3] this surveillance is patient based instead of unit based. The infection rates have been previously reported to the participating hospitals, in a Dutch journal [4] and in abstract form [5]. All ICU-acquired infections were recorded, but because most infections at the ICU are device associated, we have chosen to present results of device-associated infections only.

Here we report the rates of VAP, CR-BSI, urinary catheter a demeure (CAD)-associated urinary tract infection (CA-UTI), mortality and the effects of various risk factors. We also investigate the effect that the duration of the use of invasive devices has.

MATERIAL AND METHODS

PREZIES, established in 1996, is a cooperation of participating hospitals, the Dutch Institute for Healthcare Improvement (CBO) and the National Institute for Public Health and the Environment (RIVM). During the period July 1997- December 2000 19 Dutch hospitals (c. 20 % of all hospitals in The Netherlands) with 23 ICUs prospectively collected data of intensive care patients on a daily basis according to the PREZIES protocol. Both university and other hospitals participated, but university hospitals were relatively better represented (three out of seven). The study period varied between 2 and 39 months, with a median of 14. The average capacity of the participating ICUs was 8 beds (range 5 to 12).

Experts in the field of intensive care medicine and nosocomial infections developed the protocol in consultation with the participating hospitals. In each hospital a multidisciplinary team of the infection control professional, ICU nurses, the medical microbiologist, and the ICU physician performed the surveillance. The procedure of data collection and the tasks of the involved persons were established within each hospital. The definitions of pneumonia, sepsis, UTI and risk factors were standardized and based

on those of the CDC/NNIS system. An infection was deemed device-associated when the day of or the day before the infection occurred was a device day.

All patients who stayed at the ICU for 48 hours or more were included in the surveillance and followed from admission until discharge, death, or the day of withholding treatment because of their moribund condition. The study period per patient was restricted up to 56 days. After discharge from the ICU patients were followed-up for infection for another 24 h. The surveillance included 4,105 patients, for 3,921 of whom sufficient data were available. Of these patients 1,277 (33%) had an infection when entering the ICU and were analyzed separately (data not shown). The remaining 2,644 patients remained at the ICU for a total of 25,432 days. Median ICU stay was 6 days, interquartile range (IQR) 6 days. Patient characteristics of patients with and without a device-associated infection are presented in the Electronic Supplementary Material (ESM; Appendix A).

The following patient characteristics were recorded: demographic data, medical discipline treating the patient (specialty), Acute Physiology and Chronic Health Evaluation (APACHE) II score, immunity status (normal immunity, leukopenia (leukocytes polymorphonuclear cells < 0.5 x 10^9/l), and otherwise impaired immunity (defined as a chronic low or recent high dose of corticosteroids, chemotherapy, dialysis or systemic diseases such as leukemia or AIDS in patients with leukocytes polymorphonucelair cells > 0.5 x 10^9/l), origin (e.g. community, ward) and whether admission was acute or elective. The use of medical devices (mechanical ventilation (including intubation without ventilation and/or having a tracheostoma); CVC and indwelling transurethral or suprapubic catheter), systemic antibiotics and selective decontamination of the digestive tract (SDD) were recorded daily. Two or more central venous catheters on 1 day were counted as one CVC day. For each nosocomial infection the infection date, type of infection, and microbiological test result were recorded. Pneumonias registered within 4 days from an earlier pneumonia in the same patient, and sepsis and UTI occurring within 7 days after the same kind of infection were not regarded as new infections, according to the European protocol for nosocomial infection surveillance [6]. This led to the exclusion of about 2.5% of infections but did not affect the calculation of risk factors, as only the first VAP, CR-BSI, or CA-UTI was included in the regression analysis. Any new pathogens with these excluded infections were presented with the former infection. In patients who developed a device-related infection the time at risk was defined as the number of days from the first day the device was used until the day on which the device-related infection was diagnosed or, if no infection occurred, until the last day of device use. Observations were censored if the device was no longer used or if the patients with the device were transferred to other hospitals, deceased or when active (life-supporting) treatment was

withheld. Before aggregation individual data were checked for completeness and consistency. Patient and treatment characteristics were determined in patients with and without infection. The incidence of infections per 1,000 device days was calculated. To calculate the incidence density of subsequent periods the numbers of days at risk of a patient were divided over and thus contributed to the subsequent categories, as described by McLaws and Berry [7].

Kaplan Meier survival analysis and Cox regression in SAS 9.1 [8] were used to calculate the relative risk of acquiring infection for patient and treatment characteristics with regard to the time at risk. Logistic regression was used to determine the effect of duration of device use on infection and the effect of risk factors on mortality. For uniformity we used the same categories of risk factors for all infections. Risk factors with a p-value of 0.20 or less in the univariate regression were initially included in the multiple regression models. The model was reduced by means of manual backward elimination. Risk factors, contributing significantly to the goodness of fit of the model but not statistically significant independent risk factors in themselves are also shown. Statistical significance was defined at $p \leq 0.05$.

RESULTS

Device-related infection rates, and ICU stay

Overall 58% of patients were mechanically ventilated (568 days per 1,000 ICU days), 61% had a CVC (506 days per 1,000 ICU days) and 86% had an indwelling catheter (818 days per 1,000 ICU days). As many as 71% of the patients had two or more different devices during (part of) their ICU stay and 43% had all three.

Of all pneumonia cases 86% were associated with mechanical ventilation. VAP occurred in 19% of ventilated patients, with an incidence of 25 per 1,000 ventilator days. Of all sepsis cases 34% were related to a central vascular catheter. Of the patients with a CVC 3% developed CR-BSI, with an incidence of 4 per 1,000 CVC days. Of all UTI cases 95% were associated with the use of an indwelling catheter. CA-UTI occurred in 8% of the patients with an indwelling urinary catheter, with an incidence of 9 per 1,000 CAD days. Median ICU stay was 7 days (IQR 7) in ventilated patients without VAP and 17 days (IQR 17) in those with infection; 6 days (IQR 8) in patients with a central vascular catheter without CR-BSI and 24 days in those with infection; and 6 days (IQR 6) in patients with a urinary catheter without CA-UTI and 18.5 days (IQR 16.5) in those who developed infection. Table 1 shows the median duration of device use and the IQR. Patients who developed a device-associated infection had significantly longer ICU stays.

Table 1: Median duration of device use for all patients, those that develop infection and up to infection.

Median duration of device use (interquartile range)	for all patients on device	for all patients that developed the device-associated infection	up to the first device-associated infection
ventilation	6 (9)	14 (15)	6 (5)
central venous catheterization	5 (5)	21 (16)	9 (13)
urinary catheterization	6 (7)	17 (17.5)	8 (9)

Duration of device use as a risk factor for infection

Figure 1 shows the incidence densities of patients at risk that developed an infection, according to the duration of mechanical ventilation, central vascular catheterization or urinary catheterization. The incidence density of CR-BSI and CA-UTI varied relatively little according to duration of CVC and CAD use, but that of VAP decreased when the ventilation lasted longer than 9 days. We also calculated the VAP risk per day. Figure 2 presents the risk of patients expressed as a proportion of those at risk for at least the number of indicated days.

The risk increased until day 5, remained more or less constant unto day 10 and decreased thereafter. There were too few patients at risk for more than 3 weeks to draw conclusions. Therefore we summarize these. Cox regression takes into account the effect of time at risk, but its relative risks do not give insight into its effect. Logistic regression does not integrate the time at risk in the calculation of its odds ratios. However, this makes it possible to express the effects of discerned periods at risk. Therefore Table 2 shows the odds ratios of increased device use (until infection), determined by univariate logistic regression. Prolonged device use significantly increased the risk of acquiring a device-associated infection. The risk of CR-BSI was affected most: the odds ratio for a CVC in situ for 5-9 days was 4.3 and for a period of 10 days or longer 8.4. Device use affected the risk of VAP the least. Being on a ventilator for at least 10 days was not associated with a higher risk than being ventilated for 5-9 days. This is reflected in the decreasing incidence density in Figure 1.

Other risk factors for infection

Incidence densities for different categories of patients are given in the ESM (Appendix B). Table 3 presents the relative risks determined by multivariate Cox regression (univariate results in the ESM, Appendix C). Female sex and SDD use were associated with lower VAP risk. An APACHE II score of 20 or greater was associated with a higher risk. Only SDD use affected the VAP risk significantly. The only independent risk factor for CR-BSI was acute admission. Acutely admitted patients had a lower risk for CR-BSI. Independent risk factors for CA-UTI were female sex, impaired immunity, acute admission, and systemic

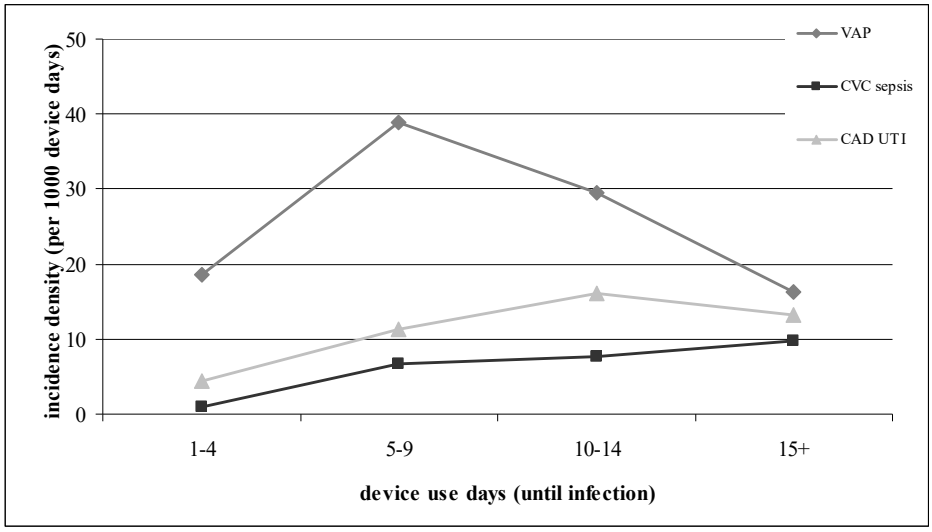


Figure 1: Incidence densities of device-associated infections per 1,000 device days, according to duration of device use.

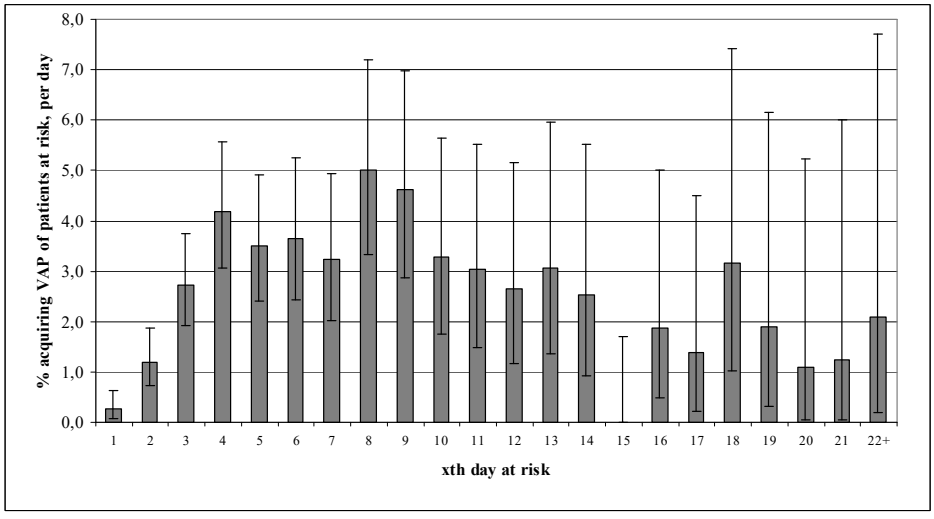


Figure 2: The proportion of all patients ventilated for x days or longer that develop VAP at day x and 95% confidence intervals.

Table 2: Odds ratios for duration of device use, determined by univariate logistic regression and 95% confidence intervals.

Device use	Duration of device use		
	1-4 days	5-9 days (95% CI)	≥ 10 days (95% CI)
ventilation	1	1.9* (1.4-2.6)	1.6* (1.1-2.2)
central venous catheterization	1	4.3* (1.7-10.7)	8.4* (3.4-20.4)
urinary catheterization	1	1.6* (1.0-2.4)	3.3* (2.2-4.9)

* p< 0.05

antibiotics. Acute admission had no proportional hazard over time, indicating that the effect of this risk factor changed over time. To account for this an interaction term with time at risk was included in the analysis. The effect of acute admission was highest at the start of the urinary catheterization and decreased with continuing ICU stay/catheterization at a factor of 10% per day.

Mortality

Developing VAP was not associated with a higher crude mortality (26.0% and 23.2% in patients with and without infection, respectively). Developing a CR-BSI or a CA-UTI was associated with a (nearly) significantly higher crude mortality: 30.9% versus 20.2% (p=0.06) in patients with a CVC and 26.7% versus 16.7% (p=0.002) in patients with a CAD. In multivariate regression developing a device-associated infection was not associated with mortality (Table 4).

Micro-organisms

Only the culture of the first infection of its kind is given here. During the first 4 days of ventilation 37% of the isolates for VAP were flora associated with early-onset VAP: *Staphylococcus aureus, Streptococcus pneumoniae,* and *Haemophilus influenzae.* In pneumonia patients ventilated for 5 days or more less *H. influenzae* was isolated and more *Pseudomonas aeruginosa* and Enterobacteriaceae. In CA-UTI patients intestinal flora contributed 69% in the first 4 days. This decreased to 44%, whereas *P. aeruginosa* and *Klebsiella pneumoniae* increased in frequency. Staphylococci were found in 60% of the isolates of CR-BSI patients in the first 2 weeks. After 2 weeks they were only found in 41% of the isolates whereas Enterobacteriaceae were more frequently found with increasing duration of CVC.

Table 3: Relative risks (RR) for infection, with 95% confidence intervals (CI), based on multivariate Cox regression.

	VAP		CR-BSI		CA-UTI	
	RR	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
Sex						
Male	**1**				**1**	
Female	**0.8***	(0.6-1.0)			**1.4***	(1.0-1.8)
APACHE II score						
0-19	**1**					
≥20	**1.2**	(1.0-1.5)				
Immunity						
Not impaired					**1**	
Leucopenia					**‡**	
Otherwise impaired immunity					**2.5****	(1.5-4.0)
Admission						
Planned			**1**		**1**	
Acute			**0.5****	(0.3-1.0)	**1.8***	(1.0-3.3)
Interaction with time					**0.9****	(0.9-1.0)
SDD use						
no SDD-use	**1**					
SDD use	**0.6****	(0.4-0.9)				
Systemic antibiotics at admission						
no SAB use					**1**	
SAB use					**0.5****	(0.3-1.0)

*0.05 < p < 0.1
**p < 0.05
‡No cases in category
Analysis of risk factors for which interaction with time was significant was executed with interaction terms included for all categories. However only significant interactions are shown.

DISCUSSION

This is one of the few prospective studies to investigate both the incidence of and the risk factors for different types of device-related ICU-acquired infections as well as their effect on mortality in the same patient population. Nearly every fifth ventilated patient without a preexisting infection, admitted for 48 hours or more at Dutch ICUs developed VAP. Infection rates in patients with a CVC or CAD were 3% and 8% respectively. Longer device use increased the risk of acquiring an infection, especially CR-BSI, and CA-UTI. Device-associated infections did not significantly increase the mortality of device-assisted patients after adjustment for case-mix.

Device utilization rates and infection rates

Device use was high in our population. The overall mean ventilator use rate reported by the NNIS was approximately 40% [9] whereas this was 58% in our study. The same applies for central line use (approx. 50% and 61%, respectively) and urinary catheter use

Table 4: Multivariate odds ratios (OR) for mortality, with 95% confidence intervals (CI)

	Ventilated patients (n=1516)		**Patients with a CVC** (n=1604)		**Patients with a urinary catheter** (n=2259)	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Age						
≤39 years	1		1		1	
40-70 years	1.7**	(1.1-2.8)	1.3	(0.8-2.2)	1.6**	(1.0-2.5)
≥ 70 years	3.0**	(1.9-4.8)	2.7**	(1.6-4.5)	2.8**	(1.8-4.4)
APACHE II score						
0-19	1		1		1	
≥20	1.9**	(1.5-2.4)	1.7**	(1.3-2.3)	1.9**	(1.5-2.4)
Specialty						
Surgery/traumatology	1		1		1	
Internal medicine	1.7**	(1.5-2.7)	2.1**	(1.5-2.9)	1.9**	(1.4-2.7)
Cardiology/-surgery	2.4**	(1.6-3.6)	2.4**	(1.6-3.6)	2.6**	(1.8-3.8)
Neurology/-surgery	1.8**	(1.2-2.8)	1.9**	(1.2-3.2)	1.8**	(1.2-2.7)
Other	1.3	(0.8-2.1)	1.8**	(1.1-2.8)	1.4	(0.9-2.2)
Admission						
Planned					1	
Acute					1.4**	(1.0-1.8)
Systemic antibiotics at admiss.						
No	1		1		1	
Yes	1.6**	(1.1-2.4)	1.4	(0.9-2.1)	1.5**	(1.1-2.3)
Ventilation						
No			1		1	
Yes			3.9**	(2.5-6.0)	4.8**	(3.3-7.0)
CVC						
No	1				1	
Yes	1.7**	(1.2-2.3)			1.8**	(1.3-2.5)
Duration of device use						
< 4 days	1		1			
5-14 days	1.5**	(1.1-2.0)	1.6**	(2.0-4.0)		
>15 days	1.6**	(1.1-2.2)	2.8**	(2.5-6.0)		

*0.05 < p < 0.1; ** p < 0.05

(70% and 86%, respectively). These differences could be the result of different selections of patient populations (all ICU patients in NNIS vs. patients staying at least 48 h in this study) which is likely to be reflected in their need of device assistance, but also of differences in patient management. The inclusion criterion of ICU stay 48 h or longer in our study probably resulted in higher infection incidence rates. Also, some publications report incidence density rates calculated with all ICU or device days instead of the number of days up to infection, resulting in lower rates, as pointed out for ventilated patients by Eggimann et al [10]. This is the case with figures derived from NNIS data [9].

Our pneumonia rate of 19% in ventilated patients and 25 per 1,000 ventilator days falls within the reported rates in more recent studies with comparable methods of diagnosing VAP (cultures usually from endotracheal aspirates or sputum): 9.8/1,000

ventilator days [9], 15% [11], 15% [12] and 44.0 per 1,000 ventilator days at risk [10], although it seems relatively high. In our study a pneumonia was considered ventilator-associated when the infection day or the day before was a ventilator day. Many studies consider VAP when a patient is ventilated longer than 48 h [13]. This difference may account in part for a relatively high VAP rate. The CR-BSI rate among patients with a central line was 3%. This figure is comparable to rates in other studies [14-16]. Our CA-UTI rate of 8% was also in accordance with earlier reported CA-UTI rates [17-19].

Risk factors for infection

The increased VAP, CR-BSI and CA-UTI risk as a consequence of device use (in general) and the effects of some of the other risk factors, for example, sex, were comparable to those reported previously [13;20;21]. After much debate [22-24] a recent Cochrane review concluded that SDD, aimed at eradicating colonization of aerobic, potentially pathogenic micro-organisms from the oropharynx, stomach, and gut, does benefit the ventilated patient [25]. In accordance with this, we found a decreased relative risk of acquiring VAP when receiving SDD. Although reported in several other studies the use of systemic antibiotics was not associated with VAP in this group. Ibrahim et al [12] found that multiple central venous line insertions increased the VAP risk, but in our data a central vascular catheter was not associated with a higher VAP risk. Also, in CVC patients, ventilation did not affect the risk of CR-BSI, unlike the findings in another study [20]. An unexpected and unaccountable finding was acute admission lowering the risk of CR-BSI. Impaired immunity increased the CA-UTI risk whereas the use of systemic antibiotics at admission was associated with a lower risk. Ventilation or a central vascular catheter did not affect the CA-UTI risk in our study.

Duration of device use

Our data showed that a longer time at risk increased the chance of infection. However, this association was less for VAP, when ventilation lasted longer than approx. 10 days, indicating that ventilation provokes pneumonia relatively early, rendering patients remaining ventilated without infection as ‘survivors’ with lower intrinsic risk for VAP [26]. The incidence density was highest in patients ventilated for 5-9 days (Figure 1). Figure 2 shows that the proportion of patients developing VAP increased until day 5. Thereafter the percentage remained more or less constant until day 10 and declined slightly thereafter, although this was not statistically significant. An increase in VAP risk during the first 5 days or so, as we observed, has been reported by almost all studies [26-28]. The results in patients ventilated for a longer period are less consistent. Unfortunately, the different ways of expressing the daily risk complicates comparisons between studies.

Duration of CVC use was a major risk factor for CR-BSI (OR 5-9 days 4.3 and ≥ 10 days 8.4 vs. 1-4 days). This is consistent with the results of other studies: a duration of a central vascular catheter longer than 7 days was associated with an up to 8.7 times increased risk for CR-BSI [20]. Duration of urinary catheterization of 5 days or longer was a risk factor for urinary tract infection, which is in accordance with other findings [21]. These risk factors are of importance when stratifying nosocomial infection risks for interhospital comparison. Furthermore, some of them can be modified as to lower the infection risk. Several studies have reported that the duration of ventilation was successfully reduced without adverse patient outcomes [29-31]. Although less complex to achieve and perhaps therefore not a subject of explicit study, the timely removal of central vascular catheters and urinary catheters is of great importance because reducing the device duration can also reduce these patients' risk of developing an infection [32].

Mortality

Nosocomial pneumonia is associated with a high crude mortality, ranging from 20% to 71% [13]. We found that VAP was associated with a relatively low crude mortality of 26%, not significantly different from that in ventilated patients without VAP. Crude mortality was significantly higher for patients with CR-BSI and CA-UTI. However, neither VAP, CR-BSI nor CA-UTI was associated with mortality when adjusted for other risk factors. Some studies found VAP to be an independent risk factor for mortality while others did not [12;33-35]. Some authors conclude this to be related to the used diagnostics. In recent studies CR-BSI is not associated with a significant attributable mortality. Case-control studies have found similar crude as well as adjusted mortality rates in patients with and without CR-BSI [36-38].

Laupland et al [18] studied ICU-acquired UTI in a large cohort of ICU patients over 90% of whom had a urinary catheter and also found a comparable difference in crude mortality between patients with and without UTI. An ICU-acquired UTI was, however, not an independent risk factor for death. In CA-UTI this may be due to the fact that UTI can simply be a marker of other serious conditions [21]. There are very few other studies which include both nosocomial infection and duration of device use as risk factors for mortality. Increased duration of device use was an independent risk factor for mortality with ventilated patients and patients with a central line, but not in patients with a urinary catheter. In patients on a ventilator or with a CVC the duration of device use is related to the development of the patient's condition at the ICU and therefore closely associated with mortality. Being in need for both ventilation and a CVC increased the mortality risk, compared with needing ventilation or a CVC only. For ventilation this association was stronger than that with APACHE II score determined within the first 24 h. When all

patients, both device-assisted and not, were considered, developing nosocomial sepsis or two or more nosocomial infections independently increased mortality (data not shown).

Pros and cons of this surveillance based study

The patient-based surveillance of ICU-acquired infections in 19 hospitals, taking into account duration of device use, resulted in an extensive, detailed database. Surveillance using a standard protocol with standardized infection definitions for prospective surveillance on a daily basis has been shown to present the greatest sensitivity and specificity for the identification of nosocomial infections [39]. A drawback of observational studies is that not all confounding variables can be taken into account. Furthermore, we included the use of all three devices in our analyses, but we did not adjust for the occurrence of a possible earlier infection of another type. Data on antibiotic resistance of the cultured micro-organisms were not collected. However, mean resistance levels in Dutch hospitals and ICUs are known to be low [40].

CONCLUSIONS

Duration of device use was an important risk factor for VAP, CR-BSI, and CA-UTI. The risk for VAP increased until day 5 and remained fairly constant until day 10. Device-associated infections were not independently associated with mortality, but (duration of) ventilation and (duration of) CVC use were. When investigating which patient groups in an institution would benefit most of infection prevention strategies, factors such as device use, time at risk, APACHE II score, intravenous antibiotics at admission, immunity, sex, acute admission must be considered. These risk factors are also of importance when stratifying for device-associated infection risks for interhospital comparison. The protocol that we used was designed for comparing the incidence of different types of ICU-acquired infections and therefore included a broad range of risk factors. The surveillance results formed a good basis to develop more specified protocols. Now Dutch hospitals can use specific surveillance protocols for CR-BSI and VAP which take more treatment specific risk factors into account and may better support infection prevention policy on the ICU.

SUPPLEMENTARY DATA

Appendix A: Patient characteristics for device assisted patients with a device-associated infection and without an infection.

	Ventilated patients n = 1516				**Patients with a CVC n = 1604**				**Patients with a urinary catheter n = 2259**			
	no VAP		**VAP**		**no CR-BSI**		**CR-BSI**		**no CA-UTI**		**CA-UTI**	
	n	*%*	n	*%*	n	*%*	n	*%*	n	*%*	n	*%*
	1235	*81.5*	281	*18.5*	1549	*96.6*	55	*3.4*	2087	*92.4*	172	*7.6*
Male	773	*62.9*	201	*71.8*	989	*64.1*	32	*58.2*	1307	*62.9*	99	*57.9*
Age												
0-39 years	167	*13.5*	50	*17.8*	140	*9.0*	6	*10.9*	254	*12.2*	20	*11.6*
40-69 years	534	*43.2*	135	*48.0*	704	*45.4*	28	*50.9*	946	*45.3*	88	*51.2*
70 years and older	534	*43.2*	196	*34.2*	705	*45.5*	21	*38.2*	887	*42.5*	64	*37.2*
APACHE II score												
0-9	173	*14.0*	30	*10.7*	314	*20.3*	8	*14.6*	422	*20.2*	31	*18.0*
10-19	483	*39.1*	91	*32.4*	620	*40.0*	14	*25.5*	848	*40.6*	56	*32.6*
20-29	368	*29.8*	117	*41.6*	424	*27.4*	27	*49.1*	543	*26.0*	56	*32.6*
30-39	131	*10.6*	26	*9.3*	114	*7.4*	3	*5.5*	167	*8.0*	20	*11.6*
=>40	50	*4.1*	13	*4.6*	51	*3.3*	1	*1.8*	60	*2.9*	7	*4.1*
Unknown	30	*2.4*	4	*1.4*	26	*1.7*	2	*3.6*	47	*2.3*	2	*1.2*
Immunity												
nothing in particular	1137	*92.1*	263	*93.9*	1426	*92.2*	52	*94.6*	1953	*93.7*	152	*88.4*
leucopenia	7	*5.7*	0	*0.0*	13	*0.8*	1	*1.8*	14	*0.7*	0	*0.0*
otherwise immunocompromised	90	*7.3*	17	*6.1*	108	*7.0*	2	*3.6*	118	*5.7*	20	*11.6*
SDD use	204	16.5	37	13.2	161	10.4	10	18.2	221	10.6	23	13.4

	no VAP		VAP		no CR-BSI		CR-BSI		no CA-UTI		CA-UTI	
	n	*%*	n	*%*	n	*%*	n	*%*	n	*%*	n	*%*
Systemic antibiotics at admission	107	8.7	24	8.6	164	10.6	5	9.1	182	8.7	11	6.4
Systemic antibiotics during ICU stay	890	72.1	256	91.1	1013	65.4	54	98.2	1312	62.9	143	83.1
Specialty												
surgery/trauma	606	49.1	143	50.9	787	50.8	33	60.0	1063	50.9	83	48.3
Internal	242	19.6	54	19.2	278	17.9	9	16.4	374	17.9	36	20.9
cardiology/-surgery	116	9.4	16	5.7	236	15.2	2	3.6	193	9.2	12	7.0
neurology/-surgery	159	12.9	46	16.4	113	7.3	4	7.3	294	14.1	33	19.2
other	111	9.0	22	7.8	135	8.7	7	12.7	163	7.8	8	4.7
Origin												
Community	573	46.4	148	52.7	667	43.1	24	43.6	917	43.9	81	47.1
Re-admission	16	1.3	0	0.0	19	1.2	1	1.8	25	1.2	3	1.7
Other ward	534	43.2	101	35.9	742	47.9	27	49.1	969	46.4	69	40.1
Other hospital no ICU	55	4.5	23	8.2	60	3.9	2	3.6	95	4.6	16	9.3
Other ICU same hospital	16	1.3	3	1.1	16	1.0	0	0.0	22	1.1	0	0.0
ICU other hospital	41	3.3	6	2.1	45	2.9	1	1.8	59	2.8	3	1.7
Admission												
Planned	322	26.1	62	22.1	482	31.1	18	32.7	647	31.0	41	23.8
Acute	913	73.9	219	77.9	1067	68.9	37	67.3	1440	69.0	131	76.2
ICU stay												
3-4 days	316	*25.6*	2	*0.7*	472	*30.5*	1	*1.8*	704	*33.7*	5	*2.9*
5-14 days	709	*57.4*	102	*36.3*	787	*50.8*	9	*16.4*	1092	*52.3*	58	*33.7*
15 days or longer	210	*17.0*	177	*63.0*	290	*18.7*	45	*81.8*	291	*13.9*	109	*63.4*
Mortality (incl. withdrawal of life-sustaining devices)	287	*23.2*	73	*26.0*	313	*20.2*	17	*30.9*	349	*16.7*	46	*26.7*

Appendix B: Incidence rates (per 1000 days) of device-associated infections

Incidence rate	VAP			CR-BSI			CA-UTI		
	cases	vent. days	**incid.**	cases	CVC days	**incid.**	cases	CAD days	**incid.**
Sex									
Male	201	7474	**27**	32	7988	**4**	99	12212	**8**
Female	79	3741	**21**	23	4235	**5**	72	6652	**11**
Age									
0-39	50	1623	**31**	6	1277	**5**	20	2546	**8**
40-69	135	5488	**25**	28	5814	**5**	88	9009	**10**
70 years and older	96	4163	**23**	21	5186	**4**	64	7379	**9**
APACHE II score									
0-9	30	1574	**19**	8	1988	**4**	31	3180	**10**
10-19	91	3962	**23**	14	4516	**3**	56	6903	**8**
20-29	117	3939	**30**	27	4111	**7**	56	6222	**9**
30-39	26	1144	**23**	3	1048	**3**	20	1660	**12**
40+	13	448	**29**	1	426	**2**	7	614	**11**
Immunity									
nothing in particular	263	10472	**25**	52	11323	**5**	152	17694	**9**
leucopenia	0	66	**0**	1	92	**11**	0	134	**0**
otherwise imm. compromised	17	728	**23**	2	858	**2**	20	1090	**18**
SDD									
no SDD	244	8934	**27**	45	10457	**4**	149	15890	**9**
SDD	37	2340	**16**	10	1820	**5**	23	3044	**8**
Systemic AB at admission									
no SAB	256	10232	**25**	50	10840	**5**	161	17117	**9**
SAB	24	1034	**23**	5	1433	**3**	11	1801	**6**
Specialty									
surgery/trauma	143	5589	**26**	33	6757	**5**	83	9763	**9**
internal	54	2366	**23**	9	2172	**4**	36	3377	**11**
cardiology/-surgery	16	892	**18**	2	1381	**1**	12	1495	**8**
neurology/-surgery	46	1446	**32**	4	940	**4**	33	2889	**11**
other	22	977	**23**	7	1027	**7**	8	1410	**6**
Origin									
Community	148	5387	**27**	24	5297	**5**	81	8558	**9**
Re-admission	0	186	**0**	1	178	**6**	3	263	**11**
Other ward	101	4502	**22**	27	5762	**5**	69	8057	**9**
Other hospital no ICU	23	614	**37**	2	537	**4**	16	1219	**13**
Other ICU same hospital	3	140	**21**	0	114	**0**	0	194	**0**
ICU other hospital	6	445	**13**	1	389	**3**	3	643	**5**

Incidence rate	VAP			CR-BSI			CA-UTI		
	cases	vent. days	**incid.**	cases	CVC days	**incid.**	cases	CAD days	**incid.**
Admission									
Planned	62	2326	**27**	18	3098	**6**	41	4656	**9**
Acute	219	8948	**24**	37	9179	**4**	131	14278	**9**

Appendix C: Univariately determined relative risks for infection, based on Cox regression

	VAP		CR-BSI		CA-UTI	
	RR	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
Sex						
Male	**1**		**1**		**1**	
Female	**0.8***	(0.6-1.0)	**1.4**	(0.8-2.5)	**1.4****	(1.0-1.9)
Age						
0-39	**1**		**1**		**1**	
40-69	**0.8**	(0.6-1.1)	**1.1**	(0.4-2.6)	**1.3**	(0.8-2.1)
70 years and older	**0.8**	(0.5-1.1)	**1.0**	(0.4-2.4)	**1.2**	(0.7-2.0)
Device use						
No device use	**1**		**1**		**1**	
Ventilation			**1.8**	(0.5-5.8)	**1.4**	(0.9-2.4)
CVC	**0.9**	(0.7-1.2)			**1.1**	(0.7-1.5)
CAD	**1.1**	(0.5-2.2)	**Δ**			
APACHE II score						
0-19	**1**		**1**		**1**	
≥20	**1.2***	(1.0-1.6)	**1.4**	(0.8-2.4)	**1.0**	(0.7-1.4)
Specialty						
surgery/traumatology	**1**		**1**		**1**	
internal medicine	**0.9**	(0.6-1.2)	**1.4**	(0.3-6.3)	**1.3**	(0.9-1.9)
cardiology/-surgery	**0.7**	(0.4-1.1)	**0.1**	(0.0-1.4)	**1.0**	(0.6-1.9)
interaction with time			**1.1***	(1.0-1.3)		
neurology/-surgery	**1.2**	(0.9-1.7)	**16.1****	(1.4-190)	**1.3**	(0.9-2.0)
interaction with time			**0.7***	(0.4-1.0)		
other	**0.9**	(0.6-1.4)	**2.3**	(0.5-11.7)	**0.7**	(0.3-1.4)
Immunity						
not impaired	**1**		**1**		**1**	
leucopenia	**‡**		**3.0**	(0.4-22.1)	**‡**	
otherwise imm. compromised	**0.9**	(0.6-1.5)	**0.5**	(0.1-2.1)	**2.3****	(1.4-3.6)

	VAP		CR-BSI		CA-UTI	
	RR	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
Origin						
community	**1**		**1**		**1**	
re-admission	**‡**		**1.2**	(0.2-9.2)	**1.6**	(0.2-12.7)
other ward	**0.8**	(0.7-1.1)	**1.1**	(0.6-1.8)	**0.8**	(0.4-1.4)
other hospital (no ICU)	**1.4**	(0.9-2.1)	**0.8**	(0.2-3.2)	**0.5**	(0.2-1.3)
interaction with time					**1.1****	(1.0-1.1)
other ICU same hospital	**0.7**	(0.2-2.3)	**‡**		**‡**	
ICU other hospital	**0.5**	(0.2-1.2)	**0.5**	(0.1-3.9)	**0.2**	(0.0-1.7)

*0.05 < p < 0.1
**p < 0.05
‡No cases in category
Δ Collinearity
Analysis of risk factors for which interaction with time was significant was executed with interaction included for all categories. However only (marginally) significant interactions are shown or those that affected the relative risk of a risk factor substantially (SDD with UTI).

REFERENCES

1. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, Wolff M, Spencer RC, Hemmer M (1995) The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. JAMA 274:639-644
2. Gaynes R, Richards C, Edwards J, Emori TG, Horan T, Alonso-Echanove J, Fridkin S, Lawton R, Peavy G, Tolson J (2001) Feeding back surveillance data to prevent hospital-acquired infections. Emerg Infect Dis 7:295-298
3. Gastmeier P, Geffers C, Sohr D, Dettenkofer M, Daschner F, Ruden H (2003) Five years working with the German nosocomial infection surveillance system (Krankenhaus Infektions Surveillance System). Am J Infect Control DOI 10.1067/mic.2003.66
4. Groot AJ, Geubbels EL, Beaumont MT, Wille JC, de Boer AS (2001) [Hospital infections and risk factors in the intensive care units of 16 Dutch hospitals, results of surveillance of quality assurance indicators]. Ned Tijdschr Geneeskd 145:1249-1254
5. Kooi, TII van der, Wille, JC, and Hof, S van den (2005) ICU acquired infections and their risk factors in the Dutch surveillance system. Abstract nr. 78. 15th Annual scientific meeting of the Society for Healthcare Epidemiology of America: 80
6. HELICS (Hospitals in Europe link for infection control through surveillance) (2005) Surveillance of nosocomial infections in Intensive Care Units. HELICS-ICU Statistical Report 2000-2004
7. McLaws ML, Berry G (2005) Nonuniform risk of bloodstream infection with increasing central venous catheter-days. Infect Control Hosp Epidemiol 26:715-719
8. SAS 9.1 2002-2003. Cary, NC, SAS Institute Inc.
9. NNIS/CDC (2001) National Nosocomial Infections Surveillance (NNIS) System Report, Data Summary from January 1992-June 2001, issued August 2001. Am J Infect Control DOI 10.1067/mic.2001.119952
10. Eggimann P, Hugonnet S, Sax H, Touveneau S, Chevrolet JC, Pittet D (2003) Ventilator-associated pneumonia: caveats for benchmarking. Intensive Care Med 29:2086-2089
11. Tejerina E, Frutos-Vivar F, Restrepo MI, Anzueto A, Abroug F, Palizas F, Gonzalez M, D'Empaire G, Apezteguia C, Esteban A (2006) Incidence, risk factors, and outcome of ventilator-associated pneumonia. J Crit Care 21:56-65
12. Ibrahim EH, Tracy L, Hill C, Fraser VJ, Kollef MH (2001) The occurrence of ventilator-associated pneumonia in a community hospital: risk factors and clinical outcomes. Chest DOI 10.1378/chest.120.2.555
13. Bergmans DCJJ, Bonten MJM (2004) Nosocomial pneumonia. In: Mayhall GM (ed) Hospital epidemiology and infection control. Lippincott Williams & Wilkins, Philadelphia, pp 311-339
14. Renaud B, Brun-Buisson C (2001) Outcomes of primary and catheter-related bacteremia. A cohort and case-control study in critically ill patients. Am J Respir Crit Care Med 163:1584-1590
15. Rupp ME (2004) Nosocomial bloodstream infections. In: Mayhall GM (ed) Hospital Epidemiology and Infection Control. Lippincott Williams & Wilkins, Philadelphia, pp 253-265
16. Maki DG, Crnich CJ (2003) Line sepsis in the ICU: prevention ,diagnosis and management. Seminars in respiratory and critical care medicine 24:23-36
17. Fernández-Crehuet R, Díaz-Molina C, De Irala J, Martínez-Concha D, Salcedo-Leal I, Masa-Calles J (1997) Nosocomial infection in an intensive-care unit: identification of risk factors. Infect Control Hosp Epidemiol 18:825-830
18. Laupland KB, Bagshaw SM, Gregson DB, Kirkpatrick AW, Ross T, Church DL (2005) Intensive care unit-acquired urinary tract infections in a regional critical care system. Crit Care 9:R60-65

19. Craven DE, Kunches LM, Lichtenberg DA, Kollisch NR, Barry MA, Heeren TC, McCabe WR (1988) Nosocomial infection and fatality in medical and surgical intensive care unit patients. Arch Intern Med 148:1161-1168
20. Safdar N, Kluger DM, Maki DG (2002) A review of risk factors for catheter-related bloodstream infection caused by percutaneously inserted, noncuffed central venous catheters: implications for preventive strategies. Medicine 81:466-479
21. Burke JP, Tsin Wen Yeo (2004) Nosocomial urinary tract infections. In: Mayhall GM (ed) Hospital Epidemiology and Infection Control. Lippincott, Williams & Wilkins, Philadelphia, pp 267-286
22. D'Amico R, Pifferi S, Leonetti C, Torri V, Tinazzi A, Liberati A (1998) Effectiveness of antibiotic prophylaxis in critically ill adult patients: systematic review of randomised controlled trials. BMJ 316:1275-1285
23. Nieuwenhoven CA van, Buskens E, Tiel FH van, Bonten MJ (2001) Relationship between methodological trial quality and the effects of selective digestive decontamination on pneumonia and mortality in critically ill patients. JAMA 286:335-340
24. Jonge E de, Schultz MJ, Spanjaard L, Bossuyt PM, Vroom MB, Dankert J, Kesecioglu J (2003) Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. Lancet 362:1011-1016
25. Liberati A, D'Amico R, Pifferi, Torri V, Brazzi L (2005) Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care (Review). The Cochrane Library, 3
26. Cook DJ, Walter SD, Cook RJ, Griffith LE, Guyatt GH, Leasa D, Jaeschke RZ, Brun-Buisson C (1998) Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. Ann Intern Med 129:433-440
27. Langer M, Mosconi P, Cigada M, Mandelli M (1989) Long-term respiratory support and risk of pneumonia in critically ill patients. Intensive Care Unit Group of Infection Control. Am Rev Respir Dis 140:302-305
28. Chevret S, Hemmer M, Carlet J, Langer M (1993) Incidence and risk factors of pneumonia acquired in intensive care units. Results from a multicenter prospective study on 996 patients. European Cooperative Group on Nosocomial Pneumonia. Intensive Care Med DOI 10.1007/BF01690545
29. Kollef MH, Shapiro SD, Silver P, St John RE, Prentice D, Sauer S, Ahrens TS, Shannon W, Baker-Clinkscale D (1997) A randomized, controlled trial of protocol-directed versus physician-directed weaning from mechanical ventilation. Crit Care Med 25:567-574
30. Marelich GP, Murin S, Battistella F, Inciardi J, Vierra T, Roby M (2000) Protocol weaning of mechanical ventilation in medical and surgical patients by respiratory care practitioners and nurses: effect on weaning time and incidence of ventilator-associated pneumonia. Chest DOI 10.1378/chest.118.2.459
31. Dries DJ, McGonigal MD, Malian MS, Bor BJ, Sullivan C (2004) Protocol-driven ventilator weaning reduces use of mechanical ventilation, rate of early reintubation, and ventilator-associated pneumonia. J Trauma DOI 10.1097/01.TA.0000124462.61459.45
32. Leone M, Albanese J, Garnier F, Sapin C, Barrau K, Bimar MC, Martin C (2003) Risk factors of nosocomial catheter-associated urinary tract infection in a polyvalent intensive care unit. Intensive Care Med DOI 10.1007/s00134-003-1767-2
33. Safdar N, Dezfulian C, Collard HR, Saint S (2005) Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. Crit Care Med 33:2184-2193
34. Kollef MH (1993) Ventilator-associated pneumonia. A multivariate analysis. JAMA 270:1965-1970
35. Girou E, Stephan F, Novara A, Safar M, Fagon JY (1998) Risk factors and outcome of nosocomial infections: results of a matched case-control study of ICU patients. Am J Respir Crit Care Med

157:1151-1158

36. Blot SI, Depuydt P, Annemans L, Benoit D, Hoste E, De Waele JJ, Decruyenaere J, Vogelaers D, Colardyn F, Vandewoude KH (2005) Clinical and economic outcomes in critically ill patients with nosocomial catheter-related bloodstream infections. Clin Infect Dis 41:1591-1598
37. Garrouste-Orgeas M, Timsit JF, Tafflet M, Misset B , Zahar JR, Soufir L, Lazard T, Jamali S, Mourvillier B, Cohen Y, De Lassence A, Azoulay E, Cheval C, Descorps-Declere A, Adrie C, Costa de Beauregard MA, Carlet J (2006) Excess risk of death from intensive care unit-acquired nosocomial bloodstream infections: a reappraisal. Clin Infect Dis 42:1118-1126
38. Eggimann P, Pittet D (2002) Overview of catheter-related infections with special emphasis on prevention based on educational programs. Clin Microbiol Infect 8:295-309
39. Glenister H, Taylor L, Bartlett C, Cooke M, Sedgwick J, Leigh D (1991) An assessment of selective surveillance methods for detecting hospital-acquired infection. Am J Med 91:121S-124S
40. Carlet J, Ben Ali A, Chalfine A (2004) Epidemiology and control of antibiotic resistance in the intensive care unit. Curr Opin Infect Dis DOI 10.1097/01/qco.0000136927.29802.68

Chapter 3

Catheter application, insertion vein and length of ICU stay prior to insertion affect the risk of catheter-related bloodstream infection

T.I.I. van der Kooi, J.C. Wille, B.H.B. van Benthem

Journal of Hospital Infection 2012(80): 238-244

ABSTRACT

Background: The Dutch PREZIES surveillance scheme for catheter-related bloodstream infection (CR-BSI) collects data on infection rates and related risk factors.

Aim: To evaluate risk factors for CR-BSI.

Methods: Hospitals collected data for intensive care units (ICU) or for the entire hospital. All short-term central venous catheters (CVC), including Swan-Ganz catheters, present for ≥ 48 hours were surveyed, except in cases when bacteraemia was present at insertion. CVCs were monitored until infection, removal or death for up to 28 days. Data were collected on 3,750 catheters and 29,003 CVC days.

Findings: Of the CVCs surveyed, 1.6% (95% confidence interval (CI) 1.2-2.0) resulted in CR-BSI, representing 2.0/1000 CVC days (95% CI 1.6-2.6). Multi-variate analysis revealed that the length of ICU stay prior to CVC insertion, insertion in the jugular or femoral vein, and use of the CVC to deliver total parenteral nutrition increased the risk of CR-BSI, whereas use of the CVC to deliver antibiotics decreased the risk of CR-BSI.

Conclusion: Attention to these risks has the potential to reduce the incidence of CR-BSI.

INTRODUCTION

In the Netherlands, 7% of patients admitted to acute care hospitals subsequently have a central venous catheter (CVC).[1] These are mainly used in patients in intensive care units (ICU). Critically ill and other patients who are in need of a CVC are at increased risk of acquiring bloodstream infection (BSI). The risk of acquiring a CVC-related bloodstream infection (CR-BSI) ranged from 2 to 4/1000 CVC days in recent studies.[2-6] CR-BSIs increase the duration of ICU and hospital stay, and are associated with increased medical costs varying in different studies between $4200 to €13500 per patient.[7-9] The aging population in the Netherlands (14% aged ≥ 65 years in 2006, predicted to increase to 24% in 2040),[10] and the consequent increase in the number of hospital admissions, will result in a growing burden of nosocomial infections. From this perspective, the importance of preventing nosocomial infections is even more apparent.

Many studies have evaluated interventions aimed at reducing the incidence of CR-BSI, including technical innovations as well as behavioural changes.[11-25] Surveillance is necessary in order to gain insight into the incidence of CR-BSI. Effective surveillance can also result in a decrease in infection rates.[4 26]

In the Netherlands, PREZIES, the national nosocomial infection surveillance network, commenced surveillance of CR-BSI in 2000. A national patient safety initiative began in 2009, focusing, among other things, on CR-BSI prevention. As such, the data presented in this paper can be considered as national baseline data.

METHODS

PREZIES, established in 1996, is a collaboration of participating hospitals, the Dutch Institute for Healthcare Improvement and the National Institute for Public Health and the Environment (RIVM). In 2000, having offered an ICU-wide surveillance module for four years[27], PREZIES invited hospitals to participate in more targeted surveillance of CR-BSI. This included collection of a larger and more targeted range of potential risk factors for CR-BSI. As in most European surveillance systems, the definitions used are based on those of the former Centers for Disease Control and Prevention/National Nosocomial Infections Surveillance System, nowadays the National Healthcare Safety Network definitions. In Dutch clinical practice, CR-BSI is usually investigated by culturing both peripheral blood and the catheter tip. Other laboratory methods such as paired blood cultures are uncommon. The diagnostic criteria are summarized below (box 1).
Based on international literature and the preceding ICU surveillance, a protocol was developed by a working group consisting of an intensivist and an anaesthesiologist (representative of their societies), epidemiologists and infection control professionals.

All uncuffed CVCs and Swan-Ganz catheters present for ≥ 48 hours in patients over one year of age were included, unless they were inserted during a culture-proven bacteraemia.

Box 1: PREZIES criteria for central venous catheter-related bloodstream infection (CR-BSI)

PREZIES criteria for CR-BSI:

- clinical symptoms (fever (> 38°), shivers, hypotension (systolic pressure<100)) *and*
- absence of other infection with identical micro-organism *and*

either
- positive (semi) quantitative culture of the catheter tip (>15 cfu) *and*
- peripheral venous blood culture positive for identical micro-organism *or*

or
- positive (semi) quantitative culture of the catheter tip (>15 cfu) *and*
- arterial blood culture positive for identical micro-organism *or*
- no blood culture done

or
- positive qualitative culture of the catheter tip *and*
- peripheral venous blood culture positive for identical micro-organism

or
- no cultures done *or*
- positive qualitative culture of the catheter tip only *or*
- positive peripheral venous blood culture only *and*
- fever disappears within 24 hrs after removal of the catheter

or
- positive peripheral venous blood culture *and*
- catheter remains in situ *and*
- fever disappears within 48 hrs after start of antibiotic treatment

Broviac/Hickman catheters and Port-a-Caths were excluded. Hospitals could choose to record all such patients or only those in specific ICU(s). Multiple hospital admissions per patient could be included as well as multiple concurrent central lines per patient. Each central line was monitored until infection or removal for up to 28 days.

The following data were recorded: type of hospital (university hospital or not); ICU level (level 1-3, indicating increasing complexity of care); demographic data; specialty of the treating physician; APACHE II score if in ICU; dates of hospital admission and discharge; ICU admission and discharge; CVC insertion and removal; insertion ward (operating room/recovery room, ICU or other); insertion vein; coating; surgery (in the week before insertion of the first CVC); single or multi-lumen; acute or elective insertion ('acute' being defined as an emergency insertion with suboptimal infection prevention measures); replacement ≤ or > 24 h; CVC application [total parenteral nutrition (TPN),

hemodynamic monitoring, administration of antibiotics, dialysis or, if none of these, other uses]; and, if present, infection criteria, infection date and microbiological results.

CVC surveillance was continued for 28 days or until a CR-BSI occurred, the CVC was removed, the patient was transferred to another hospital, died or when active (life-supporting) treatment was withheld. When ICU patients with a CVC *in situ* were discharged to another ward in the same hospital surveillance was continued. Mortality was an optional variable, recorded by some hospitals.

Hospitals participated voluntarily and received feedback reports with case-mix-adjusted infection rates. These reports were usually discussed by the infection control committee with ICU and other staff as appropriate. Quality assurance included annual workshops for participants and visits from an external validation team.

Data were recorded locally but were checked for completeness and consistency on receipt by RIVM.

Infection rates were expressed as the number of infections per 1000 CVC days. Time at risk (in days) was defined as removal date minus insertion date.

Poisson and Cox regression in SAS 9.2 (Cary, USA) were used to calculate relative risks. All variables were fixed except for whether the patient with CVC was in the ICU on each specific day which was determined daily and was therefore time dependent. Length of ICU stay prior to CVC insertion was analysed as a categorical factor. Risk factors were tested for proportional hazards and plausible interactions. Risk factors with $P \leq 0.20$ in the univariate regression analyses were initially included in the multiple regression models. The model was reduced with manual backward elimination. Confounding was investigated in this model. Statistical significance was defined at $P \leq 0.05$.

RESULTS

Data from the first two years of surveillance were of poor quality and were therefore excluded. Nine hospitals (9% of all Dutch hospitals), including one university medical centre, collected data for one to four years between 2002 and 2009. Most hospitals collected data from adult ICU wards. In total, data were collected on 2565 patients, reflecting 3750 CVCs and 29,003 CVC-days; 9.5% of these patients were not in an ICU, and 56.4% of the catheters were inserted in men. The median age of patients was 67 years.

The median CVC duration was six days (interquartile range 4-10). Overall, 1.6% of CVCs [95% confidence interval (CI) 1.2–2.0] resulted in CR-BSI, representing 2.0/1000 CVC-days (95% CI 1.6–2.6), and 2.3% of patients (95% CI 1.8–3.0) developed CR-BSI. The average incidence rate varied between hospitals from 0.9 to 3.0/1000 CVC-days. Of the 59 infections that occurred, 44% were based on both (semi) quantitative culture of the

catheter tip and a peripheral venous blood culture, and 53% were based on (semi) quantitative culture of the catheter tip and a blood culture drawn from an arterial catheter or no blood culture. Table I shows the most relevant patient and CVC characteristics, including the infection frequencies.

Figure 1 shows the risk of CR-BSI over time, averaged per four days. Prolonged catheterisation was significantly associated with the risk of developing infection [odds ratio of one extra CVC-day 1.1, 95% CI 1.07–1.14] in univariate logistic regression (Proc logistic in SAS)). Multi-level Poisson regression (Proc glimmix in SAS) revealed that both hospital and patient level were not significant. Therefore, Cox regression (Proc phreg in SAS) was used to

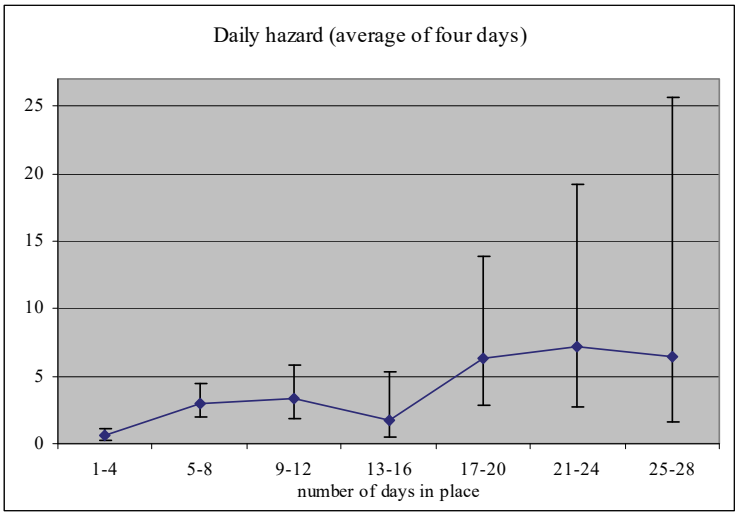


Figure 1: Daily hazard for the development of catheter-related bloodstream infection, averaged per four days, with 95% confidence intervals.

obtain the presented results. The time-dependent 'ICU presence' was not included in the multi-variate analysis (hazard ratio 1.3, 95% CI 0.7–2.4), but length of ICU stay prior to insertion was significantly associated with the risk of CR-BSI. Table II presents the hazard ratios of univariate and multi-variate analyses. The results of multi-variate analysis were adjusted for the confounding variable 'lumen' (single vs multi-lumen). When adjusted for lumen, the effect of prolonged ICU stay was more pronounced. Insertion in the jugular (P=0.06) or femoral vein compared with the subclavian vein, (prolonged) ICU-stay prior to CVC insertion (up to 20 days) and TPN through the CVC were associated with an increased risk of CR-BSI, whereas administration of antibiotics through the CVC was associated with a lower risk of infection.

Table I: Patient and central venous catheter characteristics.

	Number of CVCs	% of total number of CVCs	Number of CVC days	Catheter-related bloodstream infection	
				Incidence rate per 1000 CVC-days	95% CI[a]
Total	3750		29,003	2.0	(1.5 – 2.6)
Age (years)					
1-10	4	0.1	29	0.0	(0.0 - 158)
11-20	57	1.5	444	2.3	(0.3 - 16.0)
21-40	228	6.1	1800	1.7	(0.5 - 5.2)
41-60	910	24.3	7253	2.2	(1.4 - 3.6)
61-80	2112	56.3	16,213	1.9	(1.3 - 2.7)
>80	439	11.7	3264	2.5	(1.2 - 4.9)
Apache II score (of first ICU stay)					
0-20	1633	43.5	12,232	2.3	(1.5 – 3.3)
21-40	1519	40.5	11,369	2.0	(1.3 – 3.0)
>40	141	3.8	1023	2.0	(0.2 – 7.1)
Missing	186	5.0	1247	2.4	(0.5 – 7.0)
Patient not in ICU	271	7.2	3132	1.0	(0.2 – 2.8)
ICU level (1, 2 or 3)[b]					
1	0				
2	1083	28.9	8036	1.2	(0.7 – 2.3)
3	2667	71.1	20,967	2.3	(1.8 – 3.1)
ICU stay (until CVC insertion)[c]					
not in ICU (before insertion)	370	9.9	4092	1.0	(0.3 – 2.6)
1-5 days	2246	59.9	15,643	2.0	(1.3 – 2.8)
6-20 days	649	17.3	5597	3.4	(2.0 – 5.3)
> 20 days	206	5.5	2067	1.5	(0.3 – 4.2)
not determinable[d]	279	7.4	1604	1.2	(0.1 – 4.5)
Insertion department					
ICU	2795	*74.5*	21,540	2.2	(1.6 – 2.9)
OR / recovery	818	*21.8*	5840	1.5	(0.7 – 2.9)
Other	132	*3.5*	1573	1.9	(0.4 – 5.6)
Missing	5	*0.1*	50	0.0	(0.0 – 92.3)
Insertion vein					
Subclavian vein	1420	*37.9*	12,337	1.5	(0.9 – 2.4)
Jugular vein	992	*26.4*	7126	2.2	(1.3 – 3.6)
Femoral vein	1314	*35.0*	9395	2.6	(1.6 – 3.8)
Other veins	24	*0.6*	145	0.0	(0.0 – 32.0)
Lumen					
Single	298	*7.9*	2957	1.7	(0.5 – 3.9)
Multiple	3414	*91.0*	25,625	2.0	(1.5 – 2.7)
Missing	38	*1.0*	421	4.8	(0.5 – 17.2)
Coating					
No coating	3464	*92.4*	26,685	1.9	(1.5 - 2.5)
Coating	280	*7.5*	2257	2.7	(1.2 - 5.9)
Unknown	6	*0.2*	61	32.8	(8.2 - 131)

	Number of CVCs	% of total number of CVCs	Number of CVC days	Catheter-related bloodstream infection	
				Incidence rate per 1000 CVC-days	95% CI[a]
Use					
Parenteral nutrition	736	*19.6*	7197	3.1	(1.9 – 4.6)
Dialysis	413	*11.0*	3336	3.9	(2.1 – 6.7)
Hemodynamic monitoring	1999	*53.3*	13,897	1.5	(0.9 – 2.3)
Antibiotics	1760	*46.9*	13,858	1.6	(1.0 – 2.4)
Other (none of above)	1931	*51.5*	14,160	1.6	(1.0 – 2.4)

[a] 95% CI according to Rothman/Greenland. With zero infections in a category the Byar poisson approach was used.
[b] *1 = suited for low complex patients; 3 = suited for high complex patients*
[c] CVC insertion not necessarily directly after ICU stay
[d] Either a ICU admission or ICU discharge date were known but not both. One hospital did not collect ICU discharge dates, contributing to 272 of these 279 cases.

Table II: Risk factors for the development of catheter-related bloodstream infection in univariate and multi-variate Cox regression analyses.

	Univariate analysis		**Multivariate analysis**	
	Hazard ratio	95% CI	Hazard ratio	95% CI
Insertion vein				
Subclavian vein	Ref.[£]		Ref.[a]	
Jugular vein	1.7	0.9 - 3.3	1.9*	1.0 - 3.8
Femoral vein	2.0**	1.1 - 3.7	2.0**	1.0 - 3.8
Antibiotics through CVC	0.6	0.4 - 1.1	0.5**	0.3 - 0.9
Parenteral nutrition through CVC	1.5	0.9 - 2.5	2.3**	1.3 - 4.1
Duration of ICU stay until CVC insertion				
0 days (no ICU stay)	Ref.		Ref.	
1 - 5 days	3.0**	1.1 - 8.7	4.4**	1.2 - 16.1
6 - 20 days	4.5**	1.5 - 13.3	6.6**	1.7 - 25.5
> 20 days	1.7	0.4 - 7.4	2.4	0.4 - 12.9
not determinable[b]	2.3	0.4 - 12.9	2.5	0.4 - 16.5
Dialysis through CVC	2.2**	1.2 - 4.0		
Other CVC use (Other than TPN, dialysis, AB or hemodynamic monitoring)	0.7	0.4 - 1.2		
ICU level (complexity of care)				
2	Ref.			
3	1.8*	0.9 - 3.6		

All variables with p < 0.2 were included in the initial multivariate regression model and are shown here. Results of the multivariate analysis were corrected for confounding by the variable lumen (single versus multilumen).
[a] Reference
[b] Either a ICU admission or ICU discharge date were known but not both.
** p = < 0.05
* 0.05 < p <0.1

DISCUSSION

The incidence of CR-BSI in the study cohort was comparable with or lower than that found in other recent multi-centre studies,[2-6] but higher than the infection rate attained in some intervention studies.[25,28] However, the different infection criteria used (catheter-associated bloodstream infection or CR-BSI or variations thereupon) also affect these rates.

The effects of antibiotics, TPN and insertion vein in the surveillance cohort have frequently been shown to be associated with CR-BSI.[29] L'Hériteau[2] *et al* also found a higher risk of CR-BSI associated with insertion in the jugular vein, and a lower risk when the CVC was used for administration of antibiotics. Selective digestive tract decontamination with four days of intravenous cefotaxime, as practiced in some Dutch hospitals in order to reduce mortality, was also associated with a reduced rate of ICU-acquired bacteraemia.[30] There could be several reasons for the negative association between antibiotics and CR-BSI, apart from their antimicrobial effect. CR-BSI may be underdiagnosed in patients on antibiotics because clinicians may apply a higher threshold before taking blood cultures. This is less likely to account for the association in the present data, because it was possible to diagnose an infection without blood cultures. It is not possible to assess the extent to which false-negative blood cultures for patients on antibiotic therapy played a role. Similar to the present results, Wylie *et al* and Tacconelli *et al* found an increased risk for CR-BSI associated with TPN.[31,32]

However, L'Hériteau *et al* did not find an increased risk for CR-BSI associated with CVC insertion through the femoral vein although haemodialysis catheters were excluded in that study.[2] In the present cohort, CVC insertion in the femoral vein was strongly associated with dialysis (71% of the CVCs used for dialysis were inserted in a femoral vein), and therefore, although not significant in the multi-variate analysis, an independent deleterious effect of dialysis cannot be excluded. In a randomized trial with dialysis catheters alone, no difference was found in the infection rates for femoral and jugular access.[33]

An increased APACHE II score was not significantly associated with increased risk of CR-BSI in the present study, but patients in the ICU with a CVC inserted had a higher risk of CR-BSI than patients in other departments, and prolonged ICU stay prior to CVC insertion increased the risk. APACHE II scores are determined during the first 24 h of ICU admission, whereas the length of stay in the ICU prior to CVC insertion is associated with recovery or deterioration of the patient while at the ICU. However, when adjusted for APACHE II score, the effect of a prolonged ICU stay was reduced, as higher APACHE II scores tended to be associated with higher risk of infection (data not shown).

Other studies have demonstrated an association between prolonged catheterization and increased risk of CR-BSI[2,3,34]. The increased risk of infection associated with longer CVC duration may be attributed to risk factors being greater in CVCs that remain *in situ* for a relatively long time. However, this was not the case in the study cohort, except for CVCs used for TPN (17.8% of TPN CVCs *in situ* for over 14 days compared with 8.7% of other CVCs).

This study had the following limitations. CVC that were inserted when patients were experiencing a bacteraemia were excluded. The risk factors for CR-BSI in a CVC in a bacteraemic patient may differ from the ones in the surveillance population, and the rate may have been higher if these CVCs had been included. The hospitals in this study participated because they were aware of the risk of CVC use and were keen to prevent CR-BSI; as such, these hospitals may not be widely representative. The participating hospitals diagnosed the infections themselves and this may have led to differences in interpretation of the infection criteria. However, with validation visits from PREZIES, annual meetings for participants, a clear protocol and case histories on the PREZIES website, this is unlikely to have been a major source of bias.

Participating hospitals received benchmark reports with adjusted rates. The authors adjusted the rates for risk factors that hospital staff cannot substantially influence, and which were significantly associated with the risk of CR-BSI in the study data. Based on earlier analyses, rates were adjusted for the distribution of CVC applications in three categories: TPN, dialysis and other applications. Feedback reports were used to evaluate CVC insertion procedures, CVC care and general infection prevention practices. From 2009 onwards, participation increased as Dutch hospitals committed themselves to reduce CR-BSI rates as part of a national patient safety initiative (www.vmszorg.nl). CR-BSI rates are monitored, as is adherence to a bundle of best practices, based on those recommended by the Centers for Disease Control and Prevention and selected by Pronovost *et al*.[35] This bundle consists of:

- subclavian access as the preferred insertion site, followed by the jugular vein (another vein can be chosen instead of the subclavian, e.g. in the case of expected increased risk of mechanical complications, but this should be documented). The current guideline of the Dutch Associaton of Intensive Care does not routinely advise ultrasound guidance of CVC insertion.
- skin antisepsis with alcohol-based chlorhexidine;
- hand hygiene (all people actively involved with CVC insertion must disinfect their hands);
- maximal barrier precaution measures at CVC insertion (sterile gloves, cap, gown and a large drape);

- need for CVC evaluated daily; and
- insertion site checked daily for signs of infection.

The data presented in this article can be considered as a national baseline for this programme. Regarding the results on the effect of the chosen insertion vein and considering the frequencies of insertion in the femoral (35.0%) and jugular veins (26.4%), increased compliance with the bundle of best practices introduced in the Dutch national patient safety program has the potential to reduce the incidence of CR-BSI. Depending on alertness to the assessment of the ongoing need for a CVC, especially for risk-associated uses such as TPN, additional improvement is possible.

Although antibiotic-coated catheters can reduce the incidence of CR-BSI, their use is not preferred in the Netherlands because of the possible increase in antibacterial resistance.[36,14] Administering antibiotics through a CVC solely to reduce the CR-BSI rate does not seem well-advised.

In conclusion, ICU stay and prolonged ICU stay prior to CVC insertion, insertion in the jugular and femoral vein, and TPN increased the risk of CR-BSI in this study, whereas administration of antibiotics through the CVC decreased the risk of infection. Increased compliance with the bundle of best practices introduced in the national patient safety program has the potential to reduce the incidence of CR-BSI in Dutch hospitals.

ACKNOWLEDGEMENTS
This study was possible thanks to the efforts of infection control professionals, medical specialists, nurses and other hospital staff who dedicated their time and attention to the surveillance and prevention of CR-BSI in their hospitals.

Conflict of interest statement
None declared.

Funding sources
None.

REFERENCES

1. van der Kooi TI, Mannien J, Wille JC, van Benthem BH. Prevalence of nosocomial infections in The Netherlands, 2007-2008: results of the first four national studies. *J Hosp Infect* 2010; **75**: 168-172. doi:10.1016/j.jhin.2009.11.020 .
2. L'Heriteau F, Olivier M, Maugat S *et al*. Impact of a five-year surveillance of central venous catheter infections in the REACAT intensive care unit network in France. *J Hosp Infect* 2007; **66**: 123-129. doi:10.1016/j.jhin.2007.03.014.
3. Garnacho-Montero J, Aldabo-Pallas T, Palomar-Martinez M *et al*. Risk factors and prognosis of catheter-related bloodstream infection in critically ill patients: a multicenter study. *Intensive Care Med* 2008; **34**: 2185-2193. DOI 10.1007/s00134-008-1204-7.
4. Gastmeier P, Geffers C, Brandt C *et al*. Effectiveness of a nationwide nosocomial infection surveillance system for reducing nosocomial infections. *J Hosp Infect* 2006; **64**: 16-22. doi:10.1016/j.jhin.2006.04.017.
5. Templeton A, Schlegel M, Fleisch F *et al*. Multilumen central venous catheters increase risk for catheter-related bloodstream infection: prospective surveillance study. *Infection* 2008; **36**: 322-327.
6. Agodi A, Auxilia F, Barchitta M *et al*. Building a benchmark through active surveillance of intensive care unit-acquired infections: the Italian network SPIN-UTI. *J Hosp Infect* 2010; **74**: 258-65. doi:10.1016/j.jhin.2009.08.015.
7. Blot SI, Depuydt P, Annemans L *et al*. Clinical and economic outcomes in critically ill patients with nosocomial catheter-related bloodstream infections. *Clin Infect Dis* 2005; **41**: 1591-1598. doi:10.1053/jhin.2002.1329.
8. Higuera F, Rangel-Frausto MS, Rosenthal VD *et al*. Attributable cost and length of stay for patients with central venous catheter-associated bloodstream infection in Mexico City intensive care units: a prospective, matched analysis. *Infect Control Hosp Epidemiol* 2007; **28**: 31-35. DOI: 10.1097/01.CCM.0000178190.89663.E5 .
9. Tacconelli E, Smith G, Hieke K, Lafuma A, Bastide P. Epidemiology, medical outcomes and costs of catheter-related bloodstream infections in intensive care units of four European countries: literature- and registry-based estimates. *J Hosp Infect* 2009; **72**: 97-103. doi:10.1016/j.jhin.2008.12.012.
10. Hollander AEM, Hoeymans N, Melse JM, Oers JAMv, Polder JJ. Zorg voor Gezondheid . Volksgezondheid Toekomst Verkenning 2006 (Care for Health. Exploration of the Future of Public Health 2006). Bilthoven: National Institute of Public Health and the Environment (RIVM), 2006.
11. Harbarth S, Sax H, Gastmeier P. The preventable proportion of nosocomial infections: an overview of published reports. *J Hosp Infect* 2003; **54**: 258-266. doi:10.1016/S0195-6701(03)00150-6.
12. Gastmeier P, Geffers C. Prevention of catheter-related bloodstream infections: analysis of studies published between 2002 and 2005. *J Hosp Infect* 2006; **64**: 326-335. doi:10.1016/j.jhin.2006.07.005.
13. Al Raiy B, Fakih MG, Bryan-Nomides N *et al*. Peripherally inserted central venous catheters in the acute care setting: A safe alternative to high-risk short-term central venous catheters. *Am J Infect Control* 2010; **38**: 149-153.
14. Casey AL, Mermel LA, Nightingale P, Elliott TS. Antimicrobial central venous catheters in adults: a systematic review and meta-analysis. *Lancet Infect Dis* 2008; **8**: 763-776.
15. Esteve F, Pujol M, Limon E *et al*. Bloodstream infection related to catheter connections: a prospective trial of two connection systems. *J Hosp Infect* 2007; **67**: 30-34. doi:10.1016/j.jhin.2007.05.021.
16. Schuerer DJ, Zack JE, Thomas J *et al*. Effect of chlorhexidine/silver sulfadiazine-impregnated central

venous catheters in an intensive care unit with a low blood stream infection rate after implementation of an educational program: a before-after trial. *Surg Infect* 2007; **8**: 445-454. DOI: 10.1089/sur.2006.073.

