Cost-effectiveness of Hospital Infection Control Interventions in Resource-limited Settings

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Abstract

Background

Hospital-acquired infections (HAIs) are a major cause of morbidity and mortality among hospitalised patients. The main economic burden arises from the longer hospital stays and additional treatments and healthcare services. In addition, HAI also causes a health burden. Up to 25% of patients admitted to hospitals in some locations may acquire an HAI and the mortality rate attributable to some types of HAI could be as high as 50%. Hand hygiene amongst healthcare workers is believed to be one of the most effective measures to reduce the incidence of such infections, but compliance is often poor. A multimodal strategy has been developed by the World Health Organization consisting of five components (WHO-5): system change; training and education; observation and feedback; reminders in the hospital; and a hospital safety climate. However, evidence of effectiveness of this and other interventions intended to improve hand hygiene is still unclear. Previous systematic reviews have found too few high quality studies to draw firm conclusions about the effectiveness of such interventions in improving hand hygiene. In addition, little is known about the circumstances under which such interventions are cost-effective, particularly in resource-constrained hospital settings.

Objectives

The aim of this research is to develop and apply a framework for the economic evaluation of hand hygiene promotion interventions in resource-limited hospital settings. This study has three main objectives:

- To estimate the cost and effectiveness of documented hand hygiene promotion interventions in hospital settings in relation to levels of investment in these interventions.
- To quantify life expectancy from the long-term survival of post intensive care unit (ICU) patients in a resource-limited hospital setting.

- To evaluate the cost-effectiveness of hand hygiene promotion as a hospital infection control strategy in resource-limited hospital settings as a function of baseline hand hygiene compliance.

Methods

A systematic review with random effects network meta-analysis was performed to assess efficacy of the WHO-5 intervention and other combinations of the different intervention components. Studies implementing hand hygiene promotion amongst healthcare workers in hospital settings that met the Cochrane Effective Practice and Organisation of Care Group (EPOC) quality inclusion criteria were included. The effect size of different interventions were analysed separately for different study designs. Information on resources used for interventions was extracted in order to investigate the relationship between resource use and improvement in compliance.

In order to quantify the life years lost due to mortality attributable to HAI in ICU settings the average life expectancy was estimated from a large population of post-ICU hospitalised patients in Thailand using linked records from the local hospital database and the national death registry. Adults and paediatric patients who survived ICU stays were separately analysed. These data were used to derive estimates of QALYs gained for each HAI-related death in the ICU prevented.

Transmission dynamic and decision analytic models were developed to simulate the dynamics of MRSA carriage in ICU patients, predict the impact of hand hygiene interventions on the number of MRSA bloodstream infection (MRSA-BSIs), and evaluate the cost-effectiveness of such interventions. Two ICU settings were considered: a 7-bed paediatric intensive care unit (PICU) and a 10-bed adult intensive care unit (adult ICU). Willingness to pay for health benefits was based on those recommended for Thailand. Epidemiological and economic parameters were derived from detailed local data from a typical tertiary hospital in North-east Thailand and literature. The maximum level of investment in the intervention at which it would still be cost-effective was calculated. A series of hypothetical scenarios with different transmissibility and prevalence of MRSA colonization at admission was also considered.

Results

Meta-analysis of two randomised controlled trials showed the addition of goal-setting to WHO-5 was associated with improved compliance (pooled odds ratio [OR]=1.39, (95% CI: 1.15, 1.67); I^2 = 80.0%). Network meta-analysis from 13 interrupted time series studies indicated considerable uncertainty in the relative efficacy of interventions, but nonetheless provided evidence that WHO-5 is effective. In addition, there was evidence that further improvement in hand hygiene compliance could be achieved by adding interventions including goal-setting, reward incentives and accountability. It was not possible to reach firm conclusions about the relationship between resources used and compliance improvement due to lack of reporting of resource use data.

Of 7,070 adults and 1,935 paediatric patients discharged alive from ICUs in the hospital, the mean life expectancy was estimated as 18.3 years and 43.8 years (unpublished data) in post-ICU adult and paediatric populations respectively.

In the cost-effectiveness analysis, under base case assumptions (pre-intervention hand hygiene compliance 10%), a WHO-5 intervention was found to be cost-effective when compared with the standard practice in both PICU and adult ICU settings solely as a result of MRSA-BSI prevented. In the base case, when hand hygiene compliance increased to 40% as a result of the intervention, the total costs per year were $US 623.73 with 1.04 QALYs gained and $US 633.41 with 1.47 QALYs in the PICU and adult ICU, respectively. However, if baseline compliance was assumed to be 40% in both wards, to be cost-effective the intervention would need to have impacts on other infections in addition to MRSA-BSI.

In hypothetical scenarios analyses, for a typical situation in low-middle income-countries where the transmissibility is moderate, prevalence of MRSA colonization at admission is five percent, if baseline compliance is not greater than 20% the intervention is always cost-effective even with only a 10% compliance improvement. When the baseline compliance is not greater than 20%, the intervention will always be cost-effective if the intervention cost per year is less than $US 1,557 in the PICU and $US 888 in the adult ICU providing the intervention increases compliance by 10% or more.

Conclusions

The WHO-5 multimodal hand hygiene intervention is effective at increasing hand hygiene compliance in healthcare workers. There is evidence that adding goal-setting, reward incentives and accountability strategies can lead to greater improvements.

The WHO-5 intervention is also likely to be cost-effective in ICU settings in typical middle-income countries where baseline compliance is low solely as a result of reduced incidence of MRSA-BSI. Where baseline compliance is already moderate or high, the cost-effectiveness of interventions to improve it further will depend on the impact on HAIs other than MRSA-BSI. Further work is required to estimate these.

Key Words

Healthcare-associated infection, nosocomial infection, infection control, hand hygiene intervention, health economics, economic evaluation, cost-effectiveness, health technology assessment, decision-making, transmission dynamic model, mathematical model, decision analytic model, value of information, resource limited settings

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List of Abbreviations

AHR	Alcohol hand rub
BSI	Bloodstream infection
CAUTI	Central line-associated urinary tract infection
CBAs	Controlled before and after trials
CCTs	Controlled clinical trials
CDC	Centers for Disease Control and Prevention
CEA	Cost-effectiveness analysis
CLABS	Central line-associated bloodstream infection
CMA	Cost-minimisation analysis
CRBSI	Catheter related bloodstream infection
CUA	Cost-utility analysis
DALY	Disability adjusted life year
ECDC	European Centre for Disease Prevention and Control
EPOC	The Cochrane Effective Practice and Organisation of Care
HAI	Healthcare associated infection
HCW	Healthcare worker
ICD10	International Classification of Diseases (ICD)
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IMNB	Incremental monetary net benefits
ITS	Interrupted time series
LE	Life expectancy
LY	Life year
LOS	Length of stay
MNB	Monetary net benefits
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRSA-BSI	Methicillin-resistant *Staphylococcus aureus* bloodstream infection
NICU	Neonatal intensive care unit
NPV	Net present value
PICU	Paediatric intensive care unit
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
RCT	Randomised control trial
RTI	Respiratory tract infection
SSI	Surgical site infection
UTI	Urinary tract infection
VAP	Ventilator associated infection
WTP	Willingness to pay
WHO	World Health Organization

List of Publications

Luangasanatip N, Hongsuwan M, Lubell Y, Limmathurotsakul D, Teparrukkul P, Chaowarat S, Day NP, Graves N, Cooper BS. Long-term survival after intensive care unit discharge in Thailand: a retrospective study. Crit Care. 2013 Oct 3;17(5):R219.