17. Barsuk JH, Cohen ER, Feinglass J, McGaghie WC, Wayne DB. Use of simulation-based education to reduce catheter-related bloodstream infections. *Arch Intern Med* 2009; **169**: 1420-1423.
18. Sannoh S, Clones B, Munoz J, Montecalvo M, Parvez B. A multimodal approach to central venous catheter hub care can decrease catheter-related bloodstream infection. *Am J Infect Control* 2010; **38**: 424-429. doi:10.1016/j.ajic.2009.07.014.
19. Peredo R, Sabatier C, Villagra A *et al*. Reduction in catheter-related bloodstream infections in critically ill patients through a multiple system intervention. *Eur J Clin Microbiol Infect Dis* 2010; **29**: 1173-1177. DOI 10.1007/s10096-010-0971-6.
20. Shuman EK, Washer LL, Arndt JL *et al*. Analysis of central line-associated bloodstream infections in the intensive care unit after implementation of central line bundles. *Infect Control Hosp Epidemiol* 2010; **31**: 551-553.
21. Guerin K, Wagner J, Rains K, Bessesen M. Reduction in central line-associated bloodstream infections by implementation of a postinsertion care bundle. *Am J Infect Control* 2010; **38**: 430-433. doi:10.1016/j.ajic.2010.03.007.
22. Perez Parra A, Cruz Menarguez M, Perez Granda MJ, Tomey MJ, Padilla B, Bouza E. A simple educational intervention to decrease incidence of central line-associated bloodstream infection (CLABSI) in intensive care units with low baseline incidence of CLABSI. *Infect Control Hosp Epidemiol* 2010; **31**: 964-967.
23. Marra AR, Cal RG, Durao MS *et al*. Impact of a program to prevent central line-associated bloodstream infection in the zero tolerance era. *Am J Infect Control* 2010; **38**: 434-439. doi:10.1016/j.ajic.2009.11.012.
24. Bizzarro MJ, Sabo B, Noonan M, Bonfiglio MP, Northrup V, Diefenbach K. A quality improvement initiative to reduce central line-associated bloodstream infections in a neonatal intensive care unit. *Infect Control Hosp Epidemiol* 2010; **31**: 241-248.
25. Pronovost P. Interventions to decrease catheter-related bloodstream infections in the ICU: the Keystone Intensive Care Unit Project. *Am J Infect Control* 2008; **36**: S171.e1-5. doi:10.1016/j.ajic.2008.10.008.
26. Gaynes R, Richards C, Edwards J *et al*. Feeding back surveillance data to prevent hospital-acquired infections. *Emerg Infect Dis* 2001; **7**: 295-298.
27. van der Kooi TI, de Boer AS, Mannien J *et al*. Incidence and risk factors of device-associated infections and associated mortality at the intensive care in the Dutch surveillance system. *Intensive Care Med* 2007; **33**: 271-278. doi:10.1016/j.jhin.2009.11.020 .
28. Zingg W, Imhof A, Maggiorini M, Stocker R, Keller E, Ruef C. Impact of a prevention strategy targeting hand hygiene and catheter care on the incidence of catheter-related bloodstream infections. *Crit Care Med* 2009; **37**: 2167-2173. DOI: 10.1097/CCM.0b013e3181a02d8f.
29. Safdar N, Kluger DM, Maki DG. A review of risk factors for catheter-related bloodstream infection caused by percutaneously inserted, noncuffed central venous catheters: implications for preventive strategies. *Medicine (Baltimore)* 2002; **81**: 466-479.
30. De Smet, A. M., Kluytmans, J., Blok, H., Bonten, M., and Bootsma, M. Effects of selective digestive and selective oropharyngeal decontamination on bacteraemia and respiratory tract colonization with highly resistant micro-organisms. *20th European Congress of Clinical Microbiology and Infectious Diseases* 2010

31. Wylie MC, Graham DA, Potter-Bynoe G *et al*. Risk factors for central line-associated bloodstream infection in pediatric intensive care units. *Infect Control Hosp Epidemiol* 2010; **31**: 1049-1056.
32. Tacconelli E , Tumbarello M, Pittiruti M *et al*. Central venous catheter-related sepsis in a cohort of 366 hospitalised patients. *Eur J Clin Microbiol Infect Dis* 1997; **16**: 203-209.
33. Parienti JJ, Thirion M, Megarbane B *et al*. Femoral vs jugular venous catheterization and risk of nosocomial events in adults requiring acute renal replacement therapy: a randomized controlled trial. *JAMA* 2008; **299**: 2413-2422. doi:10.1001/jama.299.20.2413.
34. Garcia-Teresa MA, Casado-Flores J, Delgado Dominguez MA *et al*. Infectious complications of percutaneous central venous catheterization in pediatric patients: a Spanish multicenter study. *Intensive Care Med* 2007; **33**: 466-476. DOI 10.1007/s00134-006-0508-8.
35. Pronovost P, Needham D, Berenholtz S *et al*. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med* 2006; **355**: 2725-2732.
36. Dutch working party on Infection Prevention (WIP). Guideline on Flebitis and intravenous catheter-related bloodstream infections. Dutch working party on Infection Prevention (WIP), 2010.

Chapter 4

Using flexible methods to determine risk factors for ventilator-associated pneumonia in the Netherlands

Tjallie I.I. van der Kooi, Hendriek Boshuizen, Jan C. Wille, Sabine C. de Greeff, Jaap T. van Dissel, Annelot F. Schoffelen, Rolina D. van Gaalen

---

PLoS ONE 2019 14(6): e0218372.

ABSTRACT

Seven hospitals participated in the Dutch national surveillance for ventilator-associated pneumonia (VAP) and its risk factors. We analysed time-independent and time-dependent risk factors for VAP using the standard Cox regression and the flexible Weighted Cumulative Effects method (WCE) that evaluates both current and past exposures. The prospective surveillance of intensive care patients aged ≥16 years and ventilated ≥48 hours resulted in the inclusion of 940 primary ventilation periods, comprising 7872 ventilation days. The average VAP incidence density was 10.3/1000 ventilation days. Independent risk factors were age (16-40 years at increased risk: HR 2.42 95% confidence interval 1.07-5.50), COPD (HR 0.19 [0.04-0.78]), current sedation score (higher scores at increased risk), current selective oropharyngeal decontamination (HR 0.19 [0.04-0.91]), jet nebulizer (WCE, decreased risk), intravenous antibiotics for selective decontamination of the digestive tract (ivSDD, WCE, decreased risk), and intravenous antibiotics not for SDD (WCE, decreased risk). The protective effect of ivSDD was afforded for 24 days with a delay of 3 days. For some time-dependent variables, the WCE model was preferable over standard Cox proportional hazard regression. The WCE method can furthermore increase insight into the active time frame and possible delay herein of a time-dependent risk factor.

INTRODUCTION

Invasively ventilated patients are at an increased risk of acquiring pneumonia, leading to longer hospital stays and increased mortality. Ventilator-associated pneumonia (VAP) rates ranging from 2 to over 20/1000 ventilation days have been reported[1-3] with attributable mortality of 1-13%, depending on the method used and patient specialty[4-7]. Cassini et al estimated that healthcare-associated pneumonia, including VAP, leads to a burden of 169 (95%CI 149-192) disability-adjusted life years per 100,000 total population, more than any other healthcare-associated infection[8]. Several patient and treatment characteristics have been demonstrated to be associated with the risk to develop VAP, such as Glasgow coma scale, Apache II score, intubation site, length of hospital/ICU stay before ventilation, neutropenia, stress ulcer prophylaxis, corticosteroids, systemic antibiotics and enteral feeding[9-18].

Some of these patient and treatment characteristics are time-dependent. Longer exposure or treatment will modify the (cumulative) risk, but it is less clear and often not evaluated how the association of these time-dependent risks develop during and following exposure[9, 10, 12, 16, 17, 19-21]. In this manuscript we present the VAP surveillance results and evaluate the risk factors. For the time-dependent risk factors we use both standard Cox regression and the flexible Weighted Cumulative Effects (WCE) approach that evaluates both current and past exposures[22]. The WCE approach allows estimation of the timeframe during which a risk factor is (still) relevant.

MATERIAL AND METHODS

Study setting and set up

PREZIES (Prevention of HAI through Surveillance) is the Dutch national surveillance network for healthcare associated infections, hosted by the National Institute for Public Health and the Environment (RIVM), in which hospitals participate voluntarily. Since 1996, PREZIES offers Dutch hospitals the possibility to participate in the surveillance of hospital-acquired infections with attendant benchmarks. The VAP surveillance module was offered from January 2004–December 2011.

The VAP surveillance protocol was developed by a working group of relevant professionals (intensivist, infectious disease specialist, pulmonologist, anaesthesiologist, epidemiologist and infection control professional) and was based on international literature, the preceding ICU-surveillance conducted by PREZIES [23] and a pilot study. The VAP definition used (Fig 1) was a simplified version of that used by the former Centers for Disease Control and Prevention/National Nosocomial Infections Surveillance system, currently the National Healthcare Safety Network definitions. In Dutch clinical

practice, a VAP diagnosis is most often based on positive cultures of tracheal aspirates, in combination with clinical symptoms. With a negative culture, the diagnosis of a clinical pneumonia was still possible.

All patients ventilated invasively for two days (48 hours) or more, aged 16 years or older, and present in the ICU were included in the study. Successive ventilation periods of at least two days were recorded until a VAP occurred or until the end of follow-up, 28 days after the start of each ventilation period. Each ICU admission was assigned a unique identifier that could not be used to link admissions at the patient level. Therefore, patients admitted more than once to the ICU were included as separate patients (termed "admissions"). For this manuscript, we considered only data from the first ventilation period of each admission. Data were recorded prospectively, with infection control professionals checking the patients and patient records in the ICU on average twice a week. Suspected VAPs were usually discussed with a dedicated radiologist or intensivist.

- Per admission were recorded: sex, age, admission and discharge dates of hospital and ICU, Apache II score, specialism, type of ICU and reason for end of follow-up.
- Per ventilation period were recorded: start and end date, intubation site, intubation department, stress ulcer prophylaxis, post-surgical ventilation, inhalation trauma, COPD, corticosteroid use (daily dose > 10 mg prednisone) and neutropenia (< 500 granulocytes).
- Per ventilation day were recorded: sedation score (Ramsay score[24] (see Table A in S1 File), feeding mode (>12 hours), oropharyngeal prophylaxis (SOD), intestinal prophylaxis, systemic antibiotics for selective digestive tract decontamination (ivSDD), systemic antibiotics (therapeutic, not for ivSDD) (ivAB), inhalation therapy (metered dose inhaler (MDI), jet nebulizer or none).
- Per infection were recorded: infection date, infection criteria and a maximum of three micro-organisms. When a clinical or possible pneumonia was later followed by respectively a possible and/or ('confirmed') pneumonia (for the same infectious episode), the latter were recorded as final diagnosis. In this paper, we do not distinguish between these diagnostic categories.

According to Dutch legislation, written consent from each individual patient was not required because the data from the PREZIES network is anonymized and was collected as a legal task of the National Institute for Public Health and the Environment.

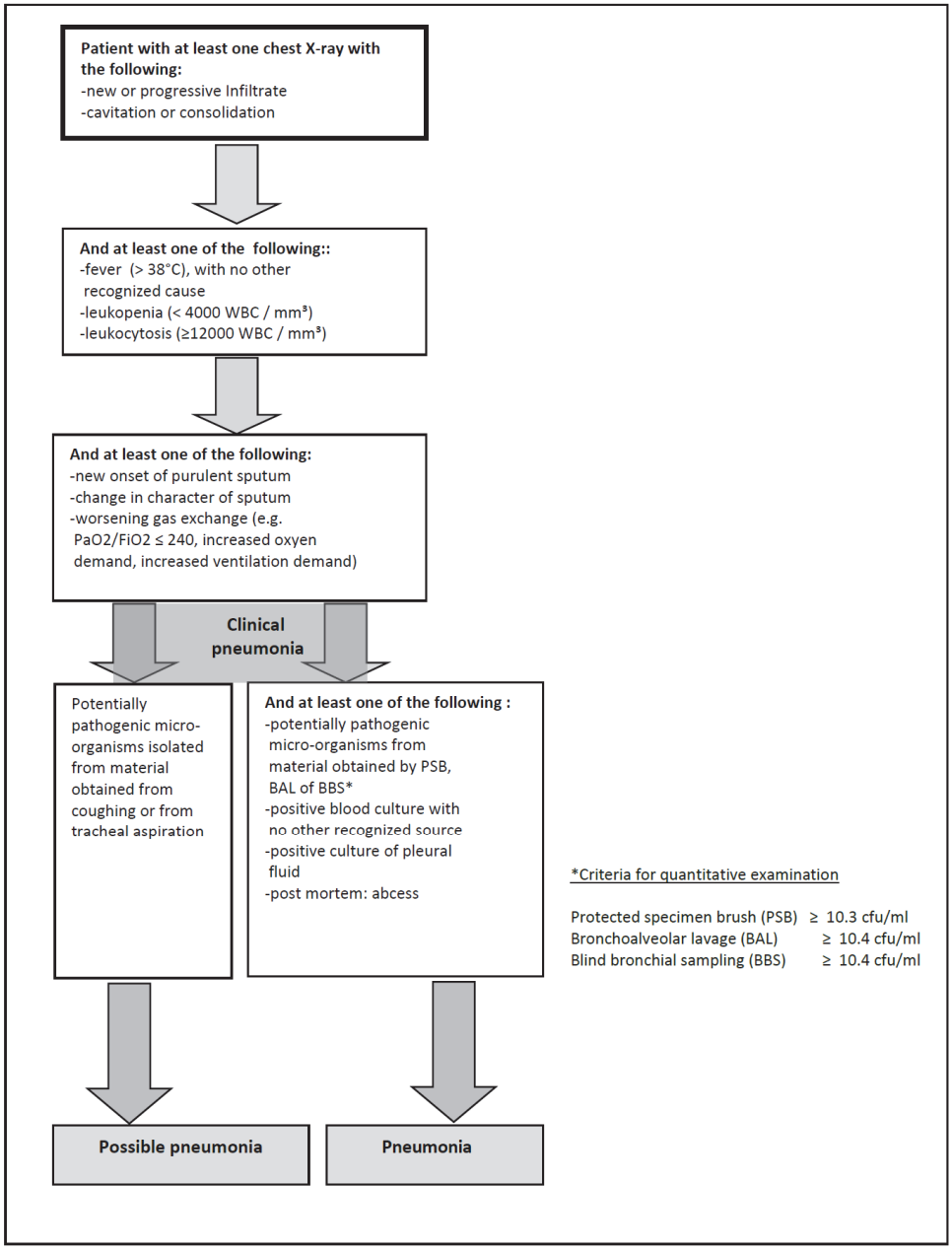


Figure 1: Diagnostic diagram for ventilator-associated pneumonia, based on the definitions of the former Centers for Disease Control and Prevention/National Nosocomial Infections Surveillance system, currently the National Healthcare Safety Network.

Statistical analysis

Data are expressed as median (interquartile range (IQR)) and absolute and relative frequencies, as appropriate. A non-parametric test (Kruskal-Wallis) was used to compare median ventilation durations.

We first calculated cause-specific hazards using univariate Cox regression models, adjusted for hospital as a fixed effect. Time-fixed, non-linear, or continuous covariates as well as duration of participation were modelled categorically in separate models using dummy variables. Separately for each time-dependent covariate, we fitted four regression models to determine if, and in which form, the covariate should be included in a multivariate analysis. The four models included three Cox models (current effects and delayed effects of one or two days) and one flexible Cox model using the WCE approach[22]. The WCE approach estimates not only the current effect of a covariate, but also the cumulative delayed effects of past exposures, and provides the timeframe for which a covariate is significantly associated with the studied event. See Box 1 for more details[25]. We assessed which of these four models fitted best using the Akaike information criteria (AIC)[26]. A difference of less than four suggested that the models fit the data equally well, a difference between four and ten suggested a slight difference, and a difference greater than ten suggested a major difference in model fit[27]. We chose the WCE model as the best-fitting model when it yielded a slight or major improvement in model fit to all of the three non-cumulative models.

All risk factors with p-value<0.2 in the univariate analysis were included in the initial multivariate Cox PH model, using the best-fitting univariate models. The final multivariate model was selected manually by backward selection using the likelihood ratio test. At each iteration, we removed from the model the variable that was associated with the highest p-value>0.05, except when the 95% CI for that variable did not include the null.

The WCE model requires complete data for the entire follow-up of each admission. Since some *time-dependent* data were missing for only 32 ventilation days (0.4%) in 24 admissions (2.6%), we used the last observation carried forward approach to fill in these values for missing days in our regression analyses. The sensitivity of our results to this approach for completing missing data was assessed by removing admissions with missing time-varying data from the dataset and rerunning the multivariate model. Admissions with data missing on *time-fixed* patient or ventilation period characteristics were excluded from the specific analysis.

Analyses were done with SAS 9.4 and R 3.4.1 software using the survival and WCE packages[28-30].

Box 1: The WCE method in more detail

The WCE model uses the Cox PH framework and time-varying covariates to generate, for each covariate, a function that describes the delayed and immediate effect of (past) exposures/levels on the outcome[22].The WCE model requires as input (1) the time-window in which past exposures are considered to have an impact on the risk of the outcome, (2) a pre-specified number of internal knots, which determine the flexibility of the cubic B-spline, and (3) whether the impact of past exposures reaches zero at the earliest point of the time-window (i.e., constraining the effect of the covariate to the null at that point). When insufficient prior information is available to make an informed choice on these inputs, as in our case, the data may be used to determine which inputs provide the best model fit. The approach used to select the optimal WCE model for each factor involved fitting multiple WCE models using all possible time-windows (up to 2, 3, 4, …, 28 days back); 1, 2 or 3 internal knots; and with the effect of the exposure at the most historical time point included in the time-window either unconstrained or constrained to the null.
From these 162 (27 x 3 x 2) models, the best-fitting WCE model for each factor was selected as the WCE model with the lowest Akaike information criteria (AIC). Since we selected the best of multiple models, p-values for WCE univariate models are likely to be artificially low. For each factor, we therefore simulated 1000 datasets in which there was no association, keeping the exposure patterns and outcome times consistent with the original dataset. For each of the 1000 simulated datasets, we ran the same set of WCE models (with alternative time-windows, numbers of internal knots, and weight-function constraints), and selected the best-fitting model using the AIC, as above. The distribution of the 1000 p-values was plotted and the proportion of the 1000 p-values that were smaller than the p-value of the optimal WCE model was recorded as the p-value corrected for multiple testing[25].

RESULTS

Participating hospitals

Seven hospitals (9% of all Dutch hospitals) participated for different periods (1-3.5 years) during the eight years of the VAP surveillance module (2004–2011). Four of the seven hospitals were top clinical (“high cure”) hospitals and three were general hospitals. University hospitals did not participate. The nation-wide distribution of the three hospital types is 29 (top clinical), 61 (general) and 10% (academic).

In the Netherlands, three ICU levels are discerned, ranging from I (relatively low complex care) to III (high complex care). The participating hospitals had ICU level I (1), II (3) and III (3) (see Table B in S1 File for hospital-specific results). Median ventilation duration differed significantly between hospitals ($p<0.0001$), ranging from four to eight days. Four of the five hospitals that participated for two years or more demonstrated a reduction in VAP (Fig 2), of which two significantly so.

Ventilation periods

The surveillance included 940 first ventilation periods of 940 ICU-admissions, all in mixed medical/surgical ICUs, comprising 7872 ventilation days, including all calendar days. The median ventilation duration for all admissions was 6 days (interquartile range (IQR) 4–10 days) (Table B in S1 File); for patients without VAP, 6 days (4–11); and for those that developed VAP, 5 days (3–7) until VAP. During follow-up, the number of patients that were still on the ventilator each day declined exponentially (Figure A in S1 File). Of the 940 admissions, 81 developed a VAP during follow-up (8.6%) and 23 were still on the

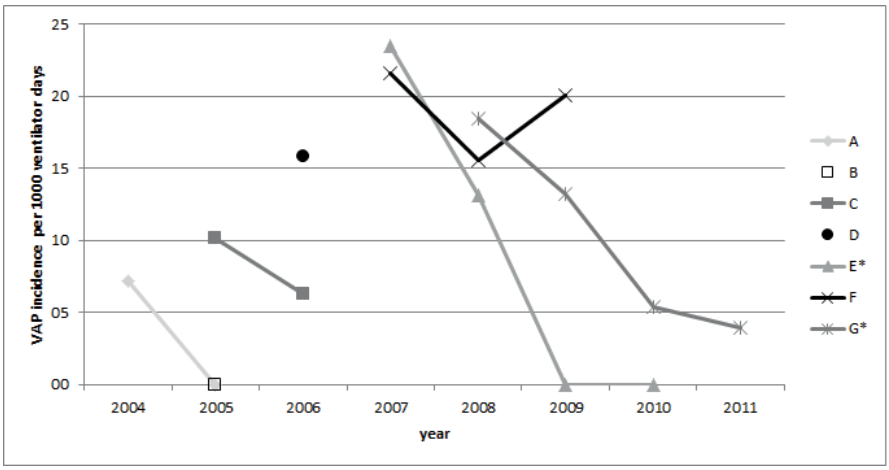


Figure 2: Average yearly incidence density, per 1000 ventilation days, of ventilator-associated pneumonia, per hospital. Hospitals with significant reduction are indicated with an * .

ventilator on day 28. The average VAP incidence density was 10.3/1000 ventilation days (range between hospitals 0.0 to 20.1).

Admission characteristics

Our study population included more men (59.3%, median age 68 [IQR 59-76] and APACHE II score 20 [15-26.5]) than women (median age 70 [59-78] and APACHE II score 22 [17-28]), and men developed VAP more often (10.1%; 95% confidence interval (CI) (8.2-12.0%) versus 6.5% (4.9-8.1%)). The median age was 69 (IQR 59–77) years for all

admissions and the median Apache II score 21 (IQR 16–27). See Table 1 and 2 and Table B in S1 File. The median age and Apache II scores were comparable for admissions with and without a VAP.

The routines and regimens offered to patients differed between hospitals. Apart from one hospital, hospitals preferred either MDI or nebulizers, four of them exclusively. IvSDD was used in three hospitals, intestinal prophylaxis in three, and SOD in five (see Figure B in S1 File). In hospital G, SOD was given for one year, followed by a complete SDD regimen (oropharyngeal and intestinal prophylaxis and four days ivSDD), as part of a study. In hospital E, SOD was initially given occasionally and subsequently extended to all admissions.

Univariate results

Of the time-independent covariates, age, length of hospital stay before start of the ventilation, COPD, intubation department, and duration of participation with the surveillance (in years) were significantly associated with VAP (Table 1). All time-dependent variables were significantly associated with the risk of acquiring VAP except for type of inhalation therapy (Table 2).

Fig. 3 shows the WCE results for the univariate analyses. The overall hazard ratio of specific exposure patterns compared with uniformly non-exposure can be calculated by multiplying the hazard ratios for all days where, for example, systemic antibiotics (Fig 3C) were administered. Suppose a patient was ventilated for 6 days and treated with ivAB on the first four ventilation days (day -5 to -2), but not on the last two ventilation days (day -1 and 0). The hazard ratio for this patient on the present day (day 0) is a multiplication of the hazards on days -5, -4, -3, and -2. Note that the hazard ratio before day -4 in Fig 3C is assumed to be 1. The WCE model for ivAB suggests a harmful effect of antibiotics taken on the present day (day 0), which is probably a result of reverse causation since system antibiotics were likely taken on the day of a VAP to *treat* the pneumonia. Further, the narrower confidence intervals shown at the left (e.g. Fig 3A) may be seen as counterintuitive since the number of patients declines with increasing follow-up duration (Figure A in S1 File), but are an artefact of the analysis since the best-fitting model for ivAB was one where the hazard ratio was constrained to the null at this point.

Multivariate results

After backward selection to step-wise exclude covariates from the model, the final multivariate model included age, COPD, current sedation score, current SOD, inhalation therapy (WCE), ivSDD (WCE), and ivAB (WCE) (Table 3).

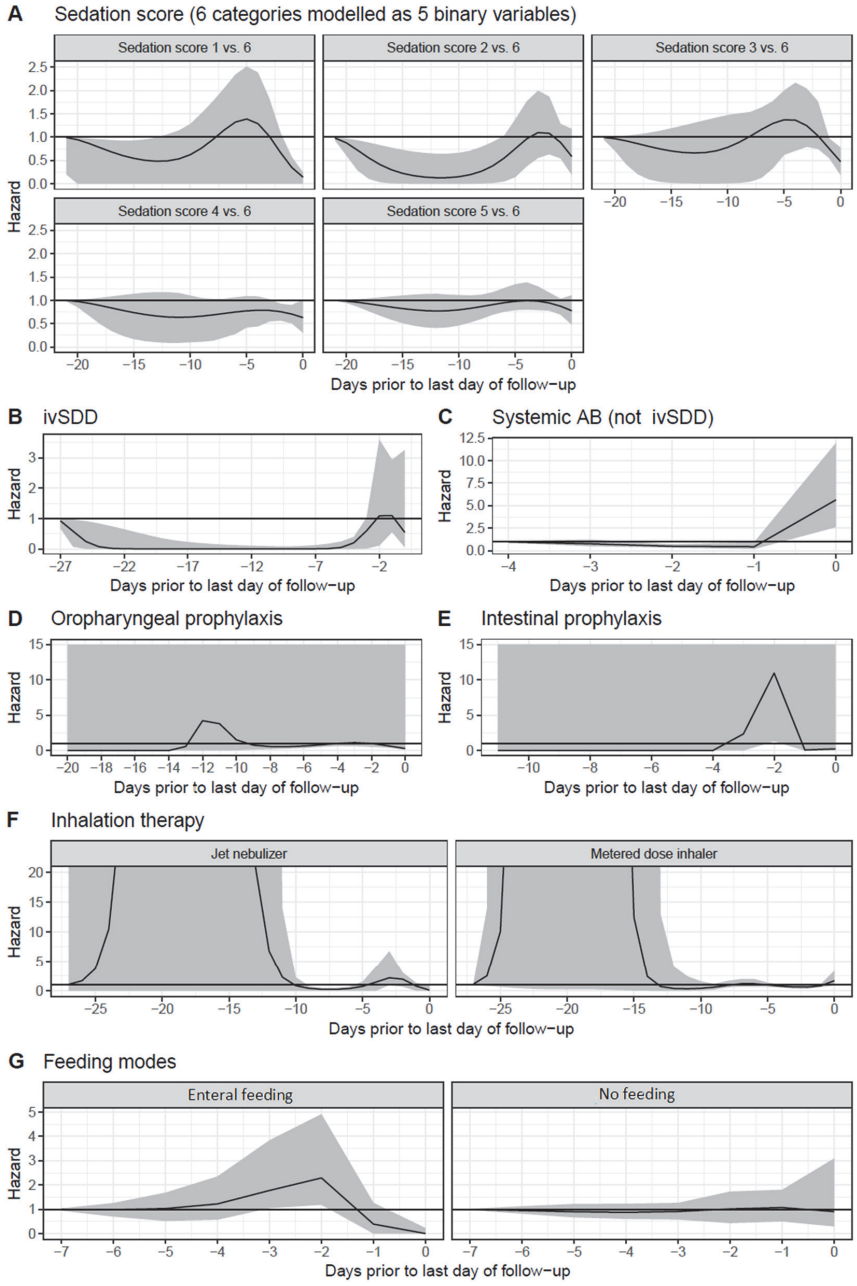


Figure 3: Daily hazards of time-dependent covariates, in univariate models.
The curve shows the estimated risk attributed to exposures on each day prior to the last day of follow-up (i.e., the event date or the censoring date) and the grey ribbon shows the 95% confidence interval. A value of one indicates no effect of the exposure at that time. At times where the grey ribbon includes one, the effect is considered to be statistically insignificant.

Table 1: Patient and ventilation characteristics and hazard ratios, including 95% confidence intervals and adjusted for hospital, of time-independent covariates.

	Patients	*Perc. of patients*	Ventilator days	*Perc. of ventilator days*	Number of VAPs	Perc. patients with VAP	Incidence density per 1000 ventilator days	HR (95% CI)	p-value
Total	940		7872		81	**8.6%**	**10.3**		
Sex									
Man	557	*59.3*	4691	59.6	56	**10.1**	**11.9**	**Ref**	
Woman	382	*40.6*	3175	40.3	25	**6.5**	**7.9**	**0.64 (0.40 – 1.02)**	0.06
Missing	1	*0.1*	6	0.1	0	**0.0**	**0.0**		
Age									
16 – 40	66	*7.0*	409	5.2	13	**19.7**	**31.8**	**3.79 (1.72 – 8.38)**	0.001
41 – 60	207	*22.0*	1614	20.5	12	**5.8**	**7.4**	**Ref**	
61 – 80	529	*56.3*	4675	59.4	45	**8.5**	**9.6**	**1.38 (0.72 – 2.61)**	0.33
> 80	138	*14.7*	1174	14.9	11	**8.0**	**9.4**	**1.60 (0.68 – 3.74)**	0.28
Apache II score									
≤ 10	143	*15.2*	1248	15.9	10	**7.0**	**8.0**	**Ref**	
11-20	339	*36.1*	2850	36.2	26	**7.7**	**9.1**	**0.61 (0.26 – 1.41)**	0.25
21-30	330	*35.1*	2790	35.4	34	**10.3**	**12.2**	**0.82 (0.36 – 1.87)**	0.63
> 30	128	*13.6*	984	12.5	11	**8.6**	**11.2**	**0.95 (0.36 – 2.51)**	0.92
Specialty									
Abdominal surgery	359	*38.2*	3443	43.7	34	**9.5**	**9.9**	**Ref**	
Cardiology	92	*9.8*	515	6.5	5	**5.4**	**9.7**	**1.30 (0.50 – 3.38)**	0.60
Cardiothoracic surgery	37	*3.9*	226	2.9	0	**0.0**	**0.0**	-	
Internal medicine	150	*16.0*	1418	18.0	7	**4.7**	**4.9**	**0.60 (0.28 – 1.31)**	0.20
Neurology	56	*6.0*	369	4.7	5	**8.9**	**13.6**	**1.33 (0.51 – 3.44)**	0.56
Neurosurgery	53	*5.6*	323	4.1	10	**18.9**	**31.0**	**1.66 (0.76 – 3.65)**	0.20
Other surgery	93	*9.9*	790	10.0	10	**10.8**	**12.7**	**1.10 (0.53 – 2.28)**	0.80
Pulmonology	47	*5.0*	314	4.0	1	**2.1**	**3.2**	**0.31 (0.04 – 2.26)**	0.25
Traumatology	30	*3.2*	316	4.0	8	**26.7**	**25.3**	**1.92 (0.81 – 4.53)**	0.14
Other specialties	21	*2.2*	147	1.9	1	**4.8**	**6.8**	**0.56 (0.08 – 4.12)**	0.57
Missing	2	*0.2*	11	0.1	0	**0.0**	**0.0**	-	

	Patients	*Perc. of patients*	Ventilator days	*Perc. of ventilator days*	Number of VAPs	Perc. patients with VAP	Incidence density per 1000 ventilator days	HR (95% CI)	p-value
LOS (before ventilation)									
0 days	322	*34.3*	2553	32.4	34	**10.6**	**13.3**	**Ref**	
1	168	*17.9*	1446	18.4	17	**10.1**	**11.8**	**0.98 (0.54 – 1.78)**	0.96
2	94	*10.0*	791	10.0	10	**10.6**	**12.6**	**0.99 (0.49 – 2.01)**	0.97
3-5	132	*14.0*	1175	14.9	6	**4.5**	**5.1**	**0.38 (0.16 – 0.92)**	0.03
6-10	104	*11.1*	834	10.6	7	**6.7**	**8.4**	**0.61 (0.27 – 1.39)**	0.24
>10	120	*12.8*	1073	13.6	7	**5.8**	**6.5**	**0.55 (0.25 – 1.18)**	0.13
LOS_IC (before ventilation)									
0 days	746	*79.4*	5953	75.6	64	**8.6**	**10.8**	**Ref**	
1	113	*12.0*	1109	14.1	12	**10.6**	**10.8**	**1.02 (0.55 – 1.91)**	0.94
2-5	55	*5.9*	558	7.1	3	**5.5**	**5.4**	**0.43 (0.14 – 1.38)**	0.16
>5	26	*2.8*	252	3.2	2	**7.7**	**7.9**	**0.63 (0.20 – 2.02)**	0.44
COPD									
No	808	*86.0*	6786	86.2	79	**9.8**	**11.6**	**Ref**	
Yes	131	*13.9*	1079	13.7	2	**1.5**	**1.9**	**0.15 (0.04 – 0.60)**	0.008
Missing	1	*0.1*	7	0.1	0	**0.0**	**0.0**		
Postsurgical ventilation									
No	468	*49.8*	3612	45.9	**35**	**7.5**	**9.7**	**Ref**	
Yes, abdominal surgery	338	*36.0*	3231	41.0	**33**	**9.8**	**10.2**	**0.97 (0.60 – 1.56)**	0.88
Yes, thoracical surgery	30	*3.2*	178	2.3	**1**	**3.3**	**5.6**	**2.31 (0.32 – 16.9)**	0.41
Yes, other surgery	104	*11.1*	851	10.8	**12**	**11.5**	**14.1**	**0.88 (0.44 – 1.74)**	0.71
Intubation site									
Oral	918	*97.7*	7641	97.1	**79**	**8.6**	**10.3**	**Ref**	
Nasal	6	*0.6*	53	0.7	**0**	**0.0**	**0.0**	**0.00 (0.00 – inf)**	0.99
Tracheostoma	14	*1.5*	167	2.1	**1**	**7.1**	**6.0**	**0.37 (0.05 – 2.68)**	0.32
Other	2	*0.2*	11	0.1	**1**	**50.0**	**90.9**	**6.73 (0.92 – 49.1)**	0.06

	Patients	*Perc. of patients*	Ventilator days	*Perc. of ventilator days*	Number of VAPs	Perc. patients with VAP	Incidence density per 1000 ventilator days	HR (95% CI)	p-value
Intubation department									
ICU	417	*44.4*	3618	46.0	**25**	**6.0**	**6.9**	**Ref**	
OR	396	*42.1*	3505	44.5	40	**10.1**	**11.4**	**1.45 (0.88 -2.38)**	0.14
Recovery	5	*0.5*	50	0.6	**0**	**0.0**	**0.0**	**0.0 (0.00 – inf)**	1.00
Other	122	*13.0*	699	8.9	16	**13.1**	**22.9**	**2.31 (1.19 – 4.48)**	0.01
Inhalation trauma									
No	924	*98.3*	7738	98.3	**79**	**8.5**	**10.2**	**1**	
Yes (burns & other)	15	*1.6*	131	1.7	**2**	**13.3**	**15.3**	**1.89 (0.44 – 7.84)**	0.40
burns	1	*0.1*	4	0.1	**0**	**0.0**	**0.0**		
other	14	*1.5*	127	1.6	**2**	**14.3**	**15.7**		
Missing	1	*0.1*	3	<0.1	**0**	**0.0**	**0.0**		
Stress Ulcer prophylaxis									
No	346	*36.8*	2316	29.4	22	**6.4**	**9.4**	**Ref**	
Protonpump inhibitors	561	*59.7*	5296	67.3	56	**10.0**	**10.6**	**1.07 (0.62 – 1.87)**	0.80
H_2-antagonists	33	*3.5*	260	3.3	3	**9.1**	**11.5**	**1.77 (0.45 – 6.89)**	0.41
Sucralphate	0	*0.0*	0	0.0					
Corticosteroid use (eq. > 10 mg prednisone)									
No	489	*52.0*	4139	52.6	50	**10.2**	**12.1**	**Ref**	
Neutropenia									
No	905	*96.3*	7535	95.7	77	**8.5**	**10.2**	**Ref**	
Yes	32	*3.4*	322	4.1	3	**9.4**	**9.3**	**0.71 (0.22 – 2.26)**	0.59
Missing	3	*0.3*	15	0.2	1	**33.3**	**66.7**		
Participation year									
1	370	*39.4*	2996	38.1	35	**9.5**	**11.7**	**Ref**	
2	284	*30.2*	2435	30.9	26	**9.2**	**10.7**	**0.70 (0.41 – 1.19)**	0.19
3	203	*21.6*	1687	21.4	18	**8.9**	**10.7**	**0.52 (0.29 – 0.95)**	0.03
4	83	*8.8*	754	9.6	2	**2.4**	**2.7**	**0.17 (0.04 – 0.72)**	0.02
Yes	451	*48.0*	3733	47.4	31	**6.9**	**8.3**	**0.69 (0.43 – 1.12)**	0.13

	Patients	*Perc. of patients*	Ventilator days	*Perc. of ventilator days*	Number of VAPs	Perc. patients with VAP	Incidence density per 1000 ventilator days	HR (95% CI)	p-value
Ventilation duration*									
3 calendar days	153	*16.3*	2820	35.8	22	**14.4**	**7.8**		
4-5 days	256	*27.2*	1429	18.2	21	**8.2**	**14.7**		
6-10 days	299	*31.8*	1897	24.1	31	**10.4**	**16.3**		
> 10 days	232	*24.7*	1726	21.9	7	**3.0**	**4.1**		

* Calculated according to Mc Laws.

Table 2: Ventilation day characteristics and hazard ratios for univariate models of time-dependent covariates

			Best-fitting *** non-cumulative exposure-risk model (current effect of the current or delayed value of the time-dependent variable)					WCE exposure-risk model (current effect of the current and past values of the time-varying variable for the best-fitting model)				Exposure-risk model selected **** for inclusion in final model
	Original ventilator days (%) *	**LOCF ventilator days (%) ******	**Optimal model**	**HR**	**95% CI**	**p-value**	**AIC**	**Relevant exposure window & number of knots for best-fitting model**	**HR & 95%CI**	**Adjusted p-value (**multiple testing)*****	**AIC**	
Sedation score			Current				977	22 days	Fig 3A	0.162	980	Current
1	737 (9.4)	741 (9.4)		0.07	(0.01, 0.52)	0.010		1 knot for all 5				
2	1095 (13.9)	1095 (13.9)		0.44	(0.19, 1.01)	0.051						
3	944 (12.0)	944 (12.0)		0.39	(0.18, 0.87)	0.020						
4	1207 (15.3)	1208 (15.3)		0.41	(0.20, 0.83)	0.013						
5	1929 (24.5)	1932 (24.5)		0.67	(0.38, 1.19)	0.175						
6	1950 (24.8)	1952 (24.8)		Ref								
missing	10 (0.1)	0 (0.0)										
Feeding mode			2-day delay				969	8 days	Fig 3G	0.929	972	2-day delay
No feeding	592 (7.5)	592 (7.5)		2.26	(1.06, 4.78)	0.034		1 knot for both		(combined)		
Parenteral	1238 (15.7)	1248 (15.9)		Ref								
Enteral & Both	6001 (76.2)	6032 (76.6)		0.88	(0.46, 1.67)	0.692						
missing	41 (0.5)	0 (0.0)										
Inhalation therapy			2-day delay				987	28 days	Fig 3F	0.048	975	WCE
None	2694 (34.2)	2695 (34.3)		Ref				3 knots for both		(combined)		
Jet nebulizer	1506 (19.1)	1506 (19.1)		1.44	(0.48, 4.27)	0.513						
Metered dose inhaler	3671 (46.6)	3671 (46.6)		0.62	(0.35, 1.11)	0.107						
missing	1(<0.1)	0 (0.0)										
Systemic AB (not ivSDD)			2-day delay				983	5 days	Fig 3C	0	961	WCE
Yes	5226 (66.4)	1469 (18.7)		0.56	(0.36, 0.89)	0.015		1 knot				
No	2645 (33.6)	6403 (81.3)		Ref								
missing	1 (0.01)	0 (0.0)										

	Original ventilator days (%) *	LOCF ventilator days (%) **	Optimal model	HR	95% CI	p-value	AIC	Relevant exposure window & number of knots for best-fitting model	HR & 95%CI	Adjusted p-value (multiple testing)*****	AIC	
ivSDD			2-day delay				986	28 days	Fig 3B	0.003	973	WCE
Yes	1160 (14.7)	1160 (14.7)		0.43	(0.15, 1.26)	0.123		1 knot				
No	6710 (85.2)	6712 (85.3)		Ref								
missing	2 (0.03)	0 (0.0)										
Intestinal prophylaxis			Current				970	12 days	Fig 3E	0	965	WCE
Yes	2395 (30.4)	2395 (30.4)		0.12	(0.04, 0.41)	0.0007		2 knots				
No	5475 (69.6)	5477 (69.6)		Ref								
missing	2 (0.03)	0 (0.0)										
Oropharyngeal prophylaxis			Current				967	21 days	Fig 3D	0	971	Current
Yes	4783 (60.8)	4784 (60.8)		0.14	(0.05, 0.38)	0.0001		1 knot				
No	3087 (39.2)	3088 (39.2)		Ref				(unconstrained)				
missing	2 (0.03)	0 (0.0)										

* The total number of ventilation days was 7872.

** The number of ventilation days after reducing the numbers of missings for time-dependent covariates with the 'last observation carried forward (LOCF) approach

*** Selected as the model with the lowest AIC among the current exposure-risk, 1-day delay exposure-risk, and 2-day delay exposure-risk models in Table C in S1 File.

**** Preference given to a non-cumulative model. WCE model selected if the WCE model had an AIC that was 4 units lower than that of the best-fitting non-cumulative model.

***** The p-value was estimated using 1000 bootstrapped data sets to account for multiple testing when selecting the best-fitting WCE model.

Table 3: Hazard ratios of patient and ventilation characteristics – results of multivariate analysis.

	Hazard ratio (95% CI)	p-value
Age		
16 – 40	2.42 (1.07, 5.50)	0.036
40 – 60	Ref	
60 – 80	1.21 (0.62, 2.34)	0.567
> 80	1.58 (0.66, 3.75)	0.305
COPD	0.19 (0.04, 0.78)	0.003
Sedation score, per day (current)		
1	0.08 (0.01, 0.58)	< 0.001
2	0.67 (0.30, 1.54)	0.335
3	0.46 (0.20, 1.03)	0.048
4	0.43 (0.21, 0.90)	0.062
5	0.77 (0.43, 1.39)	0.388
6	Ref	
Oropharyngeal prophylaxis (current)	0.19 (0.04, 0.91)	0.017
Intravenous antibiotics for SDD (ivSDD) - (WCE)	See Fig 4A	0.062
Other systemic AB (not for ivSDD) - (WCE)	See Fig 4B	< 0.001
Inhalation therapy - (WCE) • Jet nebulizer (compared to no inhalation therapy) • Metered dose inhaler (MDI) (compared to no inhalation therapy)	See Fig 4C	0.009

The model suggests that, compared to patients between 40 and 60 years of age, patients ≤ 40 had an over two-fold higher risk of developing VAP. Patients were also at an increased risk when their sedation scores were high. Patients who were on SOD, ivSDD or ivAB and patients with COPD had a lower VAP risk. The model further demonstrates a delayed protective effect of ivSDD by three days. This protective effect is afforded for 24 days (up to 27 days back) (Fig 4A). IvAB was protective for two days, with the protection being afforded after a delay of one day. The effect from inhalation therapy was minimal, with jet nebulizers showing a delayed protective effect for days 6 to 8 back. Our results were not sensitive to using the last observation carry forward approach for completing missing data. Similar results were obtained when we removed admissions with missing time-varying data from the dataset and reran the multivariate model.

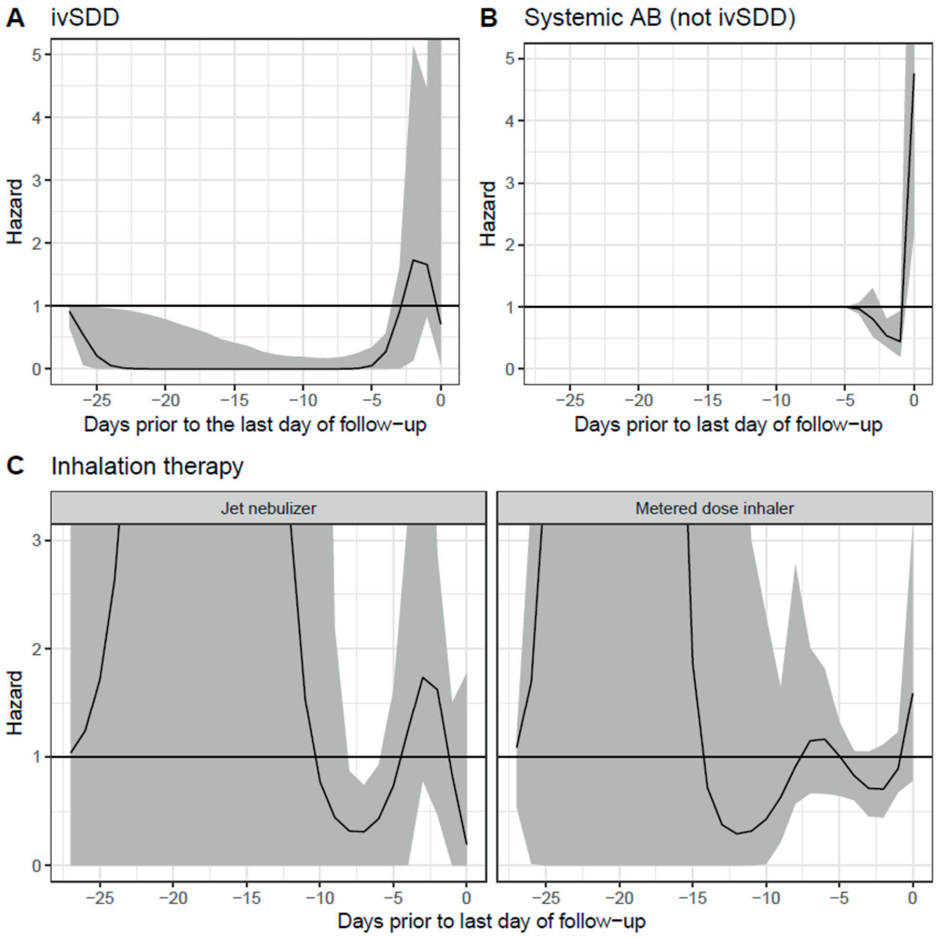


Figure 4: Daily hazard ratios attributed to past values of the covariates assessed with a weighted cumulative effects approach in the multivariate Cox regression model: (A) ivSDD, (B) ivAB, (C) Jet nebulizer (compared to no inhalation therapy) and metered dose inhalers (MDI) (compared to no inhalation therapy).
The curve shows the estimated risk attributed to exposures on each day prior to the last day of follow-up (i.e., the event date or the censoring date) and the grey ribbon shows the 95% confidence interval. A value of one indicates no effect of the exposure at that time. At times where the grey ribbon includes one, the effect is considered to be statistically insignificant.

DISCUSSION

In this manuscript, we presented data generated by the VAP surveillance module of the Dutch PREZIES network. The VAP rates reported by the hospitals participating in the surveillance (0-20.1/1000 ventilation days) are in the expected range[1-3]. The observed variation between hospitals could be partly due to the inter-observer reliability of a VAP diagnosis, which is known to be low[31, 32]. However, this applies less to intrahospital comparisons where only one intensivist or radiologist was usually dedicated to surveillance. Four of the five hospitals that participated ≥2 years demonstrated a reduction in VAP, two of which significantly so. Apart from a possible effect of the surveillance itself[33], various changes during the follow-up could have caused this reduction. Several hospitals (C-G) implemented interventions (SOD and/or ivSDD, Evac cuffs, closed suctioning system, VAP bundle), sometimes temporarily. Although the increase in VAP incidence in hospital F was duly investigated at that time, no cause was found. Hospital A did not introduce any interventions. Hospital B, with zero VAPs, used a complete SDD regimen during the surveillance. Therefore, while hospitals appear to be able to reduce VAP, either by introducing an intervention or by surveillance alone, success does not seem to be guaranteed.

The observed effects of patient and treatment characteristics vary among studies[9, 11-18], resulting from differences in the other measured covariates and case mix, and, frequently, low statistical power. In our results, Apache II score, specialty, intubation site, length of hospital/ICU stay before ventilation, postsurgical ventilation, inhalation trauma, stress ulcer prophylaxis, corticosteroids, neutropenia, intestinal prophylaxis, and feeding method were not significantly associated with VAP. Although the overall study population in our study was relatively large, low numbers of patients in certain categories could explain failures to detect associations. In our data, a higher Ramsay score was associated with an increased VAP risk, which corresponds with the increased risk associated with coma or increased Glasgow coma scale[9-12, 16, 17]. Systemic antibiotics (not for ivSDD) appeared to lower the VAP risk, as identified by others[9, 10]. In most analyses where antibiotic use was not analysed as a time-dependent variable, 'prior antibiotic use' (or variations) was not found to be associated with VAP[12, 16, 17]. Our results demonstrated that both ivSDD and SOD were associated with a VAP reduction. De Smet et al, performing a multicenter randomized clinical trial, concluded that both SOD and SDD (full regimen) led to a reduction in respiratory tract colonisation with highly resistant microorganisms[21]. As intestinal prophylaxis partly coincided with ivSDD and SOD, we evaluated a model without ivSDD/SOD. Intestinal prophylaxis was not significantly associated with VAP in this model either.

More surprisingly, because unlike other studies where the risk for older patients was similar or increased[3, 11, 17, 18] younger patients (16-40 years) appeared to be at increased risk. This may have resulted from an overrepresentation of young patients in neurosurgery and traumatology, both specialties with high VAP rates. This association remained borderline significant when adjusted for specialty and Apache II score or when these two specialties were excluded from the analysis. When excluding one center, where 11 of the 32 patients aged 16-40 developed pneumonia, the association was still present (HR 3.2 (0.49 – 21.2), although not significant anymore. While COPD is generally found to be either unassociated with VAP[3, 16], or to increase the VAP risk[11, 17], here COPD appeared to be associated with a lower risk. Our model did not detect a significant interaction with systemic antibiotics. In previous studies, COPD patients had longer ventilation durations relative to patients without COPD[3, 34]. In our study, the first ventilation periods for patients with and without COPD were similar in duration (average of 8.2 and 8.4 days, respectively), as was the total ventilated duration (9.3 and 8.7 days) and the proportion of ventilation periods lasting 28 days(1.4 and 2.8%, respectively), suggesting that the similarities in ventilated duration are not subject to censoring bias. Furthermore, mortality data, available from five hospitals, showed that mortality was comparable (40.4% and 38.5%, respectively). The lower risk in our study may reflect differences in criteria for COPD diagnosis[35], but also improved care. For example, Funk analysed the outcomes of COPD patients admitted in ICU, for the period 1998–2008, and found that risk-adjusted mortality had improved[36].

The use of jet nebulizers demonstrated a slightly reduced risk compared to no inhalation therapy, whereas MDI did not. Appropriate delivery of medication is reported to be more challenging with MDI than with jet nebulizers. In one study no difference in VAP risk was found between both methods, but the population size was small[37].

For the daily measured ivAB, ivSDD, and inhalation therapy, the WCE approach explained the associated VAP risk better than the standard Cox regression analysis. Additionally, this method provides insight into the cumulative effect over time and the relevant retrospective timeframe in which exposures are associated with a VAP. IvSDD affected this hazard for 24 days. It must be noted that in one hospital many patients received ivSDD throughout the entire ventilation period instead of the currently recommended first four days only. Although differences in the AIC were usually small (Table C in S1 File) the WCE approach identified ivSDD as an independent factor affecting the risk to develop VAP whereas standard Cox regression of current values or of one or two days earlier did not. The WCE approach is worth considering in future analysis of time-dependent risk factors of VAP, and for other device-associated infections.

Our study has some limitations. First, while the relatively large study population and the availability of daily data on time-varying risk factors represent strengths, our study made use of surveillance data and therefore missed more detailed clinical data, e.g. type of ivAB or the presence of sepsis, that could also be associated with VAP and affect estimated associations for other factors. Second, hospital-level treatment preferences resulted in low variability within individual hospitals, reducing the power to detect associations on these variables. Third, our results may not be generalizable to other settings. VAP in the Netherlands is usually diagnosed and treated based upon clinical features and/or tracheal aspirate cultures. Therefore, some risk factors may differ when VAP is diagnosed in a more invasive way. Top clinical hospitals were overrepresented in the sample of participating hospitals, whereas academic hospitals did not participate. Along with the variation in VAP rates observed this implies the average VAP incidence density may not be representative of all hospitals. Fourth, we could not distinguish between new and recurrent ICU admissions, which may have led to some overrepresentation of complex patients. Fifth, including only the first ventilation episode may have led to some bias in the assessment of risk factors. Lastly, in-house infection control professionals collected the data. Apart from the low inter-observer reliability of diagnosing VAP[31, 32], this may have led to differences in the application of the surveillance protocol. We aimed to minimize this possible bias by arranging meetings for the involved professionals to discuss data collection and infection criteria.

Surveillance results are limited for clinical use or pathophysiological insight but the data of Dutch ICUs participating in the VAP surveillance system revealed risk factors on both patient (age, sedation score) and treatment level (SDD, oropharyngeal prophylaxis, other antibiotics, nebulizer type) that can be useful for case mix adjustment and evaluation of VAP prevention strategies. The introduction of SDD or oropharyngeal prophylaxis was associated with low or zero VAP incidences. Surprisingly, COPD was associated with a reduced VAP risk, which merits further evaluation. For some time-dependent covariates, the WCE approach was preferable over standard Cox proportional hazard regression and additionally provided insight into the relevant retrospective timeframe of past exposures.

ACKNOWLEDGEMENTS

We would like to thank the infection control practitioners, intensive care nurses, intensivists and other involved staff in the participating centers for their interest in monitoring VAP in their patients and their willingness to share this information.

SUPPLEMENTARY DATA

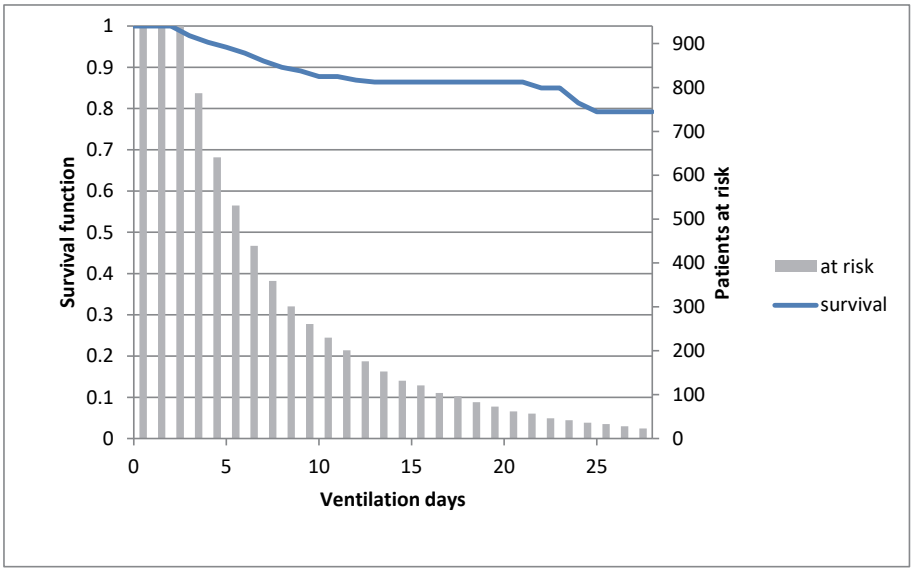


Figure A: Survival without VAP and number of patients per day (still) on the ventilator

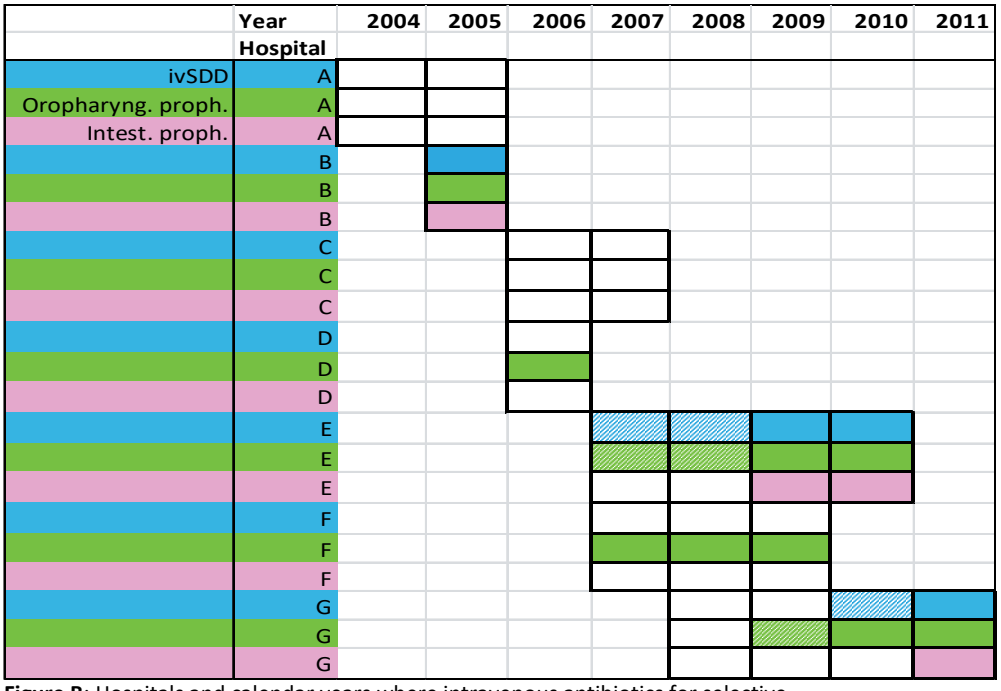


Figure B: Hospitals and calendar years where intravenous antibiotics for selective decontamination of the digestive tract (ivSDD), oropharyngeal and intestinal prophylaxis were given.

Table A: Ramsay sedation score

Awake
1. Patient anxious, agitated or restless or both
2. Patient co-operative, orientated and tranquil
3. Patient responds to commands only
Asleep levels depend on the patient's response to a light glabellar tap or loud auditory stimulus
4. Brisk response
5. Sluggish response
6. No response

Table B: Patient and ventilation characteristics of individual hospitals.

	Total	**A**	**B**	**C**	**D**	**E**	**F**	**G**
ICU level (I low, III highly complex care)		II	III	I	II	III	III	II
Patients	940	89	*140*	61	21	210	265	154
% Men*	*59*	*69*	*60*	*67*	*52*	*58*	*58*	*55*
Median age (IQR)	69 (59-77)	70 (58-79)	67.5 (58-75)	71 (60-81)	68 (56-78)	73 (63-79)	63 (51-72)	71 (63-79)
Median Apache II score (IQR)	21 (16-27)	not recorded	26 (19-31)	15 (11-23)	22 (20-27)	21 (16-27)	21 (16-26)	20 (16-26)
% COPD*	*14*	*24*	*0*	*10*	*24*	*20*	*14*	*13*
Median ventilation duration (IQR)	6 (4-10)	7 (5-12)	4 (3-6)	8 (5-19)	7 (5-13)	7 (4-12)	6 (4-9)	7 (4-12)
Median duration of ventilation in case of VAP (IQR)	5 (3-7)	12 (7-21)	no VAP	7.5 (6-10)	5 (3-5)	6 (4-8)	4 (3-7)	4 (3-9)

* = Missing for one patient

Table C: Hazard ratios for univariate models of time-dependent covariates

		Current exposure-risk model (current effect of the current value of the time-dependent variable)			1-day delay exposure-risk model (current effect of the current value of the time-dependent variable)			2-day delay exposure-risk model (current effect of the current value of the time-dependent variable)			WCE exposure-risk model (current effect of the current and past values of the time-dependent variable for the best-fitting model)				Exposure -risk model selected for final model
	LOCF venti-lator days (%) [1]	HR 95% CI	p-value	AIC	HR 95% CI	p-value	AIC	HR 95% CI	p-value	AIC	Relevant exposure window & number of knots[2]	HR & 95% CI	p-value [3]	AIC	
Sedation score				977			983			986	22 days	Fig 3A	0.162	980	Current
1	741 (9.4)	0.07 (0.01, 0.52)	0.010		0.11 (0.01, 0.83)	0.032		0.16 (0.02, 1.22)	0.077		1 knot for all 5				
2	1095 (13.9)	0.44 (0.19, 1.01)	0.051		0.50 (0.20, 1.26)	0.141		0.47 (0.16, 1.37)	0.167						
3	944 (12.0)	0.39 (0.18, 0.87)	0.020		0.31 (0.12, 0.77)	0.012		0.47 (0.20, 1.14)	0.094						
4	1208 (15.3)	0.41 (0.20, 0.83)	0.013		0.52 (0.27, 1.02)	0.058		0.39 (0.18, 0.84)	0.015						
5	1932 (24.5)	0.67 (0.38, 1.19)	0.175		0.67 (0.38, 1.18)	0.167		0.70 (0.41, 1.20)	0.192						
6	1952 (24.8)	Ref			Ref			Ref							
Feeding mode				989			990			969	8 days	Fig 3G	0.929	989	2-day delay
No feeding	592 (7.5)	0.00 (0.00, inf)	0.998		0.46 (0.06, 3.39)	0.445		2.26 (1.06, 4.78)	0.034		1 knot for both		(comb ined)		
Parenteral	1248 (15.9)	Ref			Ref			Ref							
Enteral&Both	6032 (76.6)	0.92 (0.51, 1.65)	0.772		0.87 (0.48, 1.58)	0.651		0.88 (0.46, 1.67)	0.692						

		Current exposure-risk model (current effect of the current value of the time-dependent variable)			1-day delay exposure-risk model (current effect of the current value of the time-dependent variable)			2-day delay exposure-risk model (current effect of the current value of the time-dependent variable)			WCE exposure-risk model (current effect of the current and past values of the time-dependent variable for the best-fitting model)				Exposure -risk model selected for final model
	LOCF ventilator days (%) [1]	**HR 95% CI**	**p-value**	**AIC**	**HR 95% CI**	**p-value**	**AIC**	**HR 95% CI**	**p-value**	**AIC**	**Relevant exposure window & number of knots[2]**	**HR & 95% CI**	**p-value [3]**	**AIC**	
Inhalation therapy				989			989			987	28 days 3 knots for both	Fig 3F	0.048 (combined)	975	WCE
None	2695 (34.3)	Ref			Ref			Ref							
Nebulizer	1506 (19.1)	0.41 (0.09, 1.98)	0.269		0.69 (0.18, 2.63)	0.590		1.44 (0.48, 4.27)	0.513						
Metered dose inhaler	3671 (46.6)	0.94 (0.55, 1.61)	0.833		0.74 (0.43, 1.23)	0.288		0.62 (0.35, 1.11)	0.107						
Systemic AB (not ivSDD)				985			986			983	5 days 1 knot	Fig 3C	0	961	WCE
Yes	5227 (66.4)	1.71 (0.99, 2.98)	0.056		0.67 (0.42, 1.07)	0.093		0.56 (0.36, 0.89)	0.015						
No	2645 (33.6)	Ref			Ref			Ref							
ivSDD				988			987			986	28 days 1 knot	Fig 3B	0.003	973	WCE
Yes	1160 (14.7)	0.65 (0.22, 1.92)	0.44		0.51 (0.18, 1.51)	0.23		0.43 (0.15, 1.26)	0.13						
No	6712 (85.3)	Ref			Ref			Ref							

		Current exposure-risk model (current effect of the current value of the time-dependent variable)			1-day delay exposure-risk model (current effect of the current value of the time-dependent variable)			2-day delay exposure-risk model (current effect of the current value of the time-dependent variable)			WCE exposure-risk model (current effect of the current and past values of the time-dependent variable for the best-fitting model)				Exposure -risk model selected for final model
	LOCF venti-lator days (%) [1]	**HR 95% CI**	**p-value**	**AIC**	**HR 95% CI**	**p-value**	**AIC**	**HR 95% CI**	**p-value**	**AIC**	**Relevant exposure window & number of knots[2]**	**HR & 95%CI**	**p-value [3]**	**AIC**	
Intestinal prophylaxis				970			970			975	12 day	Fig 3E	0	965	WCE
Yes	2395 (30.4)	0.12 (0.04, 0.41)	0.0007		0.13 (0.04, 0.42)	0.0008		0.19 (0.06, 0.54)	0.002		2 knots				
No	5477 (69.6)	Ref			Ref			Ref							
Oropharyngeal prophylaxis				967			968			973	21 days	Fig 3D	0	965	Current
Yes	4784 (60.8)	0.14 (0.05, 0.38)	0.0001		0.14 (0.05, 0.39)	0.0002		0.20 (0.08, 0.51)	0.0006		1 knot				
No	3088 (39.2)	Ref			Ref			Ref			(unconstrained)				

1 The number of ventilation days after reducing the numbers of missings for time-dependent covariates with the 'last observation carried forward (LOCF) approach'.
The total number of ventilation days was 7872

2 for best-fitting model

3 The p-value was estimated using 1000 bootstrapped data sets to account for multiple testing when selecting the best-fitting WCE model.

REFERENCES

1. ECDC. Surveillance of healthcareassociated infections in Europe, 2007. Stockholm: European Centre for Disease Prevention and Control; 2012.
2. Edwards JR, Peterson KD, Mu Y, Banerjee S, Allen-Bridson K, Morrell G, et al. National Healthcare Safety Network (NHSN) report: data summary for 2006 through 2008, issued December 2009. Am J Infect Control. 2009;37(10):doi:10.1016/j.ajic.2009.10.001.
3. Koulenti D, Tsigou E, Rello J. Nosocomial pneumonia in 27 ICUs in Europe: perspectives from the EU-VAP/CAP study. Eur J Clin Microbiol Infect Dis. 2016:doi:10.1007/s10096-016-2703-z.
4. Bekaert M, Timsit JF, Vansteelandt S, Depuydt P, Vesin A, Garrouste-Orgeas M, et al. Attributable mortality of ventilator-associated pneumonia: a reappraisal using causal analysis. Am J Respir Crit Care Med. 2011;184(10):doi:10.1164/rccm.201105-0867OC.
5. Melsen WG, Rovers MM, Groenwold RH, Bergmans DC, Camus C, Bauer TT, et al. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. Lancet Infect Dis. 2013;13(8):doi:10.1016/S1473-3099(13)70081-1.
6. Muscedere JG, Martin CM, Heyland DK. The impact of ventilator-associated pneumonia on the Canadian health care system. J Crit Care. 2008;23(1):doi:10.1016/j.jcrc.2007.11.012.
7. Timsit JF, Zahar JR, Chevret S. Attributable mortality of ventilator-associated pneumonia. Curr Opin Crit Care. 2011;17(5):doi:10.1097/MCC.0b013e32834a5ae9.
8. Cassini A, Plachouras D, Eckmanns T, Abu Sin M, Blank HP, Ducomble T, et al. Burden of Six Healthcare-Associated Infections on European Population Health: Estimating Incidence-Based Disability-Adjusted Life Years through a Population Prevalence-Based Modelling Study. PLoS Med. 2016;13(10):doi:10.1371/journal.pmed.1002150.
9. Cook DJ, Walter SD, Cook RJ, Griffith LE, Guyatt GH, Leasa D, et al. Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. Ann Intern Med. 1998;129(6):doi:433-40.
10. Kollef MH, Afessa B, Anzueto A, Veremakis C, Kerr KM, Margolis BD, et al. Silver-coated endotracheal tubes and incidence of ventilator-associated pneumonia: the NASCENT randomized trial. JAMA. 2008;300(7):doi:10.1001/jama.300.7.805.
11. Tejerina E, Frutos-Vivar F, Restrepo MI, Anzueto A, Abroug F, Palizas F, et al. Incidence, risk factors, and outcome of ventilator-associated pneumonia. J Crit Care. 2006;21(1):doi:10.1016/j.jcrc.2005.08.005.
12. Alp E, Guven M, Yildiz O, Aygen B, Voss A, Doganay M. Incidence, risk factors and mortality of nosocomial pneumonia in intensive care units: a prospective study. Ann Clin Microbiol Antimicrob. 2004;3:doi:10.1186/1476-0711-3-17.
13. Krag M, Perner A, Wetterslev J, Wise MP, Hylander Moller M. Stress ulcer prophylaxis versus placebo or no prophylaxis in critically ill patients. A systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. Intensive Care Med. 2014;40(1):doi:10.1007/s00134-013-3125-3.
14. Sofianou DC, Constandinidis TC, Yannacou M, Anastasiou H, Sofianos E. Analysis of risk factors for ventilator-associated pneumonia in a multidisciplinary intensive care unit. Eur J Clin Microbiol Infect Dis. 2000;19(6):doi:460-3.
15. Apostolopoulou E, Bakakos P, Katostaras T, Gregorakos L. Incidence and risk factors for ventilator-associated pneumonia in 4 multidisciplinary intensive care units in Athens, Greece. Respir Care. 2003;48(7):doi:681-8.
16. Pawar M, Mehta Y, Khurana P, Chaudhary A, Kulkarni V, Trehan N. Ventilator-associated pneumonia: Incidence, risk factors, outcome, and microbiology. J Cardiothorac Vasc Anesth. 2003;17(1):doi:10.1053/jcan.2003.4.

17. Al-Dorzi HM, El-Saed A, Rishu AH, Balkhy HH, Memish ZA, Arabi YM. The results of a 6-year epidemiologic surveillance for ventilator-associated pneumonia at a tertiary care intensive care unit in Saudi Arabia. Am J Infect Control. 2012;40(9):doi:10.1016/j.ajic.2011.10.004.
18. Myny D, Depuydt P, Colardyn F, Blot S. Ventilator-associated pneumonia in a tertiary care ICU: analysis of risk factors for acquisition and mortality. Acta Clin Belg. 2005;60(3):doi:10.1179/acb.2005.022.
19. Chen W, Cao Q, Li S, Li H, Zhang W. Impact of daily bathing with chlorhexidine gluconate on ventilator associated pneumonia in intensive care units: a meta-analysis. J Thorac Dis. 2015;7(4):doi:10.3978/j.issn.2072-1439.2015.04.21.
20. Wang L, Li X, Yang Z, Tang X, Yuan Q, Deng L, et al. Semi-recumbent position versus supine position for the prevention of ventilator-associated pneumonia in adults requiring mechanical ventilation. Cochrane Database of Syst Rev [Internet]; 2016 [2018 Dec 06]. Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009946.pub2/epdf/full.
21. de Smet AM, Kluytmans JA, Blok HE, Mascini EM, Benus RF, Bernards AT, et al. Selective digestive tract decontamination and selective oropharyngeal decontamination and antibiotic resistance in patients in intensive-care units: an open-label, clustered group-randomised, crossover study. Lancet Infect Dis. 2011;11(5):doi:10.1016/S1473-3099(11)70035-4.
22. Sylvestre MP, Abrahamowicz M. Flexible modeling of the cumulative effects of time-dependent exposures on the hazard. Stat Med. 2009;28(27):doi:10.1002/sim.3701.
23. van der Kooi TI, de Boer AS, Mannien J, Wille JC, Beaumont MT, Mooi BW, et al. Incidence and risk factors of device-associated infections and associated mortality at the intensive care in the Dutch surveillance system. Intensive Care Med. 2007;33(2):doi:10.1007/s00134-006-0464-3.
24. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. Br Med J. 1974;2(5920):doi:656-9.
25. Mahmud M, Abrahamowicz M, Leffondré K, Chaubey Y. Selecting the optimal transformation of a continuous covariate in Cox's regression: Implications for hypothesis testing. Communications in Statistics - Simulation and Computation. 2006;35:doi:27–45.
26. Akaike H. A new look at the statistical model identification. IEEE Transactions on Automatic control. 1974;19(6):doi:716-23.
27. Quantin C, Abrahamowicz M, Moreau T, Bartlett G, MacKenzie T, Tazi MA, et al. Variation over time of the effects of prognostic factors in a population-based study of colon cancer: comparison of statistical models. Am J Epidemiol. 1999;150(11):doi:1188-200.
28. R Core Team. R: A language and environment for statistical computing. In: Computing RFfS, editor. Vienna, Austria. 2016.
29. Sylvestre MP, Beauchamp ME, Kyle RP, Abrahamowicz M. WCE: Weighted Cumulative Exposure Models. Version 1.0. 2015.
30. Therneau T. A Package for Survival Analysis in S. version 2.38. 2015.
31. Klompas M, Branson R, Eichenwald EC, Greene LR, Howell MD, Lee G, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2014;35(8):doi:10.1086/677144.
32. Kerlin MP, Trick WE, Anderson DJ, Babcock HM, Lautenbach E, Gueret R, et al. Interrater Reliability of Surveillance for Ventilator-Associated Events and Pneumonia. Infect Control Hosp Epidemiol. 2017;38(2):doi:10.1017/ice.2016.262.
33. Zuschneid I, Schwab F, Geffers C, Behnke M, Ruden H, Gastmeier P. Trends in ventilator-associated pneumonia rates within the German nosocomial infection surveillance system (KISS). Infect Control Hosp Epidemiol. 2007;28(3):doi:10.1086/507823.