Luangasanatip N, Hongsuwan M, Limmathurotsakul D, Lubell Y, Lee AS, Harbarth S, Day NP, Graves N, Cooper BS. Comparative efficacy of hospital hand hygiene promotion interventions: a systematic review and network meta-analysis. BMJ. 2015:351:h3728.

Luangasanatip N, Hongsuwan M, Lubell Y, Limmathurotsakul D, Srisamang P, Day NP, Graves N, Cooper BS. Cost-effectiveness of hand hygiene promotion for MRSA bloodstream infection in ICU settings. (Under review)

Statement of Original Authorship

The work contained in this thesis has not been previously submitted to meet requirements for an award at this or any other higher education institution. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made.

QUT Verified Signature

Signature:

Date: 7 August 2015

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Chapter 1: Introduction

1.1 Background

1.1.1 Healthcare associated infections (HAIs)

More than 1.4 million patients around the world suffer from healthcare associated infections (HAIs) at any point in time.[1] HAI causes not only morbidity but is also associated with increased mortality.[2, 3] In general, the burden of HAI in low and middle-income countries is higher than developed countries.[4] Recently, a systematic review and meta-analysis estimated the pooled prevalence of HAI in developing countries to be 15.5 per 100 patients, which is much higher than those reported from Europe and USA, which were 4.5 and 7.1 per 100 patients, respectively.[5] The difference between these settings is much higher in intensive care units (ICU).[5, 6] In Thailand, the point prevalence of nation-wide nosocomial infection has been estimated to be about 6.5% and it has been estimated that 250,000 patients have an HAI each year.[7]

Several studies have shown such infections also represent a large economic burden to health care systems.[8, 9] Patients suffering from HAI are likely to have slower recoveries and to require longer hospital stays while additional antibiotics and supplemental material and services for additional stay at hospital are required.[2, 8, 10] HAIs not only cause additional costs due to the extra health care services but also impose a large health burden amongst the hospitalized patients particularly due to increased mortality. For quantifying appropriate levels of investment in interventions to reduce the burden of HAI it is important to have accurate measurement of both economic and health burdens. However, studies using appropriate methodology to estimate costs due to HAI and to quantify life years lost due to HAI mortality are lacking from resource-limited settings.[11]

1.1.2 Interventions

A report by the WHO in 2008 concluded that identifying effective interventions to prevent HAIs in developing countries was a major health priority.[4, 12] Several infection control interventions are routinely used in high income countries and there are varying degrees of evidence in support of these. Such interventions include use of topical antiseptics, patient isolation using barrier precautions (gloves and gowns), and targeted interventions (such as decolonisation or isolation) for those screening positive for target organisms.[13-16] Some of these may have very high resource implications especially those requiring screening, therefore, they might not be appropriate outside high income settings. However, hand hygiene promotion is considered as an essential infection control intervention. The advantages of hand hygiene promotion are that it is a simple intervention, which is relatively easy to implement, and requires only limited investment. Therefore, this approach is especially appropriate where resources are very limited.

Hand hygiene promotion

Direct patient contact with health-care workers (HCWs) who are transiently contaminated with nosocomial pathogens is believed to be the primary route of transmission for many nosocomial pathogens and can lead to patients becoming either colonized or infected. Improving health-care workers' hand hygiene compliance can minimize the impact of this transmission route and can potentially prevent hospitalised patients from acquiring nosocomial infection.[17-19] Although hand hygiene is widely thought to be the most important activity for the prevention of nosocomial infections, [20-23] a review of hand hygiene studies by the World Health Organization (WHO) found that baseline hand hygiene compliance among HCWs varied widely ranging from below 10% to almost 90%.[24]

In 2005, the WHO World Alliance for Patient Safety launched a campaign, the First Global Patient Safety Challenge, "Clean Care is Safer Care" aiming to improve hand hygiene in healthcare.[24] This campaign promotes a multimodal strategy (WHO-5) consisting of five components: system change; training and education; observation and feedback; reminders in the hospital; and a hospital safety climate. Details of each component are shown in Table 1.1. However, previous evaluations of the evidence for the efficacy of different hand hygiene interventions have several important limitations. First of all, most evaluations of hand hygiene promotion interventions use non-randomized study designs, and in many cases the reported analysis is inappropriate or methodological quality is too low to allow meaningful conclusions to be drawn.[25-27] Next, there is wide variation between studies in the hand-hygiene promotion activities used in both implementation and comparison groups. Finally, direct head-to-head comparisons of most interventions are lacking.[28] In addition, previous systematic review studies were also unable to draw firm conclusions on the effectiveness of such interventions.[25-28] However, recently, United Kingdom and Australia have introduced national hand hygiene campaigns. These two campaigns have been associated with substantial reduction in HAI rates, especially for drug resistant organisms.[20, 23] In addition, the national campaign in Germany reported the an improvement in hand hygiene compliance.[29] The promising conclusion from these observational studies may help convince other settings to consider implementing similar campaign especially in resource-limited settings. [30]

Table 1.1: Description of hand hygiene intervention components.

Type of Hand hygiene intervention component	Description
1. System change	Ensuring necessary infrastructure is available including a) access to water, soap and towels and b) alcohol-based handrub at the point of care.
2. Education and Training	Providing training or educational programme on the importance of hand hygiene and the correct procedures for hand hygiene, for healthcare workers.
3. Feedback	Monitoring hand hygiene practices among healthcare workers while providing the compliance feedback to staff.
4. Reminders at workplace	Prompting healthcare workers either through printed material, verbal reminders, electronic communications or other methods, to remind them about the importance of hand hygiene and the appropriate indications and procedures.
5. Institutional safety climate	Active participation at institutional level, creating an environment allowing prioritization of hand hygiene.

1.1.3 Policy decision-making for an infection control program in resource-limited settings

Healthcare decision-makers are often faced with the situation where they need to choose whether to adopt a new intervention or carry on with current practice. Because healthcare resources are limited, they need to assess not only the effectiveness of such an intervention but also the associated costs of the new program. Economic evaluation aims to promote efficiency in resource allocation by maximizing the benefits.[31] This framework has an increasing role in prioritising healthcare funding for new interventions.[32-35]

One outcome representing health benefits obtained from a particular intervention commonly used in economic analysis is the number of quality adjusted life years (QALYs) gained by the intervention. This is the number of life years gained where each life year gained is weighted by a health-related quality of life measure. The health-related quality of life weighting values range from zero (equivalent to death) to one (equivalent to full health). QALYs are recommended for health technology assessment in several countries including Thailand.[32-35] QALYs gained by interventions that reduce hospital mortality can be quantified by estimating the number of life years lost (adjusted with quality of life weights) due to early death in the hospital setting. If patients discharged from hospital have full health the QALYs gained per hospital death averted is simply the life expectancy following hospital discharge. More realistically, not all patients discharged from the hospital will have full health and the QALYs gained by preventing a hospital death must be adjusted downwards to account for quality of life weighting values below one.

Mathematical and decision analytic models are valuable tools for such economic evaluations: they aim to simplify complex clinical situations while describing the key features of a system. They allow us to combine evidence of effectiveness and associated costs in the same analysis and perform hypothetical scenario analyses, where we use the model to describe expected health and economic consequences of different decisions.[36, 37] For infectious disease studies, transmission dynamic models are particularly useful tools to help understand the likely impact of interventions. They are particularly useful when trials are difficult to conduct or when we wish to generalize the results of trials to different settings.[37] Moreover, their use in health-economic evaluations of interventions that reduce transmission is essential to fully capture the intervention benefits.[38] While several studies have used dynamic models to consider hospital infections,[39] economic studies of hand hygiene interventions have used only static models and neglected developing countries where the need for appropriate investment is most.[40-43]

Given limited information concerning the value for money of hand hygiene interventions in resource-limited hospital settings, health economic evidence about the intervention will not only aid local hospital decision-makers, but should also, at a national level, provide crucial guidance to ensure appropriate levels of investment in future national hand hygiene campaigns.