34. Rouze A, Cottereau A, Nseir S. Chronic obstructive pulmonary disease and the risk for ventilator-associated pneumonia. Curr Opin Crit Care. 2014;20(5):doi:10.1097/MCC.0000000000000123.
35. Luize AP, Menezes AM, Perez-Padilla R, Muino A, Lopez MV, Valdivia G, et al. Assessment of five different guideline indication criteria for spirometry, including modified GOLD criteria, in order to detect COPD: data from 5,315 subjects in the PLATINO study. NPJ Prim Care Respir Med. 2014;24:doi:10.1038/npjpcrm.2014.75.
36. Funk GC, Bauer P, Burghuber OC, Fazekas A, Hartl S, Hochrieser H, et al. Prevalence and prognosis of COPD in critically ill patients between 1998 and 2008. Eur Respir J. 2013;41(4):doi:10.1183/09031936.00226411.
37. Dubosky MN, Chen YF, Henriksen ME, Vines DL. Vibrating Mesh Nebulizer Compared With Metered-Dose Inhaler in Mechanically Ventilated Subjects. Respir Care. 2017;62(4):doi:10.4187/respcare.04823.

Chapter 5

Prevalence of nosocomial infections in the Netherlands, 2007-2008: results of the first four national studies

T.I.I. van der Kooi, J. Manniën, J.C. Wille,
B.H.B. van Benthem

Journal of Hospital Infection 2010(75): 168–172

ABSTRACT

The PREZIES national network for the surveillance of nosocomial infections (NI) in The Netherlands has organised a national prevalence study twice a year since 2007. This paper presents the results of the first four surveys. Of 95 hospitals in The Netherlands, 41 participated in 92 surveys and 26 937 patients were included. On the survey day 6.2% had an NI (prevalence of infections 7.2%). The prevalence of infections varied from 1.4% to 16.5% between hospitals. The prevalence of surgical site infections was 4.8%, pneumonia 1.1%, primary bloodstream infection 0.5% and symptomatic urinary tract infection 1.7%. On admission to hospital, 3.3% of patients had an NI. On the day of the survey, 30.9% of the patients were receiving antibiotics. The use of antibiotics as well as medical devices differed considerably between hospitals. Both the prevalence of NI in The Netherlands and the use of antibiotics and devices were comparable to other European countries.

INTRODUCTION

The surveillance of nosocomial infections (NIs) is necessary for assessing how hospitals perform regarding infection prevention and patient safety. The number of Nis can be measured by incidence and prevalence studies. Prevalence studies, although not suitable for in-depth analysis, are useful instruments as they are less time-consuming than incidence studies. This means that they can be conducted throughout the hospital – thus providing an overview of possible problem areas that merit further analysis. At the national level, prevalence surveys give insight into the total burden of NI.

European studies show the prevalence of nosocomial infections to vary between 6.1% and 10.7%.[1–7] In The Netherlands, PREZIES– which is a national, non-mandatory network for the surveillance of NI – collects data on the occurrence of NI. PREZIES is the Dutch acronym for 'prevention of hospital-acquired infections by surveillance'. Before national NI prevalence data for The Netherlands became available, data from the incidence-based PREZIES surveillance of surgical site infections(SSI), central venous catheter-related bloodstream infection(CR-BSI) and ventilator-associated pneumonia (VAP) indicated that the burden of NI appeared to be comparable with that of neighbouring countries.

Nosocomial infections are associated with increased morbidity, hospital stay, mortality and costs.[8,9] Superficial SSIs in The Netherlands have been associated with additional costs of €900 to €2700 per infection and deep SSI as high as €3200 to €19900.[10] Data on the extra costs involved for other types of NI are not available for The Netherlands but these are also expected to be substantial.

Many Dutch hospitals have in the past performed prevalence surveys, conducted according to different local protocols, but only a few have published their data.[11] Therefore in order to obtain national estimates of the prevalence of NIs for all types of infection and to increase inter-hospital comparability, the PREZIES network collaborated with ZIEN (working party for Hospital Acquired Infection Epidemiology in The Netherlands) and developed a national protocol in 2007. In accordance with this protocol, national prevalence surveys are organized twice yearly, in March and October. This article discusses the results of the first four surveys in 2007 and 2008.

METHODS

Setting

After a pilot study involving five hospitals, all hospitals in The Netherlands were invited to participate and attend a workshop where the PREZIES protocol and definitions were explained. Collecting the surveillance data was usually done by a team of infection control practitioners (ICPs) and medical microbiologists. These ICPs then visited the

wards, checked the medical records and laboratory results of patients and discussed these with the relevant nursing and medical staff. Patients with infections and complex cases were discussed by the whole surveillance team. From 2008 onwards, ten hospitals a year were visited by two PREZIES staff members who validated the way the protocol was used. This was done by discussing the surveillance process and studying 20 patient records from prescribed specialties including at least five from patients with NI. Preliminary results of this validation showed a negative predictive value of 97.6% and a positive predictive value of 75%.

Study design and data collection

All inpatients one year and older, who had been admitted before the day of the survey, were included except for patients in psychiatric and day units, such as dialysis. The surveillance took place during one whole month (March and/or October) and all patients from one ward were surveyed on the same day. Initially, March was the only proposed survey month but October was added at the request of participants who were used to surveying twice a year.

Demographic and additional details were collected from patients at the time of the survey and included: presence of NI on hospital admission (related to an earlier hospital stay; not included in the prevalence), surgery, and type, treating specialty, the presence of and category of NI on the survey day, risk factors and anti-infective use (excluding antifungals and antivirals). Also, the presence of peripheral, central venous, arterial, urinary, suprapubic and epidural catheters, ventricular drains and invasive ventilation were also recorded. An NI was defined as an infection that occurred following hospital admission, without any evidence that the infection was present or had been incubating on admission. An infection was considered to be present or active as long as the patient was symptomatic or receiving antimicrobial or other therapy for the infection on the day of the survey. There is a national working party on antibiotic policy (SWAB: Stichting Werkgroep Antibioticabeleid) that issues guidelines and these serve as a starting point for hospital guidelines.

All types of infections, according to the Centers for Disease Control and Prevention (CDC) criteria, were recorded. Adapted CDC criteria were used for SSI, CR-BSI and VAP (Table I). CR-BSI, VAP and catheter-related urinary tract infection (UTI) were deemed device-associated when the devices had been present for at least 48h. Only symptomatic UTIs were recorded. Where necessary, results on cultures taken on or before the survey day were collected after the survey day. Data were collected in a web-based questionnaire. In order to increase data quality, checks for logical data sequence

Table I Criteria for surgical site infection, central venous catheter-related bloodstream infection and ventilator-associated pneumonia[a]

Surgical site infection (SSI)

All infections should meet the following criteria:

for superficial SSI:

1. Infection of skin or subcutaneous tissue develops within 30 days after the operative procedure *and*
2. Purulent drainage from incision *or*
   Clinical symptom(s) (pain, tenderness, localised swelling, redness or heat) *and*
   - a positive culture *or*
   - surgeon opens incision deliberately (unless wound culture is negative).

for deep SSI (including SSI from organ/ anatomical space):

1. Infection of fascia, muscle or organ/antomical space develops within 30 days after the operative procedure *or* within a year when non-human-derived material was implanted *and*
2. Purulent drainage from deep incision or drain *or*
   Abscess or other sign of infection on direct observation, during reoperation or by histopathological or radiological investigation *or*
   Clinical symptom(s) (pain, tenderness, localised swelling, redness, heat, fever>38 °C) *and*
   - spontaneous wound dehiscence *or*
   - surgeon opens incision deliberately (unless wound culture is negative) *or*
   - positive culture of fluid or tissue (in case of surgery in organ/anatomical space)

Central venous catheter-related bloodstream infection (CR-BSI)

All infections should meet the following criteria:

1. Central venous catheter present for at least 48 h or was present until at most 24 h ago *and*
2. Fever (>38 °C), hypotension (<100 mmHg) or chills *and*
3. One of the following:
   - Positive blood culture by venepuncture or from an arterial catheter and positive semiquantitative culture of a catheter segment with the same micro-organism *or*
   - positive blood culture by venepuncture and positive qualitative culture of a catheter segment with the same micro-organism *or*
   - positive blood culture by venepuncture and central venous catheter remains in situ and symptoms disappear within 48 h after start of therapy *or*
   - no blood and/or catheter segment culture done and symptoms disappear within 24 h after removal of central venous catheter *and*
4. No infection with the same micro-organism present at another body site.

Ventilator-associated pneumonia (VAP)

All infections should meet the following criteria:

1. Patient ventilated for at least 48 h or ventilated until at most 24 h ago *and*
2. At least one chest X-ray with new or progressive infiltrate or cavitation or consolidation *and*
3. At least one of the following symptoms:
   - fever (>38 °C) without other apparent reason
   - leucopaenia (<4000 leucocytes/mm^3)
   - leucocytosis (2:12 000 leucocytes/mm^3) *and*
4. At least one of the following symptoms:
   - production of purulent sputum
   - change in character of sputum
   - worsening gas exchange.

   Patients fulfilling these criteria are registered as having clinical pneumonia. When a positive culture of tracheal aspirate, bronchoalveolar lavage liquid, etc., is present this leads to different categories of pneumonia but for this prevalence survey no distinction was made.

[a] Adapted from the Centers for Disease Control and Prevention criteria.

were built into the questionnaire. Hospitals received a detailed report on their data and the overall results.

Statistical analysis

All data were checked for completeness prior to statistical analysis. Confidence intervals were calculated with the Wilson score. All descriptive analyses were conducted using Excel and SAS 9.1.

RESULTS

Participation

In total, 92 surveys were conducted (Figure1) by 41 different hospitals – representing 43% of all the hospitals in The Netherlands. The number of surveys conducted for each hospital was as follows: 10 institutions participated once, 20 participated twice, two participated three times and nine, four times. Figure1 also shows the distribution of hospital size, based on the average number per period: 32% of the hospitals had ≤200patients, 51% 200–400 and 17% >400. Six of the eight Dutch university medical centres participated. The consecutive numbers of patients included per period were 8424, 3497, 9449 and 5567.

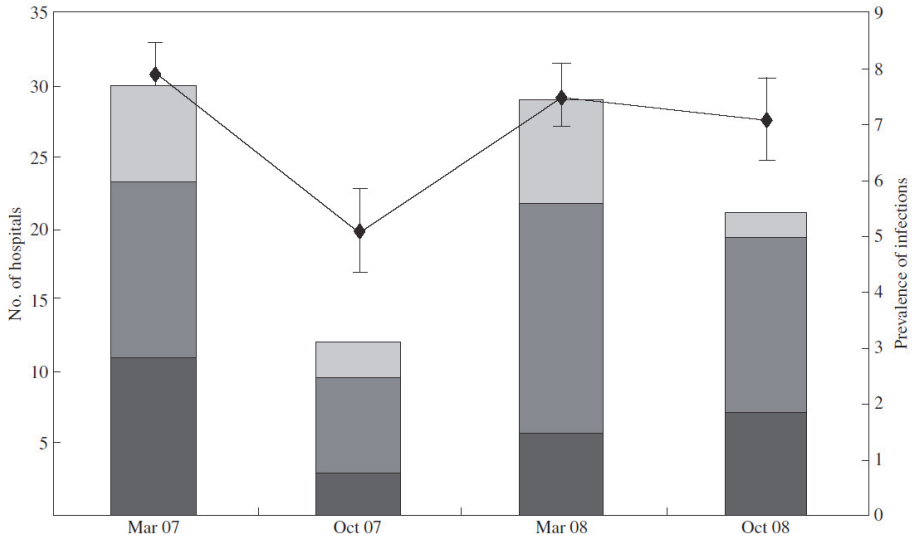


Figure 1: Prevalence of infections per period (filled diamonds), with 95% confidence interval [≤200 patients per survey (dark grey bars), 200–400 patients per survey (mid-grey bars) and >400 patients per survey (light grey bars)].

Prevalence of infection

The four studies surveyed 26937 patients. Table II outlines the patient characteristics and the corresponding NI frequencies. There was a total of 1934 Nis in 1667 patients. Thus, the prevalence of patients with NI was 6.2% (95% confidence interval: 5.9–6.5) and the prevalence of infection was 7.2% (6.9–7.5). The prevalence of infection varied from 1.4% to 16.5% between hospitals. Figure1 shows the prevalence per period. In October 2007, the prevalence was significantly lower than in other periods. The distribution of hospitals or infection types did not seem to explain the observed differences (data not shown).The nine hospitals that participated in all four periods had a comparable trend (data not shown).

The four major NIs, i.e. SSI, pneumonia, primary BSI and symptomatic UTI accounted for 70.3% of all NIs. Table III gives the prevalence per type. Secondary bloodstream infection occurred in 0.5% of patients and originated from symptomatic UTI (20%), SSI (36%), pneumonia (10%) and other infection types (33%).

The prevalence of infections on the ICU was 25.5%, the prevalence of pneumonia 9.9%, primary BSI 2.4%, symptomatic UTI 2.2% and SSI 8.6%. In other clinical areas the prevalence of infection was 6.2%; pneumonia 0.6%, primary BSI 0.4%, symptomatic UTI 1.7% and SSI 4.5%. Among the patients with NI, 1443 (86.6%) had one infection, 187 (11.2%) had two, and 37 (2.2%) had three or four.

The median length of stay before the day of the survey was six days for all patients, and for those patients without NI. It was 19 days for patients with NI. On admission, 3.3% of the patients had an NI of which 65.2% were acquired in the same hospital. Of these, SSI was the most common infection type (75.1%).

Device use

Data on the use of medical devices and NI are outlined in Table II. In 36.9% of patients one device was present, 12.2% had two, and 5.3% had three to six. The presence of a urinary catheter varied between hospitals from 10.2% to 28.6%, CVC from 1.7% to 18.6%, invasive ventilator assistance from 0% to 6.3% and peripheral catheter use from 26.2% to 56.4%.

Antibiotic use

On the day of the survey, 30.9% of patients were receiving anti-infectives. This ranged between hospitals from 20.7% to 42.9%. Of the patients with NI, 71.9% were on antibiotics, and for those without NI, 28.8%. Antibiotic use in the ICU was 56.9% and 29.6% outside the ICU.

Table II: Characteristics of patients, including device use and nosocomial infection prevalence

	No. of patients	% of patients	No. of infections	Prevalence of infections (95% CI)
Male	12802	47.5	1043	8.1 (7.7-8.6)
Female	14133	52.5	891	6.3 (5.9-6.7)
Age (years)				
1-39	4271	15.9	147	3.4 (2.9-4.0)
40-59	5660	21.0	360	6.4 (5.8-7.0)
≥60	17006	63.1	1427	8.4 (8.0-8.8)
Specialty				
Anaesthetics	87	0.3	16	18.4 (11.6-27.8)
Cardiology	3116	11.6	118	3.8 (3.2-4.5)
Cardiothoracic surgery	782	2.9	107	13.7 (11.5-16.3)
Dermatology	101	0.4	5	5.0 (2.1-11.1)
Ear/Nose/Throat	454	1.7	21	4.6 (3.0-7.0)
Haematology	324	1.2	37	11.4 (8.4-15.3)
Internal medicine	5081	18.9	313	6.2 (5.5-6.9)
Neurology	2279	8.5	172	7.5 (6.5-8.7)
Neurosurgery	595	2.2	57	9.6 (7.5-12.2)
Obstetrics & gynecology	1658	6.2	29	1.7 (1.2-2.5)
Ophthalmology	60	0.2	0	0.0 (0.0-6.0)
Oncology	484	1.8	37	7.6 (5.6-10.4)
Orthopedics	2174	8.1	117	5.4 (4.5-6.4)
Paediatrics	778	2.9	29	3.7 (2.6-5.3)
Plastic surgery	254	0.9	13	5.1 (3.0-8.6)
Respiratory	2571	9.5	84	*3.3 (2.6-4.0)*
Surgery	4692	17.4	661	*14.1 (13.1-15.1)*
Trauma	216	0.8	24	*11.1 (7.6-16.0)*
Urology	860	3.2	48	*5.6 (4.2-7.3)*
Unknown/different	364	1.4	46	*12.6 (9.6-16.4)*
Stay at ICU on survey day				
ICU	1342	5.0	342	*25.5 (23.2-27.9)*
not in ICU	25570	95.0	1590	*6.2 (5.9-6.5)*
Hospital status				
University hospital	5394	20.0	488	*9.0 (8.3-9.8)*
Not university hospital	21543	80.0	1446	*6.7 (6.4-7.1)*
Hospital size (mean of all periods)				
≤200 patients in survey	3697	13.7	185	*5.0 (4.3-5.8)*
200-400 patients	15447	57.3	1136	*7.4 (7.0-7.8)*
> 400 patients	7793	28.9	613	*7.9 (7.3-8.5)*
Surgical intervention[b]				
Surgery	9671	36.0	1190	*12.3 (11.7-13.0)*
No surgery	17216	63.9	743	*4.3 (4.0-4.6)*
Antibiotic use on survey day[c]				
Antibiotics	8318	30.9	1398	*16.8 (16.0-17.6)*
No antibiotics	18580	69.1	535	*2.9 (2.6-3.1)*
Nosocomial infection at admission[d]	887	3.3	132	*14.9 (12.7-17.4)*
Central venous catheter	1878	7.0	448	*23.9 (22.0-25.8)*
Peripheral intravenous catheter	11882	44.1	952	*8.0 (7.5-8.5)*
Arterial catheter	968	3.6	287	*29.6 (26.9-32.6)*
Invasive ventilation	619	2.3	232	*37.5 (33.8-41.4)*
Urinary catheter	5585	20.7	873	*15.6 (14.7-16.6)*
Suprapubic catheter	325	1.2	34	*10.5 (7.6-14.3)*
Intra- or extraventricular drain	230	0.9	31	*13.5 (9.7-18.5)*
Epidural catheter	421	1.6	29	*6.9 (4.8-9.7)*

	No. of patients	% of patients	No. of infections	Prevalence of infections (95% CI)
Length of stay until survey day				
1-2 days	8159	18.8	34	*0.4 (0.3-0.6)*
3-7 days	8552	37.6	242	*2.8 (2.5-3.2)*
8-14 days	4870	21.7	453	*9.3 (8.5-10.2)*
≥15 days	5356	13.8	1205	*22.5 (21.4-23.6)*

CI, confidence interval; ICU, intensive care unit.
[a] Unknown for 25 patients
[b] Unknown for 50 patients
[c] Unknown for 39 patients
[d] Unknown for 363 patients

Microbiology

Escherichia coli was identified as the cause of SSI in 19% followed by *Staphylococcus aureus* (not specifically meticillin-resistant *S. aureus*) (17%). Pneumonia was most commonly caused by *E. coli* (15%), *Pseudomonas aeruginosa* (15%) and *S. aureus* (14%). In patients with BSI, *S. aureus* (18%) and coagulase-negative staphylococci (25%) were most frequently found whereas *E. coli* was cultured in 44% of patients with symptomatic UTI. At 63%, *Clostridium difficile* was the main pathogen causing gastrointestinal infections (*C. difficile* infection prevalence 0.2%).

Table III: Percentage of patients infected with a specific nosocomial infection and range between hospitals.

Infection type	**Number**	**Infected patients**	**95% CI**	**Range**
Total no. of patients	26.937			
SSI[a]	464	4.8%	4.4-5.2	0.0-14.3
Pneumonia	298	1.1%	1.0-1.2	0.0-3.3
VAP	119	0.4%	0.4-0.5	0.0-1.9
Primary BSI	129	0.5%	0.4-0.6	0.0-2.5
CR-BSI	90	0.3%	0.3-0.4	0.0-1.8
Symptomatic UTI	469	1.7%	1.6-1.9	0.0-6.5
Catheter-related symptomatic UTI	344	1.2%	1.1-1.4	0.0-6.5

DISCUSSION

Prevalence of infection and device use

The NI prevalence of 7.2% (with 6.2% of patients infected) in Dutch hospitals was comparable with the infection frequencies found in most other recent European studies, although higher and lower prevalences have also been found.[1–7] However, as many of these studies included asymptomatic UTIs, caution is required when making direct comparisons. Seasonal fluctuations are known to occur for NIs but at present we cannot

explain the observed lower prevalence in October versus March. The prevalence of the different categories of infection was also comparable.[1–3,5,6]
In our study the use of devices was comparable or slightly higher than in other recent European studies.[3,5] The antibiotic use was comparable to that found in Sweden (32.5–34.9%), the UK and the Republic of Ireland (RoI) (32.1–33.1%).[3,6,12]

Microbiology
The pathogens predominantly cultured are known to be a major cause for these infections.[13,14] In The Netherlands, the prevalence of C. difficile was lower than that in the UK, RoI and Germany.[6,15,16] C. difficile has caused outbreaks in several Dutch hospitals, following the introduction of polymerase chain reaction ribotype 027, but in general these were under control prior to 2007.[17]

Methodological considerations
It is hard to draw conclusions on the relative position of Dutch hospitals because although all the cited studies were also point prevalence studies, there are other methodological differences that hamper comparison. These include the method of data collection (e.g. by hospital staff or by a visiting team), the characteristics of participating hospitals, the inclusion of patients admitted or discharged on the day of the survey, case definitions and the departments included. Issues that could belong to the past when a common protocol, like the one that is being developed by the European Centre for Disease Prevention and Control, is used.

Since the surveillance was executed by hospital staff it is likely that there were some differences between hospitals in how the protocol was applied. In order to address this, workshops explaining the protocol were organised for all the participants. Further, from 2008 onwards hospitals were visited by a validation team that checked the survey procedure.

Larger hospitals can be overrepresented in voluntary studies and this was the case in our study, where university medical centres were overrepresented and other larger hospitals slightly so (24% ≥800 beds vs 15% nationally).[18,19] This can result in an overestimated NI prevalence – as larger hospitals usually have relatively more patients with severe underlying disease that is associated with an increased NI risk.[18,20]

We compared our results only with those of recent studies. Previous data have limited value for comparison. For example, the average proportion of patients on antibiotics will have increased during the last decade because patients are now discharged earlier. From 1997 to 2006 the average use of antibiotics in Dutch hospitals increased from 47 to 62 defined daily doses per 100 patient-days whereas hospital stay

decreased from 8.2 to 6.3 days and the use per patient remained approximately the same.[21,22] Because of this development in hospital stay, fewer SSIs are found when no postdischarge surveillance is carried out. For the other infection types, a shorter hospital stay results in a weaker and more dependent hospital population – needing more devices which leads to more NIs. It is therefore possible that the prevalence of NI and of device use has changed over time, without a real change in risk on a per patient basis or vice versa. A difference in case-mix over the course of time or between institutions or countries could partly be overcome by including a comorbidity index. Other studies showed comorbidity indices to be significantly associated with the risk of acquiring an NI.[4,20] We have not recorded comorbidities, which hampers case-mix adjustment. The higher NI prevalence for increasing length of stay (until the survey day) is most likely to be at least partly a consequence of sicker patients and/or those with a nosocomial infection staying in hospital longer. In the reference data fed back to the hospitals and published on the PREZIES website, case-mix adjustment is attained by stratification.

Prevalence surveys are valuable because they can give an overall picture, including all NI types and, with that, estimate the total burden of NI. A drawback of prevalence surveys in general is the overestimation of NI occurrence because more vulnerable patients and those with an NI stay in hospital longer and are thus 'oversampled'. However, although these data do not present the actual risk per patient of developing an NI, they are valuable for creating insight into high risk populations. Hospitals that, in their feedback report, detect higher than average infection prevalences in certain populations, can decide to implement interventions or, when causes are unclear, choose to analyse this patient population further. As an option to the prevalence survey, hospitals could start recording more detailed data on antibiotic use and/or urinary catheter use and many hospitals have now done so. In addition, the majority of Dutch hospitals are now focusing on the reduction of SSI and CR-BSI, within a national patient safety programme. The large interhospital range in device use and prevalence of infections suggests that improvements are possible.

This study presents the first national estimates of the prevalence of NI in hospitals in The Netherlands. The prevalences stated are the best available estimate of the prevalence of NIs at national level. The use of devices and antibiotics as well as the prevalence of NI appeared to be comparable to that in other European countries. The results provide insight into high risk patients and could lead to the start of in-depth investigations and/or targeted interventions for reducing the burden of NIs.

ACKNOWLEDGEMENTS

The authors wish to thank all infection control practitioners, microbiologists, and other

hospital staff from the participating hospitals who contributed to this study. Their commitment to the surveillance of nosocomial infections is invaluable.

REFERENCES

1. Eriksen HM, Iversen BG, Aavitsland P. Prevalence of nosocomial infections in hospitals in Norway, 2002 and 2003. *J Hosp Infect* 2005;**60**:40–45.
2. Floret N, Bailly P, Bertrand X, et al. Results from a four-year study on the prevalence of nosocomial infections in Franche-Comte: attempt to rank the risk of nosocomial infection. *J Hosp Infect* 2006;**63**:393–398.
3. Humphreys H, Newcombe RG, Enstone J, et al. Four country healthcare associated infections prevalence survey 2006: risk factor analysis. *J Hosp Infect* 2008;**69**:249–257.
4. Kritsotakis EI, Dimitriadis I, Roumbelaki M, et al. Case-mix adjustment approach to benchmarking prevalence rates of nosocomial infection in hospitals in Cyprus and Greece. *Infect Control Hosp Epidemiol* 2008;**29**: 685–692.
5. Lyytikäinen O, Kanerva M, Agthe N, Möttönen T, Ruutu P, Finnish Prevalence Survey Study Group. Healthcare-associated infections in Finnish acute care hospitals: a national prevalence survey, 2005. *J Hosp Infect* 2008;**69**: 288–294.
6. Reilly J, Stewart S, Allardice G, et al. *NHS Scotland national prevalence survey. Final report 2007*. Glasgow: Health Protection Scotland; 2007.
7. Gordts B, Vrijens F, Peeters G, et al. Nationwide investigation into the prevalence of nosocomial infections in Belgium. Abstract at ECCMID 2009.
8. Defez C, Fabbro-Peray P, Cazaban M, Boudemaghe T, Sotto A, Daurès JP. Additional direct medical costs of nosocomial infections: an estimation from a cohort of patients in a French university hospital. J Hosp Infect 2008;**68**: 130–136.
9. Fabbro-Peray P, Sotto A, Defez C, et al. Mortality attributable to nosocomial infection: a cohort of patients with and without nosocomial infection in a French university hospital. *Infect Control Hosp Epidemiol* 2007;**28**: 265–272.
10. Goebbels ELPE. Prevention of surgical infections through surveillance. Dissertation, University of Utrecht; 2002. p. 101–116.
11. Hopmans TEM, Blok HEM, Troelstra A, Bonten MJM. Prevalence of hospital-acquired infections during successive surveillance surveys conducted at a university hospital in the Netherlands. *Infect Control Hosp Epidemiol* 2007;**28**:459–465.
12. Erntell M, Skoog G, Cars O, et al. Changes in patterns of antimicrobial use in Swedish hospitals from 2003 to 2006 following the introduction of large-scale nationwide point prevalence studies. Abstract at ECCMID 2008.
13. European Centre for Disease Prevention and Control. *Annual epidemiological report on communicable diseases in Europe 2008*. Stockholm: European Centre for Disease Prevention and Control; 2008.
14. French Prevalence Survey Study Group. Prevalence of nosocomial infections in France: results of the nationwide survey in 1996. *J Hosp Infect* 2000;**46**:186–193.
15. Smyth ETM, McIlvenny G, Enstone JE, et al. Four country healthcare associated infection prevalence survey 2006: overview of the results. *J Hosp Infect* 2008;**69**:230–248.
16. Gastmeier P, Weitzel-Kage D, Behnke M, Eckmanns T. Surveillance of Clostridium difficile-associated diarrhoea with the German nosocomial infection surveillance system KISS (CDAD-KISS). *Int J Antimicrob Agents* 2009;**33**: S19–S23.
17. Notermans DW, Kooi TII van der, Goorhuis A, Debast SB, Benthem BHB van, Kuijper EJ. Epidemiology of Clostridium difficile PCR ribotype 027 in the Netherlands 2005–present and the emergence of other subtypes. *Nederl Tijdschr Geneesk* 2008;**152**:1937–1940.
18. Gastmeier P, Kampf G, Wischnewski N, et al. Prevalence of nosocomial infections in representative

German hospitals. *J Hosp Infect* 1998;**38**:37–49.
19. Sax H, Pittet D. Résultats de l'enquête nationale de prévalence des infections nosocomiales de 2004 (snip04). *Swiss-NOSO* 2005;12:1–8.
20. Sax H, Pittet D, Swiss-NOSO network. Interhospital differences in nosocomial infection rates. Importance of case-mix adjustment. *Arch Intern Med* 2002;**162**:2437–2442.
21. Stichting Werkgroep Antibioticabeleid. *Nethmap 2003 – Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in The Netherlands*. Amsterdam: SWAB; 2003.
22. Stichting Werkgroep Antibioticabeleid. Nethmap 2008 – *Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in The Netherlands*. Amsterdam: SWAB; 2008.

Chapter 6

Mortality review as a tool to assess the contribution of healthcare-associated infections to death: results of a multicentre validity and reproducibility study, 11 European Union countries, 2017 to 2018

Tjallie van der Kooi, Alain Lepape, Pascal Astagneau, Carl Suetens, Mioara Alina Nicolaie, Sabine de Greeff, Ilma Lozoraitiene, Jacek Czepiel, Marta Patyi, Diamantis Plachouras, the HAI-Net Mortality review study group

---

Eurosurveillance 2021;26(23): pii=2000052

ABSTRACT

Introduction: The contribution of healthcare-associated infections (HAI) to mortality can be estimated using statistical methods, but mortality review (MR) is better suited for routine use in clinical settings. The European Centre for Disease Prevention and Control recently introduced MR into its HAI surveillance.

Aim: We evaluate validity and reproducibility of three MR measures.

Methods: The on-site investigator, usually an infection prevention and control doctor, and the clinician in charge of the patient independently reviewed records of deceased patients with bloodstream infection (BSI), pneumonia, *Clostridioides difficile* infection (CDI) or surgical site infection (SSI), and assessed the contribution to death using 3CAT: definitely/possibly/no contribution to death; WHOCAT: sole cause/part of causal sequence but not sufficient on its own/contributory cause but unrelated to condition causing death/no contribution, based on the World Health Organization's death certificate; QUANT: Likert scale: 0 (no contribution) to 10 (definitely cause of death). Inter-rater reliability was assessed with weighted kappa (wk) and intra-cluster correlation coefficient (ICC). Reviewers rated the fit of the measures. **Results:** From 2017 to 2018, 24 hospitals (11 countries) recorded 291 cases: 87 BSI, 113 pneumonia, 71 CDI and 20 SSI. The inter-rater reliability was: 3CAT wk 0.68 (95% confidence interval (CI): 0.61-0.75); WHOCAT wk 0.65 (95% CI: 0.58-0.73); QUANT ICC 0.76 (95% CI: 0.71-0.81). Inter-rater reliability ranged from 0.72 for pneumonia to 0.52 for CDI. All three measures fitted 'reasonably' or 'well' in >88%.

Conclusion: Feasibility, validity and reproducibility of these MR measures was acceptable for use in HAI surveillance.

INTRODUCTION

Healthcare-associated infections (HAI) are a major public health problem affecting more than 90,000 patients on any given day in European acute care hospitals, which results in an estimated 4.5 million cases each year (1). HAI are associated with increased morbidity and mortality (2). Data on attributable mortality are limited, hampering accurate estimates of the burden of HAI. The attributable mortality of HAI is difficult to assess because of various competing causes of death in severely ill patients, especially in intensive care units (ICU). In addition, death is a consequence of events that occur over a period of time, which is usually not well addressed in statistical models. Attributable mortality of HAI is usually estimated by calculating the difference in the relative risk of death between patients with and without HAI from comparative studies or by modelling approaches (3-8). However, statistical approaches are not easily applied in individual hospitals as they require detailed data on a cohort of patients and statistical expertise. Potential sources of bias, such as heterogeneity in multicentre studies and time-dependency of the observed outcome, need to be taken into account (5, 9), and the results can be difficult to assess, as they depend primarily on the availability of data on risk factors. Another approach to estimate the attributable mortality of HAI is to perform mortality review studies that entail a descriptive evaluation, for each patient who died with an HAI, of the likelihood that the HAI contributed to the death of the patient according to clinical judgement.

The European Centre for Disease Prevention and Control (ECDC) coordinates the European Healthcare-Associated Infections surveillance Network (HAI-Net). In 2013, the European Commission requested that the ECDC should collect additional data on mortality from HAI. To address the request, ECDC introduced mortality review into the HAI-Net surveillance protocols with a measure that categorises the contribution of an HAI to death in three categories: no contribution, possibly contributed and definitely contributed, based on the work of Kaoutar et al (10). As the validity of mortality reviews has never been established (e.g. through autopsy studies) and standardisation of the criteria and review process across hospitals and countries would be necessary, ECDC initiated a study to evaluate the validity, feasibility and reproducibility of the review measure.

METHODS

Preparation

An expert panel was established to support the project group in developing the study

design. This panel consisted of 12 experts that were either National Focal Points for HAI, infection prevention and control doctors, intensive care physicians, surgeons or epidemiologists, known for their clinical and research experience in HAI. The study group, including both project group and expert panel, met to discuss the three-category mortality review measure (3CAT) developed by Kaoutar et al (10) and evaluated in 16 French hospitals. We added two alternative measures: one based on the World Health Organization (WHO) death certification methodology that is widely applied by clinicians (11) (WHOCAT) and a quantitative Likert scale from 0 to 10 (QUANT), to enable a more visual assessment (12) (Box).

Pneumonia, bloodstream infection (BSI) and *Clostridioides difficile* infection were selected for evaluation as these HAI are recorded within two HAI-Net modules (European surveillance of healthcare-associated infections in intensive care units (pneumonia and BSI)(13) and European surveillance of *C. difficile* infections(14)) and are both frequent and associated with increased mortality(2). During the expert meeting, the panel evaluated the feasibility and validity of the three outcome measures with a number of case vignettes.

Hospital recruitment

The ECDC national focal points for HAI of all countries contributing to HAI-Net were invited by email to recruit hospitals in their country, preferably those performing HAI surveillance for ICU-acquired HAI, and/or CDI, applying the ECDC surveillance protocols (13-15).

Review procedure

On-site investigators attended the kick-off meeting, where the review procedure and the data to be collected were explained and discussed.

Adult patients aged 16 years and older were included if they had BSI or pneumonia (most often, but not exclusively, ICU-acquired, defined as occurring after more than 48 hours in ICU) or CDI, and subsequently died during the same hospital/ICU stay. Cases with SSI could be included but were not the focus of the study. A local team consisting of an on-site investigator (OSI; usually an infection prevention and control doctor or ICU physician) and a treating physician (TP) evaluated the patient records. The reviews were performed within ca 1 month of the death, to enable recollection of relevant details. For each deceased patient with an HAI, the OSI and TP independently assessed the contribution of the HAI to the patient's death, using the three outcome measures (Box). They subsequently discussed the case aiming to reach a consensus. Agreement or disagreement was recorded both before and after the discussion.

Data collection

The OSI entered data from the patient records in a data registration form prepared in Excel. The following data were recorded for each included patient: gender, age, hospital and ICU admission data, ward type, ICU type, date of onset and type of limitation of treatment (such as withholding or withdrawal of life-sustaining treatment), type of surgery for SSI cases, type of HAI, date of HAI and date of death, microbiology results (with a maximum of two pathogens), other HAI (BSI, pneumonia, CDI or SSI) and, in case of CDI, origin (healthcare- or community-associated) and complicated course. If more than one HAI was present, the HAI considered as the most severe was selected for the review. The assessment of the contribution was performed with the help of a checklist to increase inter-rater reliability and facilitate the interpretation of the results by the project group. This checklist included both objective and subjective items (for details see the data entry form (Supplementary Text Box S1)): expected mortality on admission when not admitted to an ICU, severity scores (Simplified Acute Physiology Score (SAPS) II or Acute Physiology and Chronic Health Evaluation (APACHE) II_III scores for ICUs, from which the expected mortality on admission was derived using ECDC HAI surveillance data from 2012 to 2015, and Sequential Organ Failure Assessment (SOFA) score), condition and comorbidities on hospital admission (McCabe score, Charlson's severity of illness and Charlson's comorbidities), American Society of Anesthesiologists (ASA) score for patients with a SSI, status of HAI on the day of death (HAI or complication thereof still active), severity of the HAI, plausible pathophysiological mechanism for contribution of the HAI to death, and presence of competing cause for the death.

In addition, we recorded selected antimicrobial resistance (AMR) phenotypes under surveillance, as specified in HAI-Net protocols (16), the perceived adequacy of antimicrobial treatment, and the contribution of AMR to the death of the patient, using scales similar to 3CAT and QUANT (Supplementary Table S1). Treatment was considered inadequate when the initiated empirical treatment, although conforming to the local antimicrobial policy, did not match the susceptibility of the cultured microorganisms, resulting in a delay in instituting adequate antimicrobial treatment. AMR could have contributed to death through a delay in adequate antimicrobial treatment or an adverse event (such as renal failure) induced by the antimicrobial prescribed to treat a HAI with a resistant organism.

For each case, reviewers answered the question "How well did [the measure] apply" independently assessing the fit of the measure (with the categories: applies well/reasonably/poorly/not). The fit indicated how well the assigned category for each

MR measure corresponded with the perceived contribution in each particular review case.

Statistical analysis

Inter-rater reliability was measured with Cohen's kappa statistic (kappa), weighted kappa statistic (wk), which accounts for ordered categories, percentage agreement and/or the intraclass correlation coefficient (ICC), depending on the measure. We calculated both the overall averaged kappa and an average kappa that controlled for hospital by adjusting for the hospital-specific variances (17).

We calculated the percentage agreement per category with the formula (2*a)/(2*a + b+c+d+g), where 'a' is the agreed number of cases for a category and 'b', 'c', 'd' and 'g' are the number of cases where only one reviewer assigned that category. In this article, 'agreement' refers to the initial agreement between the two reviewers, unless stated otherwise. We were interested in the ICC for absolute agreement and employed a two-way ICC, assuming that the raters' effects will contribute to the variability of the ratings as random effects (18). To study the association between patient and HAI characteristics and the perceived contribution, we used the consensus value of the measure. When a consensus was not reached, the assessment of the TP was used. To diagnose contribution to death (3CAT and WHOCAT), we used a random forest classifier approach. A set of the best predictors was selected to achieve an optimal prediction accuracy. Using this set, we switched to model construction in order to assess the association between the variables and the categorical outcome by means of multinomial logistic regression. In the overall analysis of 3CAT, we could perform a multilevel analysis, allowing for clustering at the hospital level. With HAI-specific subsets, these models usually did not converge. Variables that had a p-value < 0.2 in the univariate analysis were included in the multivariate analysis. The final model was attained by manual backward selection, controlling the decrease in model fit with the -2log likelihood test. We used SAS software version 9.4 of the SAS system (SAS Institute Inc., Cary, United States) and R, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical statement

The study protocol was submitted to the medical research ethics committee (MREC) of the University Medical Centre Utrecht. As the study was not interventional the need for further evaluation was waived. Participating hospitals also approved the study protocol.

RESULTS

Participating centres and reviewed cases

Thirty-seven hospitals expressed their interest in participating. Ultimately, 24 hospitals, from 11 European Union countries, submitted cases, collected during at least 7 months in the period April 2017 to February 2018 (Table 1). In total, 291 cases were reviewed, with a median age of 71 years (range: 21-97), and 55% (160/291) male, equating to a median of 7.5 cases (range 1-70) per hospital. Overall, 79% (230/291) of the patients were ICU patients and 69% (200/291) were ICU-acquired. Among all patients 113 (39%) had pneumonia with 90% (102/113) ICU-acquired, 87 (30%) had BSI with 93% (81/87) ICU-

The three mortality review measures

1**. 3CAT**: a three categories scale, with the following categories:

- Did not contribute
- Possibly contributed
- Definitely contributed

For the categories 'Possibly contributed' and 'Definitely contributed', the contribution was additionally assessed as major or minor.

2. **QUANT**: a quantitative score ranging from 0 to 10, with:

- 0 = the HAI did not contribute at all to the death of the patient, death during the current hospitalization would have occurred without the HAI
  to
- 10 = the HAI definitely caused the death of the patient, death during the current hospitalization would not have occurred without the HAI
-

3. **WHOCAT**: a scale based on the WHO death certification methodology, with four categories:

- No contribution: HAI did not contribute to the death or the contribution was redundant, i.e. the patient would have died anyway
- Contributory cause: HAI was a contributory cause but not related to the disease or condition causing the death
- Part of the causal sequence: HAI was part of the causal sequence of events that led to death but not sufficient on its own
- Sole cause: HAI was the sole cause of death – no other disease or condition causing the death was present (sufficient condition)

"Unknown or not verified: Contribution of HAI to death of the patient unknown or not verified" was added to all three outcomes.

Box: Description of the three mortality review outcome measures

acquired, 71 (24%) had CDI with 11% (8/71) ICU-acquired, and 20 (7%) had SSI with nine of 20 ICU-acquired. In 63 (22%) of all cases more than one of the evaluated HAI were present, with pneumonia and BSI most frequently selected for review (26/63 each).

Assigned scores

With 3CAT, the HAI was considered to have definitely or possibly contributed to the patient's death in 83% of cases according to the TP and 87% according to the OSI (Table 2). For the types of HAI, the responses of TP and OSI were respectively 71% and 81% for pneumonia, 94% and 95% for BSI and 82% and 85% for CDI (Supplementary Table S1). When the contribution was considered definite, it was viewed as a major contribution in, respectively, 92 (118/128) and 96% (108/113), whereas when the contribution was considered possible, it was viewed as major contribution in 30% (34/112 and 42/140) for both TP and OSI. With WHOCAT, the HAI was considered part of the causal sequence in the majority of patients (56 % for TP and 55% for OSI) and rarely viewed as the sole cause (9% and 7%, respectively). Table 2 summarises the ratings for 3CAT and WHOCAT and Figure 1 summarises the ratings for QUANT.

The measures corresponded reasonably well with each other, with Pearson correlation coefficients in the range of 0.83 (95% confidence interval (CI): 0.79-0.86) to 0.72 (95% CI: 0.65-0.77). Correlation was highest between 3CAT and QUANT and lowest between 3CAT and WHOCAT (Figure 2), independent of whether the TP or OSI performed the review. Because of the correlation some of the results will therefore be presented for 3CAT only.

Inter-rater reliability and perceived fit

The wk for 3CAT was 0.68 overall, whereas the percentage of initial agreement was 76% (Table 3). Consensus agreement after discussion was reached in 93% of cases. Percentage agreement was the highest when the contribution of the HAI was considered definitely present (> 80%, except for CDI) and lowest for the category 'did not contribute'. The wk differed between hospitals, ranging from 0.26 to 1.00 (wk) (p=0.015) and was higher in tertiary then in secondary care centres (p=0.03 for pneumonia, p=0.07 for BSI). The kappa on whether the HAI was a major or minor cause, when 3CAT assessments were 'possibly contributed' or 'definitely contributed', was 0.69 (95% CI: 0.60-0.79) and agreement was 86% (197/229).

The order of the categories of WHOCAT was less clear-cut than that of 3CAT and QUANT. In all except two hospitals, the inter-rater reliability was the same or higher when assuming that the categories of the variable were ordered than when the categories were considered not ordered. The inter-rater reliability for WHOCAT was comparable to

that of 3CAT, both overall and for each type of HAI. Kappa differed significantly between hospitals (p<0.0001).

Similar to 3CAT and WHOCAT, the ICC was highest for pneumonia and lowest for CDI. The observed agreement for QUANT (Figure 1) was higher at the extreme values of the scale than at the intermediate values. All three measures were reported to fit reasonably to well for more than 88% of the reviewed cases (Supplementary Table S2). WHOCAT and QUANT measures were considered to fit better than 3CAT.

Pathogens, antimicrobial resistance and adequacy of treatment.
Most recorded HAI were caused by *Klebsiella pneumoniae, Acinetobacter baumannii* and *Pseudomonas aeruginosa* (see Supplemental Table S3 for isolates per type of HAI). The CDI ribotype was available in ca half (38/71) of the cases. In the three centres that recorded the majority of CDI cases, PCR ribotype 027 was the main type in two centres. In the third centre PCR ribotype 198, a 027-related ribotype, predominated.

Data on AMR were available in 79% (173/220) of the cases (cases without AMR data and CDI cases excluded) and the AMR phenotypes under surveillance were present in 56% (42/75) of BSI, 62% (50/81) of pneumonia and six of 17 of SSI cases. Almost all (23/25) *A. baumannii* isolates were carbapenem-resistant. Carbapenem resistance was frequently present in *P. aeruginosa* (15/30) and *K. pneumoniae* (9/26) isolates. Among *S. aureus* isolates, five of 16 were oxacillin-resistant. For microorganisms with the AMR phenotypes under surveillance, AMR contributed “possibly” or “definitely” to death in 70-72% of cases (66/94 and 68/94, respectively, TP and OSI; “unknown” and “no antibiotics given” excluded). Overall, agreement on the contribution of AMR to death was good: wk = 0.83 (95% CI: 0.74-0.92) for the 3CAT measure for AMR. In HAI cases by organisms with the AMR phenotypes under surveillance, the contribution of the HAI to death, using 3CAT, was classified as possible or definite in 86% of TP assessments and 95% of OSI assessments (“definitely” in 57% by TP and 47% by OSI, Supplementary Table S6A). This proportion with possible or definite contribution was slightly smaller in cases of HAI caused by organisms lacking these AMR phenotypes: 84% of TP assessments and 85% of OSI assessments (p=0.34 for TP, p=0.03 for OSI), and less frequently classed as definite (41% by TP and 35% by OSI, Supplementary Table S6B).

Table 1: Hospital and patient characteristics.

Hospital				BSI					Pneumonia					CDI				SSI			
Hospital code	Type of hospital	ICU beds (n)	Cases (n)	n	Male (%)	Age (med*)	APACHE score (med*)	SAPS score (med"*)	n	Male (%)	Age (med*)	APACHE score (med*)	SAPS score (med"*)	n	Male (%)	Age (med*)	Complic. course (%)	n	Male (%)	Age (med*)	ASA score >2 (%)
Austra1	Tertiary	107	14	8	*63*	61		21.5	6	*67*	74.5		19								
Belgium1	Tertiary	28*	5						5	*40*	73	29	66								
Spain1	Tertiary	32	1	1	*0*	62	11														
Spain2	Tertiary	32	1						1	*100*	35		52								
France1	Secondary	15	2						2	*100*	66	5	57.5								
France2	Secondary	10	15	6	*83*	57.5		40	5	*40*	68		70	1	*100*	89	100	3	*67*	64	*66.7*
France3	Specialized	8	2	2	*50*	78		54													
France4	Tertiary	40	24	10	*50*	70		58.5	14	*71*	72		50.5								
Hungary1	Tertiary	15	33	1	*100*	64	27	69						32	*50*	82	3				
Italy1	Tertiary	16	13	6	*50*	70		54	7	*43*	73		45								
Italy2	Tertiary	8	7						7	*71*	57	19	46								
Lithuania1	Tertiary	36	6						6	*50*	61	17.5									
Lithuana2	Tertiary	40	70	21	*57*	69	14		33	*61*	67	18.5		16	*31*	76.5	38				
Netherlands1	Tertiary	36	9	5	*80*	51	17		2	*50*	62	18						2	*100*	64.5	*n.a.*
Poland1	Tertiary	54	27	2	*50*	86.5			6	*50*	79			19	*37*	86	68				
Portugal1	Secondary	20	8	4	*100*	58.5	24.5	55.5	4	*75*	76.5	34	55								
Portugal2	Secondary	6	1	1	*100*	57	30	69													
Portugal3	Tertiary	26	20	11	*36*	68	25	65	3	*67*	58	18	55					6	*67*	79.5	*83*
Portugal4	Tertiary	8	8	1	*0*	73	35	58	4	*0*	62	40	72	2	*100*	69	0	1	*0*	81	*100*
Portugal5	Secondary	12	3	2	*50*	68	20.5	0.5										1	*100*	66	*100*
Portugal6	Secondary	6	2						2	*100*	67	24.5	52								
Portugal7	Tertiary	11	5	1	*100*	50		66	2	*100*	57.5		48					2	*50*	67.5	*50*
Portugal8	Tertiary	17	12	5	*40*	85	30	46	1	*100*	59		49	1	*0*	88	0	5	*20*	69	*100*
Un. Kingdom1	Tertiary	12	3						3	*67*	69	24									
Total			291	87	*57*	67	23	54	113	*60*	69	20	50	71	*44*	82	30	20	*55*	68.5	*83*

APACHE: Acute physiology, age, chronic health evaluation; ASA: American Society of Anesthesiologists; BSI: bloodstream infection; CDI: *Clostridioides (Clostridium) difficile* infection; SAPS: Simplified acute physiology score; SSI: Surgical site infection; med*: median

* and 17 coronary care unit beds

Table 2: Ratings of on-site investigator (OSI) and treating physician (TP) for 3CAT and WHOCAT, overall.

3CAT		Ratings of on-site investigator (OSI)							
		Definitely		Possibly		Did not contribute		Total	%
Ratings of treating physician (TP)	Definitely	101		11		1		113	*39*
	Possibly	27		92		21		140	*48*
	Did not contribute	0		9		29		38	*13*
	Total *%*	128	*44*	112	*38*	51	*18*	291	*100*

WHOCAT		Ratings of on-site investigator (OSI)							
		Sole cause	Part of causal sequence	Contribut. but unrelated	Did not contribute	Unknown	Missing	Total	%
Ratings of treating physician (TP)	Sole cause	14	3	2	1	1	0	21	*7*
	Part of causal sequence	9	138	10	3	0	0	160	*55*
	Contributory but unrelated	1	15	25	15	0	0	56	*19*
	Did not contribute	1	7	5	35	0	0	48	*16*
	Unknown	0	0	1	1	1	0	3	*1*
	Missing	0	0	0	0	0	3	3	*1*
	Total (%)	25 *9*	163 *56*	43 *15*	55 *19*	2 *1*	3 *1*	291	*100*

Overall, antimicrobial treatment was considered adequate in 80% of the cases (210/262 for TP, 210/263 for OSI), with high agreement on the perceived adequacy (kappa 0.87, 95% CI: 0.80-0.95) when including the cases where the adequacy of antimicrobial treatment was classified as unknown. In cases of HAI with organisms with the AMR phenotypes under surveillance, the antimicrobial treatment was less often evaluated as adequate (71% (69/ 97)) compared to HAI with an organism without any of the AMR phenotypes under surveillance (91% (67/74)). The contribution of AMR was less often classified as possible or definite when the antimicrobial treatment was considered adequate than when it was inadequate (33% (50/153 for TP; 51/154 for OSI) adequate vs 25/31 and 25/28 inadequate for TP and OSI; p<0.0001).

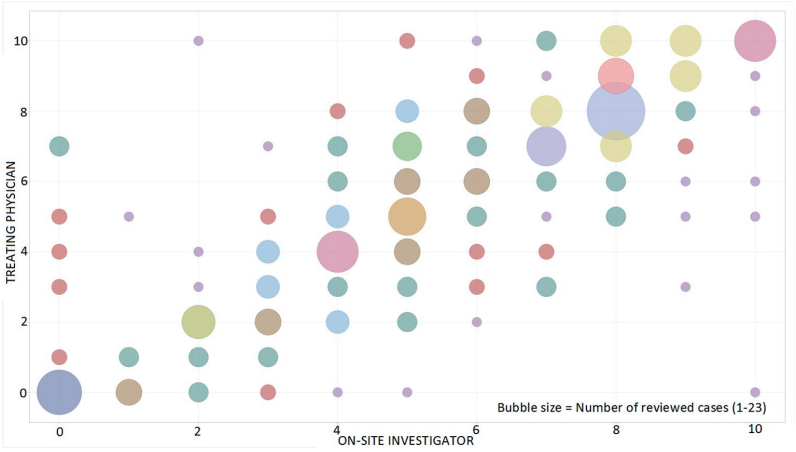


Figure 1: Agreement for ratings for the quantitative scale (QUANT), overall
Missing in 2 cases for TP; OSI: On-site investigator, TP: Treating physician

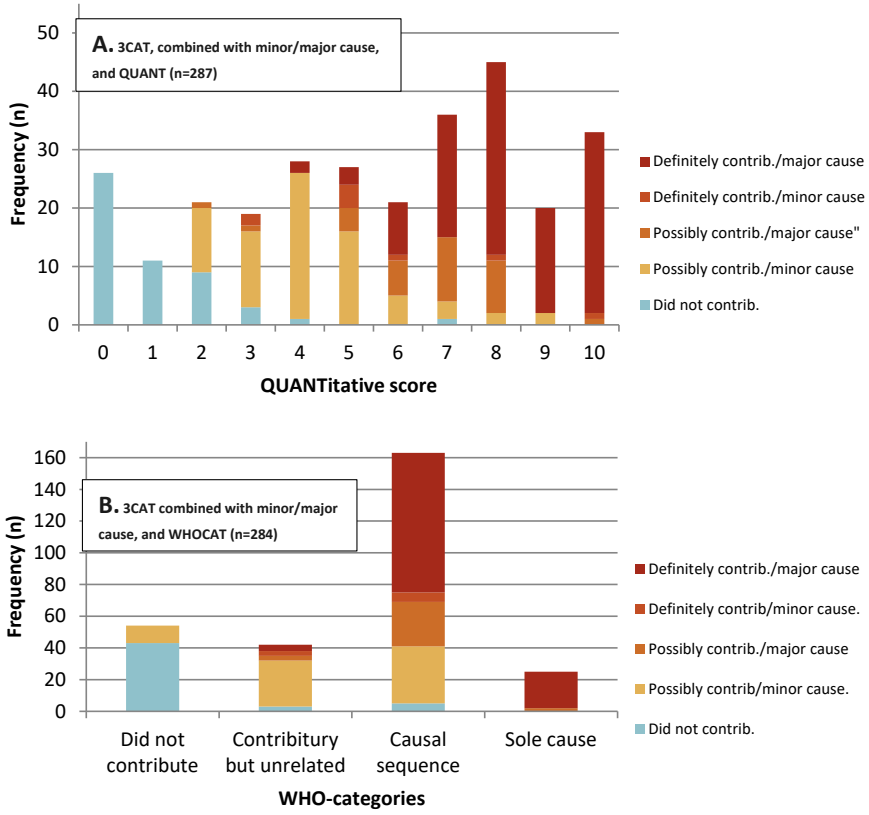


Figure 2: Correspondence between different outcome measures, assessment by the treating physician

Table 3: Inter-rater reliability of 3CAT, WHOCAT and QUANT, measured with kappa, weighted kappa, adjusted weighted kappa, percentage agreement and/or the intraclass correlation coefficient

3CAT	n	Simple Kappa (95% CI)	Weighted kappa (95% CI)	Weighted kappa, adj. for hospital[$] (95% CI)	Agreement (%)			
					Overall	Definitely	Possibly	No
Overall	291	0.62 (0.54 – 0.70)	0.68 (0.61 – 0.75)	0.63 (0.55 – 0.71)	*76*	*84*	*73*	*65*
BSI	87	0.56 (0.41 – 0.72)	0.60 (0.46 – 0.76)	0.38 (0.20 – 0.56)	*76*	*81*	*73*	*44*
Pneumonia	113	0.66 (0.55 – 0.78)	0.72 (0.62 – 0.82)	0.82 (0.74 – 0.90)	*78*	*86*	*74*	*73*
CDI	71	0.49 (0.32 – 0.67)	0.57 (0.41 – 0.73)	0.55 (0.40 – 0.70)	*69*	*74*	*69*	*58*
SSI	20	0.87 (0.65 – 1.00)	0.88 (0.70 – 1.00)	Not calc.	*95*	*100*	*89*	*0[$$]*

WHOCAT	n	Simple Kappa (95% CI)	Weighted kappa (95% CI)	Weighted kappa, adj. for hospital[$] (95% CI)	Agreement (%)				
					Overall	Sole cause	Causal sequence	Contributory cause	No
Overall	288	0.58 (0.51 – 0.66)	0.65 (0.58 – 0.73)	0.75 (0.71 – 0.80)	*74*	*62*	*85*	*51*	*69*
BSI	86	0.56 (0.41 – 0.71)	0.60 (0.43 – 0.77)	0.63 (0.55 – 0.71)	*75*	*70*	*86*	*53*	*46*
Pneumonia	110	0.66 (0.54 – 0.78)	0.72 (0.60 – 0.83)	0.89 (0.83 – 0.96)	*80*	*0[$]*	*91*	*48*	*77*
CDI	68	0.47 (0.30 – 0.64)	0.52 (0.34 – 0.70)	0.56 (0.46 – 0.66)	*65*	*36*	*76*	*53*	*62*
SSI	17	0.56 (0.22 – 0.90)	0.63 (0.29 – 0.97)	Not calc.	*72*	*83*	*80*	*0[$]*	*0[$$]*

QUANT	n	ICC (95% CI) for Absolute agreement
Overall	289	0.76 (0.71 – 0.81)
BSI	87	0.75 (0.62 – 0.83)
Pneumonia	111	0.85 (0.79 – 0.90)
CDI	71	0.54 (0.35 – 0.69)
SSI	20	0.71 (0.41 – 0.87)

$* excluding hospitals with less than six cases; *$$ 0 cases with agreement, 1 case in denominator; Cases where one of the ratings was missing or 'Unknown' excluded.
BSI: bloodstream infection; CDI: *Clostridioides (Clostridium) difficile* infection; SSI: Surgical site infection

Patient and healthcare-associated infection characteristics associated with agreement and contribution to death

Both the agreement on the initial assessments (Supplementary Table S4) and the consensus were higher for the patient and HAI characteristics that were to be assessed separately, than for the contribution of HAI to death. The agreement ranged from 81% (234/290) for the presence of pathophysiological mechanism to 95% (275/291) for whether the HAI or a complication of the HAI was active at the time of death. Agreement on the contribution to death was strongly correlated with the number of patient and HAI characteristics for which there was agreement between the TP and the OSI (Pearson correlation coefficient 0.98, 95% CI: 0.70-1.00). Agreement was associated with disease severity; it was better for the two extremes severity statuses (not or mildly ill: 43/52 and severely ill: 87/104) than for intermediate severity (68%; 91/134).

The presence of a pathophysiological mechanism for the contribution of HAI to death was most strongly associated with a contribution considered definite, for all three measures (Supplementary Table S5). Severity of HAI and presence of a competing cause for death were among the top three associated factors. The type of HAI, whether the HAI or complication of the HAI was active on the day of death, ICU admission and the Charlson's severity score were, to a lesser extent, also associated with contribution to death. HAI were considered to contribute more to the death of 'moderately ill' patients ('definitely' contributed in 51% for TP and 44% for OSI) than in 'not or mildly ill' patients (38% for TP and 38% for OSI) or 'severely ill' patients (38% for TP and 33% for OSI) (Supplementary Table S7).

DISCUSSION

Our study demonstrated that the inter-rater reliability of three mortality review measures for the contribution of HAI to death, measured with wk and percentage agreement, was moderate to strong, depending on the type of HAI. Together with the correlation between the three outcomes, 3CAT, WHOCAT and QUANT, and the perceived fit, corroborating the validity, this implies that the mortality review measures are considered acceptable for use in HAI surveillance.

Although feasibility was not evaluated in detail MR appeared feasible in the participating centres. Meeting up with the treating physicians was sometimes challenging but this could improve when MR is embedded in standard practice.

Autopsy studies are the gold standard to assess construct validity of the contribution of HAI to death, but they are few and not recent (19-22). Therefore, we applied three measures which had been proven valid before, in a single centre study(10), were based on related concepts(11) or were perceived useful by an expert panel. These measures were discussed and tested with case vignettes by the expert panel to further ensure face, content and construct validity. The correlation between the three measures supports the assumed validity. Another feature that can corroborate the content and construct validity of the measures is the perceived fit, which was reasonable or good in more than 88% for all measures. The OSI preferred WHOCAT and QUANT over 3CAT on the grounds that it better reflected the rationale (WHOCAT) or a more neutral and better fit of the mortality review (QUANT).

The inter-rater reliability varied with the type of HAI: it was the highest for pneumonia and the lowest for CDI. Differences in kappa were larger than differences in percentage agreement, which can partly be explained by the prevalence of the different categories. The reviewers agreed most often when the contribution of the HAI was assessed as definite or, slightly less, when assessed as possible, whereas agreement on 'no contribution' was lowest for BSI and CDI. The majority of CDI cases originated from three centres and 45% from one of these, which may have introduced bias. It was difficult to conclude whether the lower agreement observed in two of these centres was due to the type of infection, i.e. CDI, or resulted from factors specific for these centres. A BSI was usually considered to have contributed to the death of a patient, either 'definitely' or 'possibly', and a skewed distribution resulted in lower kappa values.

There are a few reports on the inter-rater reliability of HAI-associated mortality review outcomes. In a study by Kaoutar et al (10), the review was performed by an infection prevention and control professional who also interviewed the TP. This procedure resembles the joint discussion after the independent review in our study and the agreement of 91% reported by Kaoutar et al is close to the 93% final consensus in our results. Michel et al reported a high inter-rater reliability in a French hospital care-related study on adverse events: 92% (kappa = 0.83; 95% CI: 0.67-0.99) (23). The inter-observer reliability (kappa = 0.4) reported by Langelaan et al in a Dutch study on adverse events was considerably lower (24).

AMR was present in more than half of the BSI and pneumonia cases, which is higher than the approximately 30% expected in the overall population of patients (alive and deceased) with a HAI (estimated with the country-specific AMR percentages from the

ECDC point prevalence surveys and the number of cases contributed by each country, not accounting for the type of HAI) (25). The higher AMR rate in this population of deceased patients with HAI seems to be associated with death as AMR was perceived as definitely or possibly contributing to death in 70-72% of these patients. In a German mortality review of 215 patients deceased with a multidrug-resistant hospital-acquired infection the infection was considered the cause of death in 36% (26), which is slightly higher than the 28-30% of our cases where contribution of (not necessarily multidrug) resistance was considered definite. Overall, antimicrobial treatment was considered inadequate in 15% of the cases, in the lower ranges of what has been reported elsewhere (27). Inadequate antimicrobial treatment was associated with a higher contribution of AMR to death. Inadequate treatment is a known and confirmed risk factor for mortality of patients with infections in observational studies (28).

Our study showed that healthcare-associated BSI, pneumonia and CDI were perceived to have definitely or possibly contributed to the death of a patient in the majority of cases. The presence of a pathophysiological mechanism that explained the contribution of the HAI to the death of the patient, and the severity of the HAI, were items that were most strongly associated with the perceived contribution (Supplementary Table S5). For CDI, 'complicated course' fitted the results better than severity. In some cases, a clear pathophysiological mechanism can relate the HAI to the cause of death. However, in other cases, the perceived presence of a pathophysiological mechanism can be considered as a proxy of the assessment of the contribution and may therefore not be useful to guide a reviewer's assessment. Some but not all reviewers described the 'checklist' as helpful in gathering the relevant information. Altogether, the variables shown to be significantly associated with death may be used as tools for facilitating and standardising the assessment.

When evaluating only pneumonia, BSI and related infections in the study by Kaoutar et al. (10), the proportions of cases with definite and possible contribution of pneumonia were 29 and 40%, respectively, which is comparable to our study. For BSI, the contributions were 36 and 38% respectively, lower than in our study (51 and 43%). Differences in the patient population (more ICU patients in our study) and improvement in the prognosis of BSI since Kaoutar's study in 2000 and 2001 may account for this difference. Decoster et al. found that death was attributable to an HAI in 33% of patients with McCabe score 1 or 2 and a bacteraemia, systemic, respiratory or catheter infection (29). In the same patient category, the contribution was classified as definite in 47% (TP) and 42% (OSI). Branger et al. found that the death was 'most likely' associated with the

HAI in only 20% of the cases but this study did not exclude infections with little impact on mortality, such as UTI (30). Two earlier studies included autopsy reports in the evaluation. Hospital-acquired bacteraemia/sepsis and pneumonia were perceived as the 'immediate cause of death' in 33% of BSI and 59% of pneumonia cases in the first study (22), and in 49% pneumonia cases in the second study (21), i.e. more or equally frequent as in our results for pneumonia, but less frequent for BSI. Although the attributable mortality of CDI has been frequently documented (31-33), mortality review data are scarce for CDI. Mlangeni et al. found that CDI contributed to death in 24% of 85 cases (34), which is less than the 82% (TP) and 85% (OSI) in our study. It is difficult to conclude what reasons might explain the differences in the perceived contribution of BSI and CDI to death. The specific hospital mix of the studies might contribute to this. Although in our study, the perceived contribution of HAI to death was higher in tertiary care centres than in secondary care centres, this does not need to necessarily be the case (22). The cited studies were all performed in a single country, but countries differ with regards to the availability of ICU beds (35) and consequently the average disease severity, infection prevention and control practices (36), prevalence of AMR (25) and other, including cultural, factors that may affect the contribution of HAI to death and the assessment of this contribution.

A strength of our study was the multicentre design, including hospitals from 11 countries, which increased the generalisability of its results and insight into possible differences among countries and hospitals, but also introduced new sources of variance that cannot always be controlled for. The results for CDI are less robust as 45% of all cases originated from one centre and the majority from three. A local team performed the reviews as in routine HAI surveillance. As a consequence, there were known and unknown differences among the review practices despite initial training at the kick-off meeting and use of a standardised protocol. Strongly opinionated reviewers and other subjective factors may be sources of bias in individual centres, but are expected to average out when a large number of hospitals contribute to regular HAI surveillance. The contribution of specific types of HAI might have been overestimated as the most severe HAI, in cases with more than one HAI present, was selected for the mortality review. Our results may not be representative of all types of hospitals. The majority of the participating hospitals were tertiary care centres, and the inter-rater reliability appeared to be higher than in secondary care centres. This could be due to the smaller number of reviewed cases in secondary hospitals. Autopsies were not performed in the framework of our study.

A common criticism on the association between a HAI and the death of a patient is that patients die *with* the HAI and not *because of* the HAI (37). The present study demonstrates that clinicians frequently think otherwise and that a mortality review can be performed with reasonable inter-rater reliability. Still, clinicians sometimes fear the judgement of hospital management or medico-legal consequences if they perform a mortality review with explicit outcome statements. These anticipated consequences are a major barrier for widespread adoption of an otherwise feasible mortality review. It is important that stakeholders understand that neither the death of a patient with an HAI, nor the HAI itself are necessarily preventable, and support clinical staff, as improved insight into the contribution of HAIs to patients' morbidity and mortality is an important driver of quality improvement processes and interventions to prevent HAI.

Conclusion

Although the construct validity of mortality review is difficult to assess because there is no recent gold-standard for the assessment of the contribution of an HAI to death, this study showed that the validity and reproducibility of the three mortality review measures that were evaluated was acceptable for use in European surveillance of HAI. The performance of the three measures was comparable and the perceived fit of the three outcomes was predominantly reasonable or good. Most reviewers preferred the WHO categories (WHOCAT) that better account for the different levels of causality assessment and the quantitative scale (QUANT) which was perceived as more neutral than other measures. Further standardization of the measures for surveillance purposes through training and the use of case vignettes may increase robustness and comparability across hospitals and countries.

INVESTIGATORS

Members of the HAI-Net Mortality review study group:
Meander Sips, Maximilian Edlinger-Stanger, Michael Hiesmayr, Joke Denolf, Marc Nauwynck, Amine Si Ali,
Caroline Jannière-Nartey, Elodie Munier-Marion, Guillaume Grillet, Marie-Aline Robaux, Antonella Agodi, Giacomo Castiglione, Marinella Astuto, Davide Durì, Ieva Kisieliene, Meri Varkila, Paula van Ooik, Ed Kuijper, Monique Crobach, Grażyna Biesiada, Clara Carvalho, Camila Tapadinhas, Rita Corte-Real, Sofia Cardoso, Maria Barroso, Heloisa Castro, Ana Josefina Pinheiro Marques, Dulce Pascoalinho, Adriana Ribeiro, Filomena Freitas, J Ricardo Gimeno Costa, F Xavier Nuvials Casals, Richard Pugh, Anne Savey, David A.

Enoch, Evert de Jonge, Heinz Winkler, Jan DeWaele, Karen Burns, Mercedes Palomar Martinez, Rasmus Leistner, Susan Hopkins.

ACKNOWLEDGEMENTS

We thank the participating centres for contributing to this study, especially the on-site investigators and treating physicians: Ádám Varga, Adeline Grateau, Adrian Ionescu, Ákos Csaba Kiss, Andrea Mohos, Andrew Evans, Anna Głuszewska, Annamária Budai, Antoine Caubel, Barbara Xavier, Bartosz Brzozowski, Béatrice Lacombe, Benjamin Delwarde, Bernadetta Przepiórkowska-Hoyer, Birgit De Wulf, Bram Dewulf, Brigitta Kószó, Carlos Neves, Christophe Savry, Dániel Csőke, Danuta Owczarek, Dorottya Olajos, Eduardo Ribeiro, Endre Wórum, Erzsébet Csík, Ewa Klimek, Ferenc Papp, Francelina Rebelo, Gabriella Vén, György Gyimesi , Ildikó Csupor, Ines Gragueb-Chatti, Isabel Simões, János Tóth, Janusz Kąkol, Jean Mouline, Joana Osório, José Alonso Fajardo, József Horváth, Karolina Piotrowicz, Katalin Bihari, Katarzyna Konturek, Katarzyna Strzępek, Krzysztof Rewiuk, László Lehoczky, Laurent Argaud, Laurent Bitker, Małgorzata Wójcik-Bugajska, Marcin Krzanowski, Marco Melo, Marie Simon, Márta Juhász, Martin Cour, Máté Zatykó, Mónica Gordon Sahuquillo, Paula Pestana, Paulina Fatyga, Philippe Quinio, Pedro Matos Moreira, Pierre Bouju, Piotr Jasik, Roberto Cocconi, Rogério Matias, Roland Smonig, Romain Hernu, Thibaut Girardot, Thomas Baudry, Thomas Madeleine, Thomas Rimmele, Thomas Uberti, Thomas Verhaeghen, Wojciech Serednicki, Zoltán Fülep, Zoltán Gaál, Zsolt Dubravcsik, Zsolt Klucsik and colleagues. As reviewers, they evaluated the often difficult patient histories and therewith contributed to the knowledge on the impact of healthcare-associated infections and its measurement. We also thank the members of the expert panel for contributing to the study design

Funding: This study was commissioned by the European Centre for Disease Prevention and Control (ECDC), within Framework Contract ECDC/2016/032, and produced by the Dutch National Institute for Public Health and the Environment (RIVM) (service contracts ECD.5895, ECD.7323 and ECD.8451).

SUPPLEMENT

This supplementary material is hosted by *Eurosurveillance* as supporting information alongside the article "Mortality review as a tool to assess the contribution of healthcare-associated infections to death: results of a multicentre validity and reproducibility study", on behalf of the authors, who remain responsible for the accuracy and appropriateness of the content. The same standards for ethics, copyright, attributions and permissions as for the article apply. Supplements are not edited by Eurosurveillance and the journal is not responsible for the maintenance of any links or email addresses provided therein.

Contents:

Supplementary Textbox S1: Data collection form

There were separate (but similar) forms for on-site investigators, treating physicians and for the combined review.

<table>
<tr><td colspan="2">Patient identifier</td><td colspan="3">Age (years)</td></tr>
<tr><td>Gender</td><td>O Male
O Female</td><td colspan="3">Hospital admission date
dd/mm/yyyy</td></tr>
<tr><td colspan="2">McCabe score (without influence of HAI) on admission in the hospital. See page 7 of form for details
O 1 Non-fatal (≥5 yr survival)
O 2 Ultimately fatal (≥1 – 5 yr survival)
O 3 Rapidly fatal (<1 year survival)</td><td colspan="3" rowspan="4">Charlson’s comorbidities on admission in the hospital Please record all comorbidities that apply (not only the group as in the earlier version):
O AIDS
O metastatic solid tumor
O Moderate or severe liver disease
O Any non-metastatic solid tumor
O Malignant lymphoma
O Leukemia
O Diabetes with end organ damage
O Moderate or severe renal disease
O Hemiplegia
O Diabetes without end organ damage
O Mild liver disease
O Ulcer disease
O Connective tissue disease
O Chronic pulmonary disease
O Dementia
O Cerebrovascular disease
O Peripheral vascular disease
O Congestive heart failure
O Myocardial infarction</td></tr>
<tr><td colspan="2">Charlson’s comorbidity score – severity of illness on admission in the hospital
O Not or mildly ill
O Moderately ill
O Severely ill

Expected age-adjusted one-year mortality:
http://tools.farmacologiaclinica.info/index.php?sid=37148</td></tr>
<tr><td colspan="2">Treatment limitation
In the case that treatment options are extended again, this can be recorded in the Comment section.
O No
O Future therapy restrictions
O Partial withdrawal
O Full withdrawal</td></tr>
<tr><td colspan="2">Date of treatment limitation
dd/mm/yyyy</td></tr>
<tr><td colspan="2">ICU admission date
Please record this too for SSI and CDI patients in the SSI or CDI surveillance that are admitted in the ICU, preceding, during or following the HAI.
dd/mm/yyyy</td><td colspan="3">ICU discharge date
Please record this too for SSI and CDI patients (see admission date)
dd/mm/yyyy or not applicable</td></tr>
<tr><td colspan="5">Type of ICU
O Mixed
O Medical
O Surgical
O Coronary
O Burns
O Neurosurgery
O Other
O Unknown</td></tr>
<tr><td colspan="2">SAPS II/III score

Record -1 when unknown</td><td>SOFA score (the most recent one, before HAI developed; when available)

Record -1 when unknown</td><td colspan="2">Date of SOFA score
dd/mm/yyyy</td></tr>
</table>

Q5 Checklist: When SAPS II/III score not available: **Apache II / IV score** Record -1 when unknown	When recording **Apache II** score: Patient required emergency surgery O No O Yes

When recording **Apache II score**: please indicate reason for admission on last page.

SSI data

Date of surgery
dd/mm/yyyy

Operation code For hospitals recording SSI in SSI surveillance: Same operation codes as in SSI surveillance

O CBGB
O CBGC
O CABG
O COLO
O CHOL
O CSEC
O HPRO
O KPRO
O LAM

Operation code
For hospitals recording SSI in ICU only: Same operation codes as in PPS surveillance

O AAA
O AMP
O APPY
O AVSD
O BILI
O BRST
O CARD
O CEA
O CBGB
O CBGC
O CHOL
O COLO
O CRAN
O CSEC
O FUSN
O FX
O GAST
O HER
O HPRO
O HTP
O HYST
O KPRO
O KTP
O LAM
O LTP
O NECK
O NEPH
O OVRY
O PACE
O PRST
O PVBY
O REC
O RFUSN
O SB
O SPLE
O THOR
O THYR
O VHYS
O VSHN
O XLAP

ASA class

O 1 Healthy person.
O 2 Mild systemic disease.
O 3 Severe systemic disease.
O 4 Severe systemic disease that is a constant threat to life.
O 5 A moribund person who is not expected to survive without the operation.

CDI data

Unit specialty
(where patient was first diagnosed with CDI)

O SUR = surgical specialties
O MED = medical specialties
O ICU = Intensive care unit
O GO = gynaecology/obstetrics
O GER = geriatrics
O PSY = psychiatry
O RHB = rehabilitation
O LTC = long term care
O OTH = other
O MIX = mixed specialties

<table>
<tr><th colspan="3">HAI data</th></tr>
<tr><td colspan="2">Pneumonia
O No
O PN1
O PN2
O PN3
O PN4
O PN5</td><td>Pneumonia date
dd/mm/yyyy</td></tr>
<tr><td colspan="2">BSI
In case of secondary BSI originating from an infection that is also monitored it suffices to record the BSI only (e.g. S-SSI, in case of a surgical site infection).
O No
O central vascular catheter
O peripheral vascular catheter
O arterial catheter

Secondary to another infection:
O Pulmonary
O Urinary tract
O Digestive tract
O Surgical site
O Skin and soft tissue
O Other (central nervous system, bone (e.g. osteomyelitis, etc.)
O Unknown: BSI of unknown origin (origin was verified but no source could be found for the BSI).
O Missing, data unavailable: only use this code if data on the BSI origin is missing.</td><td>BSI date
dd/mm/yyyy</td></tr>
<tr><td colspan="2">SSI
O No
O SSI-Superficial
O SSI-Deep
O SSI-Organ/space</td><td>SSI date
dd/mm/yyyy</td></tr>
<tr><td colspan="2">Clostridium difficile infection according to HAI-Net protocol for CDI
O No
O Healthcare-associated - Present admission
O Healthcare-associated – earlier admission in same or different hospital(s)
O Community-associated</td><td>CDI date
dd/mm/yyyy</td></tr>
<tr><td colspan="2">Complicated course of CDI
In the setting of this study this has a more restricted meaning than in the CDI surveillance. The course is complicated when:
– admitted to an intensive care unit for treatment of CDI or its complications (e.g. for shock requiring vasopressor therapy);
– surgery (colectomy) for toxic megacolon, perforation or refractory colitis.

O No
O Yes</td><td>Ribotype
(If available already)</td></tr>
<tr><td colspan="2">HAI for mortality review
The HAI that is considered “worst” i.e. to have contributed most to the death of the patient is to be selected for review.
In case of a BSI secondary to another infection monitored in this study, e.g. pneumonia (S-PUL), please indicate the source infection here. Of course the septic sequelae are included in the review.</td><td>O Pneumonia
O BSI
O SSI
O CDI</td></tr>
</table>

The following items are answered for the HAI that is considered for mortality review	
Isolate_1 result: Pathogen coded as in HAI-Net protocol (Appendix C) NA = Results not available NOEXA = Examination not done NONID = Microorganism not identified STERI = Sterile examination	**Isolate_2 result:** Pathogen coded as in HAI-Net protocol (Appendix C) NA = Results not available NOEXA = Examination not done NONID = Microorganism not identified STERI = Sterile examination
CHECKLIST for Contribution of HAI to death of the patient	
Date of death dd/mm/yyyy	
Q1 Checklist: **What was the expected hospital mortality at hospital admission?** Based on the acute condition that led to admission to the hospital and the patient's comorbidities (McCabe, Charlson's comorbidity score). *For patients directly admitted in ICU at hospital admission: no need to enter as this will be based on the SAPS II/III or Apache II/IV score (at admission) in that case.*	O very low (<1%) O low (1-5%) O medium (5-25%) O high (>25%)
Q2 Checklist: To be considered for Q1 when not admitted to ICU at hospital admission – see page 1 **McCabe score**	
Q3 Checklist: To be considered for Q1 when not admitted to ICU at hospital admission - see page 1 **Charlson's comorbidity score – associated one-year mortality**	
Q4 Checklist: To be considered for Q1 when not admitted to ICU at hospital admission - see page 1 **ASA score**	
These items (Q2-Q4) and the following items are to be considered for Contribution of HAI to the death:	
Q5 Checklist: **SAPS II/III or Apache II/IV score** - when HAI developed in ICU – see page 1	
Q6 Checklist: **SOFA score** (when available) - when HAI developed in ICU. – see page 1	
Q7 Checklist: **Active infection** Was the HAI or a complication active at time of death?	O No O Yes
Q8 Checklist: **Severity of HAI** Severity of HAI: The HAI is considered severe in case of at least one organ failure, e.g. respiratory failure, septic shock or ARDS and, for CDI, in case of surgery (colectomy) for toxic megacolon, perforation or refractory colitis.	O Not severe O Severe
Q9 Checklist: **Pathophysiological mechanism for contribution of HAI** Was there a plausible pathophysiological mechanism to assume that the HAI contributed to the death of the patient (consider infection type, complication of HAI, involved microorganisms, antimicrobial resistance, whether treatment was effective)?	O No O Possibly O Yes
Q10a Checklist: **Competing cause** Was another cause for the death present during the current hospitalisation/ICU admission?	O No O Possibly O Yes

Q10b Please describe nature of competing cause:	
Contribution of HAI to death of the patient Appropriate treatment of a HAI affects the survival of the patient. However, here we do not consider the treatment. I.e. we do not distinguish between e.g. patients that die of a very severe HAI that could not be helped and a less severe HAI that, with better treatment, would not have led to the death of the patient. In both cases the HAI contributed to the death of the patient. Appropriate treatment can (in part) be addressed with the subsequent questions on adequate antimicrobial therapy and contribution of antimicrobial resistance.	
3 Category scale	O No contribution O Possibly O Definitely O Unknown/not verified
Fit of 3 Category scale How well did the 3 Category scale apply?	O Applies well O Applies reasonably O Applies poorly O Does not apply
In combination with 3 Category scale: **Major / Minor cause** If HAI contributed possibly/definitely to death: - HAI was a major cause: cause or part of sequence of events that led to death - HAI was a minor cause: not the cause or part of the sequence of events that led to death, but added to the risk of death	O Major cause O Minor cause
Fit_major/minor	O Applies well O Applies reasonably O Applies poorly O Does not apply
10 Points scale (Score 0 to 10) (0 = No contribution of HAI at all 10 = HAI definitely cause of death)	Score: O Unknown/not verified
Fit of 10 Points scale How well did the 10-Points scale apply?	O Applies well O Applies reasonably O Applies poorly O Does not apply
WHO Scale These categories are evaluated for its use in the present setting. There is no need to check or align with what was indicated on the actual death certificates of the patients.	O HAI did not contribute to the death or contribution was redundant (patient would have died anyway). O HAI was a contributory cause but not related to disease or condition causing death O HAI part of causal sequence but not sufficient on its own to cause death

	O HAI sole cause of death O Contribution unknown or not verified.
Fit of -WHO Scale How well did the WHO Scale apply?	O Applies well O Applies reasonably O Applies poorly O Does not apply
Antimicrobial resistance	
O Staphylococcus Oxa-S *O Staphylococcus* Oxa-R *O Staphylococcus* Gly-I *O Enterococcus Gly-S* *O Enterococcus Gly-R*	O Enterobacteriaceae C3G-S/Car-S O Enterobacteriaceae C3G-R/Car-S O Enterobacteriaceae C3G-R/Car-R O Pseu/Acinetob Car-S O Pseu/Acinetob Car-R O Unknown
Adequate antimicrobial treatment The antimicrobial treatment of the HAI was adequate (regarding the antimicrobial resistance, timeliness, etc.). When no antibiotics were give and you feel this was inadequate record 'No'.	O Yes O No O Unknown (no identification of pathogen)
Contribution of antimicrobial resistance (AR) – 3 Category scale	O No contribution O Possibly O Definitely O No antibiotics were given O Unknown/not verified
Contribution of antimicrobial resistance (AR) – 10 Points scale (Score 0 to 10) (0 = No contribution of AR at all 10 = AR definitely cause of death)	Score: O No antibiotics were given O Unknown/not verified
Comments on case	

McCabe score: pto

McCabe score: Classification of the severity of underlying medical conditions. Disregard the influence of an active HAI, i.e. estimate the score the patient had before the infection, in this study: at admission in the hospital. Some examples of diseases and their different McCabe score categories are given below. These examples, in particular those of the second (ultimately fatal) category, are not meant to be exhaustive but rather to serve as a guidance tool for the current protocol.

Rapidly fatal (survival < one year)	• End-stage haematological malignancies (unsuitable for transplant, or relapsed), heart failure (EF < 25%) and end-stage liver disease (unsuitable for transplant with recalcitrant ascites, encephalopathy or varices) • Pulmonary disease with cor pulmonale
Ultimately fatal: (1 ≤ survival < 5 years)	• Chronic leukaemia's, myelomas, lymphomas, metastatic carcinoma, end-stage kidney disease (without transplant) • Motor neuron disease, multiple sclerosis non-responsive to treatment • Alzheimer's/dementia • Diabetes requiring amputation or post amputation
Non-fatal (survival ≥ five years)	• Diabetes • Carcinoma/haematological malignancy with > 80% five-year survival • Inflammatory disorders • Chronic GI, GU conditions • Obstetrics • Infections (including HIV, HCV, HBV – unless in above categories) • All other diseases

EF: Ejection fraction, GI: Gastrointestinal, GU: Genitourinary, HCV: Hepatitis C virus, HBV: Hepatitis B virus

Reason for ICU admission (with Apache II score)

Respiratory: O Asthma/allergy O COPD O Pulmonary edema (non-cardiogenic) O Postrespiratory arrest O Aspiration/poisoning/toxic O Pulmonary embolus O Infection O Neoplasm **Cardiovascular:** O Hypertension O Rhythm disturbance O Congestive heart failure O Hemorrhagic shock/hypovolemic O Coronary artery disease O CABG (coronary artery bypass graft)	**Cardiovascular (continued):** O Sepsis O Postcardiac arrest O Cardiogenic shock O Dissecting thoracic/abdominal aneurysm **Trauma (non-surgical):** O Multiple trauma O Head trauma **Neurologic (non-surgical):** O Seizure disorder O ICH/SDH/SAH (intracerebral/subdural/subaracnoid hemorrhage) **Non-surgical (not otherwise specified):** O Metabolic/renal O Respiratory O Neurologic O Cardiovascular O Gastrointestinal	**Postoperative** O Multiple trauma O Chronic cardiovascular disease O Peripheral vascular surg. O Heart valve surg. O Craniotomy for neoplasm O Renal surg. for neopl. O Renal transplant O Head trauma O Thoracic surg. for neopl. O Craniotomy for ICH/SDH/SAH O Laminectomy and other spinal surgery O Hemorrhagic shock O GI bleeding O GI surgery for neoplasm O Respiratory insufficiency after OR O GI perforation/ obstruction O Postop Sepsis O Postop postarrest	**Postoperative (not otherwise specified)** O Neurologic O Cardiovascular O Respiratory O Gastrointestinal O Metabolic/renal **Other** O Drug overdose O Diabetic ketoacidosis O GI bleeding

Supplementary Table S1-A: 3CAT and WHOCAT ratings for BSI

3CAT	Definitely contributed	Possibly contributed	Did not contribute	Total (OSI)
Definitely contributed	35	4	0	39
Possibly contributed	12	29	3	44
Did not contribute	0	2	2	4
Total (TP)	47	35	5	87

WHOCAT	Sole cause	Part of causal sequence	Contributory cause	Did not contribute	Unknown	Missing	Total (OSI)
Sole cause	7	2	0	0	0	0	9
Part of causal sequence	3	47	1	0	0	0	51
Contributory cause	1	7	8	4	0	0	20
Did not contribute	0	2	1	3	0	0	6
Unknown	0	0	0	0	0	0	0
Missing	0	0	0	0	0	1	1
Total (TP)	11	58	10	7	0	1	87

OSI: On-site investigator, TP: Treating physician

Supplementary Table S1-B: 3CAT and WHOCAT ratings for Pneumonia

	Definitely contributed	Possibly contributed	Did not contribute	Total (OSI)
Definitely contributed	34	3	1	38
Possibly contributed	7	34	12	53
Did not contribute	0	2	20	22
Total (TP)	41	39	33	113

WHOCAT	Sole cause	Part of causal sequence	Contributory cause	Did not contribute	Unknown	Missing	Total (OSI)
Sole cause	0	0	0	0	0	0	0
Part of causal sequence	2	56	4	2	0	0	64
Contributory cause	0	2	8	8	0	0	18
Did not contribute	0	1	3	24	0	0	28
Unknown	0	0	1	1	1	0	3
Missing	0	0	0	0	0	0	0
Total (TP)	2	59	16	35	1	0	113

OSI: On-site investigator, TP: Treating physician

Supplementary Table S1-C: 3CAT and WHOCAT ratings for CDI

	Definitely contributed	Possibly contributed	Did not contribute	Total (OSI)
Definitely contributed	17	4	0	21
Possibly contributed	8	25	6	39
Did not contribute	0	4	7	11
Total (TP)	25	33	13	71

WHOCAT	Sole cause	Part of causal sequence	Contributory cause	Did not contribute	Unknown	Missing	Total (OSI)
Sole cause	2	1	2	1	0	0	6
Part of causal sequence	2	27	4	1	0	0	34
Contributory cause	0	6	9	3	0	0	18
Did not contribute	1	3	1	8	0	0	13
Unknown	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0
Total (TP)	5	37	16	13	0	0	71

OSI: On-site investigator, TP: Treating physician

Supplementary Table S1-D: 3CAT and WHOCAT ratings for SSI

	Definitely contributed	Possibly contributed	Did not contribute	Total (OSI)
Definitely contributed	15	0	0	15
Possibly contributed	0	4	0	4
Did not contribute	0	1	0	1
Total (TP)	15	5	0	20

WHOCAT	Sole cause	Contributory cause	Part of causal sequence	Did not contribute	Unknown	Missing	Total (OSI)
Sole cause	5	0	0	0	1	1	7
Contributory cause	0	0	0	0	0	0	0
Part of causal sequence	2	1	8	0	0	0	11
Did not contribute	0	0	1	0	0	0	1
Unknown	0	0	0	0	0	0	0
Missing	0	0	1	0	0	0	1
Total (TP)	7	1	10	0	1	1	20

OSI: On-site investigator, TP: Treating physician

Supplementary Table S2: Perceived fit of all outcome variables and agreement on the perceived fit between both reviewers

	3CAT				MajorMinor*				WHOCAT				QUANT			
	TP		**OSI**		**TP**		**OSI**		**TP**		**OSI**		**TP**		**OSI**	
Agreement	208/291		*71.5%*		156/252		*61.9%*		*188/285*		*66.0%*		208/289		*72.0%*	
	n	*%*	n	*%*	n	*%*	n	*%*	n	*%*	n	*%*	n	*%*	n	*%*
Does not fit	5	*1.7*	0	*0.0*	6	*2.5*	0	*0.0*	1	*0.0*	1	*0.4*	3	*1.0*	1	*0.3*
Fits poorly	29	*10.0*	32	*11.0*	30	*12.5*	34	*13.4*	16	*5.9*	22	*7.6*	15	*5.2*	19	*6.5*
Fits reasonably	109	*37.5*	109	*37.5*	84	*35.0*	81	*32.0*	84	*29.4*	77	*26.6*	91	*31.5*	87	*29.9*
Fits well	148	*50.9*	150	*51.6*	120	*50.0*	138	*54.6*	185	*64.7*	189	*65.4*	100	*62.3*	184	*63.2*
Missings (n)	0		0		0		0		5		2		2		0	

* if the assessment was not 'Did not contribute'
OSI: On-site investigator, TP: Treating physician

Supplementary Table S3: The most frequently isolated micro-organisms per infection type, as percentage of the cases with a known isolate

	BSI	Pneumonia	SSI
Perc. of cases with a known isolate	*97.7*	*77.9*	*95.0*
Acinetobacter baumanni	*9.4*	*19.3*	
Enterobacter aerogenes			*15.8*
Enterobacter cloacae	*10.6*		
Enterococcus faecium	*10.6*		*26.3*
Klebsiella pneumoniae	*18.8*	*18.2*	
Pseudomonas aeruginosa	*11.8*	*17.0*	*31.6*
Staphylococcus aureus		*15.9*	
Staphylococcus epidermidis	*9.4*		

Supplementary Table S4: (Weighted) kappa and percentage agreement for independantly assessed patient and HAI characteristics.
Weighed kappa for severity of HAI, presence of competing cause, presence of pathophysiological mechanism, expected mortality at hospital admission and adequacy of antibiotics.

	Overall (Weighted) kappa (95% CI)	% agreement	BSI (Weighted) kappa (95% CI)	% agreement	Pneumonia (Weighted) kappa (95% CI)	% agreement	CDI (Weighted) kappa (95% CI)	% agreement	SSI (Weighted) kappa (95% CI)	% agreement
Severity of HAI	0.70 (0.60 – 0.81)	*90.4*	0.68 (0.41 – 0.94)	*94.3*	0.67 (0.51 – 0.83)	*87.6*	0.75 (0.59 – 0.90)	*87.3*	1.00 (1.00 – 1.00)	*100.0*
Competing cause	0.67 (0.56 – 0.78)	*87.6*	0.74 (0.58 – 0.89)	*88.5*	0.49 (0.24 – 0.73)	*87.6*	0.63 (0.35 – 0.90)	*88.6*	0.73 (0.47 – 0.99)	*80.0*
Pathophysiological mechanism*	0.72 (0.65 – 0.80)	*80.7*	0.56 (0.39 – 0.74)	*77.0*	0.79 (0.70 – 0.88)	*84.1*	0.65 (0.49 – 0.80)	*75.7*	0.81 (0.48 – 1.00)	*95.0*
HAI or complication active	0.80 (0.71 – 0.90)	*94.5*	0.84 (0.63 – 1.00)	*97.7*	0.77 (0.62 – 0.93)	*93.8*	0.81 (0.67 – 0.95)	*91.5*	0.64 (0.01 – 1.00)	*95.0*
Expected mortality at hospital admission (n=232)*	0.72 (0.64 – 0.80)	*84.5*	0.74 (0.60 – 0.88)	*83.8*	0.82 (0.70 – 0.94)	*88.2*	0.49 (0.32 – 0.66)	*76.5*	1.00 (1.00 – 1.00)	*100.0*
Adequacy of AB treatment (n=260)	0.88 (0.82 – 0.95)	*95.8*	0.91 (0.80 – 1.00)	*92.0*	0.86 (0.74 – 0.98)	*94.9*	0.65 (0.20 -1.00)	*96.6*	0.91 (0.74 – 1.00)	*95.0*

* Significantly different between infection types (p=0.034 and 0.009 respectively)

Supplementary Table S5: Variables evaluated and kept (ticked, when significant) in the multivariate regression model.
The bottom line indicates the percentage of correctly predicted cases of each model (with cross validation).

	Overall				BSI				Pneumonia				CDI			
	3CAT	**3CAT**	**WHO**	**WHO**	**3CAT***	**3CAT***	**WHO***	**WHO***	**3CAT**	**3CAT**	**WHO**	**WHO**	**3CAT***	**3CAT***	**WHO**	**WHO***
Pathophysiological mechanism	X		X		X		X		X		X		X		X	
Severity of HAI	X	X	X	X	X	X	X	X		X	X	X				
HAI or complication active		X		X						X		X				
Competing cause	X	X														
HAI type			X	X												
Number of HAI	X								X							
Duration between HAI and death						X										
Length of stay before HAI		X	X	X					X	X						
LOS in ICU before HAI																
Gender											X					X
Age (categories)		X					X	X					X		X	
In ICU at anytime		X														
Treatment limitation						X										
Charlson's severity score	X	X	X	X									X		X	
McCabe score																
Sum Charlson's comorbidities	X	X							X	X						

	Overall		BSI						Pneumonia			CDI				
	3CAT	**3CAT**	**WHO**	**WHO**	**3CAT***	**3CAT***	**WHO***	**WHO***	**3CAT**	**3CAT**	**WHO**	**WHO**	**3CAT***	**3CAT***	**WHO**	**WHO***
Expected mortality at admission																
COPD			X	X												
Dementia		X														
Diabetes with end organ damage	X	X								X						
Mod/severe liver dis.										X						
Myocard. infarct						X										
Peripheral vascular disease			X	X												
Antibiotic resistance									X	X						
Adequate AB treatment	X	X														
BSI source							X	X								
Pneumonia type										X						
Unit specialty													X	X	X	X
Complicated course													X	X		X
Acq. earlier or present admission.															X	
Percent Predicted correctly	82.7	61.5	60.6	60.0	81.4	61.3	54.0	58.0	68.6	56.7	80.5	58%	84.6	72.1	78.5	57.9

*Questionable model fit because of quasi-complete separation of data points.
WHO = WHOCAT

Supplementary Table S6-A: 3CAT ratings for HAI by micro-organisms with the AMR phenotypes under surveillance (BSI, pneumonia and SSI)

	Definitely contributed	Possibly contributed	Did not contribute	Total (OSI)
Definitely contributed	43	1	0	44
Possibly contributed	11	25	9	45
Did not contribute	0	1	4	5
Total (TP)	54	27	13	94

Supplementary Table S6-B: 3CAT ratings for HAI by micro-organisms without the AMR phenotypes under surveillance (BSI, pneumonia and SSI)

	Definitely contributed	Possibly contributed	Did not contribute	Total (OSI)
Definitely contributed	23	2	0	24
Possibly contributed	5	25	4	34
Did not contribute	0	3	7	10
Total (TP)	28	29	11	68

Supplementary Table S7-A: 3CAT ratings for HAI, stratified for Charlson's severity of illness score = Not or mildly ill

	Definitely contributed	Possibly contributed	Did not contribute	Total (OSI)
Definitely contributed	18	2	0	20
Possibly contributed	2	16	5	23
Did not contribute	0	0	9	9
Total (TP)	20	18	14	52

Supplementary Table S7-B: 3CAT ratings for HAI, stratified for Charlson's severity of illness score = Moderately ill

	Definitely contributed	Possibly contributed	Did not contribute	Total (OSI)
Definitely contributed	52	6	1	59
Possibly contributed	17	30	10	57
Did not contribute	0	9	9	18
Total (TP)	69	45	20	134

Supplementary Table S7-C: 3CAT ratings for HAI, stratified for Charlson's severity of illness score = Severely ill

	Definitely contributed	Possibly contributed	Did not contribute	Total (OSI)
Definitely contributed	31	3	0	34
Possibly contributed	8	45	6	59
Did not contribute	0	0	11	11
Total (TP)	39	48	17	104

REFERENCES

1. Suetens C, Latour K, Karki T, Ricchizzi E, Kinross P, Moro ML, et al. Prevalence of healthcare-associated infections, estimated incidence and composite antimicrobial resistance index in acute care hospitals and long-term care facilities: results from two European point prevalence surveys, 2016 to 2017. Euro Surveill. 2018;23(46).
2. Cassini A, Plachouras D, Eckmanns T, Abu Sin M, Blank HP, Ducomble T, et al. Burden of Six Healthcare-Associated Infections on European Population Health: Estimating Incidence-Based Disability-Adjusted Life Years through a Population Prevalence-Based Modelling Study. PLoS Med. 2016;13(10):e1002150.
3. Schumacher M, Allignol A, Beyersmann J, Binder N, Wolkewitz M. Hospital-acquired infections--appropriate statistical treatment is urgently needed! Int J Epidemiol. 2013;42(5):1502-8.
4. Wolkewitz M, Beyersmann J, Gastmeier P, Schumacher M. Modeling the effect of time-dependent exposure on intensive care unit mortality. Intensive Care Med. 2009;35(5):826-32.
5. Wolkewitz M, Cooper BS, Palomar-Martinez M, Alvarez-Lerma F, Olaechea-Astigarraga P, Barnett AG, et al. Multilevel competing risk models to evaluate the risk of nosocomial infection. Crit Care. 2014;18(2):R64.
6. Olivieri A, Del Monte D, Benacchio L, Bonvicini D, Baiocchi M, Allegri C, et al. An Observational Veneto Research on Ventilator-Associated Pneumonia (OVeRVAP): attributable mortality and cumulative incidence of ventilator-associated pneumonia. Minerva Anestesiol. 2018;84(7):811-9.
7. Brady M, Oza A, Cunney R, Burns K. Attributable mortality of hospital-acquired bloodstream infections in Ireland. J Hosp Infect. 2017;96(1):35-41.
8. Green N, Johnson AP, Henderson KL, Muller-Pebody B, Thelwall S, Robotham JV, et al. Quantifying the Burden of Hospital-Acquired Bloodstream Infection in Children in England by Estimating Excess Length of Hospital Stay and Mortality Using a Multistate Analysis of Linked, Routinely Collected Data. J Pediatric Infect Dis Soc. 2015;4(4):305-12.
9. Timsit JF, Zahar JR, Chevret S. Attributable mortality of ventilator-associated pneumonia. Curr Opin Crit Care. 2011;17(5):464-71.
10. Kaoutar B, Joly C, L'Heriteau F, Barbut F, Robert J, Denis M, et al. Nosocomial infections and hospital mortality: a multicentre epidemiology study. J Hosp Infect. 2004;58(4):268-75.
11. World Health Organization. Medical certification of cause of death : instructions for physicians on use of international form of medical certificate of cause of death, 4th ed. Geneva : World Health Organization. 1979.
12. Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH, et al. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. J Pain Symptom Manage. 2011;41(6):1073-93.
13. European Centre for Disease Prevention and Control. Surveillance of healthcare-associated infections and prevention indicators in European intensive care units Stockholm: ECDC; 2017 [Available from: https://ecdc.europa.eu/sites/portal/files/documents/HAI-Net-ICU-protocol-v2.2_0.pdf.
14. European Centre for Disease Prevention and Control. European Surveillance of Clostridium difficile infections. Surveillance protocol version 2.3. Stockholm: ECDC; 2017 [Available from: https://ecdc.europa.eu/sites/portal/files/documents/European-surveillance-clostridium-difficile-v2point3-FINAL_PDF3.pdf.

15. European Centre for Disease Prevention and Control. Surveillance of surgical site infections and prevention indicators in European hospitals - HAI-Net SSI protocol, version 2.2. Stockholm: ECDC; 2017 [Available from: https://ecdc.europa.eu/sites/portal/files/documents/HAI-Net-SSI-protocol-v2.2.pdf.
16. European Centre for Disease Prevention and Control. Point prevalence survey of healthcareassociated infections and antimicrobial use in European acute care hospitals – protocol version 5.3 Stockholm: ECDC; 2016 [Available from: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/PPS-HAI-antimicrobial-use-EU-acute-care-hospitals-V5-3.pdf.
17. Sun S. Meta-analysis of Cohen's kappa. Health Serv Outcomes Res Method. 2011(11):145-63.
18. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull. 1979;86(2):420-8.
19. Tejerina E, Esteban A, Fernandez-Segoviano P, Maria Rodriguez-Barbero J, Gordo F, Frutos-Vivar F, et al. Clinical diagnoses and autopsy findings: discrepancies in critically ill patients*. Crit Care Med. 2012;40(3):842-6.
20. Daschner F, Nadjem H, Langmaack H, Sandritter W. Surveillance, prevention and control of hospital-acquired infections. III. Nosocomial infections as cause of death: retrospective analysis of 1000 autopsy reports. Infection. 1978;6(6):261-5.
21. Pommerenke F, Radtke A, Tessmann D, Thierbach K. [Autopsy-confirmed nosocomial infections among the deaths in an intensive care unit]. Anaesthesiol Reanim. 1993;18(1):20-3.
22. Groβer J, Meyer R, Wilbrand B, Grosse K, Uhlmann F. Investigations on the relevance and avoidability of nosocomial infections as a cause of death in hospitals. Hygiene & Medizin. 1994;19(3):132-6.
23. Michel P, Quenon JL, Djihoud A, Tricaud-Vialle S, de Sarasqueta AM. French national survey of inpatient adverse events prospectively assessed with ward staff. Qual Saf Health Care. 2007;16(5):369-77.
24. Langelaan M. dBMC, Baines R.J., Broekens M.A., Hammink K., Schilp J., Verweij L., Asscheman H., Wagner C. Monitor Zorggerelateerde schade 2011-2012. Dossieronderzoek in Nederlandse ziekenhuizen (Monitor Healthcare-related damage 2011-2012. Patient records study in Dutch hospitals). EMGO+ Institute for Health and Care Research, NIVEL, Netherlands Institute for Health Services Research; 2013.
25. European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals 2011-2012. Stockholm: European Centre for Disease Prevention and Control; 2013.
26. Neubeiser A, Bonsignore M, Tafelski S, Alefelder C, Schwegmann K, Ruden H, et al. Mortality attributable to hospital acquired infections with multidrug-resistant bacteria in a large group of German hospitals. J Infect Public Health. 2020;13(2):204-10.
27. Kariv G, Paul M, Shani V, Muchtar E, Leibovici L. Benchmarking inappropriate empirical antibiotic treatment. Clin Microbiol Infect. 2013;19(7):629-33.
28. Carrara E, Pfeffer I, Zusman O, Leibovici L, Paul M. Determinants of inappropriate empirical antibiotic treatment: systematic review and meta-analysis. Int J Antimicrob Agents. 2018;51(4):548-53.
29. Decoster A, Grandbastien B, Demory MF, Leclercq V, Alfandari S, Regional Network 'Review of nosocomial infection-related m. A prospective study of nosocomial-infection-related mortality assessed through mortality reviews in 14 hospitals in Northern France. J Hosp Infect. 2012;80(4):310-5.
30. Branger B, Durand C, Jarno P, Chaperon J, Delattre-Maillot I, Rennes lmdCd. Mortalité hospitalière imputable aux infections nosocomiales. Méd Mal Infect. 2001(32):98-106.
31. Katz KC, Golding GR, Choi KB, Pelude L, Amaratunga KR, Taljaard M, et al. The evolving epidemiology of Clostridium difficile infection in Canadian hospitals during a postepidemic period (2009-2015). CMAJ. 2018;190(25):E758-E65.

32. Olsen MA, Stwalley D, Demont C, Dubberke ER. Clostridium difficile infection increases acute and chronic morbidity and mortality. Infect Control Hosp Epidemiol. 2019;40(1):65-71.
33. Tabak YP, Zilberberg MD, Johannes RS, Sun X, McDonald LC. Attributable burden of hospital-onset Clostridium difficile infection: a propensity score matching study. Infect Control Hosp Epidemiol. 2013;34(6):588-96.
34. Mlangeni DA, Harris MD, Franklin L, Hunt P, Karas JA, Enoch DA. Death certificates provide a poor estimation of attributable mortality due to Clostridium difficile when compared to a death review panel using defined criteria. J Hosp Infect. 2011;77(4):370-1.
35. Rhodes A, Ferdinande P, Flaatten H, Guidet B, Metnitz PG, Moreno RP. The variability of critical care bed numbers in Europe. Intensive Care Med. 2012;38(10):1647-53.
36. Hansen S, Zingg W, Ahmad R, Kyratsis Y, Behnke M, Schwab F, et al. Organization of infection control in European hospitals. J Hosp Infect. 2015;91(4):338-45.
37. Morgan DJ, Lomotan LL, Agnes K, McGrail L, Roghmann MC. Characteristics of healthcare-associated infections contributing to unexpected in-hospital deaths. Infect Control Hosp Epidemiol. 2010;31(8):864-6.

Part II

Prevention of HAI: improving compliance to best practices

Chapter 7

Chapter 7 Prevention of hospital infections by intervention and training (PROHIBIT): results of a pan-European cluster-randomized multicentred study to reduce central venous catheter-related bloodstream infections

Tjallie van der Kooi[1], Hugo Sax[2,3], Didier Pittet[3], Jaap van Dissel[1], Birgit van Benthem[1], Bernhard Walder[3], Vanessa Cartier[3], Lauren Clack[2], Sabine de Greeff[1], Martin Wolkewitz[4], Stefanie Hieke[4], Hendriek Boshuizen[1], Jan van de Kassteele[1], Annemie Van den Abeele[5], Teck Wee Boo[6], Magda Diab-Elschahawi[7], Uga Dumpis[8], Camelia Ghita[9], Susan Fitzgerald[10], Tatjana Lejko[11], Kris Leleu[5], Mercedes Palomar Martinez[12], Olga Paniara[13], Márta Patyi[14], Paweł Schab[15], Annibale Raglio[16], Emese Szilágyi[17], Mirosław Ziętkiewicz[18], Albert W. Wu[19], *Hajo Grundmann[4,20]; *Walter Zingg[3,21], on behalf of the PROHIBIT consortium.

[1] RIVM National Institute for Public Health and the Environment, 3720 BA, Bilthoven, the Netherlands
[2] Division of Infectious Diseases and Hospital Epidemiology, University Hospital of Zurich, University of Zurich, 8006, Zurich, Switzerland
[3] Infection Control & World Health Organization Collaborating Center on Patient Safety, The University of Geneva Hospitals and Faculty of Medicine, 1211, Geneva, Switzerland
[4] University of Freiburg, 79085, Freiburg, Germany
[5] AZ Sint-Lucas hospital, 9000, Ghent, Belgium
[6] University Hospital Galway, Galway, H91 YR71, Ireland
[7] Medical University of Vienna, 1090, Vienna, Austria
[8] Pauls Stradins Clinical University Hospital, Riga, LV-1002, Latvia
[9] Department of Infection control, Institute for emergency cardiovascular diseases "Prof. C.C. Iliescu", Bucharest, 022328, Romania
[10] St. Vincent's University Hospital, Dublin, D04 Y8V0, Ireland
[11] University Medical Center Ljubljana, 1000, Ljubljana, Slovenia
[12] Arnau de Vilanova University Hospital, 25198, Lleida & Vall d'Hebron University Hospital and Universitat Autónoma, 08035, Barcelona, Spain
[13] Evanggelismos hospital, Athens, 106 76, Greece
[14] Bács-Kiskun County Teaching Hospital, Kecskemét, 6000, Hungary
[15] Hospital of Silesia, 43-400, Cieszyn, Poland
[16] Papa Giovanni XXIII Hospital, 24127, Bergamo, Italy
[17] Office of the Chief Medical Officer & Szent János Hospital, Budapest, 1125, Hungary
[18] John Paul II Hospital, Kraków, 30-001, Poland
[19] John Hopkins University Bloomberg School of Public Health, Baltimore, MD 21205, USA
[20] University Medical Center Groningen, 9713 GZ, Groningen, the Netherlands
[21] Imperial College London, London, SW7 2AZ, United Kingdom
*loco equo

PROHIBIT Consortium: PROHIBIT Study Group: Pittet D (principal investigator), Zingg W (coordinator), Ahmad R, Allegranzi B, Cookson B, Dettenkofer M, Gastmeier P, Grundmann H, Hansen S, Heczko PB, Holmes A, Kyratsis Y, Magiorakos A, Martin M, Richet H, Sax H, Szilágyi E, van Benthem B, van der Kooi T, Wu AW.

Intensive Care Medicine 2018(44): 48-60

ABSTRACT

Purpose: To test the effectiveness of a central venous catheter (CVC) insertion strategy and a hand hygiene (HH) improvement strategy to prevent central venous catheter-related bloodstream infections (CRBSI) in European intensive care units (ICUs), measuring both process and outcome indicators.

Methods: Adult ICUs from 14 hospitals in 11 European countries participated in this stepped-wedge cluster randomised controlled multicentre intervention study. After a six month baseline, three hospitals were randomised to one of three interventions every quarter: 1) CVC insertion strategy (CVCi); 2) HH promotion strategy (HHi); and 3) both interventions combined (COMBi). Primary outcome was prospective CRBSI incidence density. Secondary outcomes were a CVC insertion score and HH compliance.

Results: Overall 25,348 patients with 35,831 CVCs were included. CRBSI incidence density decreased from 2.4/1000 CVC-days at baseline to 0.9/1000 ($p < 0.0001$). When adjusted for patient and CVC characteristics all three interventions significantly reduced CRBSI incidence density. When additionally adjusted for the baseline decreasing trend, the HHi and COMBi arms were still effective. CVC insertion scores and HH compliance increased significantly with all three interventions.

Conclusions: This study demonstrates that multimodal prevention strategies aiming at improving CVC insertion practice and HH reduce CRBSI in diverse European ICUs. Compliance explained CRBSI reduction and future quality improvement studies should encourage measuring process indicators.

INTRODUCTION

Healthcare-associated infections (HAIs) result in increased morbidity, mortality, hospital stay, and additional healthcare costs. In Europe, an average of 6% of hospitalized patients are affected, but HAI prevalence differs between countries [1, 2]. Although some differences can be explained by case-mix variation, they may be also due to infection prevention and control (IPC) practices [3].

The Prevention of Hospital Infections by Intervention and Training (PROHIBIT) project, funded by the European Commission 7th Framework Program, aimed to address and analyze the variation of IPC practices in Europe. Through its multiple work packages, PROHIBIT generated an overview of IPC at various levels [4-7], including the present study, with the objective to measure the effectiveness of two interventions of known efficacy in the prevention of CRBSI in European intensive care units (ICUs) (https://plone.unige.ch/prohibit/publications). The results discussed here have partly been presented before, as abstracts [8-10].

METHODS

Settings

Intensive care units from European hospitals were invited either through the European Center for Disease Prevention and Control (ECDC) national contact points for the HAI surveillance network (HAI-Net), or directly if registered in the European Antimicrobial Resistance Surveillance System. Eligible hospitals had to have a sufficient density of central venous catheter (CVC) use in the ICU and adequate diagnostic microbiological capacity. Germany and the Netherlands were excluded because the national surveillance protocols differed from the study protocol. Each hospital appointed a dedicated on-site investigator (OSI) and a study nurse. PROHIBIT offered reimbursement of a 0.5 full-time equivalent study nurse salary.

Study design

This study was conducted between January 2011 and June 2013. All adult patients (≥ 16 years of age) with a CVC inserted in a study hospital and admitted to one of the participating ICUs were eligible. The study followed a stepped-wedge, cluster randomized, controlled design (Fig. 1), which allowed control for secular trends, and enabled the comparison of hospitals with other hospitals and themselves. After a baseline of 6 months for all hospitals, every subsequent quarter, three hospitals were computer-randomized to one of three interventions: 1) a comprehensive CVC insertion strategy, developed and successfully implemented at the University of Geneva Hospitals (CVCi) [11]; 2) a hand hygiene improvement strategy based on World Health Organization

(WHO) recommendations (HHi) targeting the entire ICU-unit [12]; and 3) both interventions combined (COMBi) (more information in Supp. Methods). CRBSI was the primary outcome, process indicators, i.e. a CVC insertion score and hand hygiene compliance, were secondary outcomes. Interventions targeting quality of care were implemented at ICU-ward level (cluster level) whereas ICU patients were monitored for CRBSI and healthcare professionals for compliance.

Central venous catheters and CRBSI

Surveillance was performed prospectively by the local PROHIBIT study nurse. Tunneled or peripherally-inserted central catheters, as well as CVCs already present at hospital admission or *in situ* for only one day were excluded. CVCs were followed up from insertion to removal. Dwell-time was censored in the case of CRBSI, beyond 48 hours after ICU discharge, and after fatal outcome. CRBSI was measured as an incidence density (per 1000 CVC-days). Bloodstream infection (BSI) was defined according to the US Centers for Disease Control and Prevention (CDC) criteria for laboratory-confirmed BSI. CVC relation was defined using the ECDC HAI-Net criteria for microbiologically-confirmed CVC-related BSI (CRI3) [13], with the added criterion of the timely resolution of clinical symptoms after CVC removal or after starting antimicrobial therapy (Supp. Methods and results).

Process indicator surveillance

CVC insertion compliance was measured by direct observation using a list based on the CRBSI prevention protocol developed at the University of Geneva Hospitals (Supp. Fig. 1) and expressed as the proportion of fulfilled protocol items divided by the total number of protocol items (CVC insertion score). Hand hygiene compliance was measured by direct observation according to the WHO “My five moments for hand hygiene” concept [14]. Observations of CVC insertion were randomized for date (weekdays) and place of insertion (ICU, operating theatre [if ICU patients regularly received the CVC there]) and were performed during daytime. Hand hygiene observations were randomized for date (weekdays), time slots (08-12:00, 12:00-16:00 and 16:00-20:00), and ICU beds. OSIs and study nurses were advised not to disclose any outcome or process indicator results during baseline. During the intervention, quarterly feedback reports on CRBSI and process indicator(s), according to the allocated intervention, were made available to OSIs by the project coordination team.

Co-variables

The recorded patient and CVC characteristics were age, sex, type of admission, type of ICU, length-of-stay, place of CVC insertion, insertion site, CVC type, number of lumens, indication for CVC insertion, and CVC dwell-time. Local study teams provided the Simplified Acute Physiology Score (SAPS) II or the Acute Physiology and Chronic Health Evaluation (APACHE) II score at patient admission, where available.

Training of study participants

Six weeks before the start of the study baseline the PROHIBIT study nurses were trained in the direct observation of CVC insertion and hand hygiene compliance at the University of Geneva Hospitals. Three to six months before the start of the intervention, study nurses and physicians attended a two-day PROHIBIT workshop for training best practices and implementation science. Parallel to the WHO training material on hand hygiene (http://www.who.int/gpsc/5may/tools/en/), an e-learning program developed at the University of Geneva Hospitals was adapted to the PROHIBIT protocol and made available publicly at www.carepractice.net. Hospitals were encouraged to adapt the intervention program to their local context.

Implementation activities

The hospitals adapted CVC insertion procedures and introduced material (e.g. large drapes) as needed and feasible. They promoted strategy elements through educational sessions and bed-side training, using the WHO material and/or the Carepractice e-learning program. Some CVCi hospitals filmed the 'old and new' local insertion procedure to be used in educational sessions. All HHi hospitals applied posters and/or other reminders in the workplace and many came up with various additional activities. Detailed intervention activities are described in Supp. Tables 1a and 1b.

Statistical methods

For sample size calculations, we anticipated a baseline CRBSI incidence density of 3/1000 CVC-days. We hypothesized that the HHi-, CVCi-, and COMBi interventions would reduce CRBSI by 15%, 35% [15], and 50% (alpha=0·05; approximately 60% power for HHi, and over 80% power for CVCi and COMBi), respectively. χ^2 and exact tests were used to calculate 95% confidence intervals (CIs) for CRBSI incidence densities and compliance proportions. Differences between medians were tested with the Kruskal-Wallis test. CVC removal without CRBSI, discharge from the ICU with the CVC in place, and death were modeled as competing events for CRBSI (Supp. Methods and results) [16]. The association of the three interventions (CVCi, HHi and COMBi) with CRBSI incidence

density was analyzed using a sub-distribution Cox proportional hazard analysis, stratified by hospitals. As patients can have more than one CVC, we adjusted for possible clustering at the patient level using robust covariance estimation. Records with missing values for a variable were excluded from the regression analysis of that variable. Patient and CVC characteristics with a p-value < 0.2 were included in the multivariable regression model.

Following distribution of the dependent variables, the association of the interventions with the CVC insertion score was analyzed using generalized linear mixed modeling with a binomial distribution, and with hand hygiene using generalized linear mixed modeling, with a normal distribution, both allowing for clustering at the hospital level. The association with professional category, type of ICU, shift, weekday, and activity index (number of hand hygiene opportunities per hour [17], averaged per quarter) was evaluated and these were included in the multiple regression model in case of a p-value < 0.2.

All analyses were performed 1) without assuming a time-dependent trend, and 2) with assuming a baseline hospital-specific time-dependent trend and an additional intervention-specific time-dependent trend. Time was modeled as quarters during baseline (1 to a maximum of 6), and intervention (1 to a maximum of 8), assuming a linear trend. These models were fixed models, with hospitals included as a covariate to allow interaction terms of hospitals with the time-dependent trend.

The direct association of the two process indicators (CVC insertion score and hand hygiene compliance) with CRBSI incidence was explored using the quarterly averages of the CVC insertion score and hand hygiene compliance (both as percentages) and the quarterly CRBSI numbers, using Poisson regression modeling, allowing for clustering at the hospital level. Quarterly averages of covariates associated with CRBSI in the Cox regression model were evaluated in this analysis and included in the multiple regression model in case of a p-value < 0.2. We used SAS software, version 9.3 for all statistical analyses.

Ethics

The medical ethical committees of all participating hospitals approved the study before randomization. In one center individual patient consent was deemed necessary and therefore obtained.

Study registration

We retrospectively registered the protocol at the ISRCTN registry (ISRCTN24828982).

Role of the Funding Source

The PROHIBIT study was funded by the European Commission 7th Framework Program. The study funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript. The study funder was not involved in the decision to submit the paper for publication.

RESULTS

Participating hospitals

Fifteen hospitals were selected from 18 applicants to provide an even geographical distribution across Europe. Two hospitals dropped out before study start: one due to local ethics review board requiring individual written informed consent from patients, and one due to the workload anticipated by the ICU as non-feasible. One hospital was excluded during baseline because it failed to comply with the study protocol. Two of the three drop-out hospitals were replaced. Fourteen hospitals from 11 European countries completed the study: four were randomized to HHi, five to CVCi, and five to COMBi. Seven hospitals were university-affiliated. Four centers counted >50,000 admissions per year, four between 30,000 and 50,000, and five <30,000. The median (range) number of ICU beds per hospital was 30 (10-53). Median nurse-to-patient ratio in the ICU was 0.42 (0.25-1). Median (interquartile range (IQR)) activity index was 10.7 (8.2-12.7) hand hygiene opportunities per hour.

Patients and CVC utilization

A total of 35,831 CVCs and 25,348 patients were included in the study. Patient and CVC characteristics are summarized in Tables 1 (per study arm) and Supp. Table 2 (overall). Patient and CVC characteristics differed significantly among the three intervention arms (Table 1). The APACHE II and SAPS II scores were available for only 35% and 37% of patients, respectively (Supp Table 3); and therefore excluded from the main analysis. CVC utilization decreased in all three intervention arms, but significantly only in the CVCi arm (Supp. Table 3). Median CVC dwell-times decreased in the COMBi arm (6 to 5 days, $p<0.0001$), but did not change significantly in the HHi- (6 and 7 days, $p=0.41$) and CVCi arms (5 and 5 days, $p=0.46$).

CRBSI incidence densities

The overall CRBSI incidence density decreased from 2.4/1000 CVC-days at baseline to 0.9/1000 during the intervention (rate ratio, 0.39; 95% CI, 0.32–0.48; $p<0.0001$). CRBSI incidences at baseline differed significantly between the three study arms: 2.0, 1.4, and

5.3/1000 CVC-days for HHi, CVCi and COMBi, respectively. Figure 2 shows the quarterly CRBSI incidence density for each study arm (results for each center in Supp. Fig. 2). Table 2 shows the results of the univariable and multivariable regression analyses. CRBSI incidence density reduction between baseline and intervention was significant in all study arms, when adjusted in the multivariable regression analysis: the sub-distribution hazard ratios (HR_{sub}; 95% CI) for the CVCi-, HHi-, and COMBi arms were 0.59 (0.43–0.81), 0.46 (0.28–0.74), and 0.33 (0.24–0.47), respectively.

CRBSI incidence density tended to decrease already during baseline (HR_{sub} 0.93; [0.84 – 1.02], per baseline quarter). When adjusting for possible underlying hospital-specific trends and taking into account an intervention-specific trend, CRBSI reduction remained significant in the HHi- and COMBi arms: HR_{sub} 0.37 (0.16–0.87) and 0.47 (0.27–0.83), respectively. In this model, CRBSI reduction was not significant in the CVCi arm: HR_{sub} 1.16 (0.63–2.16). The interventions did not result in significant changes of the baseline trends (Supp. Methods and results). The overall median CVC dwell-time until infection was prolonged from 10 to 11.5 days (p=0.042).

Microorganisms

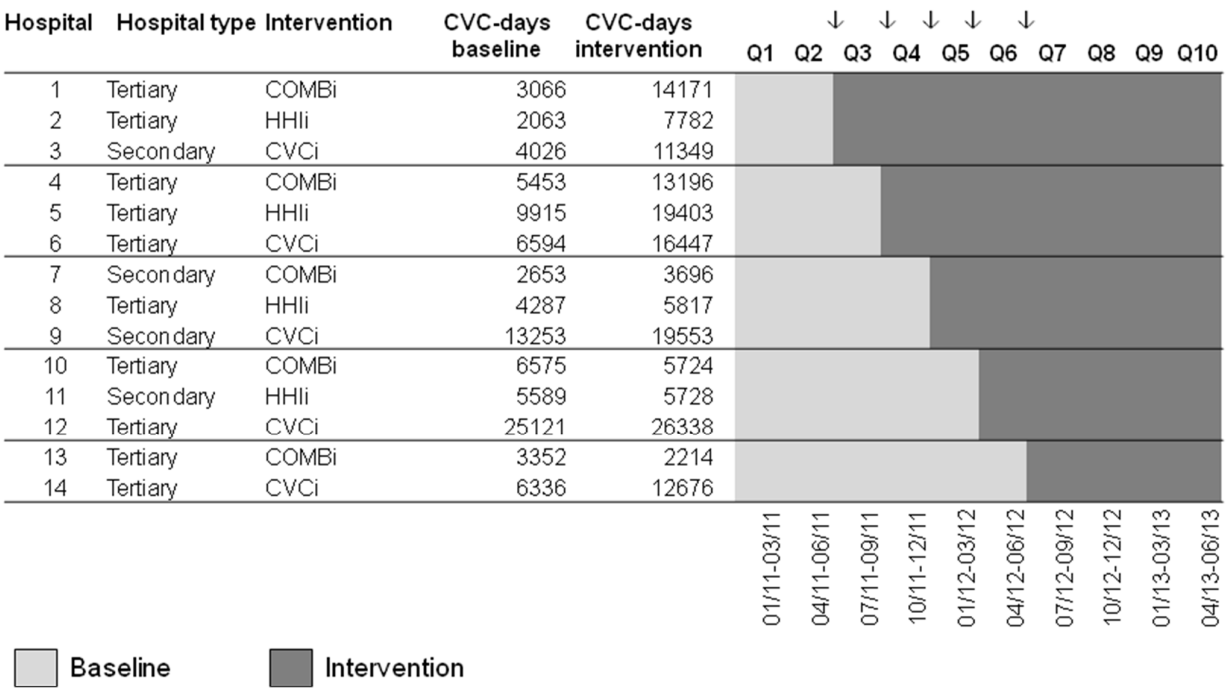
The overall distribution of isolated microorganisms was as follows: Gram negative organisms: 44.0%; Gram positive organisms: 41.6%; *Candida* spp. 6.8%; and multiple organisms: 7.6%. The most frequent species were *Acinetobacter baumannii* (17.3%), *Staphylococus epidermidis* (15.7%), other coagulase negative staphylococci (CoNS) (14.1%), *Klebsiella pneumoniae* (9.7%), *Pseudomonas aeruginosa* (9.2%), *Staphylococcus aureus* (8.4%), *Candida* spp. (7.9%), *Enterococcus faecium* (4.7%), and *E. faecalis* (4.5%). CRBSI-reduction was significant for *Acinetobacter baumannii* (HR_{sub} 0.39 [0.23-0.67]), *Staphylococcus epidermidis* (0.33 [0.19-0.56]), Pseudomonas aeruginosa (0.39 [0.18-0.83]) and CoNS other than *S. epidermidis* (0.04 [0.01-0.20]).

CVC insertion score

A total of 3,572 CVC insertions were observed, i.e. 8.9% (IQR 6.4 – 15.6%) of all study CVCs. Supp. Table 5 shows the results for each insertion score element. CVC insertion scores improved in all study arms (Fig. 2, individual hospitals in Supp. Fig. 3): between baseline and intervention period, the mean insertion scores in the CVCi-, HHi- and COMBi arms improved from 69% to 92% (OR [95%CI]: 4.0 [3.7–4.4]; p<0.0001), from 66% to 85%

Figure. 1: Study design with referral level, randomly allocated intervention, central venous catheter days, and randomly allocated start of the intervention

Hospital	Hospital type	Intervention	CVC-days baseline	CVC-days intervention
1	Tertiary	COMBi	3066	14171
2	Tertiary	HHIi	2063	7782
3	Secondary	CVCi	4026	11349
4	Tertiary	COMBi	5453	13196
5	Tertiary	HHIi	9915	19403
6	Tertiary	CVCi	6594	16447
7	Secondary	COMBi	2653	3696
8	Tertiary	HHIi	4287	5817
9	Secondary	CVCi	13253	19553
10	Tertiary	COMBi	6575	5724
11	Secondary	HHIi	5589	5728
12	Tertiary	CVCi	25121	26338
13	Tertiary	COMBi	3352	2214
14	Tertiary	CVCi	6336	12676



Q: Quarter; COMBi: hand hygiene intervention and central venous catheter intervention combined; CVC: Central venous catheter; CVCi: central venous catheter intervention; HHi: hand hygiene intervention

Table 1: Patient and central venous catheter characteristics at baseline and intervention, stratified by study arm

	HH intervention only					CVC intervention only					Both interventions				
	Baseline		Intervention		p-value	Baseline		Intervention		p-value	Baseline		Intervention		p-value
CRBSI *per 1000 CVC days (95% CI)*	2.0 (1.4 –2.6)		0.9 (0.6 – 1.2)		0.0004	1.4 (1.1 – 1.8)		0.8 (0.6 – 1.0)		0.0002	5.3 (4.3 – 6.3)		1.3 (1.0 – 1.7)		<0.0001
Dwell time *in days (median (IQR)*	6 (3 – 10)		7 (4 – 9)		0.41	5 (3 – 9)		5 (3 – 9)		0.46	6 (3 – 11)		5 (2 – 10)		<0.0001
	N	***%***	**N**	***%***	**p-value**	**N**	***%***	**N**	***%***	**p-value**	**N**	***%***	**N**	***%***	**p-value**
Patients	1506		2476			6090		9454			2004		3818		
CVCs	2898		5273			7664		12061			2669		5266		
CVC-days	21854		38730			55330		86363			21099		39001		
CRBSIs	43		34			78		65			111		51		
Sex															
Male	1856	*64.0*	3361	*63.7*	0.78	5126	*66.9*	7702	*63.9*	<0.0001	1619	*60.7*	3261	*61.9*	0.27
Female	1042	*36.0*	1912	*36.3*		2538	*33.1*	4359	*36.1*		1050	*39.3*	2005	*38.1*	
Age (years)															
< 30	227	*7.8*	331	*6.3*	0.03	273	*3.6*	393	*3.3*	0.37	112	*4.2*	133	*2.5*	<0.0001
30-49	438	*15.1*	838	*15.9*		864	*11.3*	1431	*11.9*		411	*15.4*	822	*15.6*	
50-69	1130	*39.0*	2150	*40.8*		3443	*44.9*	5350	*44.4*		1208	*45.3*	2619	*49.7*	
≥ 70	1103	*38.1*	1954	*37.1*		3084	*40.2*	4887	*40.5*		938	*35.1*	1692	*32.1*	
Type of admission[a]															
Medical	1587	*54.8*	2779	*52.7*		2200	*28.7*	3384	*28.1*		1549	*58.0*	2091	*39.7*	
Surgical	744	*25.7*	1068	*20.3*	<0.0001	4438	*57.9*	6893	*57.2*	<0.02	608	*22.8*	1993	*37.8*	<0.0001
Unscheduled surgical	567	*19.6*	1426	*27.0*		1026	*13.4*	1784	*14.8*		512	*19.2*	1182	*22.4*	

	HH intervention only					CVC intervention only					Both interventions				
		Baseline		Intervention			Baseline		Intervention			Baseline		Intervention	
	N	%	N	%	p-value	N	%	N	%	p-value	N	%	N	%	p-value
Type of ICU															
Cardiothoracic surgery	0	0	0	*0*		4478	*58.4*	6446	*53.4*		476	*17.8*	2305	*43.8*	
Infectious diseases	0	0	0	*0*	1.00	307	*4.0*	416	*3.4*	<0.0001	0	*0*	0	*0.0*	<0.0001
Intermediate care	0	0	0	*0*		16	*0.2*	12	*0.1*		0	*0*	0	*0.0*	
Medical	0	*0*	0	*0*		875	*11.4*	1179	*9.8*		565	*21.2*	440	*8.4*	
Medical-surgical	2898	*100.0*	5273	*100.0*		1582	*20.6*	3290	*27.3*		1403	*52.6*	2031	*38.6*	
Neurology	0	*0*	0	*0*		168	*2.2*	177	*1.5*		33	*1.2*	13	*0.2*	
Neurosurgery	0	*0*	0	*0*		98	*1.3*	206	*1.7*		67	*2.5*	126	*2.4*	
Surgery	0	*0*	0	*0*		140	*1.8*	335	*2.8*		0	*0*	0	*0.0*	
Vascular surgery	0	*0*	0	*0*		0	*0*	0	*0.0*		125	*4.7*	351	*6.7*	
ICU stay[b] until insertion															
0 days	222	*7.7*	256	*4.9*	<0.0001	213	*2.8*	324	*2.7*	0.58	76	*2.8*	127	*2.4*	0.21
1-5	1762	*60.8*	2996	*56.8*		6441	*84.0*	10206	*84.6*		2110	*79.1*	4225	*80.2*	
6-20	581	*20.0*	1160	*22.0*		614	*8.0*	940	*7.8*		332	*12.4*	591	*11.2*	
>20	333	*11.5*	858	*16.3*		394	*5.1*	575	*4.8*		151	*5.7*	323	*6.1*	
missing	0	*0.0*	3	*0.1*		2	*0.03*	16	*0.1*		0	*0*	0	*0.0*	
Bacteremia at insertion					0.95					0.33					<0.0001
yes	160	*5.5*	300	*5.7*		192	*2.5*	263	*2.2*		195	*7.3*	189	*3.6*	
no	2738	*94.5*	4973	*94.3*		7472	*97.5*	11798	*97.8*		2474	*92.7*	5077	*96.4*	
Insertion department															
ICU	2227	*76.8*	4157	*78.8*		2817	*36.8*	4558	*37.8*		2089	*78.3*	3373	*64.1*	
OR	398	*13.7*	682	*12.9*	0.09	4567	*59.6*	7035	*58.3*	0.20	525	*19.7*	1788	*34.0*	<0.0001
Elsewhere	273	*9.4*	434	*8.2*		280	*3.7*	468	*3.9*		55	*2.1*	105	*2.0*	
Insertion site															
Subclavian	817	*28.2*	1251	*23.7*	<0.0001	2042	*26.6*	3094	*25.7*	0.11	1063	*39.8*	1320	*25.1*	<0.0001
Jugular	1489	*51.4*	2853	*54.1*		4985	*65.0*	8012	*66.4*		1251	*46.9*	3008	*57.1*	
Femoral	454	*15.7*	1035	*19.6*		522	*6.8*	755	*6.3*		309	*11.6*	674	*12.8*	
Other	138	*4.8*	134	*2.5*		115	*1.5*	200	*1.7*		46	*1.7*	264	*5.0*	

	HH intervention only					CVC intervention only					Both interventions				
		Baseline		Intervention			Baseline		Intervention			Baseline		Intervention	
	N	%	N	%	p-value	N	%	N	%	p-value	N	%	N	%	p-value
Type of CVC															
CVC	2863	*98.8*	5194	*98.5*	0.28	7390	*96.4*	11508	*95.4*	<0.0001	2534	*94.9*	4930	*93.6*	0.02
Swan-Ganz	35	*1.2*	79	*1.5*		274	*3.6*	553	*4.6*		135	*5.1*	336	*6.4*	
Lumen															
Multi	2453	*84.6*	4974	*94.3*	<0.0001	7530	*98.3*	11837	*98.1*	0.86	2553	*95.7*	4939	*93.8*	0.003
Single	445	*15.4*	299	*5.7*		134	*1.7*	224	*1.9*		116	*4.3*	327	*6.2*	
Use of CVC															
Antibiotics[c]	1738	*71.6*	3715	*79.3*	0.32	6464	*84.3*	9861	*81.8*	<0.0001	2065	*77.4*	4177	*79.3*	0.045
Blood products	342	*11.8*	716	*13.6*	0.02	1687	*22.0*	1704	*14.1*	<0.0001	279	*10.5*	495	*9.4*	0.14
Dialysis	675	*23.3*	1142	*21.7*	0.09	341	*4.4*	706	*5.9*	<0.0001	264	*9.9*	509	*9.7*	0.75
TPN[d]	629	*21.7*	1211	*23.0*	0.19	1183	*15.4*	2285	*18.9*	<0.0001	413	*21.9*	616	*13.6*	<0.0001
Other indications[e]	325	*74.2*	3666	*75.0*	0.71	7000	*91.3*	11228	*93.1*	<0.0001	2403	*90.0*	4754	*90.3*	0.73
CVC dwell-time[f]															
1-4 days	967	*33.4*	1664	*31.6*		3662	*47.8*	5791	*48.0*		1001	*37.5*	2471	*46.9*	
5-9	1152	*39.8*	2330	*44.2*	<0.0001	2245	*29.3*	3548	*29.4*	0.49	823	*30.8*	1380	*26.2*	<0.0001
10-19	665	*22.9*	1145	*21.7*		1345	*17.5*	2032	*16.8*		708	*26.5*	1078	*20.5*	
≥ 20	114	*3.9*	134	*2.5*		412	*5.4*	690	*5.7*		137	*5.1*	337	*6.4*	

[a] according to the SAPS II criteria: medical: no surgery within 1 week of admission to ICU; scheduled surgical: surgery was scheduled at least 24 hours in advance +/- 7 days intensive care unit admission; unscheduled surgical: patients added to the operating room schedule within 24 hours of the operation.

[b] including subsequent ICU stays (max. 3) until insertion

[c] data of first two months of one hospital excluded because of invalid or missing data

[d] one hospital excluded because of invalid or missing data

[e] data of first year of three hospitals and of first four months of another hospital excluded because of different interpretation

[f] Number of CVC days per category acc. to McLaws(1)

Table 2: Subdistribution hazard ratios for the association of central venous catheter-related bloodstream infection with interventions and patient and central venous catheter characteristics – univariable and multivariable regression analyses

	Univariable regression analysis	Multivariable regression analysis with time-dependent trend	Multivariable regression analysis without time-dependent trend
HH intervention	0.46 (0.27 – 0.79)	0.37 (0.16 – 0.87)	0.59 (0.43 – 0.81)
CVC intervention	0.61 (0.44 – 0.86)	1.16 (0.63 – 2.16)	0.46 (0.28 – 0.74)
Both interventions	0.39 (0.28 – 0.56)	0.47 (0.27 – 0.83)	0.33 (0.24 – 0.47)
Sex			
Male	1	1	
Female	1.02 (0.81 – 1.28)	1.04 (0.84 – 1.28)	
Age (years)			
< 30	0.64 (0.36 – 1.14)	0.59 (0.34 – 1.03)	
30-49	0.96 (0.70 – 1.33)	0.98 (0.72 – 1.32)	
50-69	1	1	
≥ 70	0.90 (0.70 – 1.15)	0.94 (0.75 – 1.19)	
Type of admission[a]			
Medical	1.36 (1.00 – 1.87)	1.28 (0.89 – 1.84)	
Surgical	1	1	
Unscheduled surgical	1.67 (1.20 – 2.35)	1.70 (1.18 – 2.46)	
Type of ICU			
Cardiothoracic surgery & coronary care	1.02 (0.64 – 1.61)	1.71 (1.04 – 2.82)	
Infectious diseases	0.92 (0.44 – 1.91)	0.79 (0.37 – 1.68)	
Intermediate care[b]	4.26 (0.58 – 31.3)	2.75 (0.45 – 16.8)	
Medical	1.02 (0.64 – 1.65)	1.14 (0.72 – 1.82)	
Medical-surgical	1	1	
Neurology	1.26 (0.60 – 2.62)	1.99 (0.98 – 4.02)	
Neurosurgery	1.51 (0.76 – 3.01)	1.88 (1.04 – 3.40)	
Surgery	1.58 (0.49 – 5.14)	1.88 (0.54 – 6.51)	
Vascular surgery	0.46 (0.06 – 3.60)	0.80 (0.10 – 6.48)	
ICU stay[c] **until insertion (days)**			
0	1.89 (1.15 – 3.11)	1.90 (1.13 – 3.20)	
1-5	1	1	
6-20	2.80 (2.17 – 3.62)	2.31 (1.76 – 3.03)	
>20	3.02 (2.16 – 4.23)	2.17 (1.54 – 3.04)	
BSI at the time of CVC insertion			
Yes	6.84 (5.50 – 8.52)	5.86 (4.63 – 7.43)	
No	1	1	
Place of insertion			
ICU	1	1	
Operating room	0.52 (0.37 – 0.72)	0.73 (0.46 – 1.14)	
Elsewhere	0.86 (0.52 – 1.39)	0.89 (0.51 – 1.54)	

	Univariable regression analysis	Multivariable regression analysis with time-dependent trend	Multivariable regression analysis without time-dependent trend
Access site			
Subclavian	1.08 (0.84 – 1.38)	0.81 (0.63 – 1.06)	
Jugular	1	1	
Femoral	1.30 (0.92 – 1.82)	1.18 (0.81 – 1.72)	
Brachial	0.44 (0.16 – 1.24)	0.42 (0.14 – 1.22)	
Other	1.29 (0.52 – 3.18)	1.53 (0.57 – 4.08)	
CVC type			
CVC	1		
Swan-Ganz	0.59 (0.25 – 1.39)		
Lumen			
Multi	1		
Single	1.00 (0.56 – 1.72)		
Indications for CVC use			
Antibiotics[d]	1.47 (1.11 – 1.95)	1.38 (1.01 – 1.87)	
Blood products	1.15 (1.12 – 1.88)	1.32 (1.01 – 1.71)	
Dialysis	0.94 (0.67 – 1.32)		
Total parenteral nutrition[e]	1.70 (1.31 – 2.20)	1.68 (1.25 – 2.26)	
Other indications[f]	0.88 (0.65 – 1.19)		

BSI, bloodstream infection; CRBSI, central venous catheter-related bloodstream infection; CVC, central venous catheter; HH, hand hygiene; ICU, intensive care unit

[a] according to the SAPS II criteria: medical: no surgery within one week of admission to ICU; scheduled surgical: surgery was scheduled at least 24 hours in advance +/- seven days intensive care unit admission; unscheduled surgical: patients added to the operating room schedule within 24 hours of the operation.

[b] in univariable analysis the interaction term of Intermediate Care with CVC duration was significant with a HR of 0.90 (0.82-0.99, p-value = 0.02). HR for IM was 10.3 (1.2-86.4, p-value = 0.03). This effect decreased with increasing CVC duration (10% per day). In the multivariable analysis this interaction was not significant anymore.