1.2 Research aims

This research aims to provide relevant information for policy makers regarding investments in hand hygiene improvement programmes to prevent HAIs in resource-limited hospital settings using a case study of such an intervention in a hospital in northeast Thailand and generalized to other similar settings.

A rational economic framework is used to determine under what circumstances investing in hand hygiene promotion as part of an infection control programme is likely to cost-effective in resource-limited hospital settings. This framework combines three main components (research objectives 1-3 below).

Research objectives

1. To estimate the cost and effectiveness of documented hand hygiene promotion interventions in hospital settings in relation to levels of investment in these interventions.

2. To quantify life expectancy from the long-term survival of post-ICU patients in a resource-limited hospital setting. This information is needed to quantify the health benefits (in terms of life years gained and quality-adjusted life year gained) resulting from the hand hygiene intervention.

3. To evaluate the cost-effectiveness of hand hygiene promotion as a hospital infection control strategy in resource-limited hospital settings as a function of baseline hand hygiene compliance using a model-based approach.

1.3 Contribution of thesis

This thesis addresses an important knowledge gap regarding the value for money of hand hygiene interventions in developing countries.[40-43] It employs economic, mathematical, and statistical modelling approaches to evaluate an infection control strategy in a resource-limited hospital setting. It is anticipated that the findings from this research will help guide policy-makers tasked with making decision about appropriate levels of investment in hospital hand hygiene campaigns at the local and the national level, both in Thailand and other similar settings.

Peer reviewed publications as arising directly from the thesis

Luangasanatip N, Hongsuwan M, Limmathurotsakul D, Lubell Y, Lee AS, Harbarth S, Day NP, Graves N, Cooper BS. Comparative efficacy of hospital hand hygiene promotion interventions: a systematic review and network meta-analysis. BMJ. 2015;351:h3728.

Luangasanatip N, Hongsuwan M, Lubell Y, Limmathurotsakul D, Teparrukkul P, Chaowarat S, Day NP, Graves N, Cooper BS. Long-term survival after intensive care unit discharge in Thailand: a retrospective study. Crit Care. 2013 Oct 3;17(5):R219.

Luangasanatip N, Hongsuwan M, Lubell Y, Limmathurotsakul D, Srisamang P, Day NP, Graves N, Cooper BS. Cost-effectiveness of hand hygiene promotion for MRSA bloodstream infection in ICU settings.
Under review: Lancet Global Health

The author's contribution to each of these papers is documented on the first page of each chapter (Chapters 3, 4 and 5, respectively).

Peered reviewed publications related indirectly from the thesis

Hongsuwan M, Srisamang P, Kanoksil M, Luangasanatip N, Jatapai A, Day NP, Peacock SJ, Cooper BS, Limmathurotsakul D. Increasing incidence of hospital-acquired and healthcare-associated bacteremia in northeast Thailand: a multicenter surveillance study. PLoS One. 2014 Oct 13;9(10):e109324.

List of conference or abstract publication

Luangasanatip N, Hongsuwan M, Lubell Y, Limmathurotsakul D, Srisomang P, Cooper BS. (2012) "Excess Length of Stay and Mortality Due to Hospital-associated Infections in Thailand: an Analysis of 8 Years of Retrospective Data." Paper presented at 15th International Congress on Infectious Diseases (ICID), Bangkok, Thailand.

Luangasanatip N, Hongsuwan M, Lubell Y, Limmathurotsakul D, Teparrukkul P, Chaowarat S, Day N, Graves N, Cooper BS. (2013) "Long-term Survival After Intensive Care Unit Discharge in Thailand: a Retrospective study." Paper presented at International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 16th European Conference, Dublin, Ireland.

Luangasanatip N, Hongsuwan M, Lubell Y, Cooper BS. (2014) "Effectiveness of Hand Hygiene Promotion and Level of Investment: a Systematic Review." Paper presented at International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 6th Asia-Pacific Conference, Beijing, China.

Luangasanatip N, Hongsuwan M, Limmathurotsakul D, Lubell Y, Lee AS, Harbarth S, Day NP, Graves N, Cooper BS. (2015) "Comparative efficacy of hospital hand hygiene promotion interventions: a systematic review and network meta-analysis." (Podium) 25th European Congress of Clinical Microbiology and Infectious Disease (ECCMID), Copenhagen, Denmark.

Luangasanatip N, Hongsuwan M, Limmathurotsakul D, Lubell Y, Day NP, Graves N, Cooper BS. (2015) "Cost-effectiveness of hand hygiene promotion for MRSA bloodstream infection in ICU settings." (Podium) 3rd International Conference on Prevention & Infection Control (ICPIC) Geneva, Switzerland.

1.4 Outline of thesis

This thesis is in "thesis by publication" format, which consists of three papers: Systematic Review, Results Paper 1, and Results Paper 2. Each paper was written for a particular journal. Therefore, repetitiveness in their introductions, methods, and discussions may be unavoidable. This introduction (Chapter 1) provides a brief overview of this thesis. The remaining chapters are arranged as follows:

Chapter 2 is a review of the current literature on healthcare associated infection, hand hygiene promotion policies and economic evaluation to explore and summarise existing knowledge.

Chapter 3 is a systematic review paper quantifying the efficacy of different hand hygiene strategies: "Comparative efficacy of hospital hand hygiene promotion interventions: a systematic review and network meta-analysis." Information of the effectiveness of hand hygiene interventions in improving the hand hygiene compliance obtained from this review is a key input of the model-based economic analysis in Chapter 5.

Chapter 4 is results paper 1: "Long term survival after intensive care unit discharge in Thailand: a retrospective study." This estimates the life expectancy amongst patients discharged alive from hospital. This information is needed to quantify the health benefits of infection control interventions that prevent unnecessary deaths during hospital stays. The life expectancy adjusted with quality of life is used in the economic analysis in Chapter 5.

Chapter 5 is results paper 2: "Cost-effectiveness of hand hygiene promotion for MRSA bloodstream infection in ICU settings." Model-based economic analysis is performed incorporating the information from Chapter 4 and 5 as well as other local data.

Chapter 6 provides general discussion and summarises findings from these various publications. Generalisability, strengths and limitations of this research, and recommendations for future research directions are considered.

Chapter 2: Literature Review

In section 2.1, the literature related to healthcare associated infections is reviewed and appropriate definitions provided for different types of HAI.

In section 2.2 and 2.3, literature concerning the epidemiology and economic burden due to HAIs in high income and low-middle income countries including Thailand is summarised. Infection control programmes to prevent HAIs including hand hygiene promotion and the evidence of their effectiveness are reviewed in section 2.4.

In section 2.5, methods for conducting economic evaluation are discussed. Finally, in section 2.6, a review of existing economic analyses of hand hygiene promotion is performed.

2.1 Healthcare-Associated Infection

Healthcare associated infection (HAI) is a major healthcare problem worldwide in both developed and developing countries and represents one of the leading causes of death and increased morbidity among hospitalised patients.[44] By convention, infections with nosocomial pathogens at least 48 hours after hospital admission are classified as HAI or nosocomial infection[45] The risk of such nosocomial infection depends on factors including age, degree of cross contamination, immunocompromised condition, and antibiotic pressure. HAIs can be caused by pathogens including bacteria, viruses, fungi, and macroparasites. However, the most common HAIs are bacterial infections. Patients may have HAI caused by organisms carried asymptomatically on their body sites (endogenous flora). Such colonising organisms may become invasive only under appropriate conditions, which allow them to penetrate to normally sterile sites. Patient contact with healthcare workers, other patients or exposure to contaminated instruments, devices or patients' surroundings, are possible routes of transmission of HAI due to exogenous flora.