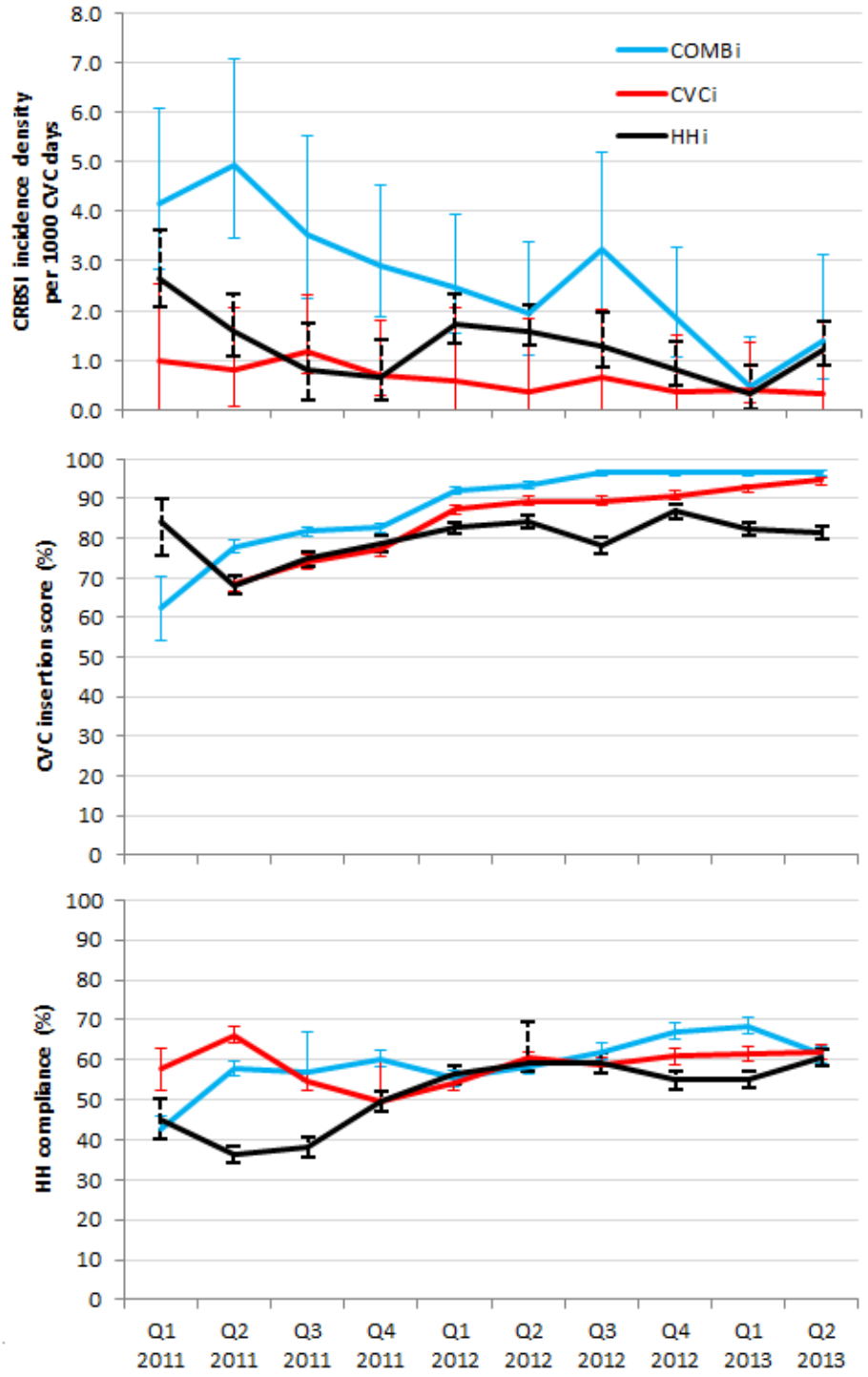
[c] including subsequent ICU stays (maximum 3) until insertion; in univariable analysis the interaction term of an ICU stay of >20 days with CVC duration was significant with a HR of 1.04 (1.004-1.08). HR for ICU stay > 20 days was 1.78 (0.99-3.20, p-value = 0.06). This effect increased with increasing CVC duration (4% per day). In the multivariable analysis, this interaction was not significant anymore.

[d] data of first two months of one hospital excluded because of invalid or missing data.

[e] one hospital excluded because of invalid or missing data; in univariable analysis, the interaction term with CVC duration was significant with a HR of 1.03 (1.005-1.71, p-value = 0.02). HR for TPN was 1.12 (0.73-1.71). This effect increased with increasing CVC duration (3% per day). In multivariable analysis this interaction was not significant anymore.

[f] data of first year of three hospitals and of first four months of another hospital excluded because of different interpretation.

Figure 2: Incidence density of catheter-related bloodstream infections (top), central venous catheter insertion scores (center), hand hygiene compliance (bottom) – stratified by intervention arm



COMBi, hand hygiene intervention and central venous catheter intervention combined; CRBSI, central venous catheter-related bloodstream infection; CVCi, central venous catheter intervention; HHi, hand hygiene intervention; Q, quarter
Of note: no CVC insertion scores during Q1.

(1.3 [1.2–1.5]; p<0.0001), and from 78% to 96% (6.0 [5.5–6.6]; p<0.0001), respectively. The CVC insertion score per quarter improved already during baseline (OR 1.05 [1.02–1.09]). When adjusting for the possible underlying hospital-specific trends and taking into account an intervention-specific trend, the odds ratios for the CVCi-, HHi-, and COMBi arms were 2.6 (2.2–3.0), 1.1 (0.6–1.3), and 3.4 (2.9–4.0), respectively. The improvement per quarter increased after the introduction of the intervention in the CVCi and COMBi arms (average additional OR 1.2 (1.1–1.5) and 1.5 (1.3–1.8), respectively), but did not change significantly in the HHi arm (OR 0.95 [0.9–1.1]).

Increasing CVC insertion scores were significantly associated with decreasing CRBSI incidence density: the incidence rate ratio (95% CI) per percentage point (PP) increase of the CVC score over the entire study was 0.97 (0.96–0.98). After adjustment for the proportions of patients with bloodstream infection at the time of insertion and of patients with prolonged ICU stay before insertion, this association remained significant with an incidence rate ratio of 0.97 (0.96–0.98) for the entire population, and for both the CVCi and COMBi arm; however, the adjusted association was not significant in the HHi arm) (Supp. Table 6).

Hand hygiene compliance

A total of 59,122 hand hygiene opportunities were observed during 6,749 observation sessions. Nurses were the main contributors (74.4%), followed by medical doctors (14.5%), auxiliaries (8.8%), and other healthcare professionals (2.3%). Overall hand hygiene compliance at baseline averaged 49%.

Between baseline and intervention period, hand hygiene compliance in the CVCi-, HHi- and COMBi arms improved from 51% (50–52%) to 62% (61–63%; p < 0.0001), from 36% (34–37%) to 58% (57–59%; p < 0.0001), and from 54% (52–55%) to 63% (62–64%; p<0.0001), respectively (Fig. 2, individual hospital data in Supp. Fig. 4). During baseline, hand hygiene compliance decreased by -1 [-2– -0.05] percentage points (PPs) per quarter. When adjusted for healthcare professional category, ICU type and activity index, improvement of hand hygiene compliance in the CVCi-, HHi-, and COMBi arms was 6 PP (4–8 PP), 20 PP (18–22 PP), and 8 PP (7–10 PP), respectively. When adjusted for underlying hospital-specific trends and taking into account an intervention-specific trend, improvement of hand hygiene compliance in the CVCi-, HHi-, and COMBi arms was 10 PP (6–14 PP), 18 PP (15–22 PP) and 6 PP (3–9 PP), respectively.

Hand hygiene compliance improved in all four healthcare professional categories in the HHi- and COMBi arms, while hand hygiene compliance in the CVCi arm improved only in nurses (Supp. Table 7). HH compliance by indication is displayed in Supp.Table 8.

As with the CVC insertion score, increasing hand hygiene compliance was associated with decreasing CRBSI incidence density: the incidence rate ratio (95% CI) per PP increase of hand hygiene compliance over the entire study was 0.99 (0.98–1.00). After adjustment for the proportions of patients with bloodstream infection at the time of insertion and of patients with prolonged ICU stay before insertion, this association did not remain significant, with an incidence rate ratio of 1.00 (0.99–1.01) for the entire population, and for the CVCi- and COMBi arms. However, the adjusted association was significant in the HHi arm (Supp. Table 6).

DISCUSSION

Our results demonstrate that the introduction of a best practice CVC insertion strategy, a WHO-based HH promotion strategy, and the combination of both, significantly improve process indicators, and reduce CRBSI incidence densities. When taking into account a decreasing trend during baseline both the HH program and the combined HH and CVC insertion strategy were still effective. The low baseline rates in the CVCi arm limited the power to demonstrate the same effect in this arm.

This is the first multinational randomized multicenter CRBSI prevention study providing sufficiently powered information on both outcome and process indicators. Many studies have reported successful CVC insertion or hand hygiene improvement initiatives [18-22]. However, most CRBSI prevention studies reported outcome data only, without mentioning process indicator data, as evidenced in a recent systematic review by Ista et al. [18]. In a randomized Canadian study, compliance with CRBSI-prevention measures increased from 10% at baseline to 70% during intervention in the intervention ICUs, while compliance increased from 31% to 52% in the control ICUs [20].The study did not report CRBSIs and numbers of CVCs were low. Non-randomized before-and-after studies, partially using retrospective data, have reported CVC “bundle” compliance in the range of 20%-37% [23], 55.2% [24], 74% [25] and 90%-100% [21, 26, 27]. An Australian multicenter study reported variation of bundle compliance between hospitals ranging from 0 to 100% (personal communication from McLaws) [21]. Most studies used an “all or nothing” approach where the outcome was met if all items of the bundle were fulfilled. Our CVC checklist consisted of 20 items, which is beyond the usual bundle promotions. Thus, in order to be discriminatory and to capture gradual quality improvement over time, we analyzed CVC insertion as a score.

Our baseline hand hygiene compliance of 48% is similar to the 52% identified by the MOSAR study in 13 European ICUs [28], and to the 40-50% reported by a review summarizing 65 ICU studies [29]. The effects of our intervention are in line with the

specific efficacy of the WHO multimodal promotion strategy [30] and other hand hygiene promotion strategies [22]. Hand hygiene improvement was highest for the HHi arm while the average increase of hand hygiene in the CVCi- and COMBi arms was moderate. Together with “HH study fatigue” in one centre, economic constraints resulting in budget and salary cuts, low staffing levels, and high workload were mentioned to play a role in prioritizing CVC-intervention over HH intervention in the COMBi arm. Nurses performed better than doctors across all study arms as has been reported by many others [29].

The average baseline CRBSI incidence density of 2.4/1000 CVC-days as seen in our study has become standard in high-income countries [31-33], although the hospital specific incidence density ranged from 0 to 10.2/1000 at baseline. This range may reflect not only real variation in CVC insertion and infection prevention practice but also differences in culturing quality and frequency. To minimize this bias we discussed these issues with the on-site investigators and study nurses during the kick-off and observer training that took place before baseline measurements began.

Meta-analyses about the effectiveness of CVC bundle or checklist interventions on central line-associated BSI (CLABSI) identified significant reductions (odds ratio of 0.34 [19], incidence rate ratio 0.45 [18]) but the lowest baseline incidence densities in both meta-analyses were higher (3.4 and 5.7/1000 CVC-days) compared to our study. However, it must be taken into account that CRBSI is a more specific definition than CLABSI [34]. CRBSI decreased already during baseline. This trend may have been the result of external factors, but probably also was a result of the concurrent study, and particularly due to direct observations of CVC insertion and hand hygiene, as shown by increasing CVC insertion scores and HH compliance. However, other aspects of care may have improved as well, e.g. catheter care due to general patient safety awareness. Feedback reports were sent only after the formal start of the intervention, and thus, are barely responsible for the observed ‘surveillance effect’ [35-37]. Alternatively, the improvement of baseline CRBSI rates and CVC insertion scores may also represent a secular trend as reported by the English ”Matching Michigan” program, which was due to pre-existing or ongoing quality improvement initiatives [38]. In contrast, many of our centers had little or no exposure to national quality improvement initiatives and adopted the PROHIBIT project as an opportunity to improve practice [39].

Measuring process indicators allows testing whether the target of an intervention is achieved, provides insight into the implementation process, and allows evaluation of direct association between process parameters and outcome. We report that one percentage point increase in compliance was associated with a two to five percentage point decrease in CRBSI. However, the magnitude of the observed associations must be

interpreted with caution as aggregated data on CVC insertion and hand hygiene compliance had to be used and other factors could be relevant [40-42].

Our study has several strengths. The multicenter design with 14 hospitals from 11 different countries embraces a range of variable IPC practices across Europe, and thus offers greater generalizability than previous studies. The number of CVC-days observed in each center was large and the combination of a shared baseline and intervention period and the randomized, stepped wedge introduction of the interventions helped to control for unknown trends and confounders. Lastly, the measurement of process indicators demonstrated that CRBSI reduction was the result of improved practice, even if some of this occurred before the formal intervention.

The study has limitations. First, our stepped-wedge design did not allow block randomization based on baseline rates. As a consequence and unfortunately, the CVCi arm had four out of the five hospitals with low baseline incidence densities. The small effect of the prevention program on CRBSI in the CVCi arm, that was significant in the before-and-after analysis, but not significant when considering the decreasing trend already observed during baseline, could well be due to the low baseline rate (1.4/1000 CVC-days), which may be partly explained by the overrepresentation of cardiothoracic surgery patients undergoing elective CVC insertions in this study arm. Second, process indicators not only improved in allocated arms, but in all study arms (HH in the CVCi arm; CVC insertion score in the HHi arm). The PROHIBIT project was a priority or the only ongoing patient safety project in many of our centers. Such project prioritization, together with Hawthorne effects [43] due to the surveillance of process indicators, may have contributed to this finding. Third, some patient- and CVC characteristics differed between baseline and intervention, and between the study arms. Although significance of many differences are due to large numbers, cardiothoracic patients and hence scheduled surgical admissions were more frequent in the CVCi arm. While we could not adjust for severity-of-illness score for the entire study population due to missing data, all other critical variables were taken into account in the multivariable models. The analysis on the subset where Apache II scores were reported showed comparable results (Supp.Methods and results). Fourth, although the study duration was 30 months in total, we did not go back to the hospitals to test for sustainability. Others have shown sustainable effects of behavioral change studies aiming at CLABSI prevention[44].

In conclusion, this study demonstrates that multimodal prevention strategies aiming at improving CVC insertion practice and hand hygiene compliance reduce CRBSI in culturally diverse European ICUs. The CVC insertion score explained the reduction of CRBSI and helped to explain the dynamics of behavior change. Future quality

improvement studies should encourage measuring process indicators.

ACKNOWLEDGEMENTS

We thank Sylvie Touveneau, Marie-Noëlle Chraïti and Benedetta Allegranzi, who devoted themselves to the training of the on-site investigators and study nurses in the workshops, both at the University Medical Center Groningen and the HUG. We thank Lauren Clack for editing. Our gratitude extends also to the participating centers for collaborating in this study, especially the on-site investigators and study nurses, physicians, (auxiliary) nurses and other healthcare professionals that responded positively to the challenge to improve their hand hygiene and CVC insertion practices and thus contributed to the increased safety of the patients in their care.

SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLES

Table S1A: A summary of implementation activities per hospital; all hospitals implementing the HH intervention, alone or in combination

			System change	Training and Education			Evaluation and Feedback		Reminders in the workplace	Institutional safety climate		
Hospital	**Intervention**	**Action plan**	**Alcohol-based handrub available at the bedside**	**Educational sessions**	**Small-group/ bedside training**	**Presentations**	**Institutional feedback of results**	**Individual feedback of compliance results (according to the allocated intervention)**	**Posters**	**Supported by hospital management**	**Supported by ICU management:**	**Additional activities**
3	Both	No	Yes	Yes	Yes	Adapted WHO material or made their own	Yes	Yes	WHO in local language	No	Supportive, ICU management in PROHIBIT team	-
4	HH	No	Yes, but in one ICU difficult to access.	Yes	Yes	Adapted WHO material or made their own	Yes	Yes	already in place (WHO)	Yes	Supportive after change of ICU head doctor	• Badges • pocket bottles with ABHR handed out
5	HH	Yes	Yes, improved as part of the intervention.	Yes (for the entire hospital)	Yes	Adapted WHO material or made their own	Yes	Yes	WHO in English	Yes	Supportive after change of ICU head doctor	• note on hospital's homepage • fluorescence testing • questionnaire
6	Both	No	Yes	Yes	Yes	Adapted WHO material or made their own	Yes	Yes	already in place	Yes	Supportive	screensaver
7	HH	Yes	Yes. Some dispensers were repositioned to improve accessibility.	Yes	Yes	Used WHO material, without adaptation	Yes	Yes	made their own	Yes	Supportive	• kick off meeting • wall of Fame, monthly prize • traffic light; HH test (May 5)

			System change	Training and Education			Evaluation and Feedback		Reminders in the workplace	Institutional safety climate		
Hospital	Intervention	Action plan	Alcohol-based handrub available at the bedside	Educational sessions	Small-group/ bedside training	Presentations	Institutional feedback of results	Individual feedback of compliance results (according to the allocated intervention)	Posters	Supported by hospital management	Supported by ICU management:	Additional activities
8	HH	Yes	Yes	Yes	No	Adapted WHO material or made their own	Yes	Yes	made their own	Yes	Yes	• questionnaire • monthly prize • screensaver • quiz "Match hand to HCW" (5 May)
10	Both	No	Yes	No	Yes	Adapted WHO material or made their own	Yes	Yes	already in place (WHO)	Yes	Supportive	-
11	Both	No	Yes, for 90% of the beds	Yes	Yes	Adapted WHO material or made their own	Yes	Yes	Locally done	No	Supportive, ICU management in PROHIBIT team	-
13	Both	Yes	Yes	Yes	for nurses, not for doctors	Adapted WHO material or made their own	Yes	Yes	WHO in English	Yes	Supportive in one ICU, ICU management in PROHIBIT team. Less support in other ICU.	• knowledge test

CVC: Central venous catheter; ICU: Intensive care unit; PROHIBIT: Prevention of hospital infection by intervention and training; WHO: World Health Organization

Table S1B: A summary of implementation activities per hospital; all hospitals implementing the CVC intervention, alone or in combination.

			System change		Training and Education			Evaluation and Feedback		Institutional safety climate		
Hospital	**Intervention**	**Action plan**	**Need to adapt existing CVC insertion procedure**	**Line cart**	**Educational sessions**	**Small group training**	**Presentations/films/ other material**	**Institutional feedback of results**	**Individual feedback of compliance results (according to the allocated intervention)**	**Supported by hospital management**	**Supported by ICU management**	**Additional activities**
1	CVC	No	No	Present	Yes	No	Locally made	Yes	No	Yes	Supportive	-
2	CVC	Yes	Minor change	Present	Yes	Yes	Locally made	Yes	Yes	Yes	Supportive	• Monthly short PPPs with results and points of interest on flat screen • Sent email with PPPs to all staff
3	Both	No	Minor change	Present	Yes	Yes	Locally made	Yes	Yes	No	Supportive, ICU management in PROHIBIT team	-
6	Both	No	Yes, major change	Introduced as part of the intervention	Yes	Yes	Translated Carepractice/HUG material	Yes	Yes	Yes	Supportive, ICU management in PROHIBIT team	-
9	CVC	Yes	Yes, major change	Present	Yes	No	Locally made	Yes	No	Yes	Supportive	-
10	Both	No	Yes, major change	Present	Yes	Yes	Carepractice/HUG material (not in national language)	Yes	Yes	Yes	Supportive	-

			System change		Training and Education			Evaluation and Feedback		Institutional safety climate		
Hospital	**Intervention**	**Action plan**	**Need to adapt existing CVC insertion procedure**	**Line cart**	**Educational sessions**	**Small group training**	**Presentations/films/ other material**	**Institutional feedback of results**	**Individual feedback of compliance results (according to the allocated intervention)**	**Supported by hospital management**	**Supported by ICU management**	**Additional activities**
11	Both	No	Yes, major change	Present	Yes	No	Carepractice/HUG material (not in national language) – live verbal translation needed by and provided for one doctor	Yes	Yes	No	Supportive, ICU management in PROHIBIT team	-
12	CVC	No	Yes, major change	Present	Yes	No	Locally made	Yes	Yes	Yes	Supportive, ICU management in PROHIBIT team	• Existing CVC kits completed with large sterile gowns.
13	Both	No	Minor change	Present	Yes	No	Locally made (but only in house-film of CVC insertion)	Yes	Yes	Yes	Supportive in one ICU, ICU management in PROHIBIT team. Less support in the other ICU.	-
14	CVC	No	Yes, major change	No	Yes	No	Locally made	Yes	Yes	Yes	Supportive, ICU management in PROHIBIT team	-

CVC: Central venous catheter; ICU: Intensive care unit; PROHIBIT: Prevention of hospital infection by intervention and training; WHO: World Health Organization

Table S2: CRBSI incidence densities for patient and central venous catheter (CVC) characteristics, based on the entire study duration

	CVC (N)	**CVC-days** (N)	**CVC-days** (%)	**CRBSI** (N)	**Incidence density** (N/1000 CVC-days)	**95% CI**
Total	35831	262377	*100.0*	382	1.5	1.3 – 1.6
Sex						
Male	22925	165983	*63.3*	232	1.4	1.2 – 1.6
Female	12906	96394	*36.7*	150	1.6	1.3 – 1.8
Age						
< 30 years	1469	11403	*4.3*	12	1.1	0.6 – 1.9
30-49	4804	37213	*14.2*	59	1.6	1.2 – 2.0
50-69	15900	113890	*43.4*	170	1.5	1.3 – 1.7
≥ 70	13658	99871	*38.1*	141	1.4	1.2 – 1.7
Type of admission[a]						
Medical	13590	116732	*44.5*	207	1.8	1.5 – 2.0
Surgical	15744	91365	*34.8*	85	0.9	0.8 – 1.2
Unscheduled surgical	6497	54280	*20.7*	90	1.7	1.3 – 2.0
APACHE II score[b]						
< 10	1971	10866	*4.1*	18	1.7	1.0 – 2.6
10-19	4133	29492	*11.2*	79	2.7	2.1 – 3.3
20-29	5116	40683	*15.5*	70	1.7	1.4 – 2.2
≥ 30	1692	13803	*5.3*	19	1.4	0.9 – 2.2
NA	22919	167533	*63.9*	196	1.2	1.0 – 1.3
SAPS II score[c]						
< 20	4529	19300	*7.4*	6	0.3	0.1 – 0.7
20-39	3983	28842	*11.0*	25	0.9	0.6 – 1.3
40-59	2263	23674	*9.0*	39	1.6	1.2 – 2.3
≥ 60	894	8847	*3.4*	24	2.7	1.8 – 4.0
NA	24162	181714	*69.3*	288	1.6	1.4 – 1.8

	CVC (N)	CVC-days (N)	CVC-days (%)	CRBSI (N)	Incidence density (N/1000 CVC-days)	95% CI
Type of ICU						
Cardiothoracic surgery & coronary care	13705	78886	*30.1*	75	1.0	0.8 – 1.2
Infectious diseases	723	7129	*2.7*	9	1.3	0.6 – 2.3
Intermediate care	43	331	*0.1*	1	3.0	0.2 – 14.9
Medical	3059	26192	*10.0*	79	3.0	2.4 – 3.7
Medical-surgical	16462	132794	*50.6*	184	1.4	1.2 – 1.6
Neurology	391	5928	*2.3*	9	1.5	0.7 – 2.8
Neurosurgery	497	4436	*1.7*	19	4.3	2.7 – 6.6
Surgery	475	4423	*1.7*	5	1.1	0.4 – 2.5
Vascular surgery	476	2258	*0.9*	1	0.4	0.02 – 2.2
ICU stay[d] until CVC insertion						
0 days	1218	12444	*4.7*	17	1.4	0.8 – 2.2
1-5	27740	176928	*67.4*	218	1.2	1.1 – 1.4
6-20	4218	42218	*16.1*	96	2.3	1.9 – 2.8
>20	2634	30591	*11.7*	51	1.7	1.3 – 2.2
NA	21	196	*0.1*	0	0.0	0.0 – 23.8
Bloodstream infection at the time of CVC insertion						
Yes	1299	11701	*4.4*	108	9.2	7.6 – 11.1
No	34532	250676	*95.5*	274	1.1	1.0 – 1.2
Place of CVC insertion						
ICU	19221	172233	*65.6*	300	1.7	1.6 – 2.0
Operating room	14995	76689	*29.2*	65	0.8	0.7 – 1.1
Elsewhere	1615	13455	*5.1*	17	1.3	0.8 – 2.0
Access site						
Subclavian	9587	89893	*34.3*	143	1.6	1.4 – 1.9
Jugular	21598	135996	*51.8*	178	1.3	1.1 – 1.5
Femoral	3749	30596	*11.7*	52	1.7	1.3 – 2.2
Brachial	628	3923	*1.5*	4	1.0	0.4 – 2.7
Other	269	1969	*0.8*	5	2.5	1.1 – 6.1

	CVC (N)	CVC-days (N)	CVC-days (%)	CRBSI (N)	Incidence density (N/1000 CVC-days)	95% CI
Type of CVC						
CVC	34419	255985	*97.6*	376	1.5	1.3 – 1.6
Swan-Ganz	1412	6392	*2.4*	6	0.9	0.4 – 2.1
Lumen						
Multi	34286	250125	*95.3*	359	1.4	1.3 – 1.6
Single	1545	12252	*4.7*	23	1.9	1.2 – 2.8
Indication						
Antibiotics[e]	28020	206018	*79.2*	323	1.6	1.4 – 1.7
No antibiotics[e]	7342	54043	*20.8*	52	1.0	0.7 – 1.3
Blood products	5223	41369	*15.8*	90	2.2	1.8 – 2.7
No blood products	30608	221008	*84.2*	292	1.3	1.2 – 1.5
Dialysis	3637	32081	*12.2*	36	1.1	0.8 – 1.6
No dialysis	32194	230296	*87.8*	346	1.5	1.4 – 1.7
TPN[f]	6337	69087	*27.6*	106	1.5	1.3 – 1.9
No TPN[f]	27983	180991	*72.4*	187	1.0	0.9 – 1.2
Other indications[g]	29376	206227	*87.5*	319	1.5	1.4 – 1.7
CVC dwell-time[h]						
1-4 days	15556	124743		53	0.4	0.3 – 0.6
5-9	11478	75081		111	1.5	1.2 – 1.8
10-19	6973	46720		167	3.6	3.1 – 4.2
≥ 20	1824	15833		51	3.2	2.4 – 4.2

[a] according to the SAPS II criteria: medical: no surgery within 1 week of admission to ICU; scheduled surgical: surgery was scheduled at least 24 hours in advance +/- 7 days intensive care unit admission; unscheduled surgical: patients added to the operating room schedule within 24 hours of the operation.

[b] APACHE=Acute Physiology and Chronic Health Evaluation; on first ICU admission

[c] SAPS=Simplified Acute Physiology Score; on first ICU admission

[d] including subsequent ICU stays (max. 3) until insertion

[e] data of first two months of one hospital excluded because of invalid or missing data

[f] one hospital excluded because of invalid or missing data

[g] data of first year of three hospitals and of first four months of another hospital excluded because of different interpretation
[h] number of CVC days per category acc. to McLaws[1]

Table S3. APACHE II scores and SAPS II scores at baseline and intervention, stratified by study arm

	HH intervention only					**CVC intervention only**					**Both interventions**				
	Baseline		**Intervention**			**Baseline**		**Intervention**			**Baseline**		**Intervention**		
	N	***%***	**N**	***%***	**p-value**	**N**	***%***	**N**	***%***	**p-value**	**N**	***%***	**N**	***%***	**p-value**
APACHE II score[b]															
<10	48	*3.2*	59	*2.4*	<0.0001	72	*1.2*	140	*1.5*	<0.0001	245	*12.2*	953	*25.0*	<0.0001
10-19	182	*12.1*	306	*12.4*	<0.0001[c]	461	*7.6*	490	*5.2*	<0.0001[c]	461	*23.0*	894	*23.4*	<0.0001[c]
20-29	120	*8.0*	358	*14.5*		1283	*21.1*	1028	*10.9*		249	*12.4*	457	*12.0*	
≥ 30	49	*3.3*	164	*6.6*		240	*3.9*	173	*6.8*		90	*4.5*	238	*6.2*	
missing	1107	*73.5*	1589	*64.2*		4034	*66.2*	7623	*80.6*		959	*47.9*	1276	*33.4*	
SAPS II score[a]															
<20	30	*2.0*	38	*1.5*	<0.0001	1611	*26.5*	2532	*26.8*	<0.0001	5	*0.2*	2	*0.05*	<0.0001
20-39	181	*12.0*	200	*8.1*	0.74[c]	927	*15.2*	1668	*17.6*	0.02[c]	28	*1.4*	22	*0.6*	0.88[c]
40-59	159	*10.6*	161	*6.5*		356	*5.8*	619	*6.5*		123	*6.1*	92	*2.4*	
≥ 60	40	*2.7*	50	*2.0*		110	*1.8*	152	*1.6*		121	*6.0*	86	*2.3*	
missing	1096	*72.8*	2027	*81.9*		3086	*50.7*	4483	*47.4*		1727	*86.2*	3616	*94.7*	

[a] APACHE=Acute Physiology and Chronic Health Evaluation; p-value based on non-missing values; on first ICU admission
[b] SAPS=Simplified Acute Physiology Score; p-value based on non-missing values; on first ICU admission
[c] p-value when missing values excluded

Table S4 CVC utilization ratios (CVC days[a]/ICU patient-days) for all three study arms together and per study arm

CVC utilization ratio	2011	2012	2013	P-value[b]
All three study arms together	88.3	80.7	73.5	0.01
CVC intervention arm	95.2	86.4	78.1	0.01
HH intervention arm	89.1	79.2	75.8	0.18
Both interventions	76.3	69.9	61.5	0.05

[a] for the CVC utilization ratio multiple CVCs on one day were counted as one CVC day
[b] based on the yearly change, in linear regression

Table S5: Individual central venous catheter (CVC) observation form elements (mean score), stratified by intervention arm

	HH intervention			CVC intervention			Both interventions		
Observation form elements	**BL**	**INT**	**P-value**	**BL**	**INT**	**P-value**	**BL**	**INT**	**P-value**
Work organization									
All material prepared for use	96.5	97.7	0.30	90.6	97.8	<0.0001	100.0	99.6	0.33
Trash bin in place	95.2	95.7	0.75	67.7	94.3	<0.0001	96.8	99.5	<0.0001
Operator never leaves the patient zone	96.9	95.7	0.41	87.7	97.0	<0.0001	98.2	98.2	1.00
Patient preparation									
Hand hygiene before patient contact	57.7	85.5	<0.0001	48.9	86.4	<0.0001	93.0	98.7	<0.0001
Patient's hair is covered by a cap	15.4	40.5	<0.0001	63.1	87.7	<0.0001	14.9	86.3	<0.0001
Skin antisepsis									
All medical devices for skin antisepsis are sterile	61.7	86.7	<0.0001	94.3	99.8	<0.0001	96.2	99.4	<0.0001
Use of alcohol-based chlorhexidine for skin antisepsis[a]	56.8	79.4	<0.0001	58.3	77.6	<0.0001	20.3	93.4	<0.0001
Use of sterile gloves for skin antisepsis	63.0	85.7	<0.0001	87.4	99.0	<0.0001	92.1	98.4	<0.0001
Skin antisepsis follows a correct technique	50.7	86.5	<0.0001	32.0	96.8	<0.0001	89.8	87.8	0.27
Skin antisepsis performed before applying MSB	18.4	41.3	<0.0001	58.7	93.8	<0.0001	95.1	98.4	0.0004

	HH intervention			CVC intervention			Both interventions		
Observation form elements	**BL**	**INT**	**P-value**	**BL**	**INT**	**P-value**	**BL**	**INT**	**P-value**
Maximum sterile barrier precautions									
Cap	46.3	74.8	<0.0001	94.0	100	<0.0001	82.8	99.4	<0.0001
Mask	70.9	94.7	<0.0001	96.3	100	<0.0001	84.0	99.5	<0.0001
Hand hygiene before gloving	56.8	81.8	<0.0001	51.4	91.7	<0.0001	87.4	99.0	<0.0001
Sterile gown	59.0	86.7	<0.0001	76.9	99.8	<0.0001	51.7	98.4	<0.0001
Large sterile drape*	43.6	81.5	<0.0001	24.0	61.5	<0.0001	23.3	94.2	<0.0001
Sequence respected	50.7	85.2	<0.0001	36.6	93.4	<0.0001	67.5	95.2	<0.0001
Catheter fixation and dressing									
Catheter correctly fixed	99.1	99.8	0.18	98.6	99.1	0.54	100.0	100.0	1.00
Insertion site disinfected	98.2	99.8	0.02	42.0	78.9	<0.0001	100.0	100.0	1.00
Insertion site fully covered by the dressing	99.1	99.8	0.18	99.1	98.9	1.00	98.6	99.7	0.02
Follow-up									
Daily evaluation of the ongoing need of the CVC[b]	94.9	99.7	<0.0001	97.9	94.7	0.02	85.9	77.7	0.0004

[a] Due to budgetary reasons, three hospitals were not able to provide large drapes and/or alcohol-based chlorhexidine; [b] Not taken into account if not applicable. BL, baseline; CVC, central venous catheter; HH, hand hygiene; INT, intervention; MSB: maximal sterile barrier (precautions)

Table S6: Incidence rate ratios (IRR) for the association of central venous catheter-related bloodstream infection with hand hygiene compliance and central venous catheter insertion compliance, multivariable regression analysis

	IRR	95% CI
All three study arms together		
Hand hygiene compliance	1.00	0.99 – 1.01
CVC insertion compliance	0.97	0.96 – 0.98
Proportion of patients with bacteraemia	1.12	1.06 – 1.18
Ratio of patients with ICU stay 5-20 / 1-5 days	3.11	-0.47 – 15.5
HH intervention[a]		
Hand hygiene compliance	0.95	0.93 – 0.98
CVC insertion compliance	1.01	0.98 – 1.03
CVC insertion[a]		
Hand hygiene compliance	1.00	0.99 – 1.03
CVC insertion compliance	0.98	0.97 – 0.99
BOTH interventions[a]		
Hand hygiene compliance	1.00	0.98 – 1.02
CVC insertion compliance	0.97	0.95 – 0.98

[a] Results for co-variables similar as to 'All three study arms together' and not shown

Table S7. Hand hygiene compliance per professional category during baseline and intervention, overall and stratified by intervention arm

Professional category	Baseline (%)	Intervention (%)	Absolute increase (PP)	95% CI
All three intervention arms together				
Nurse / student nurse	50.0	62.7	*12.7*	11.7 – 13.7
Auxiliaries	44.2	60.3	*16.1*	13.0 – 19.2
Medical doctors / students	44.9	52.6	*7.7*	5.5 – 10.0
Other healthcare professionals	41.6	67.6	*26.0*	19.5 – 32.5
HH intervention				
Nurse / student nurse	37.1	58.2	*21.1*	18.9 – 23.2
Auxiliaries	30.5	59.0	*28.5*	23.3 – 33.7
Medical doctors / students	31.9	51.3	*19.4*	15.5 – 23.2
Other healthcare professionals	45.6	74.9	*29.3*	21.2 – 37.4
CVC intervention				
Nurse / student nurse	51.8	64.0	*12.2*	10.8 – 13.6
Auxiliaries[a]	-	-	-	-
Medical doctors / students	45.1	46.3	*1.3*	-4.4 – 6.9
Other healthcare professionals	38.7	48.5	*9.8*	-4.0 – 23.5
Both interventions				
Nurse / student nurse	55.9	64.2	*8.3*	6.4 – 10.1
Auxiliaries	49.5	61.5	*12.0*	8.3 – 15.7
Medical doctors / students	50.8	57.9	*7.1*	3.9 – 10.3
Other healthcare professionals	27.8	47.2	*19.4*	0.8 – 38.1

[a] Not reported given their very limited presence in participating centres

Mean hand hygiene compliance increase is reported as percentage points (PP)

Table S8: The mean hand hygiene compliance per hand hygiene indication during baseline and the intervention phase, for all three study arms together and per study arm

Professional category	Baseline (%)	Intervention (%)	Absolute increase (PP)	95% CI
All three study arms together				
Before touching a patient	36.1	48.0	*11.9*	10.4 – 13.4
Before clean/aseptic procedure	53.3	55.4	*2.2*	0.0 – 4.3
After body fluid exposure risk	69.6	73.2	*3.6*	1.7 – 5.6
After touching a patient	64.5	75.3	*10.9*	9.4 – 12.3
After touching patient surroundings	31.2	53.7	*22.4*	20.4 – 24.5
HH intervention				
Before touching a patient	28.5	47.9	*19.4*	16.4 – 22.5
Before clean/aseptic procedure	27.2	35.7	*8.5*	4.6 – 12.4
After body fluid exposure risk	46.0	66.8	*20.8*	16.6 – 25.2
After touching a patient	48.0	65.8	*17.8*	14.5 – 21.0
After touching patient surroundings	23.8	59.3	*35.5*	31.7 – 39.3
CVC intervention				
Before touching a patient	38.4	45.1	*6.7*	4.2 – 9.2
Before clean/aseptic procedure	57.6	66.5	*8.9*	5.2 - 12.6
After body fluid exposure risk	72.5	75.6	*3.1*	0.0 – 6.3
After touching a patient	67.0	80.0	*13.0*	10.7 – 15.3
After touching patient surroundings	31.0	44.2	*13.2*	9.9 – 16.6
Both interventions				
Before touching a patient	37.8	51.2	*13.4*	11.0 – 15.8
Before clean/aseptic procedure	65.4	60.7	*-4.7*	-8.0 – -1.5
After body fluid exposure risk	84.7	76.5	*-8.2*	-6.0 – -1.3
After touching a patient	71.4	78.2	*6.8*	4.6 – 9.2
After touching patient surroundings	36.0	57.4	*21.4*	18.0 – 24.8

SUPPLEMENTARY FIGURES

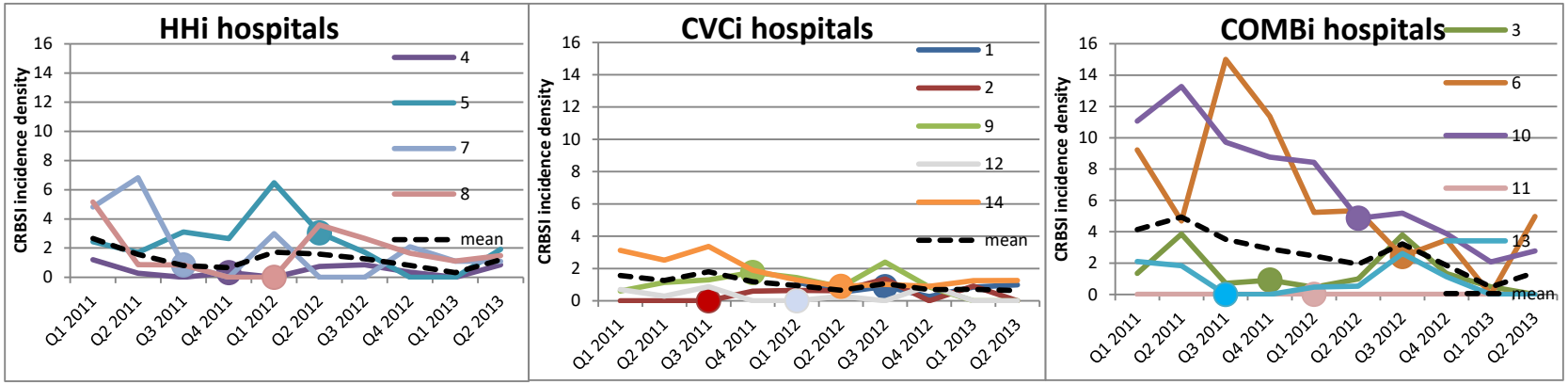
Figure S1: CVC insertion observation form

Patient identifier:
Patient birth date: ____/____/_____ **Gender: M F**
Insertion OR:
Date of insertion: ____/____/_____

	Yes	No
Emergency procedure *	□	□
Femoral insertion site	□	□
→ if yes: the femoral insertion site is justified	□	□
1. Work organization		
All material prepared for use *	□	□
Trash bin in place	□	□
Operator never leaves the patient zone *	□	□
2. Patient preparation		
Hand hygiene before patient contact	□	□
Patient's hair is covered by a cap	□	□
3. Skin antisepsis		
All medical devices for skin antisepsis are sterile	□	□
Use of alcohol-chlorhexidine for skin antisepsis	□	□
Use sterile gloves for skin antisepsis	□	□
Skin antisepsis follows a correct technique *	□	□
Skin antisepsis performed before applying maximal sterile barrier precautions	□	□
4. Maximal sterile barrier precautions		
Cap[a]	□	□
Mask[a]	□	□
Hand hygiene before gloving[a]	□	□
Sterile gown[b]	□	□
Sterile gloves[b]	□	□
Large sterile drape	□	□
Sequence respected *	□	□
Catheter fixation and dressing *		
Catheter correctly fixed	□	□
Insertion site disinfection	□	□
Insertion site fully covered by the dressing	□	□
Follow-up*: daily evaluation whether the catheter could be removed	□	□
(not applicable: n.a.)	n.a.: □	

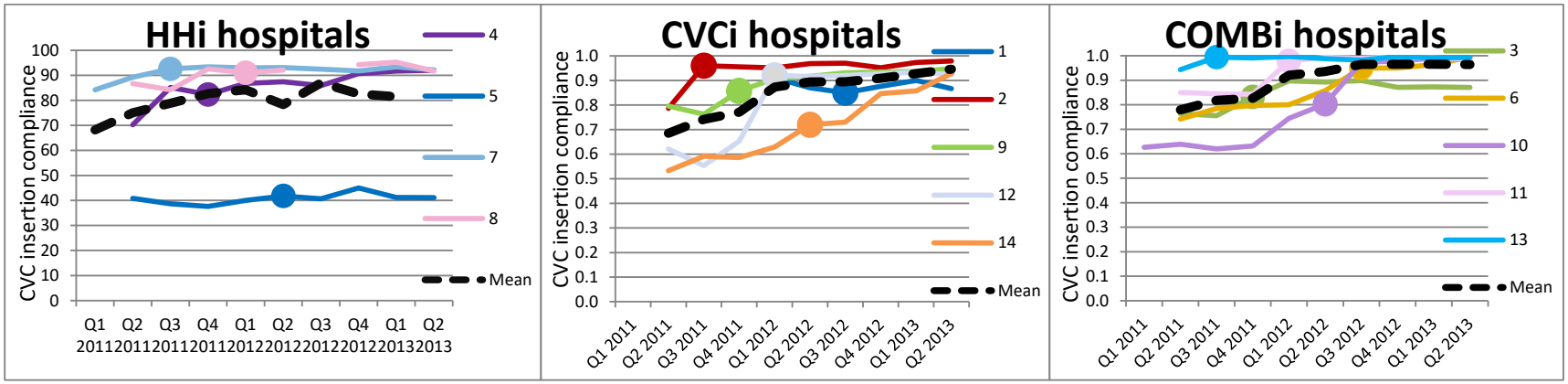
[a] Worn / done by all assisting with the procedure
[b] Worn by the operator and, if disinfecting the patient's skin, by the assistant too. Unless the assistant disinfects the patient's skin the operator changes into new sterile gloves before inserting the catheter.
* See definitions on reverse side

Figure S2. Incidence of central venous catheter-related bloodstream infection (N/1000 central venous catheter-days) per hospital, stratified by intervention arm



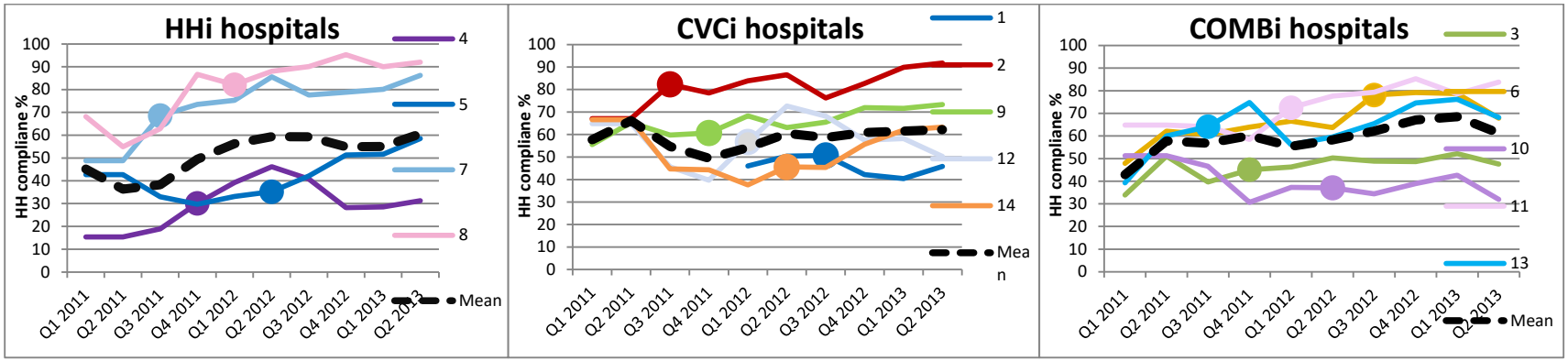
Dots indicate the first quarter of the intervention period. Hospital 1 started later as it replaced a drop out hospital.
Mean: overall mean of the study arm
COMBi, hand hygiene intervention and central venous catheter intervention combined; CRBSI, central venous catheter-related bloodstream infection; CVCi, central venous catheter intervention; HHi, hand hygiene intervention; Q, quarter

Figure S3. Central venous catheter insertion scores per hospital, stratified by intervention arm



Dots indicate the first quarter of the intervention period. Some hospitals did not collect CVC insertion scores during the first quarter. Hospital 1 started later as it replaced a drop out hospital.
Mean: overall mean of the study arm
COMBi, hand hygiene intervention and central venous catheter intervention combined; CRBSI, central venous catheter-related bloodstream infection; CVCi, central venous catheter intervention; HHi, hand hygiene intervention; Q, quarter

Figure S4. Hand hygiene compliance per hospital, stratified by intervention arm



Dots indicate the first quarter of the intervention period. Hospital 1 started later as it replaced a drop out hospital.
Mean: overall mean of the study arm
COMBi, hand hygiene intervention and central venous catheter intervention combined; CVCi, central venous catheter intervention; HH, hand hygiene; HHi, hand hygiene intervention; Q, quarter

SUPPLEMENTARY METHODS AND RESULTS

Criteria for central venous catheter-related bloodstream infections (CRBSI)

The CDC-criteria for laboratory-confirmed bloodstream infection (BSI) are used. For recording a BSI related to a catheter the HAI-Net (formerly HELICS/IPSE) criteria for CRI3 are used, with the extension of the possibility to diagnose a CRBSI based on the resolving of clinical symptoms.

A BSI is defined as bacteraemia or fungaemia without other documented source and requires:

1. one positive blood culture with a recognized pathogen
   or
2. two positive blood cultures with a common skin contaminant (coagulase negative staphylococci, Micrococcus sp., *Proprionibacterium* acnes, *Bacillus* sp., *Corynebacterium* sp.)
   and
   clinical symptoms: fever (>38°C, chills, hypotension (<100 mm Hg).

To record a CRBSI the following criteria should also be met:

1. There is a positive culture with the same micro-organism of either a quantitative culture of the catheter (≥1000 cfu/ml) or a semi-quantitative culture of the catheter (>15cu) positive for the same micro-organism as found in the blood culture and the BSI is occurring within 48 hours before or after catheter removal
   or
2. A quantitative blood culture of a CVC blood sample yields 5 fold higher in numbers of cfu than a peripheral blood sample
   or
3. CVC blood sample culture positive 2 hours or more before peripheral blood culture (blood samples drawn at the same time) = differential time-to-positivity is ≥ 2 hours
   or
4. Clinical signs of infection resolve within 24 hours after CVC removal or subside within 48 hours after antibiotic therapy refractory before removal and the BSI is occurring within 48 hours before or after catheter removal or start of antibiotic therapy
   or
5. Culture of purulent discharge of the catheter insertion site is positive for the same micro-organism as found in the blood culture.

There are several issues to consider when determining sameness of organisms.

1. If the common skin contaminant is identified to the species level from 1 culture, and a companion culture is identified with only a descriptive name (i.e., to the genus level), then it is assumed that the organisms are the same. The speciated organism should be reported as the infecting pathogen (Table M1).
2. If common skin contaminant organisms from the cultures are speciated but no antibiogrammes are done or they are done for only 1 of the isolates, it is assumed that the organisms are the same.
3. If the common skin contaminants from the cultures have antibiogrammes that are different for 2 or more antimicrobial agents, it is assumed that the organisms are not the same (Table M2).

Table M1. Examples of ''sameness'' by organism speciation

Culture	Companion Culture	Report as …
S. epidermidis	Coagulase-negative staphylococci	*S. epidermidis*
Bacillus spp (not anthracis)	*B. cereus*	*B. cereus*
S. salivarius	*S. viridans*	*S. salivarius*

Table M2. Examples of ''sameness'' by organism antibiogramme

Organism name	Isolate A	Isolate B	Interpret as …
S. epidermidis	All drugs S	All drugs S	Same
S. epidermidis	OX R CEFAZ R	OX S CEFAZ S	Different
Corynebacterium spp	PENG R CIPRO S	PENG S CIPRO R	Different
S. viridans	All drugs S	All drugs S except ERYTH R	Same

S: sensitive; R: resistant
CEFAZ: cefazolin; CIPRO: ciprofloxacin; ERYTH: erythromycin; OX: oxacillin; PENG: penicillin G

General description of the interventions

Hand hygiene intervention (HHi)
To improve awareness of and compliance to hand hygiene (HH) the World Health Organization (WHO) multimodal hand hygiene improvement strategy is used. The WHO, in cooperation with the University of Geneva, has both developed material for promoting HH and tools for evaluation of compliance (http://www.who.int/gpsc/information_centre/en/) which were used for this study. The multimodal approach identifies five key components. Hospitals formed an intervention team that evaluated these five components and intervened where necessary. The challenges they encountered differed, depending on the centre, Table 1A specifies the activities of the individual hospitals.

1. System change (infrastructure):
   - ensuring access to safe continuous water supply as well as to soap and towels
   - ensuring access to accessible alcohol-based handrub at the point of care
2. Training/education:
   - providing training on the importance of HH, based on the "My 5 moments for Hand Hygiene" approach, and the correct procedures for hand rubbing and hand washing, to all healthcare workers
     Healthcare workers were also educated on the advantages of using alcohol based handrub, which was not yet routine in all centres.
3. Evaluation and feedback:
   - monitoring hand hygiene practices and infrastructure, along with related perceptions and knowledge among healthcare workers about the appropriated indications and procedures for performing it.
     HH practices were frequently observed for study purposes. Study nurses were encouraged to give both individual and ward level feedback after the start of the intervention. Perceptions and knowledge were assessed during small-group/ bedside training and, in a few hospitals, with a questionnaire too.
4. Reminders in the workplace:
   - prompting and reminding healthcare workers about the importance of HH and about the appropriate indications and procedures for performing it.

Posters, short powerpoint presentations over the ICU nurses' station, screen savers and/or badges were used to increase awareness during daily practice.

5. Institutional safety climate:
   Creating an environment and the perceptions that facilitate awareness-raising about patient safety issues while guaranteeing consideration of HH improvement as a high priority at all levels, including:
   - active participation at both the institutional and individual levels;
   - awareness of individual and institutional capacity to change and improve (self-efficacy); and
   - partnership with patients and patient organizations.
     Creating involvement with superiors was challenging in some centres, depending highly on individuals. Partnership with patients and patient organizations was not addressed in this ICU-based study.

For all of these five key components the WHO has developed freely accessible background information, an implementation guide and tools such as power-point presentations and instruction videos (http://www.who.int/gpsc/5may/tools/en/). Three to six months before the start of the intervention, study nurses and involved physicians attended a two-day PROHIBIT workshop for training best practices and implementation science, where the implementation guide and the tools were introduced and discussed. Hospitals were encouraged to adapt the intervention program and the tools to their local context.

The Central venous catheter intervention (CVCi)
In the Hospitals of Geneva, in 2007, existing protocols related to CVC insertion and care were reviewed and updated by an interdisciplinary study group, which included members from anaesthesiology, infection control, and the nursing department. A detailed insertion checklist was defined by the study group based on evidence in the literature and by repeated practice testing in daily routine. The complete insertion procedure from patient preparation until dressing application was filmed for training purposes. For catheter care, a modular e-learning programme was developed, including assistance with CVC insertion, infusate preparation, CVC manipulation, dressing change, CVC removal, and clinical surveillance and documentation (www.carepractice.net). This modular e-learning programme was made available in English for the PROHIBIT study participants and is freely available. All modules feature detailed procedure sequences and are animated by short movies, icons, and keywords. Three to six months before the start of the intervention, study nurses and involved physicians attended a two-day PROHIBIT workshop for training best practices and implementation science, where present local CVC insertion practices and optimal CVC insertion procedure were discussed. The e-learning programme was introduced and attendants practiced CVC insertion in an intensive care unit-based skills lab. Hospitals were encouraged to adopt CVC insertion kits and line carts, where not already in use. Table 1B specifies the activities of the individual hospitals.

Methods and Results

Competing events approach
Different 'events' could happen to patients with a CVC, apart from acquiring a CRBSI. Patients could not be in need of a CVC anymore, they could be discharged to another hospital with their CVC or they could die (without a CRBSI) in the ICU. As these events can preclude the occurrence of our outcome of interest, in this case CRBSI, they are called competing events. Additionally it is possible that not only our outcome of interest is affected but (one of) the other outcome(s) as well, thus possibly leading to changes in the incidence of the outcome of interest.[2-6]
Standard Kaplan Meier curves and hazard ratios do not account for the effects of competing events, thus leading to incorrect hazards. Adjusted hazard ratios can be estimated using the sub-distribution approach, where the censoring time of the competing events is prolonged to the longest time at risk resulting in the outcome of interest (CRBSI).[7, 8]
In our data the longest time at risk resulting in an infection was 73 days. We used the following model in SAS (with CVC duration (CVCtime) set to 73 days for records without infection):

Proc phreg data=total covs(aggregate);
class hospital Patientno sex;
model CVCtime*infection2(**0**)= sex age1 age2 age3 ICUstay1 ICUstay2 ICUstay3
bacteraemia insertiondepartment1 insertiondepartment2 vein1 vein2 vein3 vein4
admissiontype1 admissiontype2 ICUtype1 ICUtype2 ICUtype3 ICUtype4 ICUtype5
ICUtype6 ICUtype7 ICUtype8 UseforAntibiotics UseforTPV UseforBloodProducts
intervention1 intervention2 intervention3 / rl;
id Patientno;
strata hospital;
run;

Table M3 shows both the hazard ratios (HR) resulting from the sub-distribution hazard analysis as well as from the event-specific hazard analysis, i.e. without taking competing events into account. As can be seen, the hazard ratios are quite similar, suggesting that the competing events were only slightly affected by the intervention. This can be checked by performing a Cox regression on these outcomes as well.

Table M3. Hazard ratios (HR) with and without taking competing events into account, with 95% confidence intervals

	Sub-distribution HR (95% CI)	Event-specific HR (95% CI)
HHint (intervention1)	0.46 (0.28 – 0.74)	0.50 (0.31 – 0.81)
CVCint (intervention2)	0.59 (0.43 – 0.81)	0.64 (0.46 – 0.89)
BOTHint (intervention3)	0.33 (0.24 – 0.47)	0.42 (0.30 – 0.58)

Trend analysis
There was a significant decreasing the baseline quarters, with a sub-distribution hazard ratio (HRsub) of 0·93 per quarter (0·84 – 1.02). Therefore we also analysed the results accounting for a baseline that is an autonomous hospital-specific trend during the entire study period (variable period 2) with a post-intervention trend on top of that (variable post period x), allowing random trends for intervention arms. The intended random multilevel Poisson model did not converge, however. Therefore a sub-distribution hazard regression, with hospital and the interaction of hospital with baseline trend as covariates was performed (again by extending the CVC duration for catheters without infection);

Proc phreg data=total covs(aggregate);
class hospital Patientno sex;
model CVCtime*infection2(**0**)= hospital – covariates as above – intervention1 intervention2 intervention3
periode2 hospital*periode2 postperiodx interventiontype*postperiodx /rl;
id Patientno;
run;

The formal start of the CVC intervention was not associated with a reduction in the CRBSI risk anymore (HR_{sub} CVCi 1·16 (0·63 –2·16) but the formal start of the interventions in both the HHi and COMBi groups successfully further reduced the CRBSI risk (HR_{sub} HHi and COMBi 0·37 (0·16 – 0·87) and 0·47 (0·27 – 0·83) respectively).

Multivariable analysis with Apache II score
Apache II scores were recorded – for limited periods only – in 11 hospitals. SAPS II scores were recorded in five hospitals. We performed the multivariable analysis allowing for trends in the subset with known Apache II scores and found comparable results (Table M4). An Apache II score of 10-19 was associated with a marginally significant hazard ratio of 1.45 (p-value 0.07) in this analysis.

Table M4 Hazard ratios (HR) for the subset with known Apache II-scores, with 95% confidence intervals.

	Sub-distribution HR (95% CI)
HHi (intervention 1)	0.11 (0.02 – 0.66)
CVCi (intervention 2)	0.93 (0.37 – 2.38)
COMBi (intervention 3)	0.22 (0.08 – 0.61)
Apache II score (first ICU admission)	
<10	1.17 (0.63 – 2.17)
10 - 19	1.45 (0.97 – 2.16)
20 -29	1
≥ 30	0.81 (0.48 – 1.38)

Intracluster correlation coefficient

- Hand hygiene compliance
  The intracluster correlation coefficient (ICC) for hospitals during the baseline period, without accounting for covariates, was 0.18. The ICC increased to 0.28 during the intervention period.

- CVC insertion score
  The ICC for hospitals during the baseline period was 0.22. The ICC increased to 0.37 during the intervention period

- CRBSI
  The ICC cannot be calculated

References Supplementary material

1. McLaws ML, Berry G (2005) Nonuniform risk of bloodstream infection with increasing central venous catheter-days. Infect Control Hosp Epidemiol 26:715-719
2. Wolkewitz M, Cooper BS, Bonten MJ, Barnett AG, Schumacher M (2014) Interpreting and comparing risks in the presence of competing events. BMJ 349:g5060
3. Beyersmann J, Gastmeier P, Schumacher M (2014) Incidence in ICU populations: how to measure and report it? Intensive Care Med 40:871-876
4. Latouche A, Allignol A, Beyersmann J, Labopin M, Fine JP (2013) A competing risks analysis should report results on all cause-specific hazards and cumulative incidence functions. J Clin Epidemiol 66:648-653
5. Lau B, Cole SR, Gange SJ (2009) Competing risk regression models for epidemiologic data. Am J Epidemiol 170:244-256
6. Schumacher M, Allignol A, Beyersmann J, Binder N, Wolkewitz M (2013) Hospital-acquired infections--appropriate statistical treatment is urgently needed! Int J Epidemiol 42:1502-1508
7. Fine JPaG, R.J. (1999) A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association 94:496-509
8. Resche-Rigon M, Azoulay E, Chevret S (2006) Evaluating mortality in intensive care units: contribution of competing risks analyses. Crit Care 10:R5

REFERENCES

1. ECDC (2013) Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals. Stockholm: European Centre for Disease Prevention and Control
2. Zingg W, Hopkins S, Gayet-Ageron A, Holmes A, Sharland M, Suetens C, group EPs (2017) Health-care-associated infections in neonates, children, and adolescents: an analysis of paediatric data from the European Centre for Disease Prevention and Control point-prevalence survey. Lancet Infect Dis 17:381-389
3. Hansen S, Schwab F, Behnke M, Carsauw H, Heczko P, Klavs I, Lyytikainen O, Palomar M, Riesenfeld Orn I, Savey A, Szilagyi E, Valinteliene R, Fabry J, Gastmeier P (2009) National influences on catheter-associated bloodstream infection rates: practices among national surveillance networks participating in the European HELICS project. J Hosp Infect 71:66-73
4. Hansen S, Schwab F, Gastmeier P, group Ps (2015) Provision and consumption of alcohol-based hand rubs in European hospitals. Clin Microbiol Infect 21:1047-1051
5. Hansen S, Zingg W, Ahmad R, Kyratsis Y, Behnke M, Schwab F, Pittet D, Gastmeier P, group Ps (2015) Organization of infection control in European hospitals. J Hosp Infect 91:338-345
6. Martin M, Zingg W, Hansen S, Gastmeier P, Wu AW, Pittet D, Dettenkofer M, group Ps (2013) Public reporting of healthcare-associated infection data in Europe. What are the views of infection prevention opinion leaders? J Hosp Infect 83:94-98
7. Martin M, Zingg W, Knoll E, Wilson C, Dettenkofer M, Group PS (2014) National European guidelines for the prevention of Clostridium difficile infection: a systematic qualitative review. J Hosp Infect 87:212-219
8. van der Kooi T, Wolkewitz M, van Benthem B, de Greeff S, Grundmann H, Zingg W, on behalf of the PROHIBIT study group (2013) Prohibit (Preventing hospital-acquired infections by intervention and training): preliminary results of a European multi-center study on the effectiveness of a hand hygiene campaign and a central venous catheter bundle (abstract O83). International Conference of Prevention and Infection Control (ICPIC), Geneva
9. van der Kooi T, Wolkewitz M, van Benthem B, de Greeff S, Grundmann H, Zingg W, on behalf of the PROHIBIT study group (2014) Unusual distribution of pathogens in a European multi-centre study about central venous catheter-related bloodstream infections (Abstract P0519). European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Barcelona
10. van der Kooi T, Wolkewitz M, van Benthem B, de Greeff S, Grundmann H, Zingg W, on behalf of the PROHIBIT study group (2014) The PROHIBIT (Preventing hospital-acquired infections by intervention and training) intervention trial - results of a cluster-randomized European multi-center study on the reduction of central-line related bloodstream infections (Abstract O198). European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Barcelona
11. Zingg W, Cartier V, Inan C, Touveneau S, Theriault M, Gayet-Ageron A, Clergue F, Pittet D, Walder B (2014) Hospital-wide multidisciplinary, multimodal intervention programme to reduce central venous catheter-associated bloodstream infection. PLoS One 9:e93898
12. Pittet D, Allegranzi B, Storr J (2008) The WHO Clean Care is Safer Care programme: field-testing to enhance sustainability and spread of hand hygiene improvements. J Infect Public Health 1:4-10
13. ECDC (2010) European surveillance of healthcare-associated infections in intensive care units - HAI-Net ICU protocol, version 1.01. Stockholm: European Centre for Disease Prevention and Control
14. Sax H, Allegranzi B, Chraiti MN, Boyce J, Larson E, Pittet D (2009) The World Health Organization hand hygiene observation method. Am J Infect Control 37:827-834

15. Eggimann P, Harbarth S, Constantin MN, Touveneau S, Chevrolet JC, Pittet D (2000) Impact of a prevention strategy targeted at vascular-access care on incidence of infections acquired in intensive care. Lancet 355:1864-1868
16. Wolkewitz M, Cooper BS, Bonten MJ, Barnett AG, Schumacher M (2014) Interpreting and comparing risks in the presence of competing events. BMJ 349:g5060
17. Pittet D, Hugonnet S, Harbarth S, Mourouga P, Sauvan V, Touveneau S, Perneger TV (2000) Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Infection Control Programme. Lancet 356:1307-1312
18. Ista E, van der Hoven B, Kornelisse RF, van der Starre C, Vos MC, Boersma E, Helder OK (2016) Effectiveness of insertion and maintenance bundles to prevent central-line-associated bloodstream infections in critically ill patients of all ages: a systematic review and meta-analysis. Lancet Infect Dis 16:724-734
19. Blot K, Bergs J, Vogelaers D, Blot S, Vandijck D (2014) Prevention of Central Line-Associated Bloodstream Infections Through Quality Improvement Interventions: A Systematic Review and Meta-analysis. Clin Infect Dis 59:96-105
20. Scales DC, Dainty K, Hales B, Pinto R, Fowler RA, Adhikari NK, Zwarenstein M (2011) A multifaceted intervention for quality improvement in a network of intensive care units: a cluster randomized trial. JAMA 305:363-372
21. Burrell AR, McLaws ML, Murgo M, Calabria E, Pantle AC, Herkes R (2011) Aseptic insertion of central venous lines to reduce bacteraemia. The Central Line Associated Bacteraemia in, N. S. W. Intensive Care Units Collaborative. Med J Aust 194:583-587
22. Schweizer ML, Reisinger HS, Ohl M, Formanek MB, Blevins A, Ward MA, Perencevich EN (2014) Searching for an optimal hand hygiene bundle: a meta-analysis. Clin Infect Dis 58:248-259
23. Jeong IS, Park SM, Lee JM, Song JY, Lee SJ (2013) Effect of central line bundle on central line-associated bloodstream infections in intensive care units. Am J Infect Control 41:710-716
24. Tang HJ, Lin HL, Lin YH, Leung PO, Chuang YC, Lai CC (2014) The impact of central line insertion bundle on central line-associated bloodstream infection. BMC Infect Dis 14:356
25. Bonello RS, Fletcher CE, Becker WK, Clutter KL, Arjes SL, Cook JJ, Petzel RA (2008) An intensive care unit quality improvement collaborative in nine Department of Veterans Affairs hospitals: reducing ventilator-associated pneumonia and catheter-related bloodstream infection rates. Jt Comm J Qual Patient Saf 34:639-645
26. Longmate AG, Ellis KS, Boyle L, Maher S, Cairns CJ, Lloyd SM, Lang C (2011) Elimination of central-venous-catheter-related bloodstream infections from the intensive care unit. BMJ Qual Saf 20:174-180
27. McLaws ML, Burrell AR (2012) Zero risk for central line-associated bloodstream infection: are we there yet? Crit Care Med 40:388-393
28. Derde LP, Cooper BS, Goossens H, Malhotra-Kumar S, Willems RJ, Gniadkowski M, Hryniewicz W, Empel J, Dautzenberg MJ, Annane D, Aragao I, Chalfine A, Dumpis U, Esteves F, Giamarellou H, Muzlovic I, Nardi G, Petrikkos GL, Tomic V, Marti AT, Stammet P, Brun-Buisson C, Bonten MJ, Team MWS (2014) Interventions to reduce colonisation and transmission of antimicrobial-resistant bacteria in intensive care units: an interrupted time series study and cluster randomised trial. Lancet Infect Dis 14:31-39
29. Erasmus V, Daha TJ, Brug H, Richardus JH, Behrendt MD, Vos MC, van Beeck EF (2010) Systematic review of studies on compliance with hand hygiene guidelines in hospital care. Infect Control Hosp Epidemiol 31:283-294

30. Allegranzi B, Gayet-Ageron A, Damani N, Bengaly L, McLaws ML, Moro ML, Memish Z, Urroz O, Richet H, Storr J, Donaldson L, Pittet D (2013) Global implementation of WHO's multimodal strategy for improvement of hand hygiene: a quasi-experimental study. Lancet Infect Dis 13:843-851
31. ECDC (2012) Annual epidemiological report. Reporting on 2010 surveillance data and 2011 epidemic intelligence data. European Centre for Disease Prevention and Control
32. Dudeck MA, Horan TC, Peterson KD, Allen-Bridson K, Morrell G, Anttila A, Pollock DA, Edwards JR (2013) National Healthcare Safety Network report, data summary for 2011, device-associated module. Am J Infect Control 41:286-300
33. Rosenthal VD, Maki DG, Mehta Y, Leblebicioglu H, Memish ZA, Al-Mousa HH, Balkhy H, Hu B, Alvarez-Moreno C, Medeiros EA, Apisarnthanarak A, Raka L, Cuellar LE, Ahmed A, Navoa-Ng JA, El-Kholy AA, Kanj SS, Bat-Erdene I, Duszynska W, Van Truong N, Pazmino LN, See-Lum LC, Fernandez-Hidalgo R, Di-Silvestre G, Zand F, Hlinkova S, Belskiy V, Al-Rahma H, Luque-Torres MT, Bayraktar N, Mitrev Z, Gurskis V, Fisher D, Abu-Khader IB, Berechid K, Rodriguez-Sanchez A, Horhat FG, Requejo-Pino O, Hadjieva N, Ben-Jaballah N, Garcia-Mayorca E, Kushner-Davalos L, Pasic S, Pedrozo-Ortiz LE, Apostolopoulou E, Mejia N, Gamar-Elanbya MO, Jayatilleke K, de Lourdes-Duenas M, Aguirre-Avalos G, International Nosocomial Infection Control C (2014) International Nosocomial Infection Control Consortium (INICC) report, data summary of 43 countries for 2007-2012. Device-associated module. Am J Infect Control 42:942-956
34. Centers for Disease Control and Prevention (CDC) / National Healthcare Safety Network (NHSN) (2017) https://www.cdc.gov/nhsn/pdfs/pscmanual/4psc_clabscurrent.pdf
35. Mannien J, van den Hof S, Muilwijk J, van den Broek PJ, van Benthem B, Wille JC (2008) Trends in the incidence of surgical site infection in the Netherlands. Infect Control Hosp Epidemiol 29:1132-1138
36. Zuschneid I, Schwab F, Geffers C, Ruden H, Gastmeier P (2003) Reducing central venous catheter-associated primary bloodstream infections in intensive care units is possible: data from the German nosocomial infection surveillance system. Infect Control Hosp Epidemiol 24:501-505
37. Almirante B, Limon E, Freixas N, Gudiol F, Program V (2012) Laboratory-based surveillance of hospital-acquired catheter-related bloodstream infections in Catalonia. Results of the VINCat Program (2007-2010). Enferm Infecc Microbiol Clin 30 Suppl 3:13-19
38. Bion J, Richardson A, Hibbert P, Beer J, Abrusci T, McCutcheon M, Cassidy J, Eddleston J, Gunning K, Bellingan G, Patten M, Harrison D, Matching Michigan C, Writing C (2013) 'Matching Michigan': a 2-year stepped interventional programme to minimise central venous catheter-blood stream infections in intensive care units in England. BMJ Qual Saf 22:110-123
39. Dixon-Woods M, Leslie M, Tarrant C, Bion J (2013) Explaining Matching Michigan: an ethnographic study of a patient safety program. Implement Sci 8:70
40. Beggs CB, Shepherd SJ, Kerr KG (2008) Increasing the frequency of hand washing by healthcare workers does not lead to commensurate reductions in staphylococcal infection in a hospital ward. BMC Infect Dis 8:114
41. Nicolau DV, Jr., Kith G, Oshmyansky A (2010) Evidence for a simple linear relationship between MRSA rates and hand-washing compliance. J Hosp Infect 75:140-141
42. Wang J, Wang L, Magal P, Wang Y, Zhuo J, Lu X, Ruan S (2011) Modelling the transmission dynamics of meticillin-resistant Staphylococcus aureus in Beijing Tongren hospital. J Hosp Infect 79:302-308

43. Srigley JA, Furness CD, Baker GR, Gardam M (2014) Quantification of the Hawthorne effect in hand hygiene compliance monitoring using an electronic monitoring system: a retrospective cohort study. BMJ Qual Saf 23:974-908
44. Pronovost PJ, Goeschel CA, Colantuoni E, Watson S, Lubomski LH, Berenholtz SM, Thompson DA, Sinopoli DJ, Cosgrove S, Sexton JB, Marsteller JA, Hyzy RC, Welsh R, Posa P, Schumacher K, Needham D (2010) Sustaining reductions in catheter related bloodstream infections in Michigan intensive care units: observational study. BMJ 340:c309

Chapter 8

Chapter 8 Hand hygiene improvement of individual healthcare workers – Results of the multicentre PROHIBIT study

Tjallie van der Kooi[1*], Hugo Sax[2,3*], Hajo Grundmann[4], Didier Pittet[5,6], Sabine de Greeff[1], Jaap van Dissel[1], Lauren Clack[2], Albert W. Wu[7], Judith Davitt[8], Sofia Kostourou[9], Alison Maguinness[10], Anna Michalik[11] , Viorica Nedelcu[12], Márta Patyi[13], Janja Perme Hajdinjak[14], Milena Prosen[14], David Tellez[15], Éva Varga[16], Fani Veini[9], Mirosław Ziętkiewicz [16,17] and Walter Zingg[2,5], on behalf of the PROHIBIT consortium.

[1] RIVM National Institute for Public Health and the Environment, Bilthoven, the Netherlands

[2] Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Zurich, Switzerland

[3] Department of Infectious Diseases, Bern University Hospital and University of Bern, Bern, Switzerland

[4] Medical Center – University of Freiburg, Freiburg, Germany

[5] University of Geneva Hospitals, Geneva, Switzerland

[6] WHO collaborating Centre on Infection Prevention and Control and Antimicrobial Resistance, Geneva, Switzerland

[7] Johns Hopkins University Bloomberg School of Public Health, Center for Health Services and Outcomes Research, Baltimore, MD, USA

[8] Galway University Hospital, Galway, Galway, Ireland

[9] Evaggelismos Hospital, Athens, Attica, Greece

[10] St. Michaels hospital, Dún Laoghaire, Ireland

[11] University of Bielsko-Biala, Faculty of Health Sciences, Bielsko-Biala, Poland

[12] Emergency Institute for Cardiovascular Diseases "Prof. C.C. Iliescu", Bucharest, Romania

[13] Bács-Kiskun Megyei Kórház (County teaching hospital), Kecskemet, Hungary

[14] University Medical Centre Ljubljana, Ljubljana, Slovenia

[15] Hospital Vall d'Hebron, Barcelona, Catalunya, Spain

[16] John Paul II Hospital, Krakow, Poland

[17] Medical College Jagiellonian University, Krakow, Poland

* These authors contributed equally to the work.

Antimicrobial resistance & Infection Control 2022(11): 123

ABSTRACT

Background: Traditionally, hand hygiene (HH) interventions do not identify the observed healthcare workers (HWCs) and therefore, reflect HH compliance only at population level. Intensive care units (ICUs) in seven European hospitals participating in the "Prevention of Hospital Infections by Intervention and Training" (PROHIBIT study provided individual HH compliance levels. We analysed these to understand the determinants and dynamics of individual change in relation to the overall intervention effect.

Methods: We included HCWs who contributed at least two observation sessions before and after intervention. Improving, non-changing, and worsening HCWs were defined with a threshold of 20% compliance change. We used multivariable linear regression and spearman's rank correlation to estimate determinants for the individual response to the intervention and correlation to overall change. Swarm graphs visualized ICU-specific patterns.

Results: In total 280 HCWs contributed 17,748 HH opportunities during 2,677 observation sessions. Overall, pooled HH compliance increased from 43.1% to 58.7%. The proportion of improving HCWs ranged from 33% to 95% among ICUs. The median HH increase per improving HCW ranged from 16 to 34 percentage points. ICU wide improvement correlated significantly with both the proportion of improving HCWs (ρ=0.82 [95%CI 0.18-0.97], and their median HH increase (ρ =0.79 [0.08-0.97]). Multilevel regression demonstrated that individual improvement was significantly associated with nurse profession, lower activity index, higher nurse-to-patient ratio, and lower baseline compliance.

Conclusions: Both the proportion of improving HCWs and their median individual improvement differed substantially among ICUs but correlated with the ICUs' overall HH improvement. With comparable overall means the range in individual HH varied considerably between some hospitals, implying different transmission risks. Greater insight into improvement dynamics might help to design more effective HH interventions in the future.

INTRODUCTION

Healthcare-associated infections (HAIs) affect on average 6% of hospitalized patients in Europe [1, 2]. Patients in hospitals are at increased risk of acquiring HAIs mainly because of invasive procedures. The proximity to other patients and frequent healthcare contacts facilitate the transmission of pathogens, and the use of broad-spectrum antibiotics increases the burden of multidrug-resistant microorganisms (MDROs) in hospital settings [3]. Hand hygiene (HH) is the most basic and essential element in the prevention of cross-transmission. Although widely promoted, HH compliance in intensive care units (ICU) remains on average 40-50% [4-7], and to sustain achieved improvements remains challenging [8-11].

All but a few small studies [12-17] on HH compliance report only pooled data across all healthcare workers (HCW). Thus there is little data on the contribution of individuals to the overall response to behavioural interventions. Individual HH compliance is relevant because average compliance does not reflect variations among HCWs and thus, might not capture overall transmission risk. Moreover, data on changes in individual HH compliance could provide insights into barriers and facilitators of a HH intervention. In the Prevention of Hospital Infections by Intervention and Training (PROHIBIT) intervention study, HH compliance was observed at the individual HCW level during baseline and intervention study periods. We analysed these data to better understand the determinants and dynamics of individual change in HH compliance in relation to the overall intervention effect.

METHODS

Methods of the PROHIBIT intervention study

The PROHIBIT intervention study tested two interventions to prevent central venous catheter bloodstream infection (CRBSI) in Intensive Care Units (ICUs) in European acute care hospitals: a central venous catheter (CVC) insertion strategy, and a HH improvement strategy. Several other work packages addressed the topic of HAI prevention more widely [18-22]. After a baseline period of at least six months, three ICUs of 14 hospitals in 11 European countries were randomly allocated every three months to start with one of the two intervention strategies or both [7]. The method and results of this step wedge randomised controlled intervention study have been reported in detail elsewhere [7, 23].

In brief, each ICU appointed one dedicated on-site investigator and one study nurse to the project. PROHIBIT offered reimbursement of a 0.5 full-time equivalent study nurse. Three to six months before the start of the intervention, local study nurses and/or infection control physicians, anaesthetists, and intensivists, depending on the

intervention, attended a two-day PROHIBIT workshop on best practices and implementation science. For the HH improvement strategy, PROHIBIT used the WHO HH training and campaign materials (http://www.who.int/gpsc/5may/tools/en/). Hand hygiene promotion included educational sessions and bedside training. In addition, the ICUs displayed posters and/or other reminders in the workplace and participants came up with various additional promotion activities. Hand hygiene compliance was measured by direct observation according to the WHO observation method.[24] PROHIBIT study nurses, most often infection prevention and control (IPC) or ICU nurses with IPC responsibilities, were trained in the methodology of direct HH observation at the University of Geneva Hospitals, Switzerland. Hand hygiene observations were randomized for date (weekdays), time slot (08-12:00, 12:00-16:00 and 16:00-20:00), and ICU bed [7]. One observation session could include observations of multiple HCWs. However, to avoid missing HH opportunities, observers were not allowed to observe more than three HCWs in one session. Hand hygiene opportunities were stratified by observation sessions and by the five WHO indications for HH [24]. HH compliance was calculated as the proportion of HH opportunities met by a HH action. Individual HCWs identity was recorded using a four-letter code, based on their given and family name, where needed retrieved from the badge and, if that proved impossible, by asking the HCW.

During the intervention on site investigators received quarterly feedback reports on the average HH compliance in their ICU and individual HCWs on their HH compliance after being observed, but not during baseline [7]. HCW codes were used for statistical analysis only.

Study population of the present analysis

Ten of the 14 ICUs agreed to capture the HCWs' identity during HH observations. Seven of these ICUs implemented the HH intervention, either alone or in combination with the CRBSI-prevention strategy and were included in the present analysis as *study ICUs*. Only data of HCWs with at least two observation sessions, during both baseline and intervention periods, were included for the individual analysis ('*study HCWs*').

Definitions

HCWs were grouped according to the change in their HH compliance between baseline and intervention. '*Improving HCW*' were defined by having improved compliance by at least 20%, '*Worsening HCW*' decreased by at least 20%, and '*Non-changing HCW*' changed less than 20%, if at all. The 20%-threshold was chosen retrospectively based on the rounded pooled mean change among all HCWs. An ‚*activity index*', defined by number of hand hygiene opportunities per hour of observation, was defined as a proxy for the intensity of care [25].

Analysis plan and statistics

To meet our study scope, we chose four analytical models. In Model 1, we evaluated the extent to which changes in the individual HH compliance between study periods were associated with ICU characteristics. We calculated Spearman rank correlation coefficients of the proportion of *Improving HCWs* with a) the nurse-to-patient ratio and b) the pooled mean baseline HH compliance of all HCWs.

In Model 2, we assessed a potential association between the intervention effect on the individual HCW and the overall ICU. We calculated the Spearman' rank correlation coefficients for the proportion and median improvement of *Improving HCWs* with the pooled change in HH compliance of all HCWs.

In Model 3, we tested the potential association of the change in HH compliance for each individual HCW (measured as change in percentage points (pp); outcome variable) with HCW characteristics (i.e., professional category, baseline compliance) and contextual factors (i.e., activity index, ICU type, ICU nurse- to-patient ratio, and proportion of improving HCWs). We used a generalized linear mixed model (GLMM) with a normal distribution, allowing for clustering at the ICU level. Variables with a P-value <0.25 in the univariable analysis were included in the multivariable model using manual backward selection. The proportion of explained variation (R^2) was calculated for this model. All changes in HH compliance were calculated as relative proportions (%) or differences in percentage points (pp), using mid-P exact tests to test for significance. We used SAS 9.4 (SAS Institute Inc., Cary, United States) for all statistical analyses.

In Model 4, we created a swarm plot with individual HH compliance at baseline and intervention for each HCW, in each category (improving, non-improving, worsening HCWs), and a bar diagram of the range in HH between HH sessions for each HCW, during the baseline and intervention phase, for visual display of individual HCW compliance patterns in the seven study ICUs.

RESULTS

Study intensive care units and healthcare worker population

Three of the seven study hospitals were university affiliated, two had >50,000 admissions per year, two between 30,000 and 50,000, and three <30,000 admissions per year. The median number of ICU beds per hospital was 17 (range, 10-40). The median nurse-to-patient ratio in the ICU during day shifts was 0.5 (range, 0.29–1.00; Additional file 1: Table S1) at baseline, i.e., one nurse for two patients. The median activity index in the ICUs was 9.0 (IQR, 6.0–15.0) HH opportunities per hour. According to the inclusion criteria, 280 study HCWs (58% nurses, 20% doctors, 18% auxiliary nurses, 4% other HCWs) contributed 17,748 HH opportunities during 2,677 observation sessions with a median number of sessions per HCW of 4 (interquartile range (IQR), 2-6) during baseline and 10 (IQR, 5-15) during intervention. During baseline 365 HCW and during intervention another 623 HCWs were excluded because they did not meet the inclusion criteria of at least two observation sessions per study period.

Hand hygiene compliance

The pooled mean HH compliance of study HCWs increased significantly from 43.1% during baseline to 58.7% during intervention (Table 1). Similarly, the compliance of the 365 excluded HCWs was 43.1% during baseline. Overall HH compliance of study HCWs and non-study HCWs increased from 43.1% to 60.8% (Additional file 1: Table S2, 61.0% for the excluded 623 HCWs). For *Improving HCWs*, *Worsening HCWs*, and *Non-changing HCWs* HH compliance changed from 35% to 57%, 50% to 41%, and 59% to 66%, respectively. Individual HH compliance per HCW for the entire study population is shown in Fig. 1 and for each study ICU in Additional file 1: Figs. S1 and S2.

Model 1: The proportion of *Improving Healthcare workers* and associated factors per ICU

The overall proportion of *Improving HCWs* was 62.1% with an inter-ICU range of 32.7% to 95.2% (Table 1). Per ICU, the proportion of *Improving HCWs* was not significantly associated

Table 1 : Hand hygiene compliance per hospital during baseline and intervention

Hospital	Number of HCWs	HH (%) during baseline	HH (%) after intervention	Percentage points change in overall HH (95% confidence interval)	Proportion of improving HCWs (%)	Proportion of non-changing HCWs (%)	Proportion of worsening HCWs (%)
A	52	44.1	48.7	4.7 (0.84–8.5)	32.7	51.9	15.4
B	64	16.7	34.7	18.0 (15.1–20.9)	82.8	4.7	12.5
C	28	36.6	49.0	12.4 (8.3–16.5)	71.4	14.3	14.3
D	21	47.1	78.6	31.5 (24.9–38.2)	95.2	4.8	0.0
E	25	62.7	90.9	28.3 (22.6–33.9)	68.0	28.0	4.0
F	36	62.2	79.8	17.5 (13.4–21.7)	61.1	38.9	0.0
G	54	55.5	69.2	13.7 (10.1–17.3)	46.3	42.6	11.1
Total	280	43.1	58.7	15.6 (14.0–17.2)	62.1	28.2	9.6

HCW, healthcare worker; HH, hand hygiene

with the nurse-to-patient ratio (ρ 0.23; CI -0.64-0.84) or the overall baseline compliance (ρ 0.37; -0.86-0.54).

The average improvement in HH compliance was negatively associated with the activity index (Additional file 1: Table S1).

Model 2: Association of the intervention effect between individual HCWs and the overall ICU

The median increase in HH compliance of *Improving HCWs* per ICU ranged from 16 pp to 34 pp (Additional file 1: Fig S2) and was significantly associated with the overall improvement among all HCWs in the corresponding ICU (ρ 0.79; CI 0.08-0.97) (Fig. 2). The overall proportion of *Improving HCWs* was 62.1% with an inter-ICU range of 32.7% to 95.2% (Table 1). This proportion of *Improving HCWs* per ICU was associated with the overall HH improvement among all HCWs (Spearman rank correlation (ρ) 0.82; 95% confidence interval (CI), 0.18-0.97) (Table 1, Fig. 3).

Model 3: Factors associated with individual HH compliance change between study periods

In multivariable analysis, a higher nurse-to-patient ratio was positively associated, and professional category 'medical doctor/ students', higher activity index, and higher individual baseline HH compliance were negatively associated with individual changes in HH compliance between study periods (Table 2). The multivariable regression model explained 43% of the variance in individual changes in HH compliance between study periods (marginal R2), 22% due to the independent variables (fixed effects) and 21% due to nested clustering on the HCWs and hospital level (random effects).

Model 4

Although lower baseline compliance overall was associated with a larger increase in HH compliance, it can be seen in Fig. 1 that *Improving HCWs* with low baseline HH compliance remained lower in intervention compared to *Improving HCWs* who were already high during baseline. Figure 1 shows different HCW compliance patterns and changes across the study ICUs. In some centres the variability in HH compliance among individual HCWs increased from baseline to intervention – resulting from higher variability in compliance between HCWs (Additional file 1: Fig. S1) and/or between sessions of individual HCWs (Additional file 1: Fig. S3).

DISCUSSION

The goal of this study was to understand the determinants and dynamics of individual HH compliance in response to an intervention. The intervention was a success, HH compliance increased significantly and importantly, overall and in each ICU. Individual compliance change was positively correlated with the overall change per ICU. However, we found large inter-ICU and inter-individual differences in the observed HH compliance and their dynamics. In some ICUs the overall result of the intervention was produced by almost exclusively improving HCWs, while in other ICUs the contribution of improving HCWs was to some extent offset by worsening or non-changing HCWs. We also found that individual compliance change was positively associated with a higher nurse-to-patient ratio, and negatively

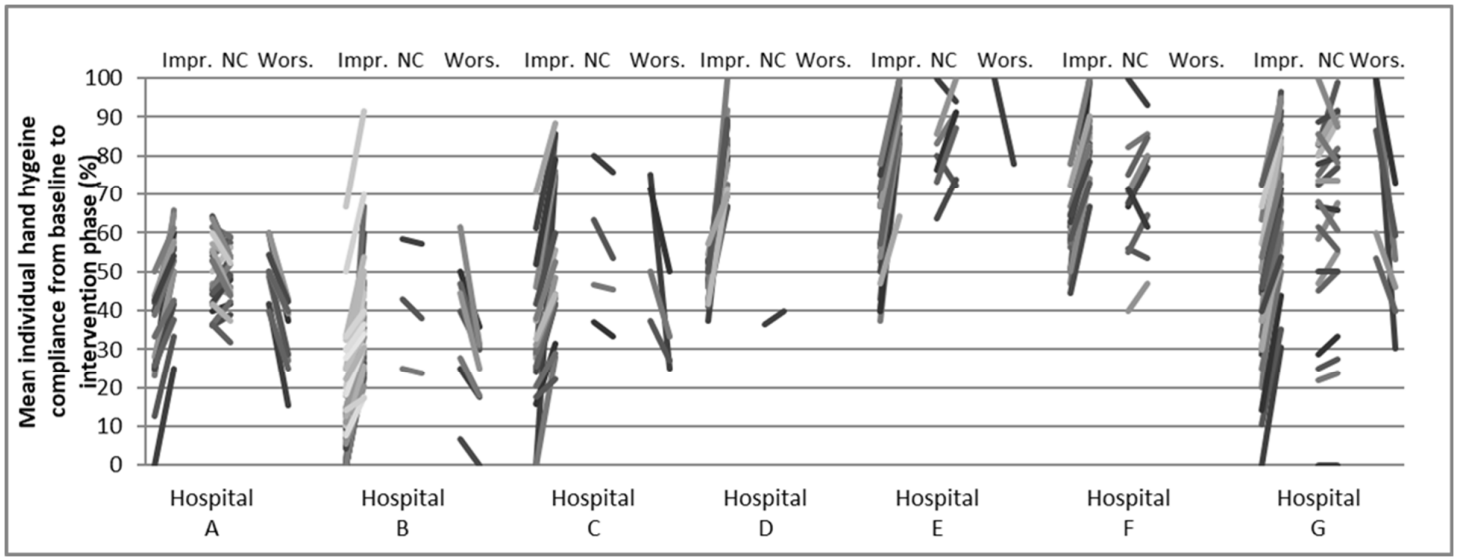


Figure 1: Individual change of hand hygiene compliance, stratified by intensive care unit. Each line represents one HCW.

Impr., improving healthcare workers; NC, Non-changing healthcare workers; Wors., Worsening healthcare workers

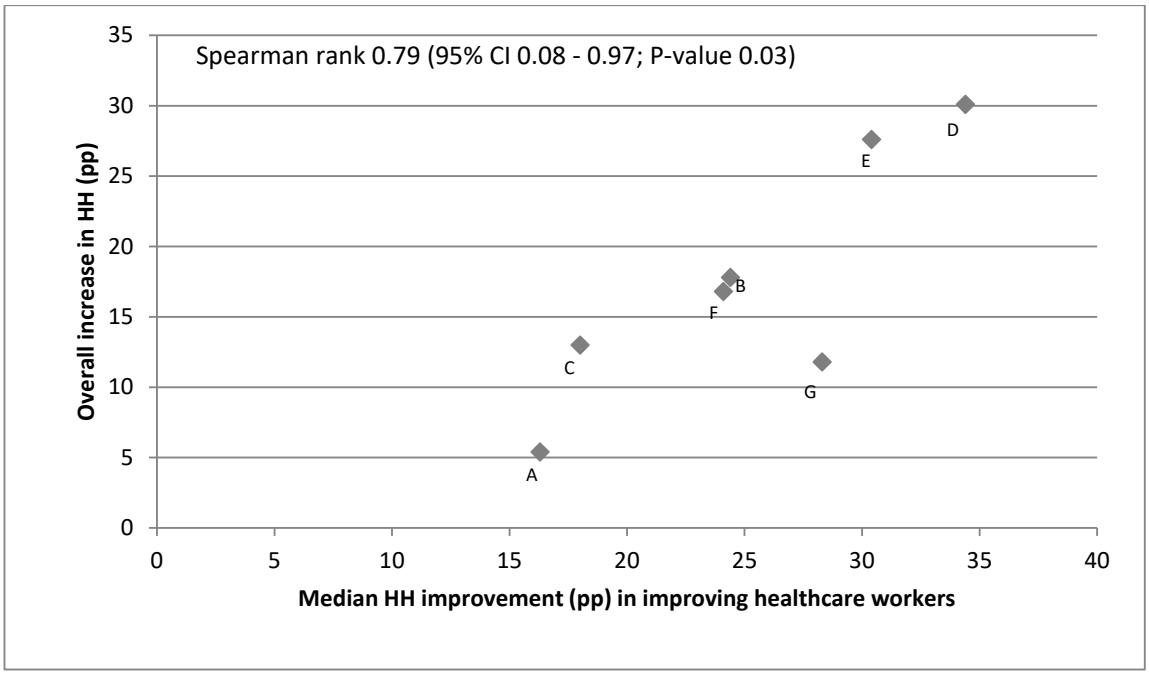


Figure 2: Correlation between median hand hygiene improvement of improving healthcare workers and overall improvement in hand hygiene compliance per hospital
HH, hand hygiene; pp, percentage points

associated with a higher activity index, with being a physician or medical student, and higher baseline HH compliance.

This study is important, because understanding the patterns and dynamics of individual HH compliance in response to an intervention might help to better tailor improvement efforts. When individual responses to the intervention diverge strongly one might suspect factors that concern HCWs individually. In the contrary case, where all HCWs respond with a similar but smaller increase in HH compliance, contributing to the same overall result, systemic factors might be sought and addressed. For example, in addition to a high baseline compliance, these might include a flawed handrub dispenser placement, a high activity index, or a low nurse-to-patient ratio. Indeed, a higher nurse-to-patient ratio was independently associated with a higher HH improvement in this study. Moreover, the ICU with the highest nurse-to-patient ratio (ICU E) was the only one in which the activity index was not negatively associated with HH compliance. This suggests that the nurse-to-patient ratio is a relevant variable to target as a risk for low HH compliance. The negative effect of a

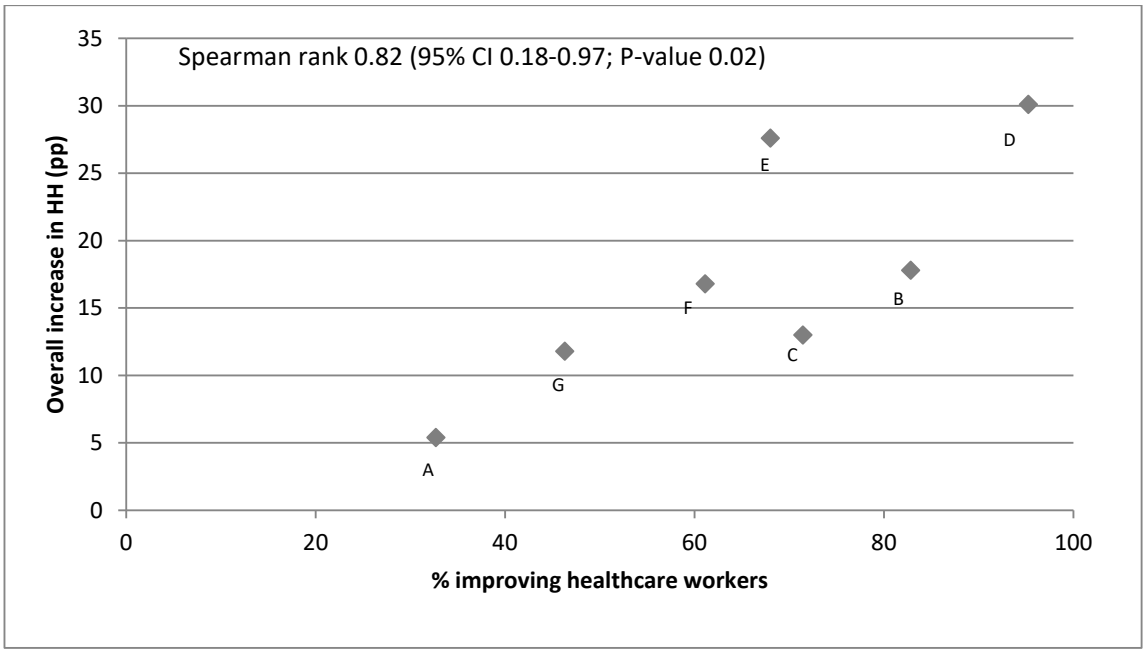


Figure 3: Correlation between the proportions of improving healthcare workers and the overall improvement in hand hygiene compliance per hospital
HH, hand hygiene; pp, percentage points

high workload on HH compliance has been reported before [25-28]. Scheithauer et al. demonstrated an inverse relationship between the daily workload and HH [29], and Lee et al. found a positive association between nurse-to-patient ratio and HH compliance [16]. Data collected by Hansen et al. demonstrate a nurse to patient ratio of 0.5 during dayshifts to be typical for European ICUs, with national averages ranging from 0.3 to 0.9 [30].

Our study reveals considerable variability in HH compliance between individual HCWs, in some ICUs more than in others. The few previous studies that have employed individualized observation found similar between-HCW variability [12-17, 31]. However, these were either based on a small number of HCWs or did not perform an intervention. Estimating from **Figure 1** and additional **Figure 1**, this between-HCW variability seems to increase in some centres, suggesting differences in the individual response to the intervention. Personal perceptions, mental models, motivation, and work organisation can influence the individual HH behaviour of each HCW and, in consequence, also their response to promotional exposure [31-34]. Early recognition of these individual factors could help in customizing HH improvement strategies to a range of typical behavioural profiles. Methods

Table 2: Univariable and multivariable estimates of the effect on the change of hand hygiene compliance

	Univariable estimate			Multivariable estimate		
	pp	CI95%	p-value	PP	CI95%	p-value
Professionals						
Nurse/student nurse	Ref.			Ref.		
Auxiliaries	0.8	(-4.1–5.7)	0.74	0.4	(-3.5–4.4)	0.84
Medical doctors / students	-2.4	(-7.3–2.5)	0.34	-5.7	(-9.7– -1.7)	0.005
Other healthcare professionals	6.3	(-2.6–15.2)	0.17	4.1	(-3.5–11.7)	0.29
Type of ICU						
Medical/surgical	Ref.			Ref.		
Cardiosurgery	-7.8	(-25.7–10.1)	0.39			
Vascular surgery	-6.3	(-23.1–10.6)	0.47			
Activity index [1,2]						
Per one extra opportunity/h	-0.6	(-0.8– -0.4)	<0.0001	-0.6	(-0.8– -0.4)	<0.0001
Baseline compliance [2]						
Per PP higher compliance	-0.6	(-0.7– -0.5)	<0.0001	-0.6	(-0.7– -0.5)	<0.0001
Nurse-to-patient ratio [2]						
Per PP increase	0.2	(-0.1–0.5)	0.25	0.5	(0.07–0.8)	0.02

[1]Activity index of the sessions during the intervention period.
[2]Differences of mean (centered)
CI95%, 95% confidence interval; PP, percentage point

from psychology and implementation science may be helpful to tailor improvement strategies to prospectively identified determinants of HH [35-37].

Data on the level of HH compliance needed to prevent cross-transmission are limited to modelling studies. Three reports identified a “threshold” of mean HH compliance above which pathogen transmission and infections would start to decline to be 48%, 66% and 87%, respectively, always assuming that each HH action results in a total eradication of pathogen transmission[38-40]. Models taking into account less than 100% efficacy, conclude that no level of HH can be identified as “good enough” to prevent transmission[41-43]. Most importantly, models have demonstrated that the

distribution of HH compliance among HCWs in a population affects the ensuing transmission risk. A single HCW with low HH compliance could play a significant role in pathogen transmission, especially if such a low-performing HCW provides care to many patients consecutively. This effect was demonstrated in two agent-based models by Temime et al. and by Hornbeck et al [44, 45]. Exemplarily, the proportion of low-performing staff in our study were predominantly doctors who typically deliver care to many different patients. This 'weakest link' mechanism challenges the usefulness of pooled means of HH compliance infectious risk in each care unit. Our real-world data support the idea that similar pooled mean HH compliance rates between observed settings can be the result of quite different distributions of high- and low-performing HCWs.

This study has limitations. First, not all observed HCWs could be included in the analysis due to the required number of observations. This could have led to an overrepresentation of permanent staff. Both the pooled baseline and intervention compliance were, however, comparable between the group of study HCWs and the excluded HCWs.

Second, the definition of *Improving HCWs* as those with ≥20% HH improvement precluded the inclusion of HCWs with >80% compliance at baseline in this category. To circumvent this problem, we evaluated the possibility of using the change in *non*-compliance, rather than compliance to distinguish HCWs. This resulted in slightly higher correlations and similar effect estimates in the univariable regression model. We therefore decided to remain with the traditional definition of HH compliance. Third, the chosen cut-off value of 20% to distinguish HCWs into the three HH compliance change categories was somewhat arbitrary. However, a multivariable model with a cut-off value of 10% provided similar results (data not shown). Fourth, some of the observed between-HCW variability could be explained by chance due to a limited number of HH observation sessions per HCW and a limited number of opportunities per session. However, our study is the largest of its kind to date and demonstrates the feasibility and benefit of this approach. It might take an advanced automatic HH monitoring system to collect a larger number of opportunities per identified HCW. Finally, like other HH observation studies, observer and observation biases cannot be entirely excluded, especially a desirability bias by the observers also being involved in the promotion of the intervention, and observation bias, also known as Hawthorne effect [46-48]. However, given the long study duration of 30 months and the focus on improvement dynamics, it is likely that neither biases influenced the results to a degree that would invalidate our findings.

CONCLUSIONS

Both the proportion of improving HCWs and the median of individual HH improvement differed substantially among hospitals. Both measures were associated with the overall success of the intervention. However, the patterns and dynamics of individual HH compliance varied considerably among ICUs, and could potentially result in different risk of pathogen transmission. Being a nurse, a low individual baseline HH compliance, a lower ICU-level activity index, and a favourable nurse-to-patient ratio were associated with a higher individual HH compliance improvement. Data on individual HH compliance could advance our understanding of improvement dynamics and inform better intervention strategies. Collecting individual level HH data on should be seriously considered in future HH research, especially in the design of interventions.

DECLARATIONS

Ethics approval and consent to participate

The Medical Ethical Research Committee of the Utrecht University Medical Center, Utrecht, the Netherlands, decided that the study was not subject to the Medical Research Involving Human Subjects Act. All institutional review boards of the study hospitals approved of the study protocol.

FUNDING

The study was funded by the European Commission 7th Framework Programme.

ACKNOWLEDGEMENTS

We thank Sylvie Touveneau, Marie-Noëlle Chraïti and Benedetta Allegranzi, who devoted themselves to the training of the on-site investigators and study nurses in the workshops. Our gratitude extends also to the participating centres for collaborating in this study, especially the management and staff of the centres that allowed the individual compliance results to be recorded and that responded positively to the challenge to improve their hand hygiene and thus contributed to the increased safety of the patients in their care.

Additional file 1

Supplementary Table 1. Association between hand hygiene and activity index during baseline and intervention.

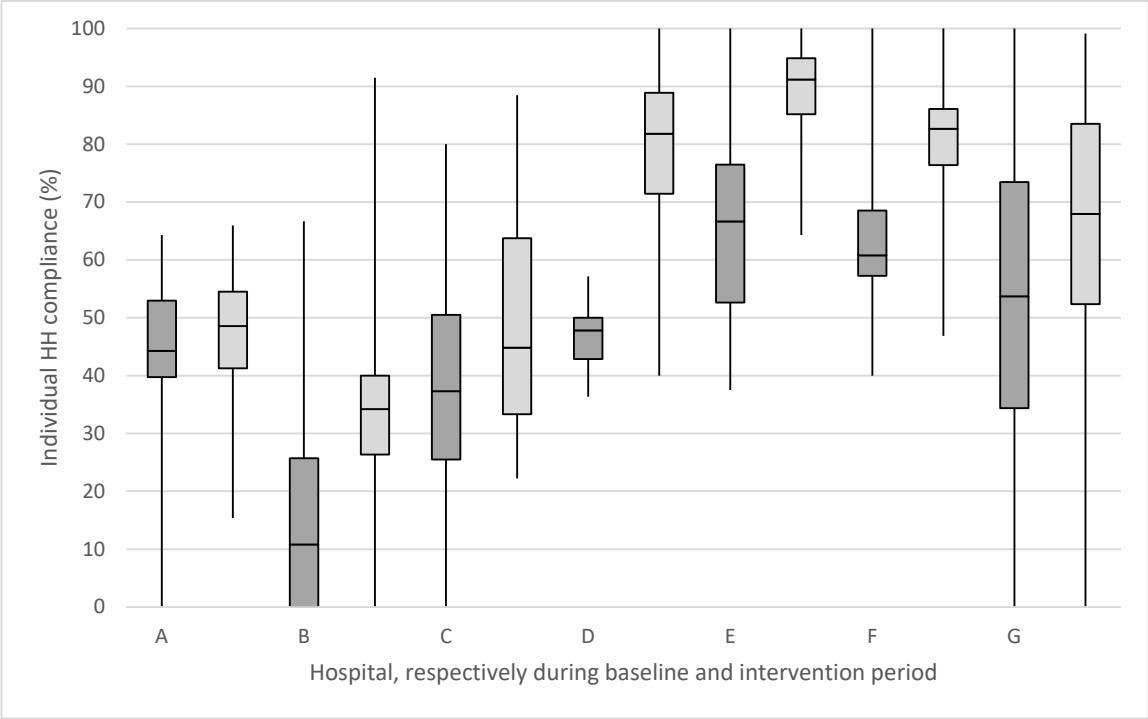
	Baseline				**Intervention**			
Hospital	Nurse to patient ratio	HH compliance	*PP change per 1 PP increase in activity index	(p-value)	Nurse to patient ratio	HH compliance	*PP change per 1 PP increase in activity index	(p-value)
A	0.50	44.1	0.82	(0.0007)	0.50	48.7	-0.55	(0.042)
B	0.33	16.7	0.20	(0.60)	0.25	34.7	-0.95	(< 0.0001)
C	0.33	36.6	-0.57	(0.18)	0.50	49.0	-1.1	(0.032)
D	0.67	47.1	0.07	(0.81)	0.67	78.6	-1.1	(0.0003)
E	1.0	62.7	-2.0	(0.005)	0.75	90.9	0.72	(0.003)
F	0.50	62.2	-2.5	(< 0.0001)	0.50	79.8	-1.9	(0.0001)
G	0.29	55.5	-0.31	(0.37)	0.25	69.2	-0.25	(0.041)

*Univariable analysis, clustered on healthcare worker level
HH, hand hygiene; PP, percentage point

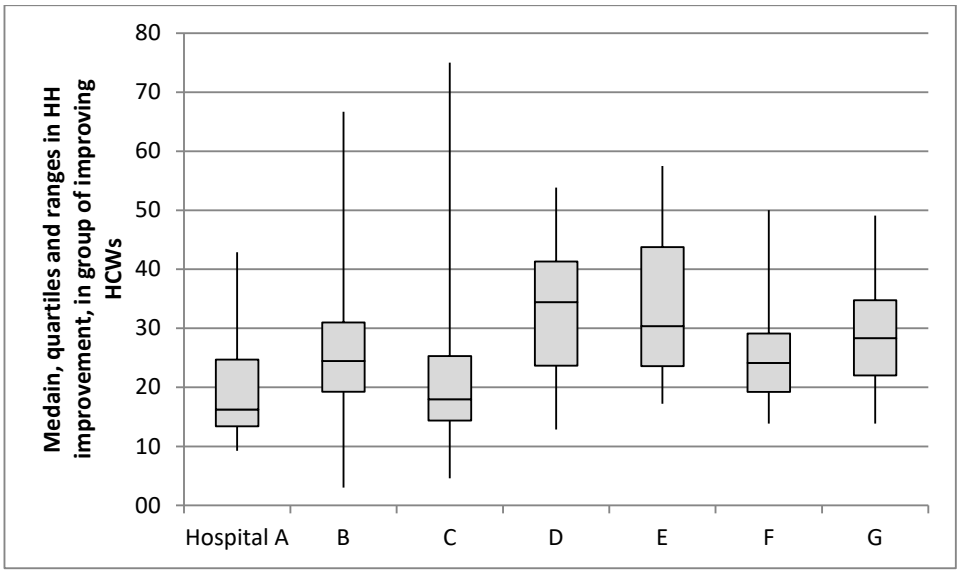
Supplementary Table 2. Overall (i.e. for all HCWs) hand hygiene compliance per hospital, during baseline and the intervention period

Hospital	**Baseline**			**Intervention**			**Change**	
	opportunities	*actions*	*compliance*	*opportunities*	*actions*	*compliance*	***PP***	*95% CI*
A	*1284*	*549*	*42.8*	*3325*	*1602*	*48.2*	***5.4***	*2.2 - 8.6*
B	1417	240	16.9	4805	1669	34.7	**17.8**	15.4 - 20.2
C	1285	444	34.6	1665	793	47.6	**13.1**	9.5 - 16.6
D	572	279	48.8	3961	3125	78.9	**30.1**	25.8 - 34.4
E	815	505	62.0	1488	1333	89.6	**27.6**	23.9 - 31.3
F	810	507	62.6	1591	1263	79.4	**16.8**	12.9 - 20.7
G	1126	625	55.5	6850	4608	67.3	**11.8**	8.7 - 14.9

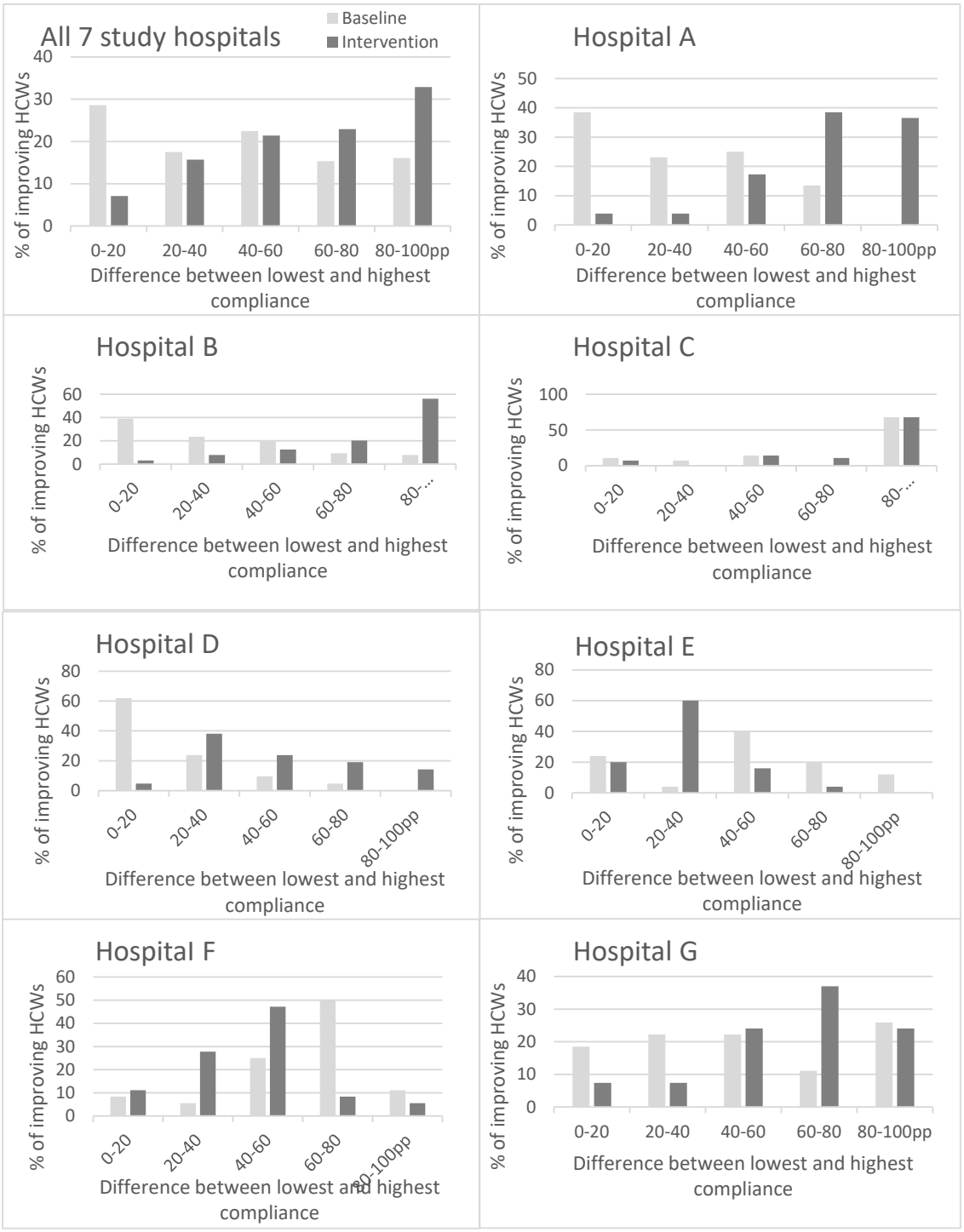
95% CI, 95% confidence interval; HCW, healthcare worker; PP, percentage point



Supplementary Figure 1: Boxplot (median, quartiles and ranges) of individual HH compliance both during baseline and intervention period



Supplementary Figure 2. Boxplot (median, quartiles and ranges) of hand hygiene increase (in percentage points) in the group of improving HCWs



Supplementary Figure 3: Variability within improving HCWs, measured as the range between the observation session with the lowest compliance and the session with the highest compliance for each HCW

REFERENCES

1. Suetens C, Latour K, Karki T, Ricchizzi E, Kinross P, Moro ML, et al. Prevalence of healthcare-associated infections, estimated incidence and composite antimicrobial resistance index in acute care hospitals and long-term care facilities: results from two European point prevalence surveys, 2016 to 2017. Euro Surveill. 2018;23(46).
2. ECDC. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals. Stockholm: European Centre for Disease Prevention and Control; 2013.
3. Versporten A, Zarb P, Caniaux I, Gros MF, Drapier N, Miller M, et al. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. Lancet Glob Health. 2018;6(6):e619-e29.
4. Moro ML, Morsillo F, Nascetti S, Parenti M, Allegranzi B, Pompa MG, Pittet D. Determinants of success and sustainability of the WHO multimodal hand hygiene promotion campaign, Italy, 2007-2008 and 2014. Euro Surveill. 2017;22(23).
5. Derde LPG, Cooper BS, Goossens H, Malhotra-Kumar S, Willems RJL, Gniadkowski M, et al. Interventions to reduce colonisation and transmission of antimicrobial-resistant bacteria in intensive care units: an interrupted time series study and cluster randomised trial. Lancet Infect Dis. 2014;14(1):31-9.
6. Erasmus V, Daha TJ, Brug H, Richardus JH, Behrendt MD, Vos MC, van Beeck EF. Systematic review of studies on compliance with hand hygiene guidelines in hospital care. Infect Control Hosp Epidemiol. 2010;31(3):283-94.
7. van der Kooi T, Sax H, Pittet D, van Dissel J, van Benthem B, Walder B, et al. Prevention of hospital infections by intervention and training (PROHIBIT): results of a pan-European cluster-randomized multicentre study to reduce central venous catheter-related bloodstream infections. Intensive Care Med. 2018;44(1):48-60.
8. Gould DJ, Chudleigh JH, Moralejo D, Drey N. Interventions to improve hand hygiene compliance in patient care. Cochrane Database Syst Rev. 2007(2):CD005186.
9. Schwadtke L, Graf K, Lutze B, von Lengerke T, Chaberny IF. [Compliance with hand hygiene guidelines on intensive care units at a university medical centre with surgical focus]. Dtsch Med Wochenschr. 2014;139(25-26):1341-5.
10. Luangasanatip N, Hongsuwan M, Limmathurotsakul D, Lubell Y, Lee AS, Harbarth S, et al. Comparative efficacy of interventions to promote hand hygiene in hospital: systematic review and network meta-analysis. BMJ. 2015;351:h3728.
11. Fonguh S, Uwineza A, Catry B, Simon A. Belgian hand hygiene campaigns in ICU, 2005-2015. Arch Public Health. 2016;74:47.
12. Kerbaj J, Toure Y, Soto Aladro A, Boudjema S, Giorgi R, Dufour JC, Brouqui P. Smartphone text message service to foster hand hygiene compliance in health care workers. Am J Infect Control. 2017;45(3):234-9.
13. Sanchez-Carrillo LA, Rodriguez-Lopez JM, Galarza-Delgado DA, Baena-Trejo L, Padilla-Orozco M, Mendoza-Flores L, Camacho-Ortiz A. Enhancement of hand hygiene compliance among health care workers from a hemodialysis unit using video-monitoring feedback. Am J Infect Control. 2016;44(8):868-72.
14. Cheng VC, Tai JW, Ho SK, Chan JF, Hung KN, Ho PL, Yuen KY. Introduction of an electronic monitoring system for monitoring compliance with Moments 1 and 4 of the WHO "My 5 Moments for Hand Hygiene" methodology. BMC Infect Dis. 2011;11:151.
15. Kurtz SL. Identification of low, high, and super gelers and barriers to hand hygiene among intensive care unit nurses. Am J Infect Control. 2017.
16. Lee A, Chalfine A, Daikos GL, Garilli S, Jovanovic B, Lemmen S, et al. Hand hygiene practices and adherence determinants in surgical wards across Europe and Israel: a multicenter observational study. Am J Infect Control. 2011;39(6):517-20.
17. Iversen AM, Kavalaris CP, Hansen R, Hansen MB, Alexander R, Kostadinov K, et al. Clinical experiences with a new system for automated hand hygiene monitoring: A prospective observational study. Am J Infect Control. 2020;48(5):527-33.
18. Martin M, Zingg W, Knoll E, Wilson C, Dettenkofer M, Group PS. National European guidelines for the prevention of Clostridium difficile infection: a systematic qualitative review. J Hosp Infect. 2014;87(4):212-9.

19. Hansen S, Schwab F, Gastmeier P, group Ps, Pittet D, Zingg W, et al. Provision and consumption of alcohol-based hand rubs in European hospitals. Clin Microbiol Infect. 2015;21(12):1047-51.
20. Hansen S, Schwab F, Gastmeier P, Zingg W, group Ps. Association of national and hospital factors to hospitals' alcohol-based handrub consumption in Europe: results of the European PROHIBIT study. Clin Microbiol Infect. 2018;24(7):778 e1- e6.
21. Hansen S, Schwab F, Zingg W, Gastmeier P, The Prohibit Study G. Process and outcome indicators for infection control and prevention in European acute care hospitals in 2011 to 2012 - Results of the PROHIBIT study. Euro Surveill. 2018;23(21).
22. Hansen S, Zingg W, Ahmad R, Kyratsis Y, Behnke M, Schwab F, et al. Organization of infection control in European hospitals. J Hosp Infect. 2015;91(4):338-45.
23. Clack L, Zingg W, Saint S, Casillas A, Touveneau S, da Liberdade Jantarada F, et al. Implementing infection prevention practices across European hospitals: an in-depth qualitative assessment. BMJ Qual Saf. 2018;27(10):771-80.
24. Sax H, Allegranzi B, Chraiti MN, Boyce J, Larson E, Pittet D. The World Health Organization hand hygiene observation method. Am J Infect Control. 2009;37(10):827-34.
25. Pittet D, Hugonnet S, Harbarth S, Mourouga P, Sauvan V, Touveneau S, Perneger TV. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Infection Control Programme. Lancet. 2000;356(9238):1307-12.
26. O'Boyle CA, Henly SJ, Larson E. Understanding adherence to hand hygiene recommendations: the theory of planned behavior. Am J Infect Control. 2001;29(6):352-60.
27. Sharma S, Sharma S, Puri S, Whig J. Hand hygiene compliance in the intensive care units of a tertiary care hospital. Indian J Community Med. 2011;36(3):217-21.
28. Stewardson AJ, Sax H, Gayet-Ageron A, Touveneau S, Longtin Y, Zingg W, Pittet D. Enhanced performance feedback and patient participation to improve hand hygiene compliance of health-care workers in the setting of established multimodal promotion: a single-centre, cluster randomised controlled trial. Lancet Infect Dis. 2016;16(12):1345-55.
29. Scheithauer S, Batzer B, Dangel M, Passweg J, Widmer A. Workload even affects hand hygiene in a highly trained and well-staffed setting: a prospective 365/7/24 observational study. J Hosp Infect. 2017;97(1):11-6.
30. Hansen S, Schwab F, Behnke M, Carsauw H, Heczko P, Klavs I, et al. National influences on catheter-associated bloodstream infection rates: practices among national surveillance networks participating in the European HELICS project. J Hosp Infect. 2009;71(1):66-73.
31. Dufour JC, Reynier P, Boudjema S, Soto Aladro A, Giorgi R, Brouqui P. Evaluation of hand hygiene compliance and associated factors with a radio-frequency-identification-based real-time continuous automated monitoring system. J Hosp Infect. 2017;95(4):344-51.
32. Smiddy MP, R OC, Creedon SA. Systematic qualitative literature review of health care workers' compliance with hand hygiene guidelines. Am J Infect Control. 2015;43(3):269-74.
33. Sax H, Clack L. Mental models: a basic concept for human factors design in infection prevention. J Hosp Infect. 2015;89(4):335-9.
34. Lutze B, Chaberny IF, Graf K, Krauth C, Lange K, Schwadtke L, et al. Intensive care physicians' and nurses' perception that hand hygiene prevents pathogen transmission: Belief strength and associations with other cognitive factors. J Health Psychol. 2017;22(1):89-100.
35. Grayson ML, Macesic N, Huang GK, Bond K, Fletcher J, Gilbert GL, et al. Use of an Innovative Personality-Mindset Profiling Tool to Guide Culture-Change Strategies among Different Healthcare Worker Groups. PLoS One. 2015;10(10):e0140509.
36. Gould DJ, Navaie D, Purssell E, Drey NS, Creedon S. Changing the paradigm: messages for hand hygiene education and audit from cluster analysis. J Hosp Infect. 2018;98(4):345-51.
37. Sassenrath C, Diefenbacher S, Siegel A, Keller J. A person-oriented approach to hand hygiene behaviour: Emotional empathy fosters hand hygiene practice. Psychol Health. 2016;31(2):205-27.
38. McBryde ES, Pettitt AN, McElwain DL. A stochastic mathematical model of methicillin resistant Staphylococcus aureus transmission in an intensive care unit: predicting the impact of interventions. J Theor Biol. 2007;245(3):470-81.
39. Grundmann H, Hori S, Winter B, Tami A, Austin DJ. Risk factors for the transmission of methicillin-resistant Staphylococcus aureus in an adult intensive care unit: fitting a model to the data. J Infect Dis. 2002;185(4):481-8.

40. Doan TN, Kong DC, Marshall C, Kirkpatrick CM, McBryde ES. Modeling the impact of interventions against Acinetobacter baumannii transmission in intensive care units. Virulence. 2016;7(2):141-52.
41. Goldstein ND, Eppes SC, Mackley A, Tuttle D, Paul DA. A Network Model of Hand Hygiene: How Good Is Good Enough to Stop the Spread of MRSA? Infect Control Hosp Epidemiol. 2017;38(8):945-52.
42. Greene C, Ceron NH, Eisenberg MC, Koopman J, Miller JD, Xi C, Eisenberg JNS. Asymmetric transfer efficiencies between fomites and fingers: Impact on model parameterization. Am J Infect Control. 2018;46(6):620-6.
43. D'Agata EM, Webb GF, Horn MA, Moellering RC, Jr., Ruan S. Modeling the invasion of community-acquired methicillin-resistant Staphylococcus aureus into hospitals. Clin Infect Dis. 2009;48(3):274-84.
44. Temime L, Kardas-Sloma L, Opatowski L, Brun-Buisson C, Boëlle P, Guillemot D. NosoSim: an agent-based model of nosocomial pathogens circulation in hospitals. Procedia Computer Science. 2012;1:2245-52.
45. Hornbeck T, Naylor D, Segre AM, Thomas G, Herman T, Polgreen PM. Using sensor networks to study the effect of peripatetic healthcare workers on the spread of hospital-associated infections. J Infect Dis. 2012;206(10):1549-57.
46. Srigley JA, Furness CD, Baker GR, Gardam M. Quantification of the Hawthorne effect in hand hygiene compliance monitoring using an electronic monitoring system: a retrospective cohort study. BMJ Qual Saf. 2014;23(12):974-80.
47. Dawson CH. Future systems of measurement for hand hygiene in healthcare. Warwick: University of Warwick; 2014.
48. Hagel S, Reischke J, Kesselmeier M, Winning J, Gastmeier P, Brunkhorst FM, et al. Quantifying the Hawthorne Effect in Hand Hygiene Compliance Through Comparing Direct Observation With Automated Hand Hygiene Monitoring. Infect Control Hosp Epidemiol. 2015;36(8):957-62.

Chapter 9

The effect of an intervention bundle to prevent central venous catheter-related bloodstream infection in a national programme in the Netherlands

T.I.I. van der Kooi*, E.A. Smid*, M.B.G. Koek, S.E. Geerlings,
L.G.M. Bode, T.E.M. Hopmans, and S.C. de Greeff

* These authors contributed equally to the work.

Journal of Hospital Infection 2023(131): 194-202

ABSTRACT

Introduction: Central venous catheters (CVC) can lead to central line-related bloodstream infections (CRBSI). A six-item bundle was introduced in 2009 to prevent CRBSI in Dutch hospitals.

Aim: This study aimed to determine the impact of an intervention bundle on CRBSI risk.

Methods: Data were obtained from hospitals participating in the national CRBSI surveillance between 2009 and 2019. Bundle compliance was evaluated as a total ("overall") bundle (all six items) and as an insertion bundle (four items) and a maintenance bundle (two daily checks). We estimated the impact of the overall and partial bundles, using multilevel Cox regression.

Findings: Of the 66 hospitals in the CRBSI surveillance 56 (84.8%) recorded annual bundle (non)compliance for >80% of the CVCs, for 1-9 years. In these 56 hospitals CRBSI incidence decreased from 4.0 to 1.6/1000 CVC days. In the intensive care units (ICU) compliance was not associated with CRBSI risk (hazard ratio (HR) for the overall, insertion and maintenance bundle were 1.14 [95% confidence interval 0.80-1.64], 1.05 [0.56-1.95] and 1.13 [0.79-1.62]), respectively. Outside the ICU the non-significant association of compliance with the overall bundle (HR 1.36 [0.96-1.93]) resulted from opposite effects of the insertion bundle, associated with decreased risk (HR 0.50 [0.30-0.85]) and the maintenance bundle, associated with increased risk (HR 1.68 [1.19-2.36]).

Conclusion: Following a national program to introduce an intervention bundle CRBSI incidence decreased significantly. In the ICU, bundle compliance was not associated with CRBSI risk, but outside the ICU improved compliance to the insertion bundle resulted in a decreased CRBSI risk.

INTRODUCTION

Central venous catheters (CVCs) are an important cause of bloodstream infections. These infections increase the length of hospital stay and medical costs [1, 2]. Dutch hospitals can participate in surveillance of central venous catheter-related bloodstream infections (CRBSI) within the national surveillance network for healthcare associated infections (PREZIES). Between 2002 and 2009 the average CRBSI incidence density in nine hospitals was 2.0/1 000 CVC days [3, 4]. There was large variation in CRBSI incidence between hospitals (range 0.9 to 3.0) and the impression was that rates were higher in hospitals that did not participate, suggesting that improvement was still possible [3]. In 2008, the Dutch Hospital Patient Safety Programme (DHPSP) was initiated to prevent adverse events and avoidable deaths in hospitalized patients [5]. One of the 10 subprogrammes included CRBSI prevention, with the goal to decrease the incidence of CRBSI to less than 3 cases per 1000 CVC days in all hospitals. To achieve this a six-item intervention bundle was introduced (Box 1), based on the successful bundle of Pronovost et al[6]. Hospital staff from infection control, quality control and intensive care departments attended national workshops, where the scientific background, implementation and surveillance of the CRBSI prevention tool was discussed. The DHPSP additionally supplied campaign material and tools to use in the hospitals.

The DHPSP was initially planned to run until 2013, but was extended for a further two years, with the aim that hospitals should achieve 90% compliance with the bundle. It was expected that increased bundle compliance would result in decreased CRBSI rates. Dutch hospitals were advised to implement the intervention bundle for all CVCs and to report compliance and outcomes within the national surveillance network. Registration of the bundle compliance was facilitated until 2019.

The goal of this study was to determine the impact of the intervention bundle on the CRBSI risk in the Netherlands.

METHODS

CRBSI surveillance

Participation in the Dutch national surveillance network is voluntarily. The incidence of CRBSI is assessed using strict criteria based on the definitions from the (European) Centre for Disease Control (Supplementary Textbox A1). Participating hospitals report data on all non-tunnelled CVCs of patients of ≥18 years, inserted for ≥48 hours in the subclavian, jugular, or femoral vein. The maximum duration of follow-up of the CVC is 28 days, but follow-up (including bundle compliance monitoring) ends in the event of a CRBSI, CVC removal, discharge, death or when treatment is discontinued due to impending death. A new hospital admission is considered a new patient. Patient characteristics (sex, date of

birth, intensive care unit (ICU) admissions), insertion and removal date, insertion vein, and CVC indication (total parenteral nutrition, hemodynamic monitoring, dialysis, antibiotics and 'other' uses, independent of the number of days or times of that specific use of the CVC) are reported. Each CVC contributes to the number of CVC days. Hospitals participating in the CRBSI surveillance could choose to participate in the DHPSP CRBSI-prevention programme and report bundle compliance.

***Box 1**: Six-item bundle to prevent CRBSI: Definitions of the bundle items*

Insertion bundle elements:

1. *Hand hygiene*: All hospital personal who took part actively in inserting the CVC must disinfect their hands.
2. *Precautions during insertion*: the patient is covered with a sterile drape to at least 80%, including the head and hair when inserting in the jugular or subclavian vein, and the clinician and assistants wear sterile gowns and gloves, a hat, and a mouth nose mask.
3. *Disinfection of the skin*: The skin should be disinfected with 0.5% chlorhexidine in 70% alcohol before insertion.
4. *Selection of insertion site*: Choose the most optimal insertion site in descending preference: 1) v. subclavian, 2) v. jugular, 3) v. femoral. Deviation of this preferred order is accepted when documented.

Maintenance bundle elements:

5. *Daily check on indication*: Every day it should be checked that the indication for the CVC is still valid; otherwise, the CVC should be removed within 24 hours.
6. *Daily check on insertion site*: Every day the insertion site should be checked for infection symptoms; when there are infection symptoms, the CVC should be removed within 24 hours.

Bundle compliance

Bundle compliance was evaluated as a total ("overall") bundle and in two partial bundles: an insertion bundle, comprising the four interventions to optimize aseptic/sterile insertion of the CVC, and a maintenance bundle, comprising the two daily checks. These maintenance items needed to be performed and recorded daily in order to be recorded as being complied with. Reporting of compliance with the bundle elements could be manual or in an electronic hospital system. For the analyses we distinguished compliance (all six bundle items were complied with) versus noncompliance (all six items recorded

but not all were complied with). For the partial bundles, the definitions were adapted accordingly.

Data selection and statistical analysis

We included data from 2009 up to and including 2019. Not all hospitals that joined the national CRBSI surveillance during this period additionally reported bundle compliance during the entire surveillance period. Some hospitals managed to record compliance only for some bundle elements or for part of the CVCs. For the analyses in this study we included only those years of a hospital where bundle recordings were complete for at least 80% of the CVCs. The trend in CRBSI rates and patient and CVC characteristics is additionally described for all hospital data in this period.

We used Cox regression to determine the association of bundle compliance as a binary variable with CRBSI risk, while accounting for clustering of data within patients and hospitals, using robust covariance estimation and stratification for hospitals. We performed the analyses for the overall bundle as well as for the insertion and maintenance bundles separately in one model. Sex, age, CVC indication and insertion vein were included as covariates to account for potential confounding. Variables were included in the initial multivariable model if the p-value was <0.25, but sex and age were retained during manual backward selection. To assess the effect of ongoing participation, results were evaluated both with and without calendar years and the number of years each hospital participated in the surveillance. We additionally analysed the association of bundle compliance with catheter duration, using multilevel analysis with a gamma distribution.

Some hospitals performed surveillance in ICUs only, but in 2016 hospital wide surveillance became mandatory when participating. Therefore, the analysis of CRBSI was also performed separately for CVC days in the ICU and ICU-acquired CRBSI (including CRBSI developed < 48 hours after ICU-discharge), and for CVC days outside the ICU and non-ICU-acquired CRBSI. Peripherally inserted CVCs can be recorded in the CRBSI surveillance from 2014 onwards but were excluded from these analyses. The statistical analyses were performed using SAS Statistical software, version 9.4 (Cary, NC, USA).

RESULTS

Participation in the surveillance

Following the start of the DHPSP the number of hospitals that took part in the national CRBSI surveillance increased from nine in 2009 to 43 (47% of all 91 Dutch hospitals) in 2014 (Figure 1). After the DHPSP ended, participation decreased to 21 hospitals in 2019. In total, 66 hospitals took part in the CRBSI surveillance, for one to 11 years with a median of five years (interquartile range (IQR) 3-7), for a total of 324 ‘hospital years’).

These 66 hospitals reported data on 62,862 CVCs and 423,316 CVC days for 49,388 patients, with 799 infections.

Of the 66 hospitals in the CRBSI surveillance, 56 (84.8%) recorded bundle (non)compliance for 80% or more of the CVCs, for one to nine years with a median of four years (IQR 3-6), summing up to 240 of the total of 324 hospital years (74.1%) in the CRBSI surveillance (Supplementary Table S1 gives the yearly participation per hospital). In these 240 hospital years, data were reported on 43,262 CVCs and 291,610 CVC days for 31,687 patients, with 507 infections (62.9% microbiologically confirmed CRBSI, 3.9% CRBSI category 1, 16.0% CRBSI category 2, 15.8% CRBSI category 3 and 1.4% CRBSI category 4).

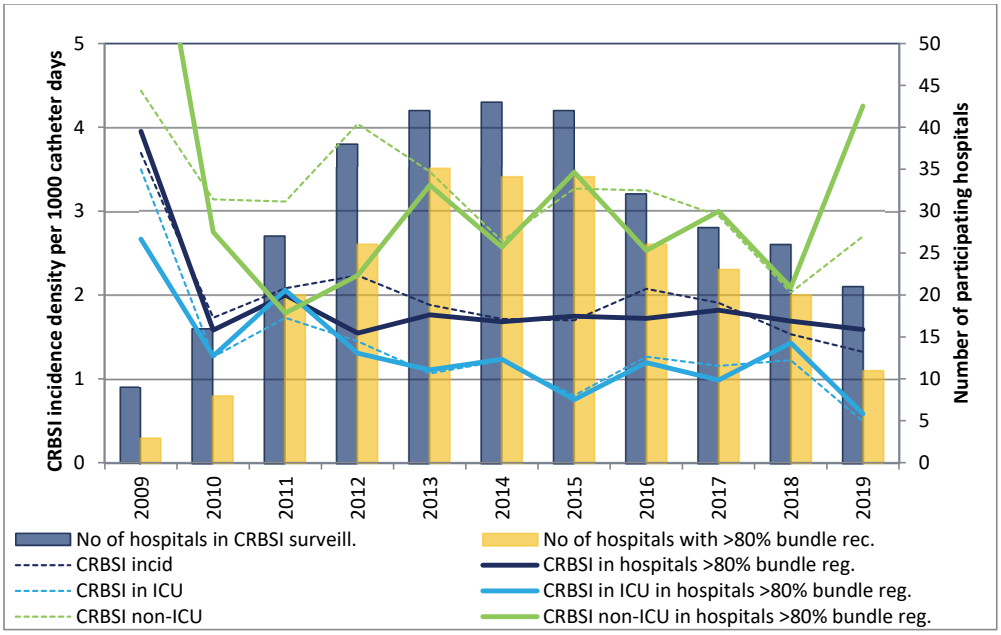


Figure 1: Central venous catheter-related bloodstream infection (CRBSI) incidence and number of hospitals per calendar year.
CRBSI incidence density overall, in and outside the ICU, overall and for those hospitals with >80% bundles recorded in a year.
The number of hospitals participating in the national CRBSI surveillance per year and the number of hospitals that recorded bundle compliance in > 80% of the CVCs (evaluated per year).

Hospital years with ≥80% bundle recordings

Patient and CVC characteristics

Table I shows the patient and CVC characteristics. Apart from sex, all patient and CVC characteristics fluctuated significantly over the years. The percentage of patients outside the ICU increased and the proportion of patients between 18 and 45 years decreased

slightly. CVCs were increasingly inserted in the jugular vein and became less frequently used for antibiotics and dialysis, and instead more often for 'other indications'. Catheter duration decreased from a median of six days (IQR 3-9) in 2009-2013 to five (3-8) thereafter. For CVC days in the ICU (of CVCs with at least one day in the ICU) this was five (IQR 3-7) and four (2-7) respectively, whereas for CVC days outside the ICU (of CVCs with at least one day outside the ICU) this was five (IQR 3-9) and five (2-9). In all 66 hospitals participating in the CRBSI surveillance, patient and CVC characteristics demonstrated comparable trends (Supplementary Table S2).

CRBSI incidence

The average CRBSI rate based on the hospital years with >80% bundles recorded, decreased from 4.0 to 1.6/1000 CVC days, resembling the overall trend from 3.7/1000 in 2009 to 1.3/1000 in 2019 (Figure 1). Figure 2 demonstrates the CRBSI incidence density against number of participation years. During the first three years the CRBSI rate decreased from 2.0 (median 1.6, IQR 0.0-3.0) to 1.5/1000 CVC days (median 1.0, IQR 0.0-2.0). Ongoing participation was associated with a further decrease.

Bundle compliance

The mean compliance to the overall bundle in the first participation year was 64% (median 75% IQR 46-92%). For the insertion bundle this was already 90% (median 93% [85-98%]). The use of 0.5% chlorhexidine in alcohol was practiced for the majority of patients in almost all hospitals. For the maintenance bundle the mean compliance was 69% (median 86% [56-96%]). During the first participation years, the insertion bundle compliance increased (Figure 3) and slightly decreased thereafter. Improving the maintenance bundle and consequently the overall bundle appeared to be more challenging at first. There were, however, substantial differences between participating hospitals. Supplementary Figure A1 shows bundle compliance per calendar year.

Association with the CRBSI risk

Hospital wide: In multivariable analysis of hospital wide data, i.e. without distinction between ICU and non-ICU, the parameters sex, insertion vein and catheter indication were significantly associated with the CRBSI risk (Table II). Male sex, insertion in the jugular and femoral vein and total parenteral nutrition were associated with increased risk whereas antibiotics and hemodynamic monitoring were associated with reduced risk.

The overall bundle compliance was not significantly associated with CRBSI risk in the multivariable model (the hazard ratio (HR) of 1.24 (95% confidence interval (CI) 0.97-

Table I: Patient and central venous catheter (CVC) characteristics per calendar year, in percentages of patients and CVCs; overall number of CVC days, central line-related bloodstream infection (CRBSI) and mean CRBSI incidence per category, for the hospital years with ≥80% bundle recordings.

	Overall				**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**p-value****
		CVC days	**CRBSI**	**incid. per 1000 CVC days**												
Total number of patients	**34081**				**155**	**731**	**2233**	**3396**	**4373**	**5010**	**5453**	**4844**	**4100**	**2644**	**1142**	
Total number of CVCs	**43262**	**291610**	**507**	**1.7**	**247**	**999**	**2977**	**4539**	**5620**	**6354**	**6818**	**5990**	**5002**	**3255**	**1461**	
Sex[*]	%				%	%	%	%	%	%	%	%	%	%	%	0.75
Men	58.9	172311	317	1.8	60.6	60.9	58.9	57.9	58.5	59.5	58.9	58.5	58.6	60.2	59.2	
Women	41.1	119299	190	1.6	39.4	39.1	41.1	42.1	41.5	40.5	41.1	41.5	41.4	39.8	40.8	
Age[*]																0.002
< 45 years of age	6.4	18212	32	1.8	10.3	8.2	7.4	7.2	7.1	6.0	6.1	5.9	5.3	6.5	6.5	
45-65	29.1	87422	141	1.6	25.2	30.8	28.0	28.4	29.4	29.5	28.7	30.7	28.8	28.3	25.9	
≥65	64.5	185976	334	1.8	64.5	61.0	64.6	64.4	63.5	64.4	65.2	63.4	65.9	65.2	66.6	
In ICU with a CVC present[*]																<0.0001
Only in ICU	63.4	194118	232	1.2	77.4	77.2	74.8	72.0	69.7	65.7	61.2	55.3	52.3	57.2	68.9	
Both in and outside ICU	19.9		divided[***]		11.0	15.6	18.5	18.5	18.3	20.8	20.1	21.6	22.6	19.0	18.3	
Only outside ICU	16.7	97492	275	2.8	11.6	7.3	6.7	9.5	12.1	13.5	18.7	23.0	25.0	23.8	12.8	
Insertion vein																<0.0001
Subclavian	28.9	97820	171	1.7	32.0	44.3	39.5	39.7	34.3	30.3	28.4	21.9	18.8	22.9	14.4	
Jugular	47.8	132781	258	1.9	28.3	25.8	31.7	32.4	39.9	46.4	49.7	58.6	62.0	57.0	61.0	
Femoral	23.3	61009	78	1.3	39.7	29.8	28.8	27.9	25.8	23.3	21.9	19.5	19.2	20.2	24.6	

	Overall				2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	p-value**
		CVC days	CRBSI	incid. per 1000 CVC days												
Application																
Total parenteral nutrition	21.4	79473	265	3.3	21.1	19.5	22.5	23.6	21.4	20.2	23.2	18.2	20.9	24.5	18.0	<0.0001
Antibiotics	47.2	146768	207	1.4	36.0	45.2	53.8	55.7	56.7	46.3	41.2	38.6	42.0	46.5	60.0	<0.0001
Dialysis	12.1	40220	54	1.3	16.6	21.0	14.9	12.7	13.4	11.1	10.6	11.1	10.8	11.8	13.8	<0.0001
Hemodynamic monitoring	55.7	149429	187	1.3	64.0	52.7	55.4	61.6	61.6	61.3	58.8	50.9	47.6	43.4	50.8	<0.0001
Other applications	10.3	24274	34	1.4	8.5	9.1	7.0	7.2	6.6	9.3	8.4	13.8	16.0	14.5	12.3	<0.0001
Catheter duration (median)	5				5	6	6	6	5	5	5	5	5	5	5	<0.0001

* Percentages for patient-based characteristics were calculated for patients.
** p-values were calculated with multinomial multilevel regression and indicate whether the distribution of the variable over the categories differed between calendar years. For this aim catheter duration was categorized into 6 categories (2-4, 5-7, 8-10, 11-13, 14-16 and > 16 days).
*** ICU days and non-ICU days of catheters present both in and outside the ICU were attributed to ICU and non-ICU respectively.

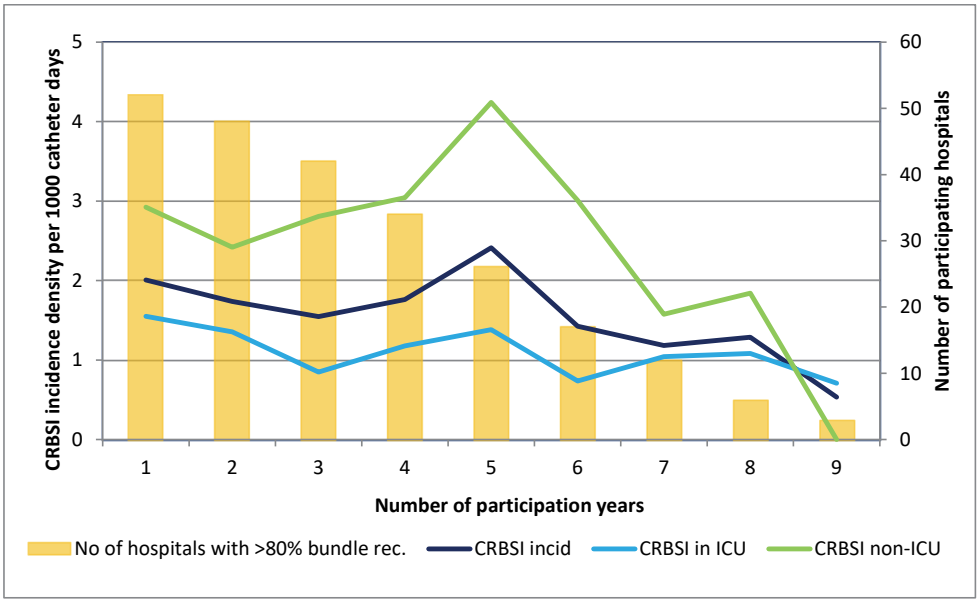


Figure 2: Central venous catheter-related bloodstream infection (CRBSI) incidence density and number of hospitals per participation year, for those hospital years with >80% bundles recorded. CRBSI incidence density overall, in and outside the intensive care unit (ICU).