HAIs produce unfavourable impacts at both the individual level and to healthcare systems. Patients suffering from HAI are likely to have slower recoveries and to require longer hospital stays. Moreover, additional treatments with antibiotic drugs and special care services are needed to support these patients. In severe infections, especially with bacteraemia, the mortality rate attributable to HAI could be as high as 50%.[3, 46] From the healthcare provider's perspective, the cost of antibiotic drug treatments, supplemental materials and services for additional stay at hospitals[2, 8, 10] affect the overall healthcare budget. This expense can be dramatically increased if the incidence of antimicrobial resistant HAI is high due to the need for new expensive antibiotic treatment.[47] Moreover, the impact of HAI also affects bed occupancy. The longer hospitalization of patients with HAI causes longer waits for other patients accessing medical services.

The identification and classification of HAI cases requires criteria combining clinical outcomes and laboratory confirmation. Some of the most widely used guidelines come from Centers for Disease Control and Prevention (CDC).[6] HAIs can be classified depending on the different sites of infection and also according to the types of medical device they are associated with. The CDC's guidelines classify HAIs as bloodstream infections (BSI), urinary tract infections (UTI), respiratory tract infections (RTI), surgical site infections (SSI), skin and soft tissue infections, central nervous system infections, infections of eye and conjunctiva and others. HAIs are also classified as device-associated and non device-associated infections. The device-associated HAIs include central line-associated bloodstream infection (CLABSI), catheter-related urinary tract infection (CAUTI) and ventilator-associated pneumonia (VAP).

2.2 Incidence and Prevalence of HAI

High-income countries

Prevalence and incidence of HAI vary worldwide depending on the healthcare system and facility. The burden of HAIs in resource-rich settings or developed countries is relatively low compared to developing countries.[48] Evidence from

USA and Europe is representative for the situation in industrialized countries. The incidence rate of HAI in the US was estimated as 4.5 per 100 admissions in 2002, or about 9.3 infections per 1000 patient-days.[6] An annual report from the European Centre of Disease Prevention and Control (ECDC)[49] reported that the overall prevalence of HAI varied between 3.5% (525 of 14,996 patients) and 10.5% (604 of 5,750 patients) across industrialised countries, and was about 7.1% on average. In addition, the prevalence of HAI is higher in intensive care units (ICUs). One multi-center point prevalence study in Europe reported that on the date of study, the proportion of patients in ICU with an HAI could be in excess of 50% (7,087 of 13,796 patients).[50] Moreover, large-scale studies in the US show that the incidence density of HAI in ICU ranged from 13.0 to 19.8 events per 1,000 patient-days.[6, 51, 52] Of note, most of these are associated with the use of invasive devices including catheters and ventilators. In general, the most common type of HAI in both US and Europe is UTI, which accounts for about 36% and 27% of all HAIs, respectively.[6, 49] In the US, the second most frequent type of HAI is SSI (20%) followed by BSI and Pneumonia (overall 11%)[6] while in the EU RTI (24%) is the second most frequent and then SSI (17%) and BSI (10%).[49]

Low and middle-income countries

In developing countries, where resources are more limited, the risk of infection has been reported to be 2 to 20 times higher than in developed countries, and the proportion of infected patients can exceed 25 percent of patients admitted to acute care hospitals.[24, 53] A recent systematic review by Allegranzi et al.[48] showed that hospital-wide prevalence of HAI combined from 22 studies in developing countries was 15.5 per 100 patients, varying from 5.7 to 19.1%. The pooled HAI density in ICUs was 47.9 per 1000 patient-days, approximately three fold higher than the number reported from the US. Moreover, a six-year study by Rosenthal et al.[3] reported that the mean prevalence and incidence of device-associated HAI in 173 ICUs in 25 countries, mostly from low and middle income countries, were 15.5 per 100 patients and 34.2 per 1000 patient-days. Overall, SSI was the most frequent type of HAI in developing countries (accounting for 29.1% of all HAI) followed by UTI, BSI, and hospital acquired pneumonia (HAP) (23.9%, 19.1 and 14.8% respectively).[48]

Thailand

In Thailand, national surveillance of nosocomial infection studies has been studied since 1988.[7, 54, 55] The trend of the prevalence is apparently decreasing. The latest surveillance study in 2006 collected data from 20 hospitals representing all sizes of hospital in Thailand, and used a 2-week period prevalence study. It showed that the overall prevalence of nation-wide nosocomial infection was about 6.5%,[7] with a tendency to be higher in university hospitals (7.6%), and slightly lower in provincial and regional hospitals, 6.5% and 4.9% respectively. This study found that the most common HAI was lower RTI followed by UTI and SSI, 36.1%, 25.5%, and 11% respectively. The highest prevalence rate was in ICUs, where about 23% of patients develop an HAI while the prevalence at other wards ranged from 1.1 to 6.8%. More than half of HAI cases were potentially related to device-associate infections. The commonest organisms causing HAIs were Gram-negative bacteria, accounting for about 75.7% of infections, including *Pseudomonas aeruginosa*, *Klebsiella spp.*, *Acinetobacter baumanni*, and *Escherichea coli*. HAI caused by Gram-positive bacteria accounted for 18.4% of infections. Most of these were *S. aureus*, of which two thirds were methicillin-resistant *S. aureus* (MRSA).[7] However, it is possible that these figures represent a substantial underestimate due to underdiagnosis of hospital infections. The total annual number of HAI cases was estimated to be about 390,000 assuming that 6 million people are admitted to hospital each year in Thailand.[56] The total number of deaths due to HAI was estimated to be 26,000 per year, assuming a mortality rate attributable to HAI of 6.7%.[55]

2.3 Economic burden of HAI

HAIs impose significant economic consequences on the healthcare system worldwide. The major costs derive from the longer stay in the hospital and also more care and treatments.[2, 8, 57] Moreover, patients with HAI are more difficult to treat when they have multiply drug resistant infections.[47] This has the potential to result in higher costs of treatment (due to more expensive antibiotics) and therefore this will affect the national healthcare expenditure.

The economic burden of HAI is believed to be high even in developed countries. Based on prevalence data from six European countries and the number of hospital admissions among 27 European countries, and taking estimates of attributable mortality due to HAI from the US CDC, HAIs have been estimated to cause 16 million extra days of hospitalisation and 37,000 attributable deaths yearly in 2008, in Europe.[49] In addition, accounting for only direct costs, HAI cost about 7 billion Euros per year.[49] However, in the US, there were 99,000 deaths attributable to HAI in 2002 and more than half of these cases were due to pneumonia and BSI.[6] The economic burden of HAI was estimated to be as high as $US 6.5 billion in 2004.[6] The cost per case of HAI has also been estimated. In the US, Stone et al.[58] estimated the cost per infection of HAI ranged from $US 1,006 for CAUTI to $US 36,441 for CLABSI. Another cost estimation study conducted in the UK by Plowman et al.[59] used a linear regression model to estimate that on average (considering all types of HAI) patients with HAI incurred hospital costs 2.9 times higher than uninfected patients, an additional £3,154 in 1995 (range from £1618 to £9,152 per case). However, the costs of HAI also varied depending on the types and number of sites of infection.

The estimated economic impacts in developing countries have a wide range and different methods have been used for the estimates. For example, the cost due to hospital acquired BSIs in India was estimated in 2009 to be $US 14,818 per case[60] from a 200-bedded private tertiary care cardiac hospital in New Delhi while in another study in the same country estimating the cost of antibiotics alone for MRSA-HAI case from a medical ICU in a 2,600-bed tertiary care hospital in Vellore, the median cost was $US 124 per case (while comparatively low, this is still enough to render effective antibiotic treatment unaffordable by a significant proportion of the Indian population, very few of whom have medical insurance).[61] The average additional cost of central-line related bloodstream infection (CRBSI) and hospital acquired pneumonia (HAP) in ICUs were estimated as $US 4,888 per event in Argentina, in 2005 prices.[57] In Malaysia, the cost of antibiotics for treating HAI was estimated to be $US 521,000 per year in an 800-bed tertiary hospital.[62] In Thailand, the cost of antibiotics for treating a single HAI was estimated using a matched case-control in the year 2001 to range from 6,000 to 16,000 baht ($US 200-500), depending on the number of infected sites.[55]

A systematic review by Stone et al.[63, 64] revealed that there is a wide range in estimated costs of HAI. Several statistical methods have been used to estimate these costs including regression models, multiple matched comparisons, and case review.[65-67] Costs of HAI have two components: the excess length of stay (LOS) i.e. the additional time spent at hospital that would not have been spent had the patient avoided the infection, and the cost per infected bed day, i.e. the costs of the extra resources used for treating the resulting HAI (such as antibiotics).

In most cases, in high income countries, most of the excess costs result from the excess length of stay (LOS), as antibiotic and other pharmaceutical costs are usually a small proportion of these.[68] Estimating the excess LOS with commonly used statistical approaches is subject to time dependent bias. This bias can arise from the fact that the analysis erroneously treats the infection as present at baseline. While an HAI probably usually does increase the length of stay (though in some cases increased associated mortality can actually decrease length of stay), a longer stay will certainly increase the risk of HAI and failure to account for this will lead to over-estimation of the increase in length of stay due to infection.[69, 70] As a result of this bias, two group comparisons, matched cohort studies, and matched cohort with matching on time of infection all tend to overestimate this additional LOS due to HAI.[71] More appropriate statistical approaches accounting for the time-varying exposure that HAI represents should be used instead.

In addition, the value of bed-days used in most of the previous studies was estimated based on the accounting approach using the hospital budget divided by the total patient bed-days over the same period.[63-67] As this accounting cost is fixed and dependent on budget decisions that have already been made, this would not reflect the opportunity cost of the occupied bed to be used.[11] A health economist would focus on the extra beds and other resources released and variable costs saved when implementing an infection control program. This would support the decision-making process when considering investment in a new infection control program to free up beds. Willingness to pay for accessing this bed-day released would reflect the value of opportunity cost. However, for a centralized healthcare system, this cost of a blocked bed should be valued by hospital management.[11] The value of a bed day based on a willingness to pay approach is generally much lower and could be only one third of the value derived using the accounting approach.[72] Using this willingness to pay approach therefore tends to reduce the estimated economic burden of extra stay due to HAI.

Both shortcomings in the literature tend to exaggerate the burden of HAIs[11] and could cause healthcare decision makers to make inappropriate budget allocations. More accurate estimation is required to support decision makers to evaluate the potential benefits of infection control interventions as a building block of cost-effectiveness analysis of infection control programmes. A few studies overcoming the problems associated with previous methods have recently been published.[10, 73, 74]

2.4 Infection control programmes

2.4.1 Hand hygiene promotion interventions

Direct patient contact with healthcare staff who are transiently contaminated with nosocomial pathogens is believed to be the primary route of transmission for several nosocomial pathogens and can lead to patients becoming either colonised or infected. Improving the healthcare team's hand hygiene compliance can reduce the impact of this transmission route.[75-77]

The first obvious evidence of effectiveness of hand hygiene intervention was in 1847. Ignaz Philip Semmelweis, a Hungarian physician, noticed a high maternal mortality rate from one of the two obstetric clinics in a general hospital in Vienna. He investigated the different factors between those settings and found that in the first clinic (with the high mortality rate), medical students attended straight from autopsy class to the delivery suite while at the other clinic midwifery students were the main staff and had no involvement with the necropsy. As he believed that the infecting particles were from the corpse and transmitted by hands, chlorinated lime as disinfection agent was introduced for those leaving the necropsy room. After this intervention the mortality declined to be comparable with the other clinic over four years (11% to 1%).[78] This is one of the earliest pieces of evidence that reveal clear benefits of hand disinfection.

Later, in 1994, a landmark study was conducted in Geneva. Pittet et al. rigorously promoted a hospital-wide campaign in the University of Geneva Hospitals, Switzerland.[79] They integrated multi-component interventions including improving hand hygiene facilities, providing individual containers of alchohol hand rub solution at all beds, using visual reminders through the display of 70 different colour posters, giving performance feedback, initiating regular meetings amongst multidisciplinary groups of healthcare workers (HCWs), and obtaining strong institutional endorsement as a package of interventions. They found an improvement in compliance from 48% to 66%, reduction in prevalence of nosocomial infection from 16.9% to 9.9%, and reduction in MRSA transmission rate from 2.16 to 0.93 episodes per 10,000 patient-days over the three years study period. These findings highlighted the importance of a multi-component hand hygiene intervention that could successfully improve HCWs' hand hygiene compliance and, therefore, reduce nosocomial infections.

Although hand hygiene is widely thought to be the most important activity for the prevention of nosocomial infections, many observational studies demonstrate poor adherence by HCWs. A review of hand hygiene studies by the WHO including both developed and developing countries [80] found that the baseline hand hygiene compliance among HCWs varied between 5% and 89%, and was on average about 38.7%. There was evidence that recorded compliance varied with workload, the ward type and observation methods. Factors commonly associated with poor hand hygiene adherence include being physicians and nurse assistants, staff workload, and use of gloves.[81-83] For physicians, adherence has been reported to be associated with awareness of being observed, the belief of being a role model for other colleagues, a positive attitude toward hand hygiene after patient contact, and easy access to a hand-rub solution.

2.4.1.1 WHO hand hygiene campaign

The WHO World Alliance for Patient Safety has been trying to improve HCWs' hand hygiene by launching a campaign, the First Global Patient Safety Challenge, "Clean Care is Safer Care", aimed to reduce HAI worldwide by increasing awareness of HAI globally, encouraging countries' commitment to keep working on this field, and trying to implement basic infection control programmes at local hospitals worldwide. Hand hygiene improvement plays a major role in this campaign. A multimodal approach with five moments for hand hygiene has been recommended in the WHO guidelines on hand hygiene in healthcare. These guidelines aim to encourage good hand hygiene practice in the real world in both developed and developing countries and are designed to be readily adapted to local settings depending on the available resources at each setting. The multimodal implementation strategy consists of five components (WHO-5), which are system change, training and education, observation and feedback among healthcare workers, reminders in the hospital, and a hospital safety climate. The guidelines also emphasise the importance of increasing the use of alcohol hand rub, which is considered as the preferred practice in most circumstances and a crucial factor for improving hand hygiene.[79, 84] The alcohol hand rub is preferred because, in most cases, it is more effective at decontaminating hands than soap.[80] Several studies have reported that introduction of alcohol hand rub as part of a multimodal strategy can decrease the HAI rate.[85]

2.4.1.2 National hand hygiene campaigns

Several countries (mostly high-income countries) have implemented similar multimodal interventions as a national hand hygiene campaign.[20, 21, 23, 29, 86, 87] A few of these have reported their findings.

In 2004, a nationwide hand hygiene promotion intervention consisting of providing alcohol hand rub at the bed-side, displaying hand hygiene promotion materials and regular audits in order to enhance hand hygiene compliance and reduce HAI across England and Wales hospital was implemented.[20] This was evaluated in a four-year interrupted time series study which showed that the MRSA bacteraemia rate fell from 1.88 to 0.91 cases per 10,000 bed days while *Clostridium difficile* infections fell from 16.75 to 9.49 cases per 10,000 bed days The procurement of soap and alcohol hand rub per patient bed day, an indirect measurement of hand hygiene compliance, increased almost 300%. Results from regression analysis also showed that an additional use of 1 mL of soap per bed day was associated with a 0.7% reduction in *Clostridium difficile* infection and a 1% reduction in MRSA bacteraemia.

In 2009, a national hand hygiene programme based on the WHO's 5 moments campaign was introduced in Australia[21] and produced similar results. The overall hand hygiene compliance increased from 43.6% to 67.8% among 521 hospitals and the mean annual rate of MRSA bacteraemia declined significantly (P=0.008) from 0.50 per 10,000 patient-days in 2008 to 0.39 and 0.35 per in 2009 and 2010, respectively. Later, more sophisticated analysis after four years of the program found similar results.[23] With segmented regression analysis, they found four of the six states showed a reduction in the infection rate; two states had an immediate reduction of 17 and 28% and another two showed a linear decreasing trend of 8% and 11% per year. However, the other two states found no change in infection rates.

In Germany, the nationwide WHO-5 intervention was implemented in 2010. The overall baseline compliance was reported as 61% from 163 hospitals. They found average compliance from 62 observed hospitals increased by 11% after the intervention. However, there was no reporting of HAIs outcomes.[29]

2.4.1.3 Hand hygiene interventions in resource-limited settings

There are no reports from studies evaluating national hand hygiene campaigns in low- or middle-income countries. However, some hospital-based studies promoting both WHO-5 and other hand hygiene strategies have been conducted in developing country settings. Key studies are considered below.

Allergranzi et al. described the implementation of a hospital-wide WHO-5 campaign in a 456-bed university hospital in Mali.[88] They found the overall compliance in HCWs from 13 hospital wards increased from 8.0% (95% CI: 6.8-9.3%) to 21.8% (95% CI: 19.9-24.0%) (P<0.001) and the overall HAI reduced from 18.7% (95% CI: 12.5-26.3%) to 15.3% (95% CI: 9.8-22.3%) (P=0.453).

Rosenthal et al.[57] conducted an intervention study at two ICUs in a hospital in Argentina. This study found that hand hygiene promotion was followed by an improvement in hand hygiene compliance from 23.1% to 64.5% and there was also an associated decrease in overall nosocomial infections (including pneumonia, bacteraemia, and urinary tract infection, both device and non device associated) in both ICUs from a combined total of 47.55 per 1000 patient-days to 27.93 per 1000 patient-days (P<0.0001).

Another study conducted at two neonatal intensive care units (NICUs) in Manila, Philippines[89] evaluated an intervention including hand hygiene promotion and reported a reduction in the overall mortality rate. Hand hygiene compliance was significantly improved and the overall mortality rate decreased by 12% from one ward and 15% from another ward. However, activities including the use of checklists, staff education, and alcohol-based hand rub introduction were also implemented during the intervention period.

In summary, a number of studies have reported findings from both national hand hygiene campaigns and campaigns in local hospital settings. These studies showed evidence that interventions improved the compliance, potentially reducing HAIs, especially for multiple drug resistant organisms including MRSA.[20, 23] However, the results from these studies should be interpreted with caution as almost all of the intervention studies in the literature are performed with quasi-experimental study designs and are vulnerable to a number of biases.

2.4.1.4 Effectiveness of hand hygiene intervention

Previous systematic reviews of hand hygiene interventions in healthcare settings have important limitations.[25-28] One of these, a Cochrane Collaboration review, found very few studies of sufficient methodological quality to reliably evaluate hand hygiene promotion interventions and was unable to reach firm conclusions.[25] The other three reviews, which included studies of much lower methodological quality, pointed out the potential effect of a multimodal approach,[27] reported associations between two specific bundles of interventions and improved hand hygiene[28] and addressed the correlation between the increase in the compliance and the number of determinants of behavior change in hand hygiene strategies.[26] However, because of methodological shortcomings of the included studies, most of which do not meet minimal inclusion criteria of Cochrane Effective Practice and Organisation of Care Group (EPOC), a causal association cannot be reliably inferred. [90, 91] Further limitations include the fact that most interventions were compared with an unspecified "standard care" baseline, and direct head-to-head comparisons of interventions were lacking. Moreover, the authors highlighted the lack of information on relative effectiveness of different components of hand hygiene promotion interventions.[25-28]

2.4.2 Other infection control strategies

Apart from hand hygiene promotion, several other infection control strategies such as quality care bundles including checklists, ward cleaning, screening and decolonization and others have been reported to be effective in preventing hospital-acquired infections. Some of these infection control interventions are briefly reviewed below.

Care bundles practice

A "care bundle" refers to the combination of several interventions which may include hand hygiene promotion, use of checklists, staff education, performance monitoring and feedback, standard and enhanced precautions.[13] Such bundles have been implemented worldwide.[76, 89, 92] One study of such a care bundle with a quasi-experimental design was conducted in Thailand[93] and aimed to evaluate the effectiveness of catheter-associated bloodstream infection (CA-BSI) prevention bundle. This bundle consisted of hospital-wide education in hand hygiene practice, education on the use of maximum sterile barrier precautions during catheter insertion, use of a chlorhexidine-based skin preparation, optimisation of central venous catheter (CVC) insertion practices, and daily review of the need for CVC in each patient. The results showed a substantial reduction of CA-BSI rate from 14 cases to 6.4 cases per 1,000 catheter day and improvement in hand hygiene compliance, from 8% to 24% and 54% during the intensive hand hygiene promotion. Another healthcare bundle was reported by Gill et al.[89] It was associated with a decline of overall mortality rate of about 50%. However, the individual effects of component interventions were impossible to estimate since the interventions were combined. Moreover, the limitations of the study design, as discussed by Apisarnthanarak,[94] included the fact that effects regarding the intervention might be interfered with by a secular or seasonal trends. This study would have provided a much higher grade of evidence if it had been analysed as an interrupted time series design (with multiple measurement for each outcome before and after the intervention) instead of as a before-after study (just a single measurement for each outcome before and after the intervention).

Ward cleaning

Ward cleaning is one of the potential interventions that could prevent HAI. Dancer et al.[95] reported that some nosocomial pathogens such as MRSA, *Clostridium difficile*, vancomycin-resistant enterococci and *Acinetobacter spp.* are able to survive on the surfaces of hospital surroundings for extended periods of time. This can be a source for transmission to patients. Cleaning the hospital environment, especially surfaces frequently touched by HCWs and patients, such as the bed rail, the bed surface and the supply cart[96] would possibly help preventing HAI. A number of studies [97, 98] have suggested the efficacy on environmental cleaning to reduce HAI. However, large prospective controlled trials are required to clarify the effect of this intervention.[99]

Screening and decolonisation

Search and destroy policies making use of routine or responsive screening of patients for asymptomatic carriage of nosocomial pathogens, especially for MRSA, coupled with decolonisation of these patients, represents another class of potential intervention to reduce infections which has been implemented in many parts of the world (though usually limited to developed countries).[100-103] A systematic review by McGinigle et al.[104] provided some evidence for the effectiveness of active surveillance, which was estimated to account for about 40 to 60% reduction of hospital-acquired MRSA incidence in ICU settings. However, these studies have limitations in several ways such as study design with no control group, possible confounders, and no intervention compliance record. For decolonisation, mupirocin nasal ointment[105] and washing with chlorhexidine are two possible treatments for reducing MRSA carriage in settings where resistance to these agents is lacking.[106] According to economic evaluation studies, it seems that this infection control approach can be cost-effective in ICUs in high-income countries.[68, 107] However, both screening and decolonisation involve extensive staff time and require more resources compared to other infection control interventions. Little is known about implementing these measures in low-middle income countries where resources are more limited and where they have traditionally not been used.

2.5 Economic Evaluation Framework

2.5.1 Forms of Economic Evaluation

Resources available for healthcare are limited, and spending should seek to maximize population health benefits. Economic evaluation is an essential economic tool to compare two or more healthcare interventions in terms of costs and outcomes. Information resulting from these analyses is helpful for policy makers who have to allocate budgets within the health sector. Economic evaluation has been described as

> ‘‘The comparative analysis of alternative courses of action in terms of both their costs and consequences in order to assist policy decisions.’’
>
> Drummond et al. [31]

Economic evaluation consists of two parts: costs and consequences. Costs are always measured in monetary terms while consequences can be measured in terms of clinical outcomes, monetary (economic) terms, or utility. Economic analyses examining both costs and effects would be defined as full economic evaluation while analyses considering only costs or outcomes of the alternatives alone or without any estimations of cost per unit of health benefit are classified as partial economic evaluation (called cost analyses, efficacy or effectiveness evaluation and cost-consequences analysis). Types of full economic evaluation in healthcare are described below.[108, 109]

Cost-Minimisation Analysis (CMA)

This form of economic evaluation is used for comparing two or more equivalent interventions assuming that the consequences of alternatives are identical. This type of analysis focuses on costs incurred from different interventions assuming the lowest cost will be preferred. However, in practice, it is unlikely that interventions will produce identical outcomes rendering this approach inappropriate in most circumstances.

Cost-Effectiveness Analysis (CEA)

The consequences of this form of analysis are measured in terms of natural effects or physical units such as number of pain free days, reduction of mmHg in blood pressure, number of infection cases averted and number of life years gained. This approach has a potential benefit in the aspect of having more flexibility in measuring outcome. However, a crucial limitation of this approach is that it usually uses disease-specific measures. Consequently, there might be difficulties in comparing results across other programmes due to the differences in outcome measurement.

Cost-Utility Analysis (CUA)

In this form of analysis, consequences or outcomes are assessed in a generic measure known as quality adjusted life years (QALYs), which captures the health change in both morbidity and mortality. Utility values or quality of life weights are attached to different health states in the analysis from 0 (death) to 1 (full health) based on individuals' preferences. Results are commonly presented as costs per QALY gained. This approach has wider applicability than CEA because the outcomes are measured in terms of long-term health combining multiple dimensions of health status and the results are comparable across different areas of illness.

Cost-Benefit Analysis (CBA)

CBA values the consequences resulting from interventions in monetary terms. The benefit of this is that the result can be used to compare health expenditure with investment in other sectors. The results of this analysis can be shown as net present value (NPV) or benefit-cost ratio.[110]

Different forms of economic evaluation have different potential uses based on the situation and purpose of analysis. The terminology of CEA and CUA are often used interchangeably. However, the most frequently used approach in the healthcare sector is CUA since this approach measures the same outcomes, and allows decision-makers to compare different interventions from several areas of disease and to maximise health benefits obtained using a fixed budget.

2.5.2 Methods in Economic Evaluation

Economic evaluation can be carried out in two main ways. One approach is to conduct the evaluation alongside or as a part of a prospective study such as a randomized controlled trial (RCT); another approach is to perform the evaluation using a decision analytic model.[36]

Economic evaluations are sometimes conducted alongside RCTs or other prospective studies. The main advantages of this approach is that patient-specific data can be obtained from real world situations with low marginal costs of collection because the economic evaluation is an add-on to the data being collected for the trial. However, there are some limitations to trial-based economic evaluations. To begin with, the time frame used in trials is usually short and measured outcomes may sometimes represent transient behaviour, not the final outcomes. Consequently, the impact of interventions on long-term outcomes such as death can sometimes not be adequately captured. Also, the population in a single trial is usually relatively small in size compared to the targeted population. This can cause difficulties in generalisation of the findings. Moreover, it is only possible to evaluate a restricted number of strategies (rarely more than three) within a single trial due to study design limitations. Therefore, while important, conducting economic evaluation alongside RCTs does not generally provide enough information to inform policy decision makers.[111]

Decision analytic modeling can overcome these limitations, though at the expense of requiring a number of assumptions. This type of analysis requires the use of a mathematical model to synthesise data on alternative clinical strategies. Multiple inputs are used to construct the model, often including epidemiological and clinical data, estimates of intervention effectiveness over an extended time-horizon, unit costs and resources used, and health state valuations. One of the main benefits of this approach is the capability of extrapolating from observed RCT data. The models can enable estimates of the benefit of the intervention in the longer term (after the trials have finished) and link intermediate clinical outcomes to final outcomes. In addition, modelling can compare several strategies or interventions at the same time or allow head to head comparisons of interventions not directly compared in trials. Models can also be used to generalize results from trials to other settings by altering the parameter inputs to fit with the population of interest. In this way modelling approaches can be used to aid decision-making processes. For these reasons, decision analytic modeling is increasingly undertaken as a valuable approach for economic evaluation of various healthcare interventions.

Choices of modeling in economic evaluations

The aim of decision analysis is to make explicit the best decision under specified criteria, and to quantify and account for the uncertainty associated with these decisions. Multiple sources of information including systematic reviews with meta-analyses, RCTs, hospital datasets, observational studies, and expert opinions can be used to develop a model. Several types of modelling techniques are available for conducting economic evaluation.[37, 38, 112] The selection of model type should depend on the clinical research questions and natural history of the disease of interest. One distinction for choosing the appropriate type is whether or not individuals in the model have independent risks of becoming diseased.[112] In case of interaction between individuals (dependence) as is expected for infectious disease (where the number of infected patients influences the infection risk of the others), discrete event simulation and compartmental dynamic models may be more appropriate.[113-115] However, in other cases (when there are no important interactions between individuals), decision trees and Markov models are frequently used[38, 116] and micro-simulation is sometimes used.[117]

Modelling in healthcare associated infections

Mathematical modelling is a useful tool to describe the essential features of a complex system. Transmission dynamic models are widely used to understand the epidemiology of infectious diseases and effects of different interventions including vaccines.[118] Different epidemiological model have been developed to simulate the spread of pathogens causing HAI. Several models have been constructed to investigate the spread of bacterial and viral infections in hospital settings, especially for antibiotic resistant bacteria including MRSA infection,[119, 120] vancomycin-resistant enterococci,[121] and *Clostidium difficile*.[122, 123] In addition, infection control measures including hand hygiene promotion, decolonization, patient isolation, and antibiotic stewardship, have been incorporated into the model to predict the consequences of implementation.[39] A number of these models have incorporated a community reservoir in the model structure as the density of colonized at admission patients will affect the hospital dynamics.[124-127] The modelling techniques used and model structure are varied based on particular research questions and data availability.

Modelling of the effects of hand hygiene interventions in hospital settings have been constructed with two populations, patients and HCWs. [128-132] These are host-vector models where HCWs act as vectors having direct contact with patients and can cause cross transmission from one colonised patient to another by carrying pathogens on their hands. These models have a useful application in describing the expected relationship between hand hygiene compliance and HAI infection rates. This relationship is difficult or impossible to derive from intervention trials. Most of the hand hygiene models have considered only a single ward, mostly in ICU settings where the incidence is higher. In addition, hospital-wide models and models incorporating community reservoirs have also been developed.[39, 133] However, the more complex the model, the more epidemiological data are required to parameterize the model.

Transmission dynamic models combined with decision analytic models to perform economic analyses have increasingly been used because dynamic models can often more fully capture health benefits than conventional static models.[115] Although, a number of studies have combined dynamic modeling and economic evaluation to assess infection control interventions,[68, 134] none of these have considered interventions intended to improve hand hygiene.

2.6 Economics of hand hygiene promotion in hospital settings

The potential benefit of hand hygiene promotion is to reduce transmission of nosocomial pathogens to patients leading to a reduction in HAI and reduced patient morbidity and mortality. Hand hygiene promotion could potentially be a highly effective intervention representing good value for money meriting increased investment. Economic analysis is a useful tool to evaluate the circumstances under which further investment would be warranted. For example, it might be that only when hand hygiene levels fall below a certain threshold, or resistant organisms above a certain threshold that further investments in hand hygiene promotion are likely to be cost-effective. Such analyses can potentially help healthcare decisions makers gain the maximum health benefits out of a limited budget.

Most of the economic analyses of hand hygiene promotion in peer-reviewed journals were conducted as business case analyses, comparing the cost of hand hygiene interventions to the potential cost savings from the HAI cases avoided.[135-138] This approach is used to illustrate the effect of intervention implementation on budgets, and does not take into consideration the health benefits to the patients from the intervention (except insofar as they affect costs). An example of a business case analysis was conducted by Cummings et al.[137] This study performed a model-based analysis predicting the relationship between the increase of hand hygiene compliance and cost saving. It combined data about hand hygiene compliance and MRSA colonization and infection with MRSA rates. The authors estimated that a one percent increase in hand hygiene will save about $US 39,650 annually, mainly due to preventing MRSA cases, in a 200-bed hospital. This study demonstrated the economic value of improving hand hygiene compliance for the healthcare provider based on a 750-bed hospital in Durham, North Carolina, USA. However, costs of hand hygiene promotion required to achieve the higher rates of compliance and the consequences in terms of patient outcomes were not measured in this analysis.

However, this kind of analysis gives no information to inform budget allocation decisions. It only informs the healthcare policy decision makers about allocation efficiency. There are two broad types of economic evaluation, partial and full economic evaluations, as mentioned in section 3.4.1. Economic evaluation studies of hand hygiene interventions using both partial and full economic evaluation are reviewed below.

Partial economic evaluation

Pittet et al.[43] reported the cost of the intervention from a hospital-wide programme at the University of Geneva Hospital, Switzerland (2,600 bed hospital). Components of the intervention in this study were provision of individual bottles of hand rub solution, visual display of the importance of hand cleaning, posters promoting hand hygiene, performance feedback, and strong support from the medical and nurse directors. Costs of the hand hygiene intervention were composed of direct costs including cost of hand rub and other materials, and indirect costs including salary and expenses for office supplies. The costs were calculated on a yearly basis (1994 to 2001) and presented as incremental costs of each year compared to the baseline year (1994). The estimated average costs ranged between $US 62,743 to $US 108,348 per year (103,526 to 178,774 Swiss Francs).

Full economic evaluation

Chen et al.[41] conducted a hospital-wide hand hygiene intervention programme focusing on promoting the use of alcohol hand rub at 2,200-bed hospital in Taiwan. This cost-benefit analysis study collected the cost of hand hygiene promotion including alcohol hand rub expense and material costs and time used according to the campaign alongside the intervention study. The additional cost of the hand hygiene programme for 4 years was estimated to be US$ 233,044 and more than 90% of the cost was from alcohol hand rub (AHR) expense as a major focus was on promoting the use of AHR. The financial benefits from the programme were estimated to be $US 5,522,408 from preventing 1,424 HAI cases. Consequently, the net benefit of the programme was calculated as $US 5,289,364 and the benefit-cost ratio was 23.7 (with 3 % discounting rate).

The National Patient Safety Agency (NPSA) in the UK conducted an economic evaluation in England considering hypothesized impacts of a national hand hygiene intervention programme.[40] In this analysis, they evaluated a planned multi-faceted campaign “CleanYourHands”, aimed at improving hand hygiene compliance among NHS clinical staff. The campaign included the provision of alcohol hand rub at each bedside and personal alcohol handrub dispensers, posters and promotional messages to staff and empowerment of patients in the hand hygiene process. Costs of the intervention were mainly from the alcohol hand rub and promotional material while the consequences were measured as financial benefits and QALYs gained from reduction in fatal and non-fatal HAIs. Costs and health benefits were discounted at an annual rate of 3.5 and 1.5%,

respectively. Compliance with hand hygiene recommendations was assumed to improve from 28% to 76% in the first year and to be sustained at this level over a 5-year time horizon. The intervention was assumed (conservatively, according to the authors) to lead to a 9% reduction of the overall HAI rate, based on a survey and an expert opinion. At one 500-bed hospital, the intervention would produce a cost saving of about £ 460,000 pounds with 12 QALYs gained, annually. At the national level (England), the cost saving was estimated to be £ 137 million pounds with 3,246 QALYs gained per year.
Recently, Huis et al.[42] conducted an economic evaluation alongside a cluster-randomised trial in 67 wards from three hospitals in the Netherlands to assess the cost-effectiveness of a multimodal hand hygiene intervention equivalent to WHO-5 plus goal-setting compared with WHO-5 alone. They found the effect of goal-setting improved the compliance by 9% with an average extra cost of €5,497 per ward. However, HAI rates could not be collected from the trial but there was assumed to be a 0.15% reduction in the HAI rate from 1% improvement in compliance. As a result, the incremental cost was reported to be €4,125 per additional percentage of HAI rate reduction.

Economic analyses of hand hygiene promotion have been conducted in different countries both at hospital and national level. The results have suggested that the investment in hand hygiene promotion is cost-saving with additional health benefits in settings where the hand hygiene compliance is low. However, all but one of these studies did not evaluate interventions using the strongest study designs, randomised trials, and the costs of HAI due to additional length of stay are likely to be overestimated due to the time-dependent bias.[11, 71] The value of a bed-day is based on the accounting approach in most studies performed. This is typically much higher than the opportunity cost for the occupied bed-day.[72] Moreover, there are no studies in the literature conducted in low-middle income countries where the higher HAI incidence and the tighter constraints on healthcare expenditure represent additional challenges.

Chapter 3: Systematic Review

Comparative efficacy of hospital hand hygiene promotion interventions: a systematic review and network meta-analysis.

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Author Contribution:

NL, BSC, YL, DL, NG, and ND contributed to the study conception and design. NL and BSC extracted data and NL performed the data analysis. NL wrote the first draft. DL, YL, MH, ASL, SH, NG, ND, and BSC critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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3.1 Abstract

Objective: Many interventions have been proposed to improve hand hygiene compliance amongst healthcare workers, and in 2005 the World Health Organization launched a campaign promoting a 5-component strategy (WHO-5). We aimed to evaluate the relative efficacy of WHO-5 and other hand hygiene promotion interventions and to summarize associated resource-use information.

Design: A search strategy was developed and electronic databases searched for studies published between 1980 and February 2014. Random effects and network meta-analyses were performed on studies considered sufficiently homogeneous with regard to interventions, participants and outcome measures. Information on resources required for interventions was extracted, and graded into three levels.

Inclusion criteria