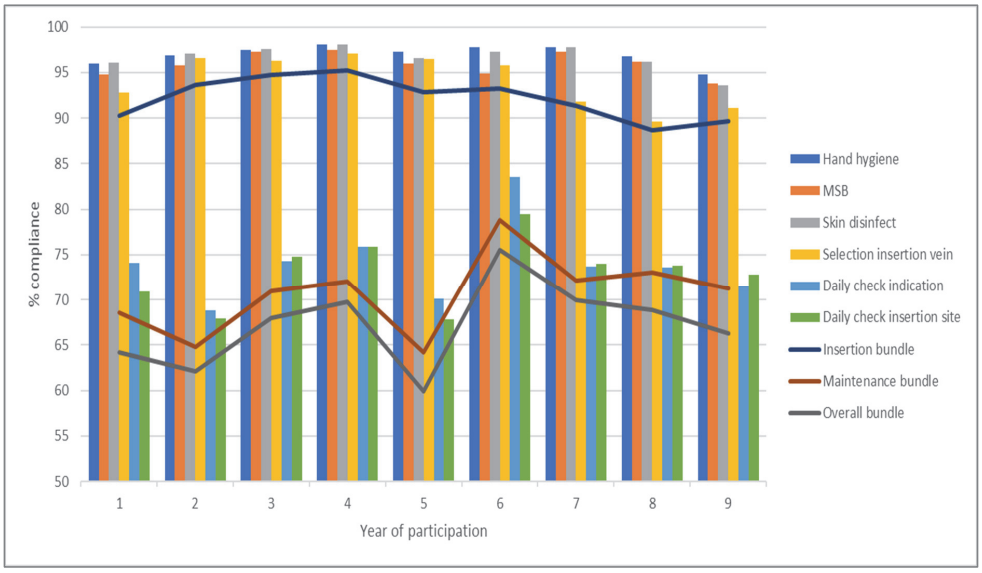


Figure 3: Mean bundle compliance per year of participation (with >80% recordings). MSB, maximum sterile barrier

1.57)); however, the trend indicated a 24% increase in CRBSI risk when all bundle items were complied with. When evaluating the partial bundles instead, the association of compliance with the insertion bundle was not associated with CRBSI risk (HR 0.84 [0.56-1.25]).

Compliance to the maintenance bundle was unexpectedly associated with a higher CRBSI risk (HR 1.31 [1.03-1.67]), i.e. the CRBSI risk was 31% higher when the maintenance bundle was complied with. To evaluate the effect of ongoing participation, the number of participation years was added to the multivariable model. This resulted in a comparable hazard ratio for the maintenance bundle (HR 1.28 [1.00-1.62]), and revealed a significant decrease with ongoing participation (HR per extra participation year 0.93 [0.87-0.99]). This reduction of 7% per year was an average with individual hospitals demonstrating a more erratic pattern over time. Adding calendar year to the model instead of the number of participation years had a similar effect. When evaluating the first four years and the remaining participation years separately, i.e. in two separate multivariable models, the effect of each extra participation year was significant in the first period of four years (HR 0.87 [0.78-0.97]) but not so thereafter (HR 0.91 [0.73-1.12]).

In the ICU: In the ICU the CRBSI incidence was lower than outside the ICU (Figure 1). Mean overall bundle compliance for CVCs in the ICU (for the entire or part of the catheter duration) was 67.6%, whereas this was 52.9% for CVCs that were in place outside the ICU only. This disparity resulted from a difference in the maintenance bundle compliance (69.7 and 49.2%, respectively), whereas the insertion bundle compliance was comparable (93.2 and 93.7%, respectively). In the ICU, neither compliance with the overall bundle, nor the separate insertion and maintenance bundle (together in a model) were independently associated with the CRBSI risk (HR 1.14 [0.80-1.64], 1.05 [0.56-1.95] and 1.13 [0.79-1.62], respectively). Ongoing participation was associated with a significant reduction of the CRBSI risk (HR 0.90 [0.82-0.98]). Calendar year instead of the number of participation years demonstrated a similar association (HR 0.89 [0.82-0.96] and explained the results slightly better. When evaluated separately for the first four and remaining years this risk reduction was significant for the first participation years only (HR 0.78 [0.65-0.94] and 0.99 [0.76-1.29]) respectively).

Outside the ICU: For CVCs outside the ICU, compliance with the overall bundle seemed associated with an increased CRBSI risk, although the association was not statistically significant (HR 1.36 [0.96-1.93]). A model with the separate insertion and maintenance

Table II: Association of patient and central venous catheter (CVC) characteristics with central line-related bloodstream infection (CRBSI) risk. Results of univariable (all variables) and multivariable regression analysis (variables retained in the final model).

	All patients and CVCs				**CVCs (when) in ICU**				**CVCs (when) outside ICU**			
	Univariable analysis		Multivariable analysis		Univar.		Multivar.		Univar.		Multivar.	
	HR[$]	(95% CI[$])	HR	(95% CI)	HR	95% CI	HR	(95% CI)	HR	95% CI	HR	(95% CI)
Sex (male vs female)	1.23	(1.02-1.48)	1.24	(1.03-1.49)	1.20	(0.91-1.59)	1.19	(0.89-1.58)	1.32	(1.04-1.69)	1.28	(1.01-1.62)
Age												
<45 years	ref.		ref.		ref.		ref.		ref.		ref.	
45-65	0.90	(0.62-1.32)	0.89	(0.61-1.30)	0.65	(0.41-1.05)	0.68	(0.42-1.11)	1.31	(0.69-2.46)	1.31	(0.69-2.48)
≥ 65 years	0.99	(0.69-1.41)	0.97	(0.68-1.39)	0.64	(0.41-0.99)	0.66	(0.42-1.03)	1.56	(0.85-2.87)	1.62	(0.88-2.98)
Insertion vein												
Subclavian	ref.		ref.		ref.		ref.		ref.			
Jugular	1.23	(1.01-1.50)	1.51	(1.24-1.85)	1.91	(1.33-2.74)	2.12	(1.47-3.05)	1.12	(0.87-1.43)		
Femoral	1.10	(0.85-1.43)	1.58	(1.18-2.11)	1.93	(1.31-2.84)	2.01	(1.36-2.9)	0.72	(0.42-1.22)		
Application												
Total parenteral nutrition	2.36	(1.98-2.82)	2.26	(1.86-2.75)	1.27	(0.92-1.76)	1.44	(1.02-2.04)	3.50	(2.61-4.69)	3.27	(2.42-4.42)
Antibiotics	0.54	(0.44-0.65)	0.54	(0.44-0.67)	0.65	(0.48-0.88)	0.64	(0.47-0.87)	0.50	(0.39-0.65)	0.61	(0.47-0.81)
Dialysis	0.78	(0.59-1.04)	0.63	(0.45-0.88)	1.01	(0.73-1.41)			0.57	(0.30-1.10)		
Hemodynamic monitoring	0.67	(0.55-0.81)	0.75	(0.61-0.92)	0.92	(0.70-1.21)			0.65	(0.48-0.90)		
Other	1.03	(0.72-1.48)			1.18	(0.70-1.99)			0.93	(0.54-1.60)		
Per additional **year of participation***	0.94	(0.89-1.00)	0.93	(0.87-0.99)	0.92	(0.84-1.00)	0.90	(0.82-0.98)	0.97	(0.89-1.06)		
Per calendar year	0.95	(0.91-1.00)	*0.91***	*(0.86-0.97)*	0.91	(0.84-0.98)	*0.89***	*(0.82-0.96)*	0.99	(0.92-1.060		
Compliance												
Overall bundle (1_6)	1.15	(0.91-1.45)			1.12	(0.78-1.60)			1.35	(0.96-1.91)		
Insertion bundle***	0.84	(0.57-1.25)			0.99	(0.54-1.81)			0.62	(0.37-1.03)	0.50	(0.30-0.85)
Maintenance bundle ***	1.23	(0.97-1.55)	1.28	(1.00-1.62)	1.11	(0.78-1.59)			1.59	(1.13-2.24)	1.68	(1.19-2.36)

$ HR = hazard ratio; CI = confidence interval

* year with >80% registration of bundles

** Multivariable results when in model instead of participation years

*** In multivariable analysis together in initial model

bundle demonstrated a significant but opposite association of the partial bundles: the HR of the maintenance bundle was 1.68 [1.19-2.36], i.e. a 68% increased CRBSI risk when the two daily checks were complied with, but the HR of the insertion bundle was 0.50 [0.30-0.85], i.e. a 50% reduced risk when the four insertion items were complied with. Ongoing participation, overall nor for the first four years only, and calendar time were not significant.

Catheter duration

Compliance to the bundle, especially the maintenance bundle, could result in shorter catheter stays, which also contributes to a smaller CRBSI risk. In our study, bundle compliance was associated with a small but significant decrease in catheter duration, when adjusted for patient and CVC characteristics: -0.15 days (95% CI -0.05 to -0.26). When the two partial bundles were modelled instead, the compliance to the maintenance bundle was associated with a significant decrease in duration: -0.29 days (-0.18 to -0.39), whereas the insertion bundle was associated with a similarly small increase: +0.29 days (0.12 - 0.47). Adding calendar time and number of participation years to the model resulted in comparable estimates (not shown).

DISCUSSION

During and following a national patient safety programme, introducing a CRBSI intervention bundle, Dutch hospitals successfully decreased their CRBSI rates. Overall bundle compliance increased from 60% in the first to 73% in the fourth bundle participation year. In the ICU there was no association between bundle compliance and CRBSI risk. Outside the ICU, where the incidence density of infection was approximately 2.5 times higher than in the ICU, compliance with the overall bundle was marginally significantly associated with the CRBSI risk. However, the effect was composed of a significant risk reduction of 50% when the insertion bundle was complied with and a significant risk increase of 68% when the maintenance bundle was complied with. This last finding might be the result of an increased awareness to diagnose CRBSI when a daily check on the insertion site was performed. The same analysis performed on CVCs with a duration of at least six days showed similar results overall and for CVCs with ≥ 6 days in ICU, but the effect of ongoing participation/calendar time was now insignificant. For CVCs with ≥ 6 days outside the ICU the effect of insertion bundle compliance was no longer significant, whereas compliance to the maintenance bundle remained significantly associated, as can be expected (data not shown).

The lack of association in the ICU might be explained by the low CRBSI incidence from the start compared with other studies at the moment the bundle was introduced [7]. In a European study (PROHIBIT), the implementation of a comparable bundle in ICUs was effective but not in one study arm (of three) where baseline CRBSI incidence was as low as 1.4/1000 CVC days already[8]. Ista et al. demonstrated in their meta-analysis that risk reduction was significantly lower in studies with a lower baseline central line-associated bloodstream infection (CLABSI) incidence than in studies with CLABSI incidence > 5/1000 CVC days[9]. Another similarity between this study and ours was the relatively high compliance with the insertion bundle at baseline: 82% and 85%, respectively. Nevertheless, ICU rates decreased over time, which may be related to the decrease in catheter duration in the ICU and other, undocumented, improvements in infection prevention practices.

Outside the ICU the CRBSI rate was higher though, possibly in part because CVCs here were more often used for total parenteral nutrition (47.9 versus 18.4%), and nursing staff probably had less experience with CVCs. In the Netherlands, central line-teams, when present, are usually not active outside the ICU. Improving CVC insertion procedures outside the ICU led to a significant reduction in the risk to develop CRBSI. Unexpectedly, compliance with the maintenance bundle, which was lower here than in the ICU, was associated with an increased risk of infection. As mentioned above, compliance with the daily checks presumably increased the awareness of CRBSI whereas some cases might have gone unnoticed previously. It is also possible that the compliance increased in the event of a suspected increased risk of CRBSI of a patient. Furuya et al. found a marginally significant protective association between ‘daily check’ and CLABSI rates in univariable analysis, but in this study the compliance and CLABSI rates were reported on ICU level[10]. The relatively few studies that reported on the effect of (varying) CRBSI prevention bundles in non-ICU wards have been mostly positive too[11-14], but did not adjust for other relevant patient and CVC characteristics.

A successful implementation of the intervention bundle, especially of the insertion bundle item regarding insertion site and the two daily checks, could also have resulted in a decrease in catheter duration and an increase in insertions via subclavian veins. The median overall catheter duration decreased from six to five days and, from four to three days in the ICU. Outside the ICU catheter duration did not decrease, but the obligation to monitor hospital-wide from 2016 onwards may have impacted this. Compliance with the overall bundle was associated with a small but significant reduction in catheter duration, as one would expect. When evaluated as partial bundles, compliance with the maintenance bundle was associated with a (larger) reduction, whereas compliance to the insertion bundle was associated with a longer duration. It is possible that precautions

taken at insertion were sometimes less when it was already expected that the CVC would be needed for a few days only. Although the subclavian vein was the preferred vein as it was associated with a lower CRBSI risk, the proportion of CVCs inserted here decreased. Insertion via the jugular vein has become popular with the increased availability of ultrasound guidance[15].

We used data from a national surveillance network that facilitated voluntary reporting of compliance with the DHPSP CRBSI intervention bundle, creating an extensive database to study the relationship between the bundle and CRBSI risk. Thus far, studies that investigate the effect of CRBSI bundles outside the ICU are relatively sparse [11-13]. Our surveillance was not limited to the ICU and comprised non-ICU wards, which allowed us to determine the bundle effect for these two settings separately.

However, as participation in the PREZIES CRBSI surveillance is voluntary, there might have been participation bias. A quarter of the Dutch hospitals did not participate in the CRBSI surveillance during the DHPSP programme. Of the 66 hospitals that did participate in this period, 56 (84.8%) reported (non)-compliance with the bundle for at least one year. Six hospitals merged to four new centres during the study period. The analysis was also performed using the merger hospitals, with respective longer participation periods, instead of the original sites, with comparable results (not shown).

Some hospitals may have been motivated to join the DHPSP programme because they experienced a problem with CRBSI. The high mean CRBSI rate during the first year of the patient safety programme might reflect this. This could result in an overestimation of the observed effect. However, analysis without 2009 led to similar results (data not shown). It is also possible that hospitals that started later, e.g. because they needed more time to prepare the practicalities of the CRBSI and/or bundle compliance registration, initially had higher CRBSI rates as well. It is known that, even in formal study set ups with a prospectively monitored baseline phase, infection rates can decrease before the actual implementation of an intervention. This probably results from increased awareness following the introduction of, and build-up to, the surveillance/study, a national programme, or political pressure[8, 16]. In our regression analyses we were not able to distinguish a participation effect from a secular trend. However, the effect of each extra participation year was only significant in the first four years, which advocates a true effect of ongoing participation.

The cut-off value of 80% was to some extent arbitrary. Including all hospital years with at least 50% recordings led to a further inclusion of 39 hospital years and comparable results (not shown).

Our data were collected in 'real life', including many hospitals, thus the results are more generalizable than data from a (limited) study setting. However, a limitation of the

voluntary surveillance is the heterogenous set of hospitals participating over the years, with different patient populations, initial CRBSI incidences, and reporting rates. This complicates straightforward interpretation of the results and multilevel analysis can only partially account for this. Second, there was no standardized way of collecting the data from the patient file (checklist or text), and it was at each hospital's discretion to decide how to organize the, sometimes challenging, recording of the compliance with the bundle elements. Checklist items are not necessarily reported correctly[17]. While word had it that a few hospitals default reported 'yes' for all bundle elements, because it was considered daily practice in their hospital, most hospitals only reported information that was available in the patient file. A hospital that by default answered 'yes' for all elements probably overestimated compliance, but hospitals only reporting information available from the patient file, may have underestimated compliance. Removing the hospital years reporting 100% compliance from the data gave highly similar results (not shown). Third, in this real-life setting hospitals may differ in culturing practices. While some hospitals culture all CVCs, others only culture the CVCs that are suspected of CRBSI. This might have changed over time in hospitals and between hospitals during the study period.

In conclusion, following a national program to introduce an intervention bundle, CRBSI incidence decreased significantly. In the ICU, with relatively low CRBSI incidence, the compliance with the CRBSI intervention bundle was not associated with CRBSI risk. Outside the ICU, the introduction of a CRBSI bundle appeared to be an effective method to reduce CRBSI rates. Hospitals and departments with relatively high CRBSI incidences will benefit from implementing the CRBSI intervention bundle to improve patient care.

ACKNOWLEDGEMENTS

The authors wish to thank all participating hospitals and hospital staff for their contribution.

Supplement

Case definition of Central venous catheter-Related Bloodstream Infection (CRBSI) in the PREZIES Surveillance

CRBSI: microbiologically-confirmed CVC-related bloodstream infection
Clinical symptoms [fever (>38°), shivers, hypotension (systolic pressure <100 mmHg)]
And
peripheral venous blood culture is positive
And
positive (semi)quantitative culture of the Central Venous Catheter (CVC)- tip [>15 colony-forming units (cfu)] with identical microorganism
or
quantitative blood culture ratio CVC blood sample/peripheral blood sample > 5;
or
differential delay of positivity of blood cultures: CVC blood sample culture positive two hours or more before peripheral blood culture (blood samples drawn simultaneously);
or
positive culture with identical microorganism from pus from CVC insertion site
And
absence of other infection with identical microorganism.

CRBSI, category 1
Clinical symptoms [fever (>38°), shivers, hypotension (systolic pressure <100 mmHg)]
And
positive qualitative culture of the CVC tip
And
peripheral venous blood culture positive with identical microorganism
And
absence of other infection with identical microorganism.

CRBSI, category 2
Clinical symptoms [fever (>38°), shivers, hypotension (systolic pressure <100 mmHg)]
And
positive (semi)quantitative culture of the CVC tip (>15 cfu)
And
no peripheral venous blood sample obtained, however arterial blood culture positive with identical microorganism
And
absence of other infection with identical microorganism.

CRBSI, category 3
Clinical symptoms [fever (>38°), shivers, hypotension (systolic pressure <100 mmHg)]
And
peripheral venous blood culture is positive or no blood cultures taken
And
positive qualitative or quantitative culture of the CVC tip with identical microorganism

or no culture of the CVC tip taken
And
fever disappears within 24h after CVC removal
And
absence of other infection with identical microorganism.

CRBSI, category 4
Clinical symptoms [fever (>38°), shivers, hypotension (systolic pressure <100 mmHg)]
And
positive peripheral venous blood culture
And
CVC remains in situ
And
fever disappears within 48 h after start of antibiotic treatment.
And
absence of other infection with identical microorganism

Notes:
- Catheter-related: the CVC was in situ < 48 hours before the onset of the BSI
- In Dutch clinical practice, CRBSI is usually investigated by culturing both peripheral blood and the CVC tip. If less optimal (laboratory) methods are used, the diagnostic CRBSI categories 1-4 are available (hierarchical structure).
- The CRBSI categories specify the laboratory method of culturing the CVC (semi-qualitative of quantitative) and the body site from which the blood culture is drawn (peripheral venous or arterial).
- The CVC and blood samples are preferentially drawn simultaneously or within 24 hours.

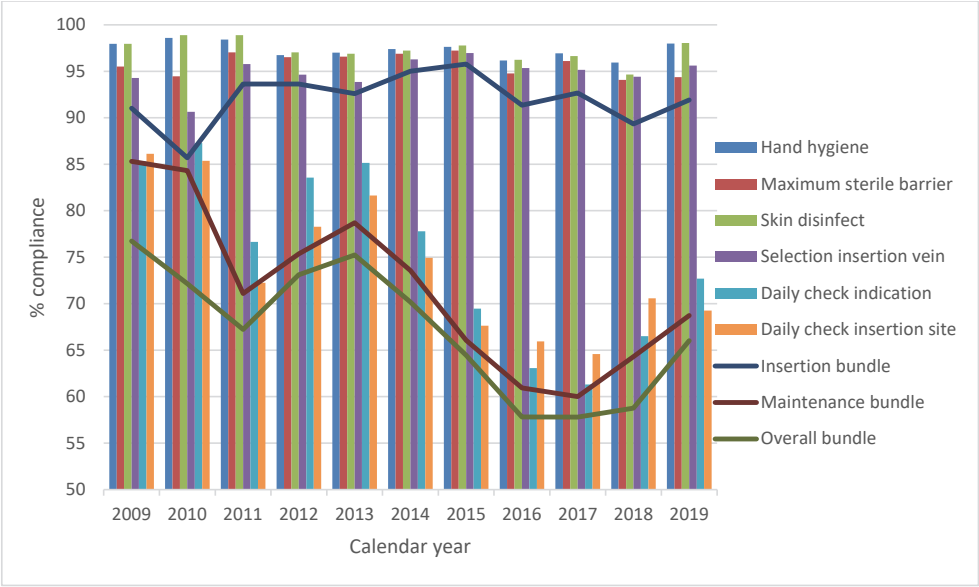


Figure S1: Mean bundle compliance per calendar year (of hospitals with >80% recordings)

REFERENCES

1. Blot SI, Depuydt P, Annemans L, Benoit D, Hoste E, De Waele JJ, et al. Clinical and economic outcomes in critically ill patients with nosocomial catheter-related bloodstream infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2005;41(11):1591-8 https://doi.org/10.1086/497833.
2. Leistner R, Hirsemann E, Bloch A, Gastmeier P, Geffers C. Costs and prolonged length of stay of central venous catheter-associated bloodstream infections (CVC BSI): a matched prospective cohort study. Infection. 2014;42(1):31-6 https://doi.org/10.1007/s15010-013-0494-z.
3. van der Kooi TI, Wille JC, van Benthem BH. Catheter application, insertion vein and length of ICU stay prior to insertion affect the risk of catheter-related bloodstream infection. The Journal of hospital infection. 2012;80(3):238-44 https://doi.org/10.1016/j.jhin.2011.11.012.
4. van der Kooi TI, Mannien J, Wille JC, van Benthem BH. Prevalence of nosocomial infections in The Netherlands, 2007-2008: results of the first four national studies. The Journal of hospital infection. 2010;75(3):168-72 https://doi.org/10.1016/j.jhin.2009.11.020.
5. VMS Veiligheidsprogramma. Prevention of CRBSI and treatment of severe sepsis (Voorkomen van lijnsepsis en behandeling van ernstige sepsis) February 2009 [Available from: https://www.vmszorg.nl/praktijkvoorbeelden-en-tools/praktijkgids-voorkomen-lijnsepsis-en-behandeling-ernstige-sepsis/.
6. Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. The New England journal of medicine. 2006;355(26):2725-32 https://doi.org/10.1056/NEJMoa061115.
7. Blot K, Bergs J, Vogelaers D, Blot S, Vandijck D. Prevention of Central Line-Associated Bloodstream Infections Through Quality Improvement Interventions: A Systematic Review and Meta-analysis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2014 https://doi.org/10.1093/cid/ciu239.
8. van der Kooi T, Sax H, Pittet D, van Dissel J, van Benthem B, Walder B, et al. Prevention of hospital infections by intervention and training (PROHIBIT): results of a pan-European cluster-randomized multicentre study to reduce central venous catheter-related bloodstream infections. Intensive care medicine. 2018;44(1):48-60 https://doi.org/10.1007/s00134-017-5007-6.
9. Ista E, van der Hoven B, Kornelisse RF, van der Starre C, Vos MC, Boersma E, et al. Effectiveness of insertion and maintenance bundles to prevent central-line-associated bloodstream infections in critically ill patients of all ages: a systematic review and meta-analysis. The Lancet Infectious diseases. 2016;16(6):724-34 https://doi.org/10.1016/S1473-3099(15)00409-0.
10. Furuya EY, Dick A, Perencevich EN, Pogorzelska M, Goldmann D, Stone PW. Central line bundle implementation in US intensive care units and impact on bloodstream infections. PloS one. 2011;6(1):e15452 https://doi.org/10.1371/journal.pone.0015452.
11. Freixas N, Bella F, Limon E, Pujol M, Almirante B, Gudiol F. Impact of a multimodal intervention to reduce bloodstream infections related to vascular catheters in non-ICU wards: a multicentre study. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2013;19(9):838-44 https://doi.org/10.1111/1469-0691.12049.
12. Garcia-Rodriguez JF, Alvarez-Diaz H, Vilarino-Maneiro L, Lorenzo-Garcia MV, Canton-Blanco A, Ordonez-Barrosa P, et al. Epidemiology and impact of a multifaceted approach in controlling central venous catheter associated blood stream infections outside the intensive care unit. BMC infectious diseases. 2013;13:445 https://doi.org/10.1186/1471-2334-13-445.

13. Klintworth G, Stafford J, O'Connor M, Leong T, Hamley L, Watson K, et al. Beyond the intensive care unit bundle: Implementation of a successful hospital-wide initiative to reduce central line-associated bloodstream infections. American journal of infection control. 2014;42(6):685-7 https://doi.org/10.1016/j.ajic.2014.02.026.

14. Wei AE, Markert RJ, Connelly C, Polenakovik H. Reduction of central line-associated bloodstream infections in a large acute care hospital in Midwest United States following implementation of a comprehensive central line insertion and maintenance bundle. J Infect Prev. 2021;22(5):186-93 https://doi.org/10.1177/17571774211012471.

15. Scholten HJ, Ten Bloemendal E, Botter B, Korsten HHM, Bouwman RA. Barriers to ultrasound guidance for central venous access: a survey among Dutch intensivists and anaesthesiologists. J Clin Monit Comput. 2019;33(6):1023-31 https://doi.org/10.1007/s10877-018-00246-z.

16. Bion J, Richardson A, Hibbert P, Beer J, Abrusci T, McCutcheon M, et al. 'Matching Michigan': a 2-year stepped interventional programme to minimise central venous catheter-blood stream infections in intensive care units in England. BMJ quality & safety. 2013;22(2):110-23 https://doi.org/10.1136/bmjqs-2012-001325.

17. van Daalen FV, Hulscher M, Minderhoud C, Prins JM, Geerlings SE. The antibiotic checklist: an observational study of the discrepancy between reported and actually performed checklist items. BMC infectious diseases. 2018;18(1):16 https://doi.org/10.1186/s12879-017-2878-7.

Chapter 10

General Discussion

This thesis provides an overview of the impact of healthcare associated infections (HAI) on patients in Dutch hospitals during the last two decades, as measured through the national surveillance program. It discusses the frequency of the major device-associated HAI and their risk factors *over time,* and, within the setting of an inter-rater reliability study, the contribution of HAI to mortality. It also presents some of the advances in HAI prevention, with a focus on CRBSI and the effect of introducing so-called "bundles" of best practices. The first part of this chapter focusses on the merits and limitations of surveillance programs and surveillance data (section 10.1), the actual HAI rates in the Netherlands (10.2), and the future of HAI surveillance (10.3). It will moreover discuss the preventability of HAI and death following a HAI, as this is connected to the contribution of HAI to mortality (10.4). The second part contains two sections: on the effectiveness of bundles (10.5) and the importance of hand hygiene, with an extension to hand hygiene in Dutch hospitals (10.6). Some concluding notes follow in 10.7.

PART I

10.1 The merits and limitations of surveillance programs and their data

All over the world a growing number of hospitals participate in HAI surveillance [1-5]. HAI surveillance has proven to be an essential instrument to lower HAI rates and thus protect patients, as demonstrated in many evaluations [1, 6-10] and this thesis. Surveillance systems, in order to be effective, need to meet a number of requirements[11]:

- Ongoing and systematic data collection. Protocols ensure uniform application of patient and procedure selections, variable recording, and infection criteria, through time. Monitoring HAI in a large-scale surveillance program in which the infection and inclusion criteria are standardised additionally allows hospitals to compare their HAI rates with other hospitals, However, despite a protocol variation in local data collection can exist and limit the quality of the surveillance data. For the Dutch surveillance surgical site infection (SSI) programme, on-site validation in the past has proven that the surveillance data are reliable [12], and the same was concluded for CRBSI. Validation visits within the European PPS demonstrated a good specificity for HAI (98-99%). The sensitivity was 72-83% [13, 14]. Although this validation study found inter-rater reliability for pneumonia was very good (kappa 1.00), most other studies reveal that inter-rater reliability for VAP is low among radiologists [15, 16]. It has furthermore been demonstrated for SSI that surveillance quality is positively associated with better detection and therefore higher SSI rates and that culturing practices, which may vary among hospitals, affect the number of CRBSI found ('the

harder you look the more you find') [17, 18]. Surveillance definitions sometimes differ from clinical definitions, and some clinicians therefore challenge the cases recorded by the surveillance team. Frequent changes of infection control staff, as observed in Dutch hospitals, may additionally affect the consistency of recording.

- Analysis and interpretation of data. To better understand trends in time and differences between centres case mix adjustment is important. To avoid interference with the infection, the collected patient and procedure/device characteristics are preferably determined at admission or at the start of the medical intervention that poses the risk. These characteristics should also be uniformly available in the electronic patient files of different hospitals. In practice, therefore, surveillance must often seek a compromise with limited data on patient and procedure/devices [19-21]. The choice of these potential risk factors is based on clinical knowledge and on earlier studies. However, studies may differ in patient population and health care setting and consequently in their findings. Apart from this, the HAI incidence in these earlier studies will most often be higher, with therefore more discriminatory risk factors than at the time a surveillance protocol is drawn up. For example, the analysis in chapter 2 and 3 demonstrated that some of the recorded risk factors, which were selected based on earlier studies, e.g. the APACHE II score, did not appear to be associated with CRBSI risk in the Dutch surveillance data. A longer ICU stay before CVC insertion, which can serve as a proxy for disease severity, was associated with a higher CRBSI risk. Again, with further decreasing CRBSI risk in the ICU, it was no longer associated (data not shown). Another possible limitation, following from the requirement that data for surveillance should be easily retrievable, is the lack of detail. For example, in the Dutch CRBSI surveillance, catheter applications are not recorded on a daily basis nor per lumen. The resulting data do not allow a very accurate assessment of e.g. the CRBSI risk of TPN. Daily recording of a relevant patient or device characteristic, as practiced in the VAP surveillance programme, enables better evaluation of the associated risk, including as a function of time (chapter 4), but proved too laborious for routine surveillance.
- Timely feedback of surveillance results to HCWs and hospital management is necessary to be able to act upon the results and improve the care in question. Hospitals that participated in the Dutch surveillance programme received feedback reports annually or more frequently if requested. For CRBSI and VAP, these included the predicted incidence given the distribution of the hospital's patient population over the major 'uncontrollable' risk factors (use of the CVC for CRBSI; specialty for VAP). Hospital participating in prevalence surveys receive a report with the prevalence stratified by a number of patient characteristics and by clinical specialty.

Results are also published on the website (PREZIES | RIVM) and in journals, serving as a reference and motivation for more hospitals to join the ongoing surveillance. The range in CRBSI incidence densities additionally served the Dutch Hospital Patient Safety Programme (DHPSP) to define attainable goals (chapter 9).

Participation in a voluntary programme such as PREZIES means that the group of participating hospitals changes from year to year. The voluntary basis also implies that hospitals may choose to monitor a certain procedure or patient category because they are interested in infection monitoring in these procedures/patients. This could result from perceived problems resulting in initially high rates, but the existing interest could already have led to lower rates, before the data collection for the national programme was accomplished, as well (chapter 9).

The variable pool of hospitals and the unknown trajectory preceding the participation in surveillance limits the straightforward interpretation of results when assessing national HAI trends. Additionally, implementing HAI surveillance may sometimes be hampered by lack of support or ownership by certain specialties [22]. This may lead to ongoing surveillance in a more cooperative discipline despite limited room for further improvement, as has been observed in some hospitals. Mandatory surveillance may divert scarce infection prevention and control (IPC) capacity to the included patient categories even when rates are already low [23]. Mandatory public reporting or even penalties for HAI, as practiced in some US states, can additionally raise concerns on underreporting [24].

Monitoring HAI, by itself—unless unobtrusively or without feedback—can increase HCW awareness and may decrease infection rates if HCWs have sufficient understanding and opportunity to prevent these infections [25]. If this is not to be expected or unknown, an intervention is called for (Part II).

10.2 HAI rates in the Netherlands: the present

This thesis begins with four papers describing the incidence of HAI and their risk factors during the first years of specific surveillance programmes. The surveillance results provided benchmarks for hospitals and targets for improvement programmes, including the CRBSI prevention component of the DHPSP discussed in chapter 9.

Since generation of the data included in these first papers, medical insight, technology, and infection prevention and control (IPC) have moved forward. During this time, many countries have reduced HAI rates with the development and implementation of healthcare technology and infection control surveillance guidelines, and intervention campaigns [5, 26, 27]. In the Netherlands, similar reductions were achieved. As described in chapter 9, the risk of developing CRBSI in the ICU decreased an average of 10% per

year. Outside the ICU, the CRBSI risk decreased with increasing compliance but was not additionally reduced with ongoing participation or calendar time. Evaluation of all hospitals in the surveillance, with the above-mentioned reservation as to the variable pool of participants, found apparent reduction outside the ICU as well (figure 1 in chapter 9). In 2019 the average risk in the ICU of the 21 participating hospitals was 0.5/1000 CVC days and outside the ICU it was 2.7/1000 CVC days.

The DHPSP not only advocated a CRBSI bundle but also an SSI bundle. Higher SSI bundle adherence appeared to lead to declining SSI rates as well [28]. VAP rates likewise seem to have improved, as the average incidence density was 25/1000 ventilator days in the ICU surveillance and 10.3/1000 in the VAP surveillance (8.6% of the patients). Firm conclusions cannot be based on these results, as few hospitals participated in VAP surveillance, and pneumonias were considered ventilator-associated only when a patient was ventilated for at least 48 hours versus 24 hours in the ICU surveillance. Of patients in eight Dutch hospitals, admitted in 2017-2019, without acute respiratory distress syndrome and expected to be ventilated for at least 24 hours, 2.1% developed "suspected" VAP (1.3% when restricted to microbiologically confirmed VAP), which suggests further improvement [29]. The point prevalence surveys (PPS) conducted since 2007 also suggest a decrease in patients with VAP, notwithstanding the less specific denominator data: from 0.7% and 0.5% in 2007 and 2008, to 0.2% and 0.1% in 2018 and 2019 (prevalence of all patients, unpublished data). Hopmans et al. reported an unadjusted OR per calendar year of 0.97 (95%CI [0.95-0.99]) in the period 2007-2016 for the total of lower respiratory tract infections [30].

With a reduction in SSI, CRBSI and VAP, it comes as no surprise that the overall prevalence of HAI decreased too. The prevalence of patients with HAI onset during hospitalisation decreased from 6.1% in 2007 (when the PPS was first organised) to 3.6% in 2016 [30]. The adjusted OR for yearly reduction until 2016 was 0.97 (95% CI [0.96 - 0.98]). The most prominent trends were seen for UTIs from 2.1% to 0.6% (unadjusted OR per year 0.85 [0.83-0.97]); CRBSIs from 0.3% to 0.1% (OR 0.90 [0.87-0.94]) and SSI from 1.6% to 0.8% (OR 0.91 [0.90-0.93]) [30]. As explained by Hopmans et al., the decrease in HAI prevalence may in part be attributed to the simultaneous decrease in length of stay (until the survey day) and to the declining percentage of patients undergoing surgery. The mean length of stay has since then not decreased further (yearly mean range 7.2-7.8 days in 2013-2019). The percentage having surgery remained stable too (around 30% overall). Obviously one can only go so far in discharging patients earlier during their convalescence, and this and the stable percentage of surgery patients may in part explain why HAI prevalence did not decrease further but remained approximately 5% [31].

10.3 HAI surveillance in the Netherlands: the future

One might wonder whether national surveillance of HAI is still necessary. The benefit for hospitals with low HAI rates is small; the discriminatory possibilities decrease, and the current level of detail may not be necessary from the viewpoint of national monitoring. In Dutch surveillance, low CRBSI incidence densities are a reason for some hospitals to stop participating: the balance between the information gained and the work expended in data collection has tipped the other way. The individual infections are still scrutinised in these hospitals. By contrast, the physicians participating in the Redline focus group study considered CRBSI benchmarking to be important [22]. There are additional reasons to continue national surveillance.

First of all to reveal further opportunities for improvement data from multiple hospitals are sometimes needed. For instance the risk of CRBSI associated with TPN was significantly higher in primary than in secondary hospitals[32], a finding which will not emerge in individual hospital data.

Secondly, a national surveillance with sufficient participating hospitals, allows the government to have a finger on the pulse. Although hospitals are keen on keeping HAI at low levels, it is conceivable that this may not always be the case. Keeping HAI rates low benefits both patients and healthcare costs.

Thirdly, a crisis such as the COVID-19 pandemic affects organisation and practices of the care system, and therefore may have impact on HAI. National surveillance contributed to the insight in these effects: not only by the regular data collection, which was in fact delayed by the overwhelming influx of SARS-CoV 2 patients to the ICU, but also because the surveillance organization acts as a central point that individual hospitals address to share and check observations. The rates of ICU-acquired infections in SARS-CoV 2 patients was considerably higher than in the usual ICU population [33-36]. In the Netherlands, the CRBSI incidence per 1000 CVC days in the ICU appeared 11 times higher with SARS-CoV 2 patients than with the average ICU patient during the four years before [36]. SARS-CoV 2 patients required long ICU stays, were treated with immunosuppressive drugs[37], and are often ventilated in a prone position, making it more difficult to access and care for their CVCs. The increased work pressure, assistance of staff from outside the ICU, and (anticipated) scarcity of materials may too have hampered infection prevention [38].

Other developments may also affect future HAI rates and thus warrant a national surveillance program, even with low incidence rates. E.g. in the coming decades, the Dutch population will continue to age. Older age per se is not an independent risk factor for each type of HAI (chapter 2-4, 7 and 9) [39-48], but the overall HAI prevalence is higher for elderly patients [8, 31]. Additionally hospital admissions increase with age [49]

as well as device use (Dutch PPS data, not shown) so HAI rates can be expected to increase. As demographic distribution differs between e.g. regions[50] this might not affect all hospitals and regions at the same rate. Understanding trends requires insight into these developments.

The present possibilities in information technology has facilitated surveillance and will continue to do so. Part of the patient and procedure data are nowadays conveniently retrieved from the electronic hospital data. Reduced infection rates in combination with the ongoing digitalisation of patient documentation and growing possibilities to retrieve data from electronic patient records has led to an increased interest in semi-automation of HAI surveillance, in both individual hospitals and the national surveillance programmes [51, 52]. Automated surveillance including automated identification of HAI or of patients at high risk of HAI reduces the workload required for surveillance and may increase inter-rater reliability in some settings [52]. Automated SSI surveillance in knee and hip arthroplasty is now being introduced in the Dutch surveillance programme [53, 54]. Likewise, with CRBSI, reduced rates have led to an increased interest in automation [55, 56], but in many hospitals the required data are not yet fully recorded in the electronic patient records.

In search of other options to reduce the workload of surveillance in the Dutch network, possibilities to simplify the CRBSI surveillance have been evaluated. Analysis of recent data demonstrate that most hospitals rate comparably when evaluating CRBSI rates per 1000 CVC days or as percentages of CVCs (not shown). With the apparent low rates, some of the risk factors can be omitted without jeopardising case-mix adjustment. In 2023 the CRBSI surveillance protocol was changed accordingly. Although reducing the time needed to perform CRBSI surveillance might convince some hospitals to start or continue participation, it may be more promising to widen the surveillance scope, leading to a larger numerator and at the same time furthering automated data collection. An outcome that might meet these demands is hospital-acquired bloodstream infection, often called hospital-onset bloodstream infection (HOB), though they are not strictly the same.

HOBs are microbiologically-confirmed BSIs that are associated with hospital stay (usually defined as developing ≥ 48 hours after admission). Microbiologically-confirmed BSIs can easily be retrieved from electronic databases and are less subject to debate. Based on larger numbers of infectious episodes, the results also allow more discrimination between hospitals [57]. The major problem is to balance clinical relevance and interpretability, for example by selecting primary bloodstream infection only which implies determining the focus of infection, against practical feasibility. Studies and surveillance programmes have made various choices in this regard [55, 57-61]. As the

existing Dutch surveillance programme for antimicrobial resistance (Infectious diseases Surveillance Information System Antimicrobial Resistance [ISIS-AR])[62] collects data on positive cultures from most Dutch laboratories, it would be very efficient if HOB rates of individual hospitals could be retrieved from these data. The admission date of the patient is currently provided by about half of the hospitals covered by the ISIS-AR laboratories, and it is in this subset that the possibility to retrieve HOB is being evaluated. Technically this is possible, but further evaluation with hospitals is required to evaluate whether the resulting HOB rates per 1000 admissions or 10,000 patient days, with limited specifications, are useful. Additionally, four hospitals in the province of Utrecht are evaluating whether they can retrieve similar but more detailed data plus information on the focus of infection. The usefulness of HOB rates to evaluate IPC and reveal possibilities for improvement is less clear-cut than for CRBSI rates. HOB-rates are sensitive to a greater array of infection prevention policies and patient characteristics than CRBSI rates. The proportion of patients with severe underlying conditions, with hematological or other oncological diagnoses and with an infection at admission, which might lead to a secondary bacteremia [63], varies between hospitals. In a US-based survey, 61% of the responding hospital epidemiologists and infection preventionists believed that HOB events are preventable, and 54% thought that HOB rates reflect quality of care [64]. Targets are set, as for example in the UK, where Public Health England set a 50% target reduction in healthcare-associated gram-negative bacterial BSIs by March 2021 [26].

Although the low CRBSI incidence rates may justify not recording some of the risk factors anymore, the increasingly electronic patient records and retrieval software offer opportunities for improved case-mix adjustment. There may be variables that are now better retrievable than before: e.g. comorbidities and admission from other healthcare settings, both probable risk factors for developing CRBSI [65]. Several variables (e.g. related to immunocompetence) were deleted from the CRBSI surveillance protocol in the past, because they were difficult to collect and/or did not seem associated with the risk to develop CRBSI in the surveillance data (chapter 3). Increasing medical insight since then may have resulted in better predictors overall or for specific patient groups, e.g. the SOFA, SAPSII and Core-10-TISS score, that were associated with primary BSI in a recent study [66].

10.4 The contribution of HAI to mortality and preventability of HAI and of its consequences.

HAI prevention leads to less morbidity and, depending on the infection type and associated pathogens, less mortality. In the ICU-acquired infection surveillance, VAP, CRBSI or CAUTI was not associated with mortality after adjusting for other risk factors, as

described in chapter 2. But when including all patients in this surveillance, i.e. those with and without an invasive device, developing nosocomial sepsis or ≥ 2 infections was associated with increased mortality. Adjustment for confounders was limited, as in many studies. Large-scale randomised clinical trials, such as those on selective decontamination of the digestive tract (SDD) and selective oropharyngeal prophylaxis (SOD), when well balanced, do not have this limitation and have demonstrated a reduced mortality by preventing bacteremia [67].

The results of the HAI-Net mortality review study demonstrated that treating physicians were of the opinion that in 39% of the assessed cases, HAI definitely contributed to the death of the patient. The WHO-based score reveals that HAI were most often considered as part of the causal sequence (56% of treating physicians) and rarely viewed as the sole cause (9%). It is imaginable that when mortality review in this form is implemented into daily practice, HAI will be found to contribute less to mortality. For one reason, in cases with more than one HAI present, the most severe HAI was selected for the mortality review. For another, the on-site investigators that participated in this study probably were convinced of the relevance of HAI. On the other hand, the treating physicians that co-reviewed the patients were not 'selected,' and [their] agreement on pneumonia and BSI was quite reasonable.

So, HAI are considered relevant with respect to this ultimate patient outcome, but to what extent are they preventable? As these two concepts are closely related, at least for [clinical] laymen, clinicians and hospital management sometimes fear legal consequences when explicitly evaluating the contribution of HAI to the death of patients (chapter 6). Therefore, it is no surprise that there are very few relevant published studies. Decoster and colleagues combined their review of the contribution of HAI to death with an assessment of preventability and concluded that death was preventable in 35 of the 182 (19%) patients (McCabe score 0 and 1 only) in whom death was attributable to HAI [68]. In the 35 cases, the HAI itself could have been prevented and/or the following death. Baines and colleagues evaluated adverse events in Dutch hospitals and found that in 31% of the 186 deceased patients with a HAI as adverse event, the adverse event had been preventable [69]. Dantes et al. recently evaluated hospital-onset bacteraemia and fungemia as a potential measure of HAI in a pilot study of 60 patients in three hospitals. Two-thirds of all HOB events and half of non-skin-commensal HOB events were judged as potentially preventable [63].

The preventability of HAI has been studied more on the system level, using data on achieved reductions in improvement studies and regression analysis on risk factors. The landmark SENIC study concluded that 32% of HAI were preventable by well-organised and highly effective infection control programmes [7]. Harbarth et al. evaluated the

achieved risk reductions over 1990-2002 and estimated that 20% of HAI were preventable, peaking up to 70% for catheter-related bacteraemia [70]. Later reviews of intervention studies often came up with similar or even higher proportions [25] [71, 72]. A more recent meta-analysis by Schreiber et al., including papers from 2005-2016 concluded that 35-55% may be preventable[73]. A drawback of this approach, especially when a long time-period is evaluated, is that it ignores the fact that medical knowledge advances in time, and with this the possibilities to prevent HAI and the associated morbidity and mortality. Therefore, this retrospective assessment may lead to an overestimation of the preventable proportion of HAI and its consequences. With best practices implemented in a growing number of hospitals, the proportion of preventable HAI may decrease over time [74]. Endogenous factors contributing to HAI remain and are more difficult to influence.

Another aspect evaluated during the HAI-Net mortality review was the contribution of antimicrobial resistance (AMR), if present. For micro-organisms with the AMR phenotypes under surveillance, AMR “possibly” or “definitely” contributed to death in 65% cases. AMR increased the risk of inappropriate empirical antibiotic therapy, which is associated with worse patient outcomes [75]. In a large US database of patients with BSIs (not necessarily hospital-onset), 19% received discordant empirical antibiotic therapy. The odds of receiving discordant therapy was 9.1 (95% CI [7.7-10.8]) in cases of infection with an antibiotic-resistant pathogen. Inappropriate therapy was associated with increased mortality [76]. This increased mortality risk was not affected by resistance in itself.

None of the Dutch cases in chapter 6 were caused by one of the AMR phenotypes in the protocol (data not shown in the paper). In a Dutch study in eight hospitals, the attributable mortality of resistant and susceptible gram-negative infections was comparable [77]. The number of people dying of AMR each year in the Netherlands is considered low [78], but may be underestimated as this is not systematically reported.

In 2015 the Dutch Ministry of Public health, Welfare and Sports initiated an extensive programme to contain antimicrobial resistance [79]. Does the limited number of deaths warrant the huge effort and cost that has since been invested in initiatives to prevent antimicrobial resistance in human healthcare in the Netherlands? Certainly, the predicted number of deaths on a global scale is of a different order [80], but infections with AMR pathogens in the Netherlands are relatively rare and trends with most pathogens are now stable [81, 82]. Developments in AMR have, however, shown clearly that AMR is not solely a problem of hospitals and other aspects of human healthcare. Large-scale antibiotic use in animal husbandry increased the prevalence of AMR in this sector, including the persons working in it and further in the food chain[80]. So far, the

AMR strains infecting livestock have not demonstrated the capacity to become a hospital pathogen, apart from settings with very vulnerable patients, such as burns centres [83]. However, a large reservoir of pathogenic micro-organisms with a range of AMR traits increases the risk of developing new resistant strains. An international and national approach was called for and has proven successful in reducing antibiotic use in animal husbandry [81]. On the other hand, travellers and refugees import AMR from countries with higher prevalence [84], so vigilance and an intersectoral approach remain important.

Part II

10.5 Bundles of best practices

Bundles of best practices to prevent CRBSI and CLABSI have been successful [85]. Evaluating multifaceted practices in a bundle demonstrates that, even when compliance to individual elements is satisfactory, the quality of overall patient care can still be lacking. The increasing attention to patient safety has fostered this more comprehensive approach. In the Michigan Keystone study, an important target was to develop a culture of patient safety, a goal often overlooked in subsequent similar interventions. Parallel to the PROHIBIT intervention study, six hospitals participated in an in-depth investigation of the main barriers, facilitators, and contextual factors relevant to the success of interventions. Apart from sufficient human and material resources, successful implementation required dedicated change agents who help make the intervention an institutional priority: these personally committed influential individuals and boundary spanners - individuals with multiple roles, traversing institutional boundaries and fostering change - helped overcome resource restrictions and intra-institutional segregations [86]. The large-scale adoption of the CRBSI bundle and commitment to the other themes in the Dutch patient safety programme was also facilitated by the introduction of a safety management system [87], that addressed safety management and culture, risk assessments and continuous safety improvements.

Bundles of best practices were developed for other HAI as well: SSI [28, 88], VAP [89], CAUTI [90, 91], CDI [92, 93] and other conditions [94-96]. Frequently included in VAP bundles are daily sedation interruption and assessment of readiness to extubate [97]. A nationwide Dutch survey to evaluate the use of currently recommended practices for preventing CDI and device-associated HAI, including VAP, revealed that ‘sedation vacation’ was used in 40% of the hospitals [98]. The VAP reduction seen in the Netherlands seems to follow the wide adoption of SDD since the study of de Smet et al. [99]. SDD has now become standard practice in Dutch ICUs [98, 100]. In most other

countries, SDD is seldom included in a bundle [101] or otherwise implemented, as the higher antibiotic resistance levels might lead to enhanced selection of resistant bacteria [102].

When the advocated best practices have become integrated in regular care ('business as usual'), one should consider updating the bundle, e.g. adding glucose control to SSI bundles [103]. Consideration is also needed when practices are less well integrated. For example, compliance to the maintenance elements of the Dutch CRBSI bundle have remained rather low. The catheter-insertion elements have, on average, been well integrated, and there are no new interventions that could become part of a "CRBSI bundle 2.0". But the maintenance bundle elements, e.g. daily assessment of the indication for the CVC, require ongoing effort to hold HCW attention.

Implementing bundles of best practices is usually effective although causal relationships may be impossible to establish due to lack of randomised controlled trials [93] or adherence measurements showing that practices were indeed better adhered to [85]. In the PROHIBIT study and the DHPSP programme, adherence was recorded and multivariable analyses demonstrated that compliance in settings with relatively high CRBSI rates was indeed associated with lowered rates. The number of confounders was limited, however, and the improvement may have come not only from bundle compliance but from other positive consequences of the interventions and programme as a whole.

Recording adherence could be a motivating part of an intervention itself, especially when giving feedback to the observed HCWs. It can also increase the insight in the success of a more challenging intervention, e.g. aiming at hand hygiene (chapter 7 and 8), and this insight could lead to more tailored interventions. However, recording compliance entails quite a lot of work/organisational effort, and its benefits should be weighed against this [28]. There is the possible drawback of the Hawthorne effect: people aware of being observed perform better than they would normally do [104-106]. The few studies on the duration of this effect have shown it to be transient [107], and as the observations in the PROHIBIT study occurred weekly over 2.5 years, we expect that HCWs soon became used to being observed. Moreover, we were interested in the *change* in bundle compliance and hand hygiene. In case the Hawthorne effect did affect our results, we expect that compliance in the beginning of the study may have been overestimated and the effect of the intervention on these process parameters underestimated.

Compliance measurements aside, well-received infection prevention interventions, in bundles or not, may have additional beneficial effects: best practices to decrease one type of HAI may incidentally decrease other types, as they improve the general health of

a patient [26], reduce risk factors for other HAI as well or increase HCWs' awareness of the importance of infection prevention [108, 109].

Changing behaviour is most feasible when it occurs at a certain single timepoint, e.g. the insertion of a catheter or the hospital- or department-wide choice for peptic ulcer prophylaxis. It is more challenging to change behaviour that needs to be repeated daily or more frequently, e.g. elevation of the head of the bed or, most notoriously, hand hygiene.

10.6 Effectiveness of hand hygiene compliance and hand hygiene in Dutch hospitals

Poor HH in hospital wards enables transmission to all kinds of body parts and invasive devices, and good HH is therefore important. Hand hygiene needs to be performed at various indications and, when attending to hospitalised patients, repeatedly so. The link between suboptimal hand hygiene of one HCW (in a team) and the occurrence of HAI is more difficult to ascertain than the link between, for example, suboptimal CVC insertion and subsequent CRBSI. Additionally, personal perceptions involving cleanliness are varied and complex and frequent hand hygiene c competes for time with other HCW duties. Increasing knowledge on hand hygiene alone is therefore often not enough to change behaviour. Relatively few well-powered studies have evaluated both HH compliance and HAI rates. Gould et al. concluded in a Cochrane review of HH interventions that the relationship between improved HH compliance and HAI reduction is not very certain [110]. Most recent studies, often evaluating a subset of HAI, have demonstrated positive results [111] [112], as did the PROHIBIT study. Other studies likewise found a reduction alongside a successful HH programme, but the initial HAI rates were relatively high [113], often limited to MRSA [114, 115] and ambiguous [115]. Eckmanns et al. evaluated transmission of pathogens by genotyping and found no correlation of the transmission rates with HH compliance (rather low in this setting) [116]. We conclude that there is evidence that increased HH compliance is associated with reduced HAI rates, but the evidence is not multifold for settings with relatively low HAI rates. Several model-based investigations have sought a bottom level for HH, as mentioned in chapter 8. Recent studies conclude that no level apart from 100% is "good enough", but these studies involved or assumed a setting with relatively high rate of baseline infection or introduction of MRSA or *Acinetobacter baumanni*, compared to Dutch settings [117-121]. Mouajou et al concluded, based on a review of 35 papers, that HH and HAI had a negative relationship up to a compliance of approximately 60%[122].

Whether improving HH in a setting with relatively low HAI levels, such as Dutch hospitals, would further reduce the infection rates remains unclear, as already pointed out by Bonten et al. in 2014[123]. When only 14.5-21.6% of nosocomial infections result

from patient-to-patient transmission (e.g. via HCW hands) as determined by Grundmann et al. in the ICUs of two German university hospitals [124], it is understandable that improved HH will not easily result in reduced HAI rates. Silvestri et al. also concluded that only 40% of all ICU-acquired infections are influenced by HH, as 60% are caused by micro-organisms with which patients are already colonised at admission [125]. In the Dutch Accomplish study, HH compliance had no significant effect on overall HAI prevalence, despite the relatively high initial prevalence of 13.4-14.2%, but perhaps the attained HH levels (35.9% in the intervention hospitals and 23.3% in the control hospitals) were still too modest [126]. What do we know about the level of HH adherence in other Dutch hospitals?

As in many other countries HCWs and IP staff in the Netherlands have become weary of trying to increase HH [127] and improving HH, although regularly addressed in audits, is for many no longer a subject of scientific interest. There have, however, been a few recent studies. In the "Roll up your sleeves" study ("Handen uit de mouwen"), HCWs of 11 centres in greater Rotterdam measured HH and received feedback on compliance along with additional training elements [128]. HH compliance at the centres increased from 42.9% in 2014 to 51.4% in 2016 and 64.6% in 2019 [129]. In another intervention study in the same period, in a university hospital, the mean baseline compliance was 46% (33-74% among various wards) and improved in some but not all wards [130]. Compliance was 33% in another university hospital, in 2012 [131]. In the earlier Helping Hands study, the attained HH levels were 46-53% [132]. Based on these results one suspects that HH is far from perfect in many Dutch hospitals, although there could be a bias, as hospitals where HH is deemed satisfactory will be less inclined to start or continue a HH improvement programme. If the above-mentioned compliance levels are indeed representative for other Dutch hospitals, there is certainly room for improvement.

As observed in the evaluation of individual HH, both the nurse-to-patient ratio and work intensity are associated with individual performance (chapter 9). However, few published intervention programmes address work pressure. Hiring more HCWs is costly and difficult, given the present nurse shortages in the Netherlands and elsewhere, but it may be more effective than interventions that address HH knowledge or intentions. Additionally important and probably related is the patient safety culture in a particular hospital or unit. In 2005-2007, HCWs from 45 hospitals who would later participate in the DHPSP completed a translated Hospital Survey on Patient Safety Culture from the Agency for Healthcare Research and Quality. In 2012, HCWs from 24 hospitals that had participated in the DHPSP also completed the Agency survey. The outcome measures included a self-reported patient safety grade and the number of errors reported in the

previous year. All dimensions improved significantly except for 'adequate staffing'. And although the patient safety culture in general was more favourable after the DHPSP, differences increased among hospital and units within hospitals [87]. A more recent study in a Dutch university hospital related unit-specific HH performance or improvement in HH to the safety culture of these units, observing correlation. Two of five units had bureaucratic or pathological (dismissive) safety cultures [130]. So there remains work to be done in this field.

10.7 Conclusions

In the past two decades, HAI surveillance has been increasingly implemented, both in the Netherlands and in other countries. In this period, surveillance of HAI has facilitated the reduction of most types of HAI. Surveillance in combination with a patient safety programme has boosted both monitoring and infection prevention activities in Dutch hospitals. The introduction of best practices in the form of a bundle and the improvement in HH have been successful tools to reduce CRBSI in settings with relatively high rates.

HAI surveillance remains relevant, particularly given the recent COVID-19 pandemic and future demographic, or possibly, other changes. However, given the nowadays low incidence of most HAI, the current developments towards automated and therefore less labour-intensive HAI surveillance is essential.

REFERENCES

1. Abbas M, de Kraker MEA, Aghayev E, Astagneau P, Aupee M, Behnke M, et al. Impact of participation in a surgical site infection surveillance network: results from a large international cohort study. J Hosp Infect. 2019;102(3):267-76 https://doi.org/10.1016/j.jhin.2018.12.003.
2. Centers for Disease Control and Prevention (CDC). About NHSN [Available from: https://www.cdc.gov/nhsn/about-nhsn/index.html.
3. Rosenthal VD, Duszynska W, Ider BE, Gurskis V, Al-Ruzzieh MA, Myatra SN, et al. International Nosocomial Infection Control Consortium (INICC) report, data summary of 45 countries for 2013-2018, Adult and Pediatric Units, Device-associated Module. Am J Infect Control. 2021;49(10):1267-74 https://doi.org/10.1016/j.ajic.2021.04.077.
4. Rosenthal VD, Maki DG, Mehta Y, Leblebicioglu H, Memish ZA, Al-Mousa HH, et al. International Nosocomial Infection Control Consortium (INICC) report, data summary of 43 countries for 2007-2012. Device-associated module. Am J Infect Control. 2014;42(9):942-56 https://doi.org/10.1016/j.ajic.2014.05.029.
5. Schröder C, Schwab F, Behnke M, Breier AC, Maechler F, Piening B, et al. Epidemiology of healthcare associated infections in Germany: Nearly 20 years of surveillance. Int J Med Microbiol. 2015;305(7):799-806 https://doi.org/10.1016/j.ijmm.2015.08.034.
6. Gastmeier P, Geffers C, Brandt C, Zuschneid I, Sohr D, Schwab F, et al. Effectiveness of a nationwide nosocomial infection surveillance system for reducing nosocomial infections. J Hosp Infect. 2006;64(1):16-22 https://doi.org/10.1016/j.jhin.2006.04.017.
7. Haley RW, Culver DH, White JW, Morgan WM, Emori TG, Munn VP, Hooton TM. The efficacy of infection surveillance and control programs in preventing nosocomial infections in US hospitals. Am J Epidemiol. 1985;121(2):182-205 https://doi.org/10.1093/oxfordjournals.aje.a113990.
8. Magill SS, O'Leary E, Janelle SJ, Thompson DL, Dumyati G, Nadle J, et al. Changes in Prevalence of Health Care-Associated Infections in U.S. Hospitals. N Engl J Med. 2018;379(18):1732-44 https://doi.org/10.1056/NEJMoa1801550.
9. Badia-Cebada L, Penafiel J, Saliba P, Andres M, Camara J, Domenech D, et al. Trends in the epidemiology of catheter-related bloodstream infections; towards a paradigm shift, Spain, 2007 to 2019. Euro Surveill. 2022;27(19) https://doi.org/10.2807/1560-7917.ES.2022.27.19.2100610.
10. Centers for Disease Control and Prevention (CDC). Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central Line Associated Bloodstream Infection) Atlanta, USA: Centers for Disease Control and Prevention; 2023 [Available from: https://www.cdc.gov/nhsn/psc/bsi/.
11. Sickbert-Bennett E.E. D, L.M. Infectious disease surveillance in healthcare settings. In: Weber D.J. TTR, editor. Mayhall's hospital epidemiology and infection control. Fifth edition ed. Philadelphia: Wolters Kluwer; 2021.
12. Mannien J, van der Zeeuw AE, Wille JC, van den Hof S. Validation of surgical site infection surveillance in the Netherlands. Infect Control Hosp Epidemiol. 2007;28(1):36-41 https://doi.org/10.1086/509847.
13. Reilly JS, Price L, Godwin J, Cairns S, Hopkins S, Cookson B, et al. A pilot validation in 10 European Union Member States of a point prevalence survey of healthcare-associated infections and antimicrobial use in acute hospitals in Europe, 2011. Euro Surveill. 2015;20(8) https://doi.org/10.2807/1560-7917.es2015.20.8.21045.
14. European Centre for Disease Prevention and Control (ECDC). Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals, 2011-2012. 2013.

15. Kerlin MP, Trick WE, Anderson DJ, Babcock HM, Lautenbach E, Gueret R, Klompas M. Interrater Reliability of Surveillance for Ventilator-Associated Events and Pneumonia. Infect Control Hosp Epidemiol. 2017;38(2):172-8 https://doi.org/10.1017/ice.2016.262.
16. Klompas M, Branson R, Eichenwald EC, Greene LR, Howell MD, Lee G, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2014;35 Suppl 2:S133-54 https://doi.org/10.1017/s0899823x00193894.
17. Niedner MF, National Association of Children's H, Related Institutions Pediatric Intensive Care Unit Patient Care FG. The harder you look, the more you find: Catheter-associated bloodstream infection surveillance variability. Am J Infect Control. 2010;38(8):585-95 https://doi.org/10.1016/j.ajic.2010.04.211.
18. Atkinson A, Eisenring MC, Troillet N, Kuster SP, Widmer A, Zwahlen M, Marschall J. Surveillance quality correlates with surgical site infection rates in knee and hip arthroplasty and colorectal surgeries: A call to action to adjust reporting of SSI rates. Infect Control Hosp Epidemiol. 2021;42(12):1451-7 https://doi.org/10.1017/ice.2021.14.
19. Jackson SS, Leekha S, Magder LS, Pineles L, Anderson DJ, Trick WE, et al. Electronically Available Comorbidities Should Be Used in Surgical Site Infection Risk Adjustment. Clin Infect Dis. 2017;65(5):803-10 https://doi.org/10.1093/cid/cix431.
20. Teng G, Wang N, Nie X, Zhang L, Liu H. Analysis of risk factors for early-onset ventilator-associated pneumonia in a neurosurgical intensive care unit. BMC Infect Dis. 2022;22(1):66 https://doi.org/10.1186/s12879-022-07053-7.
21. Harris AD, Pineles L, Anderson D, Woeltje KF, Trick WE, Kaye KS, et al. Which Comorbid Conditions Should We Be Analyzing as Risk Factors for Healthcare-Associated Infections? Infect Control Hosp Epidemiol. 2017;38(4):449-54 https://doi.org/10.1017/ice.2016.314.
22. Verberk JD, van der Kooi TI, Derde LP, Bonten MJ, de Greeff SC, van Mourik MS. Do we need to change catheter-related bloodstream infection surveillance in the Netherlands? A qualitative study among infection prevention professionals. BMJ Open. 2021;11(8):e046366 https://doi.org/10.1136/bmjopen-2020-046366.
23. Troughton R, Birgand G, Johnson AP, Naylor N, Gharbi M, Aylin P, et al. Mapping national surveillance of surgical site infections in England: needs and priorities. J Hosp Infect. 2018;100(4):378-85 https://doi.org/10.1016/j.jhin.2018.06.006.
24. MacEwan SR, Gaughan AA, Beal EW, Hebert C, DeLancey JO, McAlearney AS. Concerns and frustrations about the public reporting of device-related healthcare-associated infections: Perspectives of hospital leaders and staff. Am J Infect Control. 2022 https://doi.org/10.1016/j.ajic.2022.08.003.
25. Gastmeier P, Schwab F, Sohr D, Behnke M, Geffers C. Reproducibility of the surveillance effect to decrease nosocomial infection rates. Infect Control Hosp Epidemiol. 2009;30(10):993-9 https://doi.org/10.1086/605720.
26. Edgeworth JD, Batra R, Wulff J, Harrison D. Reductions in Methicillin-resistant Staphylococcus aureus, Clostridium difficile Infection and Intensive Care Unit-Acquired Bloodstream Infection Across the United Kingdom Following Implementation of a National Infection Control Campaign. Clin Infect Dis. 2020;70(12):2530-40 https://doi.org/10.1093/cid/ciz720.
27. Centers for Disease Control and Prevention (CDC). Data Summary of HAIs in the US: Assessing Progress 2006-2016 2016 [Available from: https://www.cdc.gov/hai/data/archive/2018-HAI-progress-report.html.
28. Koek MBG, Hopmans TEM, Soetens LC, Wille JC, Geerlings SE, Vos MC, et al. Adhering to a national surgical care bundle reduces the risk of surgical site infections. PLoS One. 2017;12(9):e0184200 https://doi.org/10.1371/journal.pone.0184200.

29. Writing C, Steering Committee for the RCG, Algera AG, Pisani L, Serpa Neto A, den Boer SS, et al. Effect of a Lower vs Higher Positive End-Expiratory Pressure Strategy on Ventilator-Free Days in ICU Patients Without ARDS: A Randomized Clinical Trial. JAMA. 2020;324(24):2509-20 https://doi.org/10.1001/jama.2020.23517.
30. Hopmans TEM, Smid EA, Wille JC, van der Kooi TII, Koek MBG, Vos MC, et al. Trends in prevalence of healthcare-associated infections and antimicrobial use in hospitals in the Netherlands: 10 years of national point-prevalence surveys. J Hosp Infect. 2019 https://doi.org/10.1016/j.jhin.2019.10.005.
31. PREZIES (Dutch national surveillance network for healthcare associated infections). PREZIES reference data Prevalence survey upto and including 2020. 2021 [Available from: https://www.rivm.nl/documenten/prezies-referentiecijfers-po-tm-2020.
32. PREZIES (Dutch national surveillance network for healthcare associated infections). Reference figures CRBSI surveillance, 2015-2019 2021 [Available from: https://www.rivm.nl/documenten/referentiecijfers-lijnsepsis-2019.
33. Ripa M, Galli L, Poli A, Oltolini C, Spagnuolo V, Mastrangelo A, et al. Secondary infections in patients hospitalized with COVID-19: incidence and predictive factors. Clin Microbiol Infect. 2021;27(3):451-7 https://doi.org/10.1016/j.cmi.2020.10.021.
34. Weiner-Lastinger LM, Pattabiraman V, Konnor RY, Patel PR, Wong E, Xu SY, et al. The impact of coronavirus disease 2019 (COVID-19) on healthcare-associated infections in 2020: A summary of data reported to the National Healthcare Safety Network. Infect Control Hosp Epidemiol. 2022;43(1):12-25 https://doi.org/10.1017/ice.2021.362.
35. Engsbro AL, Israelsen SB, Pedersen M, Tingsgaard S, Lisby G, Andersen CO, Benfield T. Predominance of hospital-acquired bloodstream infection in patients with Covid-19 pneumonia. Infect Dis (Lond). 2020;52(12):919-22 https://doi.org/10.1080/23744235.2020.1802062.
36. Verberk JDM, van der Kooi TII, Kampstra NA, Reimes N, van Rooden SM, Hopmans TEM, et al. Healthcare-associated infections in Dutch hospitals during the COVID-19 pandemic. Antimicrob Resist Infect Control. 2023;12(1):2 https://doi.org/10.1186/s13756-022-01201-z.
37. Meynaar IA, van Rijn S, Ottens TH, van Burgel ND, van Nieuwkoop C. Increased risk of central line-associated bloodstream infection in COVID-19 patients associated with dexamethasone but not with interleukin antagonists. Intensive Care Med. 2022;48(7):954-7 https://doi.org/10.1007/s00134-022-06750-w.
38. Van der Kooi T, Altorf-van der Kuil W, Schoffelen A, van Rooden S, de Greeff S, on behalf of the ISIS-AR study group. First COVID-19 wave in Dutch hospitals: effects on central venous catheter care and distribution of bacteremia pathogens (Abstract of the 6th International Conference on Prevention and Infection Control (ICPIC)). Antimicrob Resist Infect Control. 2021;10(1).
39. Lopez-de-Andres A, Lopez-Herranz M, Hernandez-Barrera V, de-Miguel-Diez J, de-Miguel-Yanes JM, Carabantes-Alarcon D, et al. Sex Differences in Hospital-Acquired Pneumonia among Patients with Type 2 Diabetes Mellitus Patients: Retrospective Cohort Study using Hospital Discharge Data in Spain (2016-2019). Int J Environ Res Public Health. 2021;18(23) https://doi.org/10.3390/ijerph182312645.
40. Daniels KR, Lee GC, Frei CR. Trends in catheter-associated urinary tract infections among a national cohort of hospitalized adults, 2001-2010. Am J Infect Control. 2014;42(1):17-22 https://doi.org/10.1016/j.ajic.2013.06.026.
41. Vincitorio D, Barbadoro P, Pennacchietti L, Pellegrini I, David S, Ponzio E, Prospero E. Risk factors for catheter-associated urinary tract infection in Italian elderly. Am J Infect Control. 2014;42(8):898-901 https://doi.org/10.1016/j.ajic.2014.05.006.

42. Aloush SM, Al Qadire M, Assmairan K, Al Sheikh H, Mosbah A, Hussien H, Al Bzoor B. Risk factors for hospital-acquired non-catheter-associated urinary tract infection. J Am Assoc Nurse Pract. 2019;31(12):747-51 https://doi.org/10.1097/JXX.0000000000000175.
43. Simon S, Hollenbeck B. Risk factors for surgical site infections in knee and hip arthroplasty patients. Am J Infect Control. 2022;50(2):214-6 https://doi.org/10.1016/j.ajic.2021.11.006.
44. Zhang X, Liu P, You J. Risk factors for surgical site infection following spinal surgery: A meta-analysis. Medicine (Baltimore). 2022;101(8):e28836 https://doi.org/10.1097/MD.0000000000028836.
45. Cai W, Wang L, Wang W, Zhou T. Systematic review and meta-analysis of the risk factors of surgical site infection in patients with colorectal cancer. Transl Cancer Res. 2022;11(4):857-71 https://doi.org/10.21037/tcr-22-627.
46. Kohno S, Hasegawa T, Aoki H, Ogawa M, Yoshida K, Yanaga K, Ikegami T. Analysis of risk factors for surgical site infection and postoperative recurrence following inguinal and femoral hernia surgery in adults. Asian J Surg. 2022;45(4):1001-6 https://doi.org/10.1016/j.asjsur.2021.08.019.
47. Gan C, Wang Y, Tang Y, Wang K, Sun B, Wang M, Zhu F. Risk factors for surgical site infection in head and neck cancer. Support Care Cancer. 2022;30(3):2735-43 https://doi.org/10.1007/s00520-021-06687-8.
48. Hoffman T, Shitrit P, Chowers M. Risk factors for surgical site infections following open versus laparoscopic colectomies: a cohort study. BMC Surg. 2021;21(1):376 https://doi.org/10.1186/s12893-021-01379-w.
49. (CBS) SN. Statline - Health and healthcare use; sex, age, personality traits: Statistics Netherlands (CBS); 2022 [Available from: https://opendata.cbs.nl/#/CBS/nl/dataset/83384NED/table?ts=1655115117270.
50. (CBS) SN. Youngsters and elderly per municipality (Jongeren en ouderen per gemeente): Statistics Netherlands (CBS); 2023 [Available from: {(CBS), 2022 #145}.
51. Verberk JDM, Aghdassi SJS, Abbas M, Naucler P, Gubbels S, Maldonado N, et al. Automated surveillance systems for healthcare-associated infections: results from a European survey and experiences from real-life utilization. J Hosp Infect. 2022;122:35-43 https://doi.org/10.1016/j.jhin.2021.12.021.
52. van Mourik MSM, van Rooden SM, Abbas M, Aspevall O, Astagneau P, Bonten MJM, et al. PRAISE: providing a roadmap for automated infection surveillance in Europe. Clin Microbiol Infect. 2021;27 Suppl 1:S3-S19 https://doi.org/10.1016/j.cmi.2021.02.028.
53. Verberk JDM, van Rooden SM, Koek MBG, Hetem DJ, Smilde AE, Bril WS, et al. Validation of an algorithm for semiautomated surveillance to detect deep surgical site infections after primary total hip or knee arthroplasty-A multicenter study. Infect Control Hosp Epidemiol. 2021;42(1):69-74 https://doi.org/10.1017/ice.2020.377.
54. PREZIES PoHtS-Dnsnfhai. PREZIES Automatisering Surveillance: POWI ORTHOpedie (PAS ORTHO) 2022 [Available from: https://www.rivm.nl/prezies/pas-ortho.
55. Gerver SM, Mihalkova M, Bion JF, Wilson APR, Chudasama D, Johnson AP, et al. Surveillance of bloodstream infections in intensive care units in England, May 2016-April 2017: epidemiology and ecology. J Hosp Infect. 2020;106(1):1-9 https://doi.org/10.1016/j.jhin.2020.05.010.
56. Kaiser AM, de Jong E, Evelein-Brugman SF, Peppink JM, Vandenbroucke-Grauls CM, Girbes AR. Development of trigger-based semi-automated surveillance of ventilator-associated pneumonia and central line-associated bloodstream infections in a Dutch intensive care. Ann Intensive Care. 2014;4:40 https://doi.org/10.1186/s13613-014-0040-x.
57. Rock C, Thom KA, Harris AD, Li S, Morgan D, Milstone AM, et al. A Multicenter Longitudinal Study of Hospital-Onset Bacteremia: Time for a New Quality Outcome Measure? Infect Control Hosp Epidemiol. 2016;37(2):143-8 https://doi.org/10.1017/ice.2015.261.

58. Baker AW, Durkin MJ, Dicks KV, Lewis SS, Moehring RW, Chen LF, et al. Methicillin-resistant Staphylococcus aureus bloodstream infection surveillance: National Healthcare Safety Network's laboratory-identified event reporting versus traditional laboratory-confirmed bloodstream infection surveillance. Infect Control Hosp Epidemiol. 2014;35(10):1286-9 https://doi.org/10.1086/678071.
59. Blot K, Hammami N, Blot S, Vogelaers D, Lambert ML. Seasonal variation of hospital-acquired bloodstream infections: A national cohort study. Infect Control Hosp Epidemiol. 2021:1-7 https://doi.org/10.1017/ice.2021.85.
60. Gubbels S, Nielsen J, Voldstedlund M, Kristensen B, Schonheyder HC, Ellermann-Eriksen S, et al. National Automated Surveillance of Hospital-Acquired Bacteremia in Denmark Using a Computer Algorithm. Infect Control Hosp Epidemiol. 2017;38(5):559-66 https://doi.org/10.1017/ice.2017.1.
61. Ridgway JP, Sun X, Tabak YP, Johannes RS, Robicsek A. Performance characteristics and associated outcomes for an automated surveillance tool for bloodstream infection. Am J Infect Control. 2016;44(5):567-71 https://doi.org/10.1016/j.ajic.2015.12.044.
62. Altorf-van der Kuil W, Schoffelen AF, de Greeff SC, Thijsen SF, Alblas HJ, Notermans DW, et al. National laboratory-based surveillance system for antimicrobial resistance: a successful tool to support the control of antimicrobial resistance in the Netherlands. Euro Surveill. 2017;22(46) https://doi.org/10.2807/1560-7917.ES.2017.22.46.17-00062.
63. Dantes RB, Rock C, Milstone AM, Jacob JT, Chernetsky-Tejedor S, Harris AD, Leekha S. Preventability of hospital onset bacteremia and fungemia: A pilot study of a potential healthcare-associated infection outcome measure. Infect Control Hosp Epidemiol. 2019;40(3):358-61 https://doi.org/10.1017/ice.2018.339.
64. Dantes RB, Abbo LM, Anderson D, Hall L, Han JH, Harris AD, et al. Hospital epidemiologists' and infection preventionists' opinions regarding hospital-onset bacteremia and fungemia as a potential healthcare-associated infection metric. Infect Control Hosp Epidemiol. 2019;40(5):536-40 https://doi.org/10.1017/ice.2019.40.
65. Khanafer N, Allaouchiche B, Argaud L, Lepape A, Guerin C, Girard R, et al. Risk factors for nosocomial bacteraemia in intensive care units vary depending on causative agents: results of a prospective surveillance study from 2003 to 2006. J Hosp Infect. 2011;79(2):184-5 https://doi.org/10.1016/j.jhin.2011.04.030.
66. Ginter K, Schwab F, Behnke M, Wolkewitz M, Gastmeier P, Geffers C, Maechler F. SAPS2, APACHE2, SOFA, and Core-10-TISS upon admission as risk indicators for ICU-acquired infections: a retrospective cohort study. Infection. 2023 https://doi.org/10.1007/s15010-022-01972-y.
67. Plantinga NL, de Smet A, Oostdijk EAN, de Jonge E, Camus C, Krueger WA, et al. Selective digestive and oropharyngeal decontamination in medical and surgical ICU patients: individual patient data meta-analysis. Clin Microbiol Infect. 2018;24(5):505-13 https://doi.org/10.1016/j.cmi.2017.08.019.
68. Decoster A, Grandbastien B, Demory MF, Leclercq V, Alfandari S, Regional Network 'Review of nosocomial infection-related m. A prospective study of nosocomial-infection-related mortality assessed through mortality reviews in 14 hospitals in Northern France. J Hosp Infect. 2012;80(4):310-5 https://doi.org/10.1016/j.jhin.2011.11.016.
69. Baines RJ, Langelaan M, de Bruijne MC, Wagner C. Is researching adverse events in hospital deaths a good way to describe patient safety in hospitals: a retrospective patient record review study. BMJ Open. 2015;5(7):e007380 https://doi.org/10.1136/bmjopen-2014-007380.
70. Harbarth S, Sax H, Gastmeier P. The preventable proportion of nosocomial infections: an overview of published reports. J Hosp Infect. 2003;54(4):258-66 https://doi.org/10.1016/s0195-6701(03)00150-6.

71. Rossello-Urgell J, Vaque-Rafart J, Hermosilla-Perez E, Allepuz-Palau A, Group EW. An approach to the study of potentially preventable nosocomial infections. Infect Control Hosp Epidemiol. 2004;25(1):41-6 https://doi.org/10.1086/502290.
72. Umscheid CA, Mitchell MD, Doshi JA, Agarwal R, Williams K, Brennan PJ. Estimating the proportion of healthcare-associated infections that are reasonably preventable and the related mortality and costs. Infect Control Hosp Epidemiol. 2011;32(2):101-14 https://doi.org/10.1086/657912.
73. Schreiber PW, Sax H, Wolfensberger A, Clack L, Kuster SP, Swissnoso. The preventable proportion of healthcare-associated infections 2005-2016: Systematic review and meta-analysis. Infect Control Hosp Epidemiol. 2018;39(11):1277-95 https://doi.org/10.1017/ice.2018.183.
74. Bearman G, Doll M, Cooper K, Stevens MP. Hospital Infection Prevention: How Much Can We Prevent and How Hard Should We Try? Curr Infect Dis Rep. 2019;21(1):2 https://doi.org/10.1007/s11908-019-0660-2.
75. Tabah A, Koulenti D, Laupland K, Misset B, Valles J, Bruzzi de Carvalho F, et al. Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study. Intensive Care Med. 2012;38(12):1930-45 https://doi.org/10.1007/s00134-012-2695-9.
76. Kadri SS, Lai YL, Warner S, Strich JR, Babiker A, Ricotta EE, et al. Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant in-vitro susceptibilities: a retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals. The Lancet infectious diseases. 2021;21(2):241-51 https://doi.org/10.1016/S1473-3099(20)30477-1.
77. Rottier WC, Deelen JWT, Caruana G, Buiting AGM, Dorigo-Zetsma JW, Kluytmans J, et al. Attributable mortality of antibiotic resistance in gram-negative infections in the Netherlands: a parallel matched cohort study. Clin Microbiol Infect. 2020 https://doi.org/10.1016/j.cmi.2020.07.014.
78. Jong de A. Toiletten lijken de bron van de hardnekkige multiresistente NDM-bacterie in het nog nieuwe Zaans Medisch Centrum. Dat zegt hoogleraar microbiologie Jan Kluytmans. Noordhollands Dagblad. 2019(1/6/2019).
79. Ministry of Public Health Welfare and Sport. Letter of the minister of Public Health, Welfare and Sport (nr 159) to the Chair of the Dutch Lower House of the States-General. 32 620. Den Haag2015.
80. O' Neill J. TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY: FINAL REPORT AND RECOMMENDATIONS. Wellcome Trust and UK Government; 2016.
81. de Greeff S, Schoffelen AF, Verduin CM. Nethmap (Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands in 2019). Dutch Foundation of the Working Party on Antibiotic Policy, Centre for Infectious disease control (National Institute for Public Health and the Environment of the Netherlands); 2020.
82. de Greeff S, Kolwijck E, Schoffelen AF, Verduin CM. Nethmap (Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands in 2021). Dutch Foundation of the Working Party on Antibiotic Policy, Centre for Infectious disease control (National Institute for Public Health and the Environment of the Netherlands); 2022.
83. Stone MJ, Swales C, Bond SE, Muthayya P, Sarma JB. An outbreak of livestock-associated meticillin-resistant Staphylococcus aureus (LA-MRSA) clonal complex 398 in a regional burns centre. J Hosp Infect. 2022;122:1-8 https://doi.org/10.1016/j.jhin.2021.12.005.
84. Landelijke Coördinatie Infectieziektenbestrijding (LCI). Refugees Ukraine and infectious diseases (Vluchtelingen Oekraïne en infectieziekten) 2022 [updated 01-06-2022. Available from: https://lci.rivm.nl/richtlijnen/vluchtelingenoekraine#:~:text=Volgens%20beperkte%20beschikbare%20gege

vens%20uit%20de%20Oekra%C3%AFne%20is,tegen%20beta-lactam%20antibiotica%20gerapporteerd%20onder%20Staphylococcus%20aureus%20%28MRSA%29.
85. Ista E, van der Hoven B, Kornelisse RF, van der Starre C, Vos MC, Boersma E, Helder OK. Effectiveness of insertion and maintenance bundles to prevent central-line-associated bloodstream infections in critically ill patients of all ages: a systematic review and meta-analysis. The Lancet infectious diseases. 2016;16(6):724-34 https://doi.org/10.1016/S1473-3099(15)00409-0.
86. Clack L, Zingg W, Saint S, Casillas A, Touveneau S, da Liberdade Jantarada F, et al. Implementing infection prevention practices across European hospitals: an in-depth qualitative assessment. BMJ Qual Saf. 2018;27(10):771-80 https://doi.org/10.1136/bmjqs-2017-007675.
87. Verbeek-van Noord I, Smits M, Zwijnenberg NC, Spreeuwenberg P, Wagner C. A nation-wide transition in patient safety culture: a multilevel analysis on two cross-sectional surveys. Int J Qual Health Care. 2019;31(8):627-32 https://doi.org/10.1093/intqhc/mzy228.
88. Pop-Vicas AE, Abad C, Baubie K, Osman F, Heise C, Safdar N. Colorectal bundles for surgical site infection prevention: A systematic review and meta-analysis. Infect Control Hosp Epidemiol. 2020;41(7):805-12 https://doi.org/10.1017/ice.2020.112.
89. Ladbrook E, Khaw D, Bouchoucha S, Hutchinson A. A systematic scoping review of the cost-impact of ventilator-associated pneumonia (VAP) intervention bundles in intensive care. Am J Infect Control. 2021;49(7):928-36 https://doi.org/10.1016/j.ajic.2020.11.027.
90. Cheng WY, Lin HL, Lin YH, Lai CC, Chao CM. Achieving zero catheter-associated urinary tract infections in a neurosurgery intensive care unit. Infect Control Hosp Epidemiol. 2014;35(6):746-7 https://doi.org/10.1086/676440.
91. Lo E, Nicolle LE, Coffin SE, Gould C, Maragakis LL, Meddings J, et al. Strategies to prevent catheter-associated urinary tract infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2014;35 Suppl 2:S32-47.
92. Yanke E, Moriarty H, Carayon P, Safdar N. A qualitative, interprofessional analysis of barriers to and facilitators of implementation of the Department of Veterans Affairs' Clostridium difficile prevention bundle using a human factors engineering approach. Am J Infect Control. 2018;46(3):276-84 https://doi.org/10.1016/j.ajic.2017.08.027.
93. Barker AK, Ngam C, Musuuza JS, Vaughn VM, Safdar N. Reducing Clostridium difficile in the Inpatient Setting: A Systematic Review of the Adherence to and Effectiveness of C. difficile Prevention Bundles. Infect Control Hosp Epidemiol. 2017;38(6):639-50 https://doi.org/10.1017/ice.2017.7.
94. Michel J, Schepan E, Hofbeck M, Engel J, Simma A, Neunhoeffer F. Implementation of a Delirium Bundle for Pediatric Intensive Care Patients. Front Pediatr. 2022;10:826259 https://doi.org/10.3389/fped.2022.826259.
95. O'Regan R, MacDonald R, Boyle JG, Hughes KA, McKenzie J. 'CPR for Feet' care bundle to improve foot assessment in inpatient diabetes. BMJ Open Qual. 2018;7(3):e000196 https://doi.org/10.1136/bmjoq-2017-000196.
96. Yilmazer T, Tuzer H. Effectiveness of a Pressure Injury Prevention Care Bundle; Prospective Interventional Study in Intensive Care Units. J Wound Ostomy Continence Nurs. 2022;49(3):226-32 https://doi.org/10.1097/WON.0000000000000875.
97. Lawrence P, Fulbrook P. The ventilator care bundle and its impact on ventilator-associated pneumonia: a review of the evidence. Nurs Crit Care. 2011;16(5):222-34 https://doi.org/10.1111/j.1478-5153.2010.00430.x.

98. Huis A, Schouten J, Lescure D, Krein S, Ratz D, Saint S, et al. Infection prevention practices in the Netherlands: results from a National Survey. Antimicrob Resist Infect Control. 2020;9(1):7 https://doi.org/10.1186/s13756-019-0667-3.
99. de Smet AM, Kluytmans JA, Cooper BS, Mascini EM, Benus RF, van der Werf TS, et al. Decontamination of the digestive tract and oropharynx in ICU patients. N Engl J Med. 2009;360(1):20-31 https://doi.org/10.1056/NEJMoa0800394.
100. Working party for Antibiotic Policy (SWAB). SWAB-guideline: selective decontamination with patients in the intensive care (revised version 2018) 2018 [Available from: https://swab.nl/nl/selectieve-decontaminatie-sdd.
101. Mastrogianni M, Katsoulas T, Galanis P, Korompeli A, Myrianthefs P. The Impact of Care Bundles on Ventilator-Associated Pneumonia (VAP) Prevention in Adult ICUs: A Systematic Review. Antibiotics (Basel). 2023;12(2) https://doi.org/10.3390/antibiotics12020227.
102. de Smet AM, Kluytmans JA, Blok HE, Mascini EM, Benus RF, Bernards AT, et al. Selective digestive tract decontamination and selective oropharyngeal decontamination and antibiotic resistance in patients in intensive-care units: an open-label, clustered group-randomised, crossover study. The Lancet infectious diseases. 2011;11(5):372-80 https://doi.org/10.1016/S1473-3099(11)70035-4.
103. de Jonge SW, Wolfhagen N, Zwinderman AH, Hollmann MW, Boermeester MA, Dijkgraaf MGW, group ECs. Enhanced PeriOperative Care and Health protection programme for the prevention of surgical site infections after elective abdominal surgery (EPO2CH): statistical analysis plan of a randomised controlled multicentre superiority trial. Trials. 2021;22(1):297 https://doi.org/10.1186/s13063-021-05202-y.
104. Dawson CH, Mackrill JB. Review of technologies available to improve hand hygiene compliance - are they fit for purpose? J Infect Prev. 2014;15(6):222-8 https://doi.org/10.1177/1757177414548695.
105. Hagel S, Reischke J, Kesselmeier M, Winning J, Gastmeier P, Brunkhorst FM, et al. Quantifying the Hawthorne Effect in Hand Hygiene Compliance Through Comparing Direct Observation With Automated Hand Hygiene Monitoring. Infect Control Hosp Epidemiol. 2015;36(8):957-62 https://doi.org/10.1017/ice.2015.93.
106. Srigley JA, Furness CD, Baker GR, Gardam M. Quantification of the Hawthorne effect in hand hygiene compliance monitoring using an electronic monitoring system: a retrospective cohort study. BMJ Qual Saf. 2014;23(12):974-80 https://doi.org/10.1136/bmjqs-2014-003080.
107. Purssell E, Drey N, Chudleigh J, Creedon S, Gould DJ. The Hawthorne effect on adherence to hand hygiene in patient care. J Hosp Infect. 2020;106(2):311-7 https://doi.org/10.1016/j.jhin.2020.07.028.
108. Cheng WY, Lin YH, Lai CC, Chao CM. Impact of catheter-associated urinary tract infection bundle on other health care-associated infections. Am J Infect Control. 2015;43(2):197-8 https://doi.org/10.1016/j.ajic.2014.09.023.
109. Fortaleza C, Filho SPF, Silva MO, Queiroz SM, Cavalcante RS. Sustained reduction of healthcare-associated infections after the introduction of a bundle for prevention of ventilator-associated pneumonia in medical-surgical intensive care units. Braz J Infect Dis. 2020;24(5):373-9 https://doi.org/10.1016/j.bjid.2020.08.004.
110. Gould DJ, Moralejo D, Drey N, Chudleigh JH, Taljaard M. Interventions to improve hand hygiene compliance in patient care. Cochrane Database Syst Rev. 2017;9:CD005186 https://doi.org/10.1002/14651858.CD005186.pub4.
111. Boyce JM, Laughman JA, Ader MH, Wagner PT, Parker AE, Arbogast JW. Impact of an automated hand hygiene monitoring system and additional promotional activities on hand hygiene performance rates and healthcare-associated infections. Infect Control Hosp Epidemiol. 2019;40(7):741-7 https://doi.org/10.1017/ice.2019.77.

112. von Lengerke T, Ebadi E, Schock B, Krauth C, Lange K, Stahmeyer JT, Chaberny IF. Impact of psychologically tailored hand hygiene interventions on nosocomial infections with multidrug-resistant organisms: results of the cluster-randomized controlled trial PSYGIENE. Antimicrob Resist Infect Control. 2019;8:56 https://doi.org/10.1186/s13756-019-0507-5.
113. Finco G, Musu M, Landoni G, Campagna M, Lai A, Cabrini L, et al. Healthcare-associated respiratory infections in intensive care unit can be reduced by a hand hygiene program: A multicenter study. Aust Crit Care. 2018;31(6):340-6 https://doi.org/10.1016/j.aucc.2017.10.004.
114. Chun JY, Seo HK, Kim MK, Shin MJ, Kim SY, Kim M, et al. Impact of a hand hygiene campaign in a tertiary hospital in South Korea on the rate of hospital-onset methicillin-resistant Staphylococcus aureus bacteremia and economic evaluation of the campaign. Am J Infect Control. 2016;44(12):1486-91 https://doi.org/10.1016/j.ajic.2016.07.009.
115. Pada S, Chee PL, Rathenam S, Ng KS, Alenton LS, Poh L, Tambyah PA. Effectiveness of a Ward level target accountability strategy for hand hygiene. Antimicrob Resist Infect Control. 2019;8:177 https://doi.org/10.1186/s13756-019-0641-0.
116. Eckmanns T, Schwab F, Bessert J, Wettstein R, Behnke M, Grundmann H, et al. Hand rub consumption and hand hygiene compliance are not indicators of pathogen transmission in intensive care units. J Hosp Infect. 2006;63(4):406-11 https://doi.org/10.1016/j.jhin.2006.03.015.
117. Doan TN, Kong DC, Marshall C, Kirkpatrick CM, McBryde ES. Modeling the impact of interventions against Acinetobacter baumannii transmission in intensive care units. Virulence. 2016;7(2):141-52 https://doi.org/10.1080/21505594.2015.1076615.
118. Goldstein ND, Eppes SC, Mackley A, Tuttle D, Paul DA. A Network Model of Hand Hygiene: How Good Is Good Enough to Stop the Spread of MRSA? Infect Control Hosp Epidemiol. 2017;38(8):945-52 https://doi.org/10.1017/ice.2017.116.
119. Greene C, Ceron NH, Eisenberg MC, Koopman J, Miller JD, Xi C, Eisenberg JNS. Asymmetric transfer efficiencies between fomites and fingers: Impact on model parameterization. Am J Infect Control. 2018;46(6):620-6 https://doi.org/10.1016/j.ajic.2017.12.002.
120. Grundmann H, Hori S, Winter B, Tami A, Austin DJ. Risk factors for the transmission of methicillin-resistant Staphylococcus aureus in an adult intensive care unit: fitting a model to the data. J Infect Dis. 2002;185(4):481-8 https://doi.org/10.1086/338568.
121. McBryde ES, Pettitt AN, McElwain DL. A stochastic mathematical model of methicillin resistant Staphylococcus aureus transmission in an intensive care unit: predicting the impact of interventions. J Theor Biol. 2007;245(3):470-81 https://doi.org/10.1016/j.jtbi.2006.11.008.
122. Mouajou V, Adams K, DeLisle G, Quach C. Hand hygiene compliance in the prevention of hospital-acquired infections: a systematic review. J Hosp Infect. 2022;119:33-48 https://doi.org/10.1016/j.jhin.2021.09.016.
123. Bonten MJ, Friedrich A, Kluytmans JAJW, Vandenbroucke-Grauls CMJE, Voss A, Vos MC. Infectiepreventie in Nederlandse ziekenhuizen. Resultaten zeggen meer dan procesindicatoren. Nederlands Tijdschrift voor Geneeskunde. 2014;158(A7395).
124. Grundmann H, Barwolff S, Tami A, Behnke M, Schwab F, Geffers C, et al. How many infections are caused by patient-to-patient transmission in intensive care units? Crit Care Med. 2005;33(5):946-51 https://doi.org/10.1097/01.ccm.0000163223.26234.56.
125. Silvestri L, Petros AJ, Sarginson RE, de la Cal MA, Murray AE, van Saene HK. Handwashing in the intensive care unit: a big measure with modest effects. J Hosp Infect. 2005;59(3):172-9 https://doi.org/10.1016/j.jhin.2004.11.005.

126. van Beeck E, Vos G, van Beeck E, Boog MB, Erasmus V, Huis A, et al. ACCOMPLISH symposium 2014 [Available from: https://www.accomplish-handhygiene.nl/download/ACCOMPLISHresultaten.pdf.
127. Vermeeren J, van Beeck E, Dorresteijn J, Vos G. Regionaal samenwerkingsproject bevordert bewustwording. Ziekenhuizen Rijnmond willen 100 procent hygiëne. Medisch Contact. 2017;37.
128. van Dijk MD, Mulder SA, Erasmus V, van Beeck AHE, Vermeeren J, Liu X, et al. A multimodal regional intervention strategy framed as friendly competition to improve hand hygiene compliance. Infect Control Hosp Epidemiol. 2019;40(2):187-93 https://doi.org/10.1017/ice.2018.261.
129. van Dijk MD, Mulder SA, Erasmus V, van Beeck AHE, Vermeeren J, Liu X, et al. "Handen uit de mouwen" programma: ABR Zorgnetwerk Zuidwest Nederland; [Available from: https://www.abrzorgnetwerkzwn.nl/wp-content/uploads/2020/03/Compliance-HUM-1.1.-tm-2.4.pdf.
130. Caris MG, Kamphuis PGA, Dekker M, de Bruijne MC, van Agtmael MA, Vandenbroucke-Grauls C. Patient Safety Culture and the Ability to Improve: A Proof of Concept Study on Hand Hygiene. Infect Control Hosp Epidemiol. 2017;38(11):1277-83 https://doi.org/10.1017/ice.2017.209.
131. Janssen M. Handhygiëne compliance Atrium Medisch Centrum Heerlen 2013.
132. Huis A, Schoonhoven L, Grol R, Donders R, Hulscher M, van Achterberg T. Impact of a team and leaders-directed strategy to improve nurses' adherence to hand hygiene guidelines: a cluster randomised trial. Int J Nurs Stud. 2013;50(4):464-74 https://doi.org/10.1016/j.ijnurstu.2012.08.004.

Closing pages

Summary

Healthcare is intended to be for the benefit of patients, but unfortunately invasive devices and procedures also form a risk for patients to acquire healthcare-associated infections (HAI). In this thesis, HAI will refer more specifically to hospital-associated infections. This thesis investigates the progress in HAI prevention over the last two decades, as measured within the national surveillance (part I), and the effect of the promotion of best practices regarding central venous catheter insertion and hand hygiene (part II).

In the introduction, **chapter 1**, I provide a short historical account of the developments in infection prevention and control in hospital care, the present incidence and aetiology of HAI and the more recent expansion of HAI surveillance programmes. Next, I present results from the Dutch HAI surveillance and a European mortality review study (part I), and describe two intervention programmes and their effect on both outcome and process parameters (part II).

Most progress in the field of infection prevention was made in the second half of the 19th century – when the importance of hygiene became increasingly acknowledged and the role of micro-organisms in infections was discovered. The level of infection treatment was not significantly improved until the discovery of antibiotics in the first half of the last century. Unfortunately, antimicrobial resistance evolved almost instantaneously, and this set the stage for professional hospital infection control programmes. In the 1960s the US Centers for Disease Control (CDC) recommended hospitals to perform surveillance of HAI, to inform the development of interventions. Since then, surveillance of HAI is considered a cornerstone of prevention and control. At present, the most frequently diagnosed and impactful HAI are surgical site infections (SSI), lower respiratory tract infections including (ventilator-associated) pneumonia (VAP); bacteraemia (bloodstream infection (BSI)), including central venous catheter-related bloodstream infection (CRBSI) and urinary tract infections (UTI), including urinary catheter-associated UTI. The acquisition of HAI is influenced by both endogenous and exogenous risk factors. Almost all HAI cause delayed or inadequate recovery, additional pain and/or anxiety or worse, and many require antibiotic treatment.

Part I

In 1996 the Dutch Institute for Public Health and the Environment (RIVM) and the former Dutch Institute for Healthcare Improvement (CBO) formed one national surveillance programme together: Prevention of Hospital infections by Interventions and Surveillance (PREZIES) (https://www.rivm.nl/prezies). PREZIES, in which hospitals and the RIVM

participate, provides the RIVM with a national overview of HAI and enables hospitals to monitor HAI according to a standardised protocol, including a limited set of relevant literature-based risk factors to allow a case mix-adjusted, benchmark. The first surveillance programme targeted SSI, complemented in 1998 by a programme focussed on the intensive care unit (ICU), where patients are at higher risk of acquiring HAI than in most other hospital wards. Lasting from 1997-2000, this programme monitored ICU-acquired infections and patient mortality. In **chapter 2** we present the results of this programme, focussing on the device-associated infections, associated mortality and their risk factors. Nineteen hospitals participated in this surveillance. Of the ventilated patients 19% developed VAP (25/1,000 ventilator days); of the patients with a CVC 3% developed CRBSI (4/1,000 CVC days) and of the catheterized patients 8% developed CAUTI (9/1,000 catheter days). Longer device use increased the risk for all infections, especially for CRBSI. Independent risk factors were sex, immunity, acute or just elective admission, selective decontamination of the digestive tract (SDD), and systemic antibiotics at admission, depending upon the infection type. Crude mortality was (statistically) significant higher in patients with CRBSI or CAUTI but not in patients with VAP, compared to patients without such an infection. Acquiring a device-associated infection was not an independent risk factor for mortality but being in need of ventilation or a central line, and the duration of these treatments, contributed significantly to mortality.

Evaluation of the ICU-programme led to the development of two more targeted programmes, one aimed at CRBSI and one at VAP, with more detailed patient and device-specific data to improve case mix correction and increase insight. The first study on the CRBSI surveillance covered the initial period 2002-2009 and in **chapter 3** we describe the CRBSI incidence rate and its risk factors. Nine hospitals, participating 1-4 years, recorded data for ICUs or for the entire hospital. Of the CVCs surveyed, 1.6% (95%CI 1.2-2.0) resulted in CRBSI, representing 2.0/1000 CVC days (95% CI 1.6-2.6). Multivariable analysis revealed that the length of the ICU stay prior to CVC insertion, insertion in the jugular or femoral vein, and use of the CVC to deliver total parenteral nutrition (TPN) increased the risk of CRBSI, whereas use of the CVC to deliver antibiotics decreased the risk of CRBSI. These data also informed the Dutch Hospital Patient Safety Programme (DHPSP) (chapter 9).

In **chapter 4** we present the results of the surveillance for VAP and its risk factors, some of which were determined daily. The prospective surveillance of ventilated patients ran from 2004 to 2011 across seven hospitals, each participating for 1-4 years. The average VAP incidence density was 10.3/1000 ventilation days. We analysed time-independent and time-dependent risk factors for VAP using the standard Cox regression and the flexible Weighted Cumulative Effects method (WCE) that evaluates both current and past

exposures. Age (16-40 years, compared to older patients) and a higher current sedation score were independently associated with increased risk to develop VAP. Inversely, COPD (surprisingly), current selective oropharyngeal decontamination, jet nebulizer (WCE), intravenous antibiotics for SDD (ivSDD, WCE), and intravenous antibiotics not for SDD (WCE) were associated with a decreased risk. ivSDD provided a protective effect for 24 days with a delay of 3 days. Using the WCE method increased our understanding of the active time frame and possible delay herein of some of the time-dependent risk factors.

The aforementioned surveillance programmes were incidence-based. Only patients that were at risk to develop a specific type of HAI due to an invasive procedure or device were studied. If the interest is in all types of HAI all hospital patients are at risk. Incidence-based surveillance of all patients would be too time-consuming and ineffective, as patients that do not belong to a risk group due to e.g. surgery or device use are generally at low risk to develop a HAI. An alternative method is the point prevalence survey (PPS) in which a cross-section of the hospital population is observed for HAI at one time-point only. Since 2007 PREZIES organizes a national PPS twice a year. In **chapter 5** we describe the results of the first four surveys. Of 95 hospitals in The Netherlands, 41 participated in 92 surveys. On the survey day 6.2% of the patients had an NI (prevalence of infections 7.2%). The prevalence of surgical site infections was 4.8%, pneumonias 1.1%, primary bloodstream infections 0.5% and of symptomatic urinary tract infections 1.7%. On admission to hospital, 3.3% of patients had an NI, which were mostly SSI developed after discharge. On the day of the survey, 30.9% of the patients were receiving antibiotics. HAI prevalence, the use of antibiotics as well as of invasive devices differed considerably between hospitals, demonstrating room for improvement.

HAI can lead to longer hospital admissions, repeated surgeries, readmissions, and increased mortality. Attributing these adverse events to a nosocomial infection is, however, often not straightforward and requires adjusting for the patient's condition by using statistical approaches. Yet, for deaths, mortality reviews (MR) are more suited for routine use in clinical settings. The European Centre for Disease Prevention and Control (ECDC) commissioned a study into the inter-rater reliability of MR for the contribution of HAI to mortality (**chapter 6**), which we organized in 2017 to 2018. The on-site investigator of each participating hospital and the clinician in charge of the patient, independently reviewed records of deceased patients with BSI, pneumonia, *Clostridioides difficile* infection (CDI) and SSI, and assessed the contribution to death using three measures: 3CAT: Definitely/Possibly/No contribution to death; WHOCAT, based on the World Health Organisation's (WHO) death certificate and QUANT, a Likert scale from 0 to 10. In total 24 hospitals from 11 countries participated and 291 cases were evaluated.

The interrater reliability was: 3CAT weighted kappa (wk) 0.68 (95%CI: 0.61-0.75); WHOCAT wk 0.65 (0.58-0.73); QUANT intra-cluster correlation coefficient 0.76 (0.71-0.81). Interrater reliability ranged from 0.72 for pneumonia to 0.52 for CDI. We concluded that feasibility, validity and reproducibility of the three MR measures was acceptable for use in HAI surveillance.

Part II

Surveillance is known to increase awareness, which in itself can lead to lower HAI rates. Nevertheless, intervention programmes are usually needed to optimize practices to prevent HAI. The concept of 'patient safety' and the notion that it should be embedded throughout the entire healthcare system was developed in the US and expanded in the late nineties. In 2004 the Institute for Healthcare Improvement (IHI) in the US initiated the 100,000 Lives Campaign to improve patient safety and outcomes. One of its six recommended interventions was the 'central line bundle' to prevent CRBSI/central line-associated BSI (CLABSI), which has been implemented in many hospitals and national surveillance programmes since. Included in these bundles is hand hygiene during the CVC insertion, as hand hygiene is a corner stone of infection prevention in general. Hand hygiene needs to be performed at various indications and, when attending to hospitalised patients, repeatedly so. Additionally, work pressure and variable personal perceptions of cleanliness challenge hand hygiene compliance.

Within the PROHIBIT (**Pr**evention **o**f **H**ospital **I**nfections **b**y **I**ntervention and **T**raining) study we evaluated whether an extensive CRBSI prevention bundle (CVCi), a WHO-based HH intervention (HHi), or both in combination (COMBi) would be effective in CRBSI prevention (**chapter 7**). ICUs from 14 hospitals in 11 European countries participated in this stepped-wedge cluster randomised study, lasting from 2011 to June 2013. After a 6-month baseline, three hospitals were randomised to one of three interventions every quarter. The primary outcome was the prospective CRBSI incidence density. Secondary outcomes were a CVC insertion score (because there were 20 items, compliance was not evaluated as a bundle but as the proportion of items adhered to) and HH compliance. The CRBSI incidence density decreased from 2.4/1000 CVC-days at baseline to 0.9/1000 ($p < 0.0001$). When adjusted for patient and CVC characteristics all three interventions significantly reduced CRBSI incidence density. When additionally adjusted for the baseline decreasing trend, the HHi and COMBi arms were still effective. CVC insertion scores and HH compliance increased significantly in each of the three interventions arms.

Traditionally, hand hygiene (HH) interventions do not identify the observed healthcare workers (HWCs), apart from their profession and student status, and therefore, reflect HH compliance only at population level. We performed analyses of individual hand hygiene data, collected in seven PROHIBIT hospitals, to better understand the determinants and dynamics of individual change in relation to the overall intervention effect (**chapter 8**). We defined improving, non-changing, and worsening HCWs with a threshold of 20% compliance change. In total 280 HCWs contributed at least two observation sessions before and after intervention and were included. The proportion of improving HCWs ranged from 33 to 95% among ICUs. The median HH increase per improving HCW ranged from 16 to 34 percentage points. ICU wide improvement in HH correlated significantly with both the proportion of improving HCWs and their median HH increase. Multilevel regression demonstrated that individual improvement was significantly associated with nurse profession (vs. doctors, auxiliary nurses and other HCWs), lower activity index, higher nurse-to-patient ratio, and lower baseline compliance. With comparable overall means the range in individual HH varied considerably between some hospitals, implying different transmission risks. Greater insight into improvement dynamics might help to design more effective HH interventions in the future.

To ensure that a large number of hospitals adopt a multifaceted intervention without too much delay, the key is a national or otherwise large-scale movement, such as the DHPSP, starting in 2009. This programme encouraged 62% of the Dutch hospitals to participate in the national CRBSI surveillance and additionally introduce a six item CRBSI prevention bundle. Using data from 2009 to 2019 we evaluated the association of the CRBSI risk with the bundle compliance as a total ('overall') bundle (all six items) and as an insertion bundle (four items) and a maintenance bundle (two daily checks) (**chapter 9**). In the ICUs, with relatively low rates already, compliance proved to be not associated with CRBSI risk, but outside the ICU improved compliance with the insertion bundle resulted in a decreased CRBSI risk.

In the general discussion (**chapter 10**) I review the merits and limitations of the surveillance and study methods. The consequences of the achieved reductions for the relevance and future set-up of HAI surveillance are considered, particularly with regard to CRBSI in the Netherlands. In the past two decades, HAI surveillance has been increasingly implemented, both in the Netherlands and in other countries. In this period, surveillance of HAI has facilitated the reduction of most types of HAI. Surveillance in combination with patient safety programmes has boosted both monitoring and infection

prevention activities. CRBSI rates were successfully reduced by introducing a bundle of best practices regarding CVC insertion and care, especially in settings with relatively high rates. Hand hygiene improvement has also proven to be effective although not all studies demonstrate an effect. Given the published HH levels in Dutch hospitals there is room for improvement.

One of the limitations of voluntary surveillance is the variable pool of participating hospitals which complicates straightforward interpretation of results when assessing national HAI trends. The reduced HAI rates has led some Dutch hospitals to cease participation with the national surveillance programme which jeopardizes representativity of the data and benchmarking possibilities. Currently automated surveillance is increasingly adopted but not all HAI, such as CRBSI, can as yet be monitored this way. Other outcomes, such as hospital-onset microbiologically-confirmed, i.e. easily retrievable, bloodstream infections (HOB) are nowadays investigated for relevance as well.

Despite the achieved reductions, surveillance of HAI remains important as both unforeseen and foreseen developments can affect HAI rates and require optimization of practices to prevent HAI.

Samenvatting

De gezondheidszorg beoogt het welzijn van patiënten, maar invasieve hulpmiddelen en procedures verhogen bij patiënten helaas ook het risico om een zorggerelateerde infectie (ZI) te ontwikkelen. In dit proefschrift worden met zorggerelateerde infecties meer specifiek ziekenhuisinfecties bedoeld. Deze thesis onderzoekt de vooruitgang in de preventie van ZI gedurende de laatste twee decennia, zoals gemeten met landelijke surveillance (deel I), en het effect van het bevorderen van 'best practices' bij het inbrengen van centraal veneuze katheters (CVK) en handhygiëne (deel II).

In de inleiding, **hoofdstuk 1**, geef ik een korte beschrijving van de historische ontwikkelingen in de infectiepreventie in ziekenhuizen, de huidige incidentie en oorzaken van ZI en de meer recente uitbreiding van ZI-surveillanceprogramma's. Vervolgens presenteer ik de resultaten van de Nederlandse ZI-surveillance en een Europese necrologiebesprekingstudie (deel I), en beschrijf twee interventieprogramma's met hun effect op zowel uitkomst- als procesmaten (deel II).

De meeste vooruitgang in het infectiepreventieveld is in de tweede helft van de 19e eeuw geboekt, toen het belang van hygiëne in toenemende mate erkend en de rol van micro-organismen ontdekt werd. Het behandelen van infecties verbeterde niet wezenlijk, tot de ontdekking van antibiotica in de eerste helft van de vorige eeuw. Resistentie tegen antibiotica ontstond helaas bijna gelijktijdig en dit vormde de aanleiding tot professionele ZI-bestrijdingsprogramma's. In de jaren zestig raadden de Centra voor Ziektebestrijding van de Verenigde Staten (VS) (US Centers for Disease Control (CDC)) ziekenhuizen aan om ZI-surveillance te gaan uitvoeren en op basis daarvan interventies te ontwikkelen. Sindsdien wordt surveillance van ZI als de hoeksteen van preventie en bestrijding gezien. Tegenwoordig zijn de meest vastgestelde en ernstige ZI postoperatieve wondinfecties (POWI), lage luchtweginfecties inclusief (beademing-gerelateerde) pneumonie, bacteriëmie (bloedbaaninfectie) inclusief CVK-gerelateerde bacteriëmie (lijnsepsis) en urineweginfecties (UWI) inclusief urinekatheter-gerelateerde UWI. Zowel endogene als exogene factoren spelen een rol bij de ontwikkeling van ZI. Bijna alle ZI leiden tot vertraagd of onvoldoende herstel, extra pijn en/of zorgen of erger, en veel ZI vereisen behandeling met antibiotica.

Deel I
In 1996 vormden het Rijksinstituut voor Volksgezondheid en Milieu (RIVM) en het voormalige Kwaliteitsinstituut voor de Gezondheidszorg (CBO) samen een landelijk surveillanceprogramma: Preventie van Ziekenhuisinfecties door Interventies en Surveillance (PREZIES) (https://www.rivm.nl/prezies). PREZIES, een samenwerking van

het RIVM en ziekenhuizen, voorziet het RIVM van een landelijk overzicht van ZI en ziekenhuizen van de mogelijkheid om ZI te monitoren aan de hand van een gestandaardiseerd protocol, inclusief een beperkte set van relevante risicofactoren, voor benchmarking. De eerste surveillancemodule richtte zich op POWIs en werd in 1998 aangevuld met een module voor de intensive care (IC), waar patiënten een hoger risico op een ZI lopen dan op veel andere ziekenhuisafdelingen. Binnen deze module, die liep van 1997 tot en met 2000, werden zowel IC-gerelateerde infecties als sterfte gemonitord. In **hoofdstuk 2** presenteren we de resultaten van deze module, met de focus op hulpmiddel-gerelateerde infecties, de daarmee geassocieerde sterfte en de risicofactoren voor beide uitkomsten. Negentien ziekenhuizen namen deel. Van de beademde patiënten ontwikkelde 19% beademing-gerelateerde pneumonie (ventilator-associated pneumonia (VAP)) (25/1000 beademingsdagen); van de patiënten met een CVK ontwikkelde 3% lijnsepsis (4/1000 lijndagen) en van de patiënten met een urinekatheter ontwikkelde 8% katheter-gerelateerde UWI (9/1000 katheterdagen). Langer hulpmiddelgebruik verhoogde het risico voor alle infecties, met name voor lijnsepsis. Onafhankelijke risicofactoren waren geslacht, immuunstatus, acute of juist electieve opname, selectieve darmdecontaminatie (SDD) en systemische antibiotica bij opname, afhankelijk van de soort infectie. De ongecorrigeerde sterfte was statistisch significant hoger bij patiënten met lijnsepsis of katheter-gerelateerde UWI, maar niet bij patiënten met VAP, vergeleken met patiënten zonder deze infectie. Een hulpmiddel-gerelateerde infectie was geen onafhankelijke risicofactor voor sterfte, maar het nodig hebben van beademing of een centrale lijn, en de duur hiervan, droeg significant bij aan de kans op overlijden.

Evaluatie van de IC-module leidde tot het opzetten van twee meer specifieke modules, één gericht op lijnsepsis en één op VAP, met gedetailleerdere patiënt- en hulpmiddelgegevens om de casemixcorrectie te verbeteren en meer inzicht te geven. De eerste lijnsepsisstudie besloeg de beginperiode, van 2002 tot en met 2009, en in **hoofdstuk 3** beschrijven we de lijnsepsisincidentie en de risicofactoren. Negen ziekenhuizen, die één tot vier jaar deelnamen, registreerden gegevens van de IC of van het hele ziekenhuis. Van de geregistreerde CVK's resulteerden 1,6% (95% betrouwbaarheidsinterval (BI) 1,2-2,0) in lijnsepsis, ofwel 2,0 gevallen per 1000 lijndagen (95% BI 1,6-2,6). Multivariabele analyse toonde aan dat de opnameduur op de IC voorafgaand aan het inbrengen van de CVK, inbrengen in de vena jugularis of femoralis en het gebruik van de lijn voor totaal parenterale voeding (TPV) het lijnsepsisrisico verhoogden, terwijl het gebruik voor antibiotica het risico verlaagde. Deze gegevens

werden, als baseline-incidentie, gebruikt bij het VMS Patiëntveiligheidsprogramma (hoofdstuk 9).

In **hoofdstuk 4** presenteren we de resultaten van de surveillance van VAP en de, deels dagelijks vastgelegde, risicofactoren hiervan. Deze prospectieve surveillance van beademde patiënten liep van 2004 tot 2011 in zeven ziekenhuizen, die elk één tot vier jaar deelnamen. De gemiddelde VAP incidentiedichtheid was 10,3/1000 beademingsdagen. We analyseerden tijdsonafhankelijke en tijdsafhankelijke risicofacoren voor VAP met standaard Cox-regressie en de flexibele 'gewogen cumulatieve effecten' methode (Weighted Cumulative Effects (WCE)). De WCE methode evalueert zowel de huidige als eerdere blootstelling. Leeftijd (16-40 jaar, vergeleken met oudere patiënten) en een hogere actuele sedatiescore waren onafhankelijk geassocieerd met een verhoogd risico op VAP. Geassocieerd met een lager VAP risico waren, verassend genoeg, COPD, actuele selectieve oropharyngeale decontaminatie, jetvernevelaars (WCE) en intraveneuze antibiotica, al dan niet voor SDD (beide WCE). Intraveneuze antibiotica voor SDD hadden gedurende 24 dagen een beschermend effect, met een vertraging van drie dagen. Het gebruik van de WCE methode vergrootte ons inzicht in de duur dat sommige tijdsafhankelijke variabelen effect hebben en de mogelijke vertraging hierin.

De hierboven genoemde surveillancemodules maten incidentie. Alleen de patiënten die risico liepen op het ontwikkelen van een bepaald soort ziekenhuisinfectie als gevolg van een invasieve procedure of dito hulpmiddel werden bestudeerd. Als de belangstelling uitgaat naar álle soorten ZI lopen alle patiënten in het ziekenhuis risico. Surveillance van alle patiënten op basis van incidentie zou te veel tijd kosten en ineffectief zijn, aangezien patiënten die niet tot een risicogroep behoren, door bijv. een operatie of invasieve hulpmiddelen, in het algemeen een laag risico op het ontwikkelen van een ZI hebben. Een alternatieve methode is de puntprevalentiestudie (PPS), waarin een dwarsdoorsnede van de ziekenhuispopulatie wordt nagelopen op een ZI, op één punt in de tijd. Sinds 2007 organiseert PREZIES twee keer per jaar een landelijk PPS. In **hoofdstuk 5** beschrijven we de resultaten van de eerste vier studies. Van de 95 ziekenhuizen in Nederland deden er 41 mee, met in totaal 92 deelnames. Op de dag van de meting had 6,2% van de patiënten een ZI (de prevalentie van infecties was 7,2%). The prevalentie van postoperatieve wondinfecties was 4,8%, pneumonieën 1,1%, primaire bacteriëmieën 0,5% en symptomatische UWIs 1,7%. Bij opname in het ziekenhuis had 3,3% van de patiënten een ZI, vooral postoperatieve wondinfecties ontwikkeld na ontslag. Op de dag van de meting kreeg 30,9% van de patiënten antibiotica. Zowel de ZI-prevalentie, het gebruik van

antibiotica en dat van invasieve hulpmiddelen verschilden aanzienlijk tussen de ziekenhuizen, wat aantoont dat er ruimte voor verbetering is.

ZI kunnen leiden tot langere ziekenhuisopnames, heroperaties, -opnames en meer sterfte. Deze ongunstige uitkomsten relateren aan een ZI is vaak niet eenvoudig en vereist correctie voor de toestand van een patiënt, door middel van statistische technieken. Bij het overlijden van patiënten zijn necrologiebesprekingen (mortality review (MR)) echter geschikter voor routinematig gebruik in de kliniek. Het Europees Centrum voor Ziektepreventie en bestrijding (ECDC) gaf opdracht tot een studie naar de interbeoordelaarsbetrouwbaarheid van MR naar de bijdrage van ZI aan sterfte (**hoofdstuk 6**), die wij in 2017 tot 2018 organiseerden. De plaatselijke onderzoeker van elk deelnemend ziekenhuis en de behandelend arts van de patiënt beoordeelden onafhankelijk van elkaar de dossiers van overleden patiënten met een bloedbaaninfectie, pneumonie, *Clostridioides difficile* infectie (CDI) of POWI, waarbij ze de bijdrage aan het overlijden bepaalden. Hiervoor gebruikten ze drie maten: 3CAT: Zeker/Mogelijk/Geen bijdrage aan overlijden; WHOCAT, gebaseerd op de overlijdensakte van de Wereldgezondheidsorganisatie (WHO), en QUANT, een Likert schaal van 0 tot 10. Er namen in totaal 24 ziekenhuizen uit 11 landen deel en er werden 291 gevallen geëvalueerd. De interbeoordelaarsbetrouwbaarheid was voor 3CAT (gewogen kappa (wk)) 0,68 (95%BI: 0,61-0,75), voor WHOCAT (wk) 0,65 (0,58-0,73) en voor QUANT (intra-cluster correlatiecoëfficiënt) 0,76 (0,71-0,81). De interbeoordelaars-betrouwbaarheid varieerde van 0.72 voor pneumonie tot 0.52 voor CDI. We concludeerden dat de uitvoerbaarheid, validiteit en reproduceerbaarheid van de drie MR maten acceptabel waren voor gebruik in ZI-surveillance.

Deel II

Van surveillance is bekend dat dit het bewustzijn van ZI vergroot, wat op zich zelf tot een lagere ZI-incidentie kan leiden. Niettemin zijn er meestal interventieprogramma's nodig om de preventie van ZI te verbeteren. Het concept 'patiëntveiligheid' en het besef dat dit ingebed zou moeten zijn in het hele zorgsysteem werd in de VS ontwikkeld en nam een vlucht in de late jaren negentig. In 2004 startte het Instituut voor Gezondheidszorg-verbetering (Institute for Healthcare Improvement (IHI)) in de VS de "100.000 Levens"campagne om de patiëntveiligheid en uitkomsten te verbeteren. Één van de zes aanbevolen interventies was de lijnsepsisbundel ter preventie van lijnsepsis, die sindsdien in veel ziekenhuizen en nationale surveillanceprogramma's in praktijk is gebracht. Eén van de elementen van deze bundels is handhygiëne tijdens het inbrengen van de CVK aangezien handhygiëne een hoeksteen van infectiepreventie in het algemeen

is. Handhygiëne moet bij diverse indicaties en, bij de zorg voor ziekenhuispatiënten, herhaaldelijk uitgevoerd worden. Werkdruk en de variatie in persoonlijke opvattingen m.b.t. hygiëne bemoeilijken de naleving van handhygiëne.

Binnen de PROHIBIT (**Pr**evention **o**f **H**ospital **I**nfections **b**y **I**ntervention and **T**raining, Preventie van Ziekenhuisinfecties door Interventie en Training) studie gingen we na in hoeverre een uitgebreide lijnsepsis-preventiebundel (CVCi), een op de WHO gebaseerde handhygiëne-interventie (HHi) of een combinatie van beide (COMBi) lijnsepsis zouden voorkómen (**hoofdstuk 7**). IC's van 14 ziekenhuizen in 11 Europese landen namen deel aan deze trapsgewijze cluster-gerandomiseerde studie, die duurde van 2011 tot halverwege 2013. Na een baseline van zes maanden werden elk kwartaal drie ziekenhuizen gerandomiseerd toegekend aan één van de drie interventies. De primaire uitkomst was de prospectieve lijnsepsisincidentie. Secundaire uitkomsten waren een lijninbrengscore (omdat er 20 onderdelen waren, evalueerde we de naleving niet als een bundel maar als de proportie nageleefde elementen) en de handhygiëne-naleving. De lijnsepsisincidentie-dichtheid daalde van 2,4/1000 lijndagen tijdens de baseline tot 0,9/1000 ($p<0,0001$). De drie interventies, gecorrigeerd voor patiënt- en lijnkenmerken, verlaagden alle drie significant de lijnsepsisincidentiedichtheid. Na aanvullende correctie voor de dalende trend gedurende de baseline waren de HHi- en de COMBi-arm nog steeds effectief. De lijninbrengscore en handhygiëne stegen significant bij alle drie de interventies.

Tot nog toe werden in handhygiënestudies zorgverleners meestal niet individueel geïdentificeerd, afgezien van hun beroep en studentstatus, en deze geven de handhygiëne-naleving dan ook alleen op populatieniveau weer. Wij analyseerden individuele handhygiënegegevens, verzameld in zeven PROHIBIT ziekenhuizen, om de determinanten en de dynamiek van individuele veranderingen, in relatie tot het algemene interventie-effect, beter te begrijpen (**hoofdstuk 8**). We deelden zorgverleners in in drie groepen: zij die beter werden ('improvers'), gelijk bleven of achteruit gingen, met een drempel van 20% verandering in de naleving. In totaal werden er 280 zorgverleners met minstens twee observatiesessies vóór en dito na de interventie geïncludeerd. Het aandeel improvers varieerde tussen de IC's van 33 tot 95%. De mediane HH-stijging per improver varieerde van 16 tot 34 percentagepunten. De IC-brede verbetering in HH correleerde significant met zowel het aandeel zorgverleners dat beter werd als met hun mediane stijging in handhygiëne. Multilevel regressie-analyse toonde aan dat de individuele verbetering significant geassocieerd was met verpleegkundigen (versus artsen, verpleeghulpen en andere zorgverleners), een lagere

activiteitsindex, hogere verpleegkundige-patiënt ratio en een lagere baseline-naleving. Met een vergelijkbaar algemeen gemiddelde verschilde het bereik in individuele handhygiëne-naleving tussen sommige ziekenhuizen aanzienlijk, wat een verschil in transmissierisico inhoudt. Meer inzicht in de verbeteringsdynamiek kan bijdragen aan het ontwikkelen van effectievere handhygiëne-interventies in de toekomst.

Om er voor te zorgen dat een veelzijdige interventie zonder al te veel vertraging door een groot aantal ziekenhuizen wordt overgenomen is een landelijke of anderszins grootschalige beweging nodig, zoals het VMS Patiëntveiligheidsprogramma dat in 2009 begon. Dit programma moedigde 62% van de Nederlandse ziekenhuizen aan om deel te nemen aan de landelijke surveillance van lijnsepsis en daarnaast een lijnsepsisbundel met zes elementen te introduceren. We evalueerden de associatie tussen het lijnsepsisrisico met de bundelnaleving als geheel (alle zes items) en als een inbreng- (vier items) en onderhoudsbundel (twee dagelijkse controles), met gegevens over 2009 tot en met 2019 (**hoofdstuk 9**). Op de IC's, waar de incidenties al relatief laag waren, bleek de naleving niet geassocieerd met het lijnsepsisrisico, maar buiten de IC leidde een betere naleving van de inbrengbundel tot een lager lijnsepsisrisico.

In de algemene discussie (**hoofdstuk 10**) bespreek ik de voordelen en beperkingen van de surveillance- en studiemethoden. Ook worden de gevolgen van de teruggebrachte incidenties voor de relevantie en toekomstige opzet van ZI-surveillance overwogen, in het bijzonder voor lijnsepsis in Nederland. In de laatste twee decennia is ZI-surveillance in toenemende mate geïmplementeerd, zowel in Nederland als in andere landen. In deze periode heeft ZI-surveillance het terugbrengen van de meeste soorten ZI mede mogelijk gemaakt. Surveillance in combinatie met patiëntveiligheidsprogramma's heeft zowel monitoring als infectiepreventie gestimuleerd. De incidentie van lijnsepsis werd succesvol teruggebracht door de introductie van een bundel best practices m.b.t het inbrengen en verzorgen van CVK's, vooral in settings met relatief hoge incidenties. Verbetering in handhygiëne is ook effectief gebleken hoewel niet alle studies een effect laten zien. Gegeven de gepubliceerde handhygiëne-nalevingscijfers in Nederlandse ziekenhuizen is er ruimte voor verbetering.

Eén van de beperkingen van vrijwillige surveillance is de variabele groep van deelnemende ziekenhuizen, die een eenvoudige interpretatie van de resultaten bij het beoordelen van landelijke ZI-trends bemoeilijkt. Door de gedaalde ZI-frequenties zijn sommige Nederlandse ziekenhuizen gestopt met deelname aan de landelijke surveillance en dit vormt een risico voor de representatitiviteit en de mogelijkheden voor

benchmarking. Er wordt inmiddels steeds meer overgegaan op geautomatiseerde surveillance, maar niet alle ZI, zoals lijnsepsis, kunnen al op deze manier gemonitord worden. Andere uitkomsten, zoals ziekenhuis-gerelateerde microbiologisch bevestigde, d.w.z. makkelijk extraheerbare, bloedbaaninfecties (hospital-onset bacteremia (HOB)), worden tegenwoordig ook op hun relevantie onderzocht.

Ondanks dat ZI succesvol teruggedrongen zijn, blijft surveillance belangrijk aangezien zowel onvoorziene als te verwachten ontwikkelingen het vóórkomen van ZI kunnen beïnvloeden. Blijvende aandacht voor een optimale preventie van ZI blijft dan ook nodig.

DANKWOORD

Twee decennia aan surveillanceresultaten betekent ook al ruim twintig jaar bij de afdeling Zorggerelateerde infecties en antimicrobiële resistentie! En dat houdt in: veel fijne collega's waar ik in de loop van de jaren mee heb samengewerkt of nog steeds een team mee vorm. Allereerst natuurlijk de collega's van PREZIES: Jan, Bert, Annette en Judith: Preziessers van (bijna) het eerste uur. Jullie zorgden er voor dat ik me snel thuis voelde in het team en in het onderwerp. Titia kwam algauw ook het team versterken en ik ging regelmatig met jou, Jan of Bert mee op validatiebezoek. Het is verrijkend om te zien waar de surveillancedata een afspiegeling van zijn en de contacten met de deskundigen infectiepreventie in de ziekenhuizen zijn altijd waardevol. Titia, jij bent niet alleen een fijne collega, maar ook onze 'harde schijf'. Als niemand het meer weet, weet jij het nog wel (op te diepen). Susan, Birgit, Mayke, Emma, Anouk, Janneke, Iralice, Nynke, Naomi en Ruben: jullie waren ook prettige en gezellige collega's. We leefden met elkaar mee, met de mooie en soms ook verdrietige gebeurtenissen in het leven.

Met Titia, Kati, Sabine, Stephanie, Wilma, Sarah, Charlotte, Manon, Robine, Cathalijne en Christel vormen we ook nu een enthousiast team van fijne collega's. Dat geldt ook voor de andere ZIA-'ers waarbij ik Anja en Mirthe met name wil noemen, en voor de datamanagers die betrokken zijn bij PREZIES, waaronder nu Wouter, Levi, Britt en Marit, en Saskia van het secretariaat. Hendriek, Jan, Maarten en Alina, jullie hulp als statistici in de afgelopen jaren was onmisbaar. Rolina, dankzij jou kreeg het artikel over beademing-gerelateerde pneumonie een waardevolle extra dimensie. Fijn dat iedereen vanuit zijn of haar expertise zo betrokken is!

Zonder de inzet van deskundigen infectiepreventie en andere betrokkenen in de ziekenhuizen geen surveillance en preventie van ziekenhuisinfecties! Dankzij jullie bereidheid om mee te denken en ons geregeld een kijkje in de infectie(preventie)praktijk van het ziekenhuis te gunnen blijft het surveillanceprogramma actueel. Dank voor de prettige samenwerking!

I would also like to thank Walter Zingg, Hugo Sax and Hajo Grundmann: I learnt a lot from you during the PROHIBIT project. I stand in awe for the zeal with which you work, Walter, and your great knowledge. Hugo, I admire your 'out of the box' thinking, and although I was not always happy with yet another round of editing or rewriting by you both, the papers improved. During the mortality review study I worked with Diamantis, Carl, Alain and Pascal and many local doctors and nurses specialized in infection prevention and control (IPC)). Thank you very much, your expertise and effort made this project a success and your amiability and humor working together a pleasure.

And of course I want to thank you, Hajo, for being my promotor. You helped me working up the leitmotiv of this thesis and your inspiring enthusiasm raised my belief that a PhD thesis was within arm's reach, even though this took me a long time after all. Additionally the COVID-19 pandemic, that demanded a lot of you and all your colleagues in IPC stalled winding up this thesis. The upside is that in the meantime I could add two more papers. Dankjewel Andreas, dat jij deze promotie mede mogelijk maakte door de rol van promotor van Hajo over te nemen.

Een woord van dank aan mijn huidige afdelingshoofd is zeker op zijn plaats: Sabine, jij bent altijd positief gebleven, ook als het promotie'project' weer lag te verstoffen, ik weer eens te optimistisch bleek over de tijd die ik nodig had om een volgende stap af te ronden of als het gewoon tegenzat. Je trad daarbij in het voetspoor van je voorgangers: Birgit en Susan.

Ik wil professor Jan Kluytmans, professor Greet Vos en professor Bahnu Sinha hartelijk bedanken voor het beoordelen van het manuscript. Ook de andere leden van de promotiecommissie: dr. Corina Glassner, dr. Karin-Ellen Veldkamp, dr. Mariëtte Lokate en dr. Susan van den Hof wil ik bedanken voor hun tijd en inzet.

Ik wil jullie, Alies en Bertine, heel hartelijk bedanken dat jullie mijn paranimfen willen zijn. Onze vriendschap, ontstaan tijdens werk en studie, en jullie betrokkenheid bij dit promotietraject betekenen veel voor me.

Het sociale aspect van het werk is voor mij altijd belangrijk geweest en tijdens de lunchwandelingen met Alies, Kees, Rudy, Ingrid, Frederika, Simeon en wie er nog meer aansluit, laad ik dan ook echt mijn batterij op. Bedankt voor jullie gezelligheid! Dat geldt natuurlijk helemaal voor jou, Alies. Bij onze gesprekken schuiven Liselotte en Michiel als 'overburen' soms ook aan.

En natuurlijk zijn er mijn vrienden die ik in Brielle, Wageningen, Nieuwegein, Zeist of elders heb leren kennen. Dankjewel voor jullie niet aflatende belangstelling en steun. Deze 'never ending story' is nu dan toch tot een gelukkig einde gebracht. Ik ben blij met jullie en hoop jullie nog vaak te zien, bijvoorbeeld tijdens een heerlijke wandeling. Dat geldt ook voor mijn dierbare zus Vanda. Ik wil ook tante Saakje hartelijk bedanken, die me altijd zo gul gesteund heeft.

Lieve papa en mama. Jullie hebben altijd meegeleefd. Mam, fijn dat jij bij congressen kwam oppassen, waardoor ik met een gerust hart weg kon. En dan natuurlijk Hong-Fen. Jij bent sinds de PROHIBIT studie, die aan het begin van het promotietraject stond, uitgegroeid van schoolkind tot een zeventienjarige zoon om trots op te zijn! Niets maakt het voortschrijden van de tijd zichtbaarder dan een kind dat boven je uitgroeit en zijn eigen verhaal begint. Op het leven!

About the author

Tjallie van der Kooi was born on the second of January 1968, on Texel, the Netherlands. After finishing secondary school at the Rijksscholengemeenschap in Brielle in 1985, she started with the study Tropical crop science at the Agricultural University (now Wageningen University). An exciting but also confronting practical training in Kenya made her decide to graduate in Crop science (targeting temperate climate zones) instead, with a major in grassland ecology. Despite a subsequent traineeship in vegetation mapping at the Dutch Institute for Ecological Research, the future appeared bleak for agricultural engineers in this field. As health sciences were always an interest of her as well, she started at the School for Higher Professional Education in Utrecht to become a nurse, combining work and study. After her graduation in 1998 she continued to work at the Sint Antonius hospital in Nieuwegein. In search of more depth she took on a job as a study nurse, in the Amsterdam University Medical Centre (AMC), and subsequently worked in the HIV outpatient clinic. A course in clinical epidemiology and biostatistics at the AMC sparked her interest in this field and she continued her epidemiological education at the EMGO institute (now EpidM).

In 2003 she started working at the National Institute for Public Health and the Environment (RIVM) , with the department of healthcare-associated infections, where she works within the national surveillance network PREZIES (PREventie van ZIEkenhuisinfecties door Surveillance). Together with her colleagues: epidemiologists, infection control professionals and data managers, she sets up surveillance protocols, evaluates the results and reports them. During 2010-13 she was given the opportunity to coordinate the European PROHIBIT (PRevention Of Hospital Infections By Intervention and Training) study and, in 2017-18, the European Centre for Disease Prevention and Control-commissioned study on the reproducibility of mortality review. Within the PREZIES network her focus is on central venous catheter-related bloodstream infection and hospital-onset bacteremia.

Tjallie lives in Zeist, with her son Hong-Fen.

List of publications discussed in this thesis

van der Kooi TI, de Boer AS, Mannien J, Wille JC, Beaumont MT, Mooi BW, van den Hof S. Incidence and risk factors of device-associated infections and associated mortality at the intensive care in the Dutch surveillance system. Intensive Care Med. 2007;33(2):271-8 https://doi.org/10.1007/s00134-006-0464-3.

van der Kooi TI, Mannien J, Wille JC, van Benthem BH. Prevalence of nosocomial infections in The Netherlands, 2007-2008: results of the first four national studies. J Hosp Infect. 2010;75(3):168-72 https://doi.org/10.1016/j.jhin.2009.11.020.

van der Kooi TI, Wille JC, van Benthem BH. Catheter application, insertion vein and length of ICU stay prior to insertion affect the risk of catheter-related bloodstream infection. J Hosp Infect. 2012;80(3):238-44 https://doi.org/10.1016/j.jhin.2011.11.012.

van der Kooi T, Sax H, Pittet D, van Dissel J, van Benthem B, Walder B, et al. Prevention of hospital infections by intervention and training (PROHIBIT): results of a pan-European cluster-randomized multicentre study to reduce central venous catheter-related bloodstream infections. Intensive Care Med. 2018;44(1):48-60 https://doi.org/10.1007/s00134-017-5007-6.

van der Kooi TII, Boshuizen H, Wille JC, de Greeff SC, van Dissel JT, Schoffelen AF, van Gaalen RD. Using flexible methods to determine risk factors for ventilator-associated pneumonia in the Netherlands. PLoS One. 2019;14(6):e0218372 https://doi.org/10.1371/journal.pone.0218372.

van der Kooi T, Lepape A, Astagneau P, Suetens C, Nicolaie MA, de Greeff S, et al. Mortality review as a tool to assess the contribution of healthcare-associated infections to death: results of a multicentre validity and reproducibility study, 11 European Union countries, 2017 to 2018. Euro Surveill. 2021;26(23) https://doi.org/10.2807/1560-7917.ES.2021.26.23.2000052.

van der Kooi T, Sax H, Grundmann H, Pittet D, de Greeff S, van Dissel J, et al. Hand hygiene improvement of individual healthcare workers: results of the multicentre PROHIBIT study. Antimicrob Resist Infect Control. 2022;11(1):123 https://doi.org/10.1186/s13756-022-01148-1.

van der Kooi TII, Smid EA, Koek MBG, Geerlings SE, Bode LGM, Hopmans TEM, de Greeff SC. The effect of an intervention bundle to prevent central venous catheter-related bloodstream infection in a national programme in the Netherlands. J Hosp Infect. 2023;131:194-202 https://doi.org/10.1016/j.jhin.2022.11.006.

List of publications not discussed in this thesis

van den Hof S, van der Kooi T, van den Berg R, Kuijper EJ, Notermans DW. Clostridium difficile PCR ribotype 027 outbreaks in the Netherlands: recent surveillance data indicate that outbreaks are not easily controlled but interhospital transmission is limited. Euro Surveill. 2006;11(1):E060126 2 https://doi.org/10.2807/esw.11.04.02882-en.

Goorhuis A, Van der Kooi T, Vaessen N, Dekker FW, Van den Berg R, Harmanus C, et al. Spread and epidemiology of Clostridium difficile polymerase chain reaction ribotype 027/toxinotype III in The Netherlands. Clin Infect Dis. 2007;45(6):695-703 https://doi.org/10.1086/520984.

Notermans DW, van der Kooi TI, Goorhuis A, Debast SB, van Benthem BH, Kuijper EJ. [Epidemiology of Clostridium difficile PCR ribotype 027 in the Netherlands 2005-present and the emergence of other subtypes]. Ned Tijdschr Geneeskd. 2008;152(35):1937-40.

van der Kooi TII, Koningstein M, Lindemans A, Notermans DW, Kuijper E, van den Berg R, et al. Antibiotic use and other risk factors at hospital level for outbreaks with Clostridium difficile PCR ribotype 027. J Med Microbiol. 2008;57(Pt 6):709-16 https://doi.org/10.1099/jmm.0.47711-0.

Vonberg RP, Kuijper EJ, Wilcox MH, Barbut F, Tull P, Gastmeier P, et al. Infection control measures to limit the spread of Clostridium difficile. Clin Microbiol Infect. 2008;14 Suppl 5:2-20 https://doi.org/10.1111/j.1469-0691.2008.01992.x.

Willemsen I, van der Kooi T, van Benthem B, Wille J, Kluytmans J. Appropriateness of antimicrobial therapy: a multicentre prevalence survey in the Netherlands, 2008-2009. Euro Surveill. 2010;15(46) https://doi.org/10.2807/ese.15.46.19715-en.

Jansen IA, Hopmans TE, Wille JC, van den Broek PJ, van der Kooi TI, van Benthem BH. Appropriate use of indwelling urethra catheters in hospitalized patients: results of a multicentre prevalence study. BMC Urol. 2012;12:25 https://doi.org/10.1186/1471-2490-12-25.

Clack L, Zingg W, Saint S, Casillas A, Touveneau S, da Liberdade Jantarada F, et al. Implementing infection prevention practices across European hospitals: an in-depth qualitative assessment. BMJ Qual Saf. 2018;27(10):771-80 https://doi.org/10.1136/bmjqs-2017-007675.

Koek MBG, van der Kooi TII, Stigter FCA, de Boer PT, de Gier B, Hopmans TEM, et al. Burden of surgical site infections in the Netherlands: cost analyses and disability-adjusted life years. J Hosp Infect. 2019;103(3):293-302 https://doi.org/10.1016/j.jhin.2019.07.010.

Hopmans TEM, Smid EA, Wille JC, van der Kooi TII, Koek MBG, Vos MC, et al. Trends in prevalence of healthcare-associated infections and antimicrobial use in hospitals in the Netherlands: 10 years of national point-prevalence surveys. J Hosp Infect. 2020;104(2):181-7 https://doi.org/10.1016/j.jhin.2019.10.005.

Verberk JD, van der Kooi TI, Derde LP, Bonten MJ, de Greeff SC, van Mourik MS. Do we need to change catheter-related bloodstream infection surveillance in the Netherlands? A qualitative study among infection prevention professionals. BMJ Open. 2021;11(8):e046366 https://doi.org/10.1136/bmjopen-2020-046366.

Verberk JDM, van der Kooi TII, Hetem DJ, Oostdam N, Noordergraaf M, de Greeff SC, et al. Semiautomated surveillance of deep surgical site infections after colorectal surgeries: A multicenter external validation of two surveillance algorithms - ERRATUM. Infect Control Hosp Epidemiol. 2023;44(7):1208 https://doi.org/10.1017/ice.2022.213.

Verberk JDM, van der Kooi TII, Kampstra NA, Reimes N, van Rooden SM, Hopmans TEM, et al. Healthcare-associated infections in Dutch hospitals during the COVID-19 pandemic. Antimicrob Resist Infect Control. 2023;12(1):2 https://doi.org/10.1186/s13756-022-01201-z.

Halonen K, van der Kooi T, Hertogh C, Haenen A, de Greeff SC, group Ss. Prevalence of healthcare-associated infections in Dutch long-term care facilities from 2009 to 2019. J Hosp Infect. 2024;143:150-9 https://doi.org/10.1016/j.jhin.2023.06.008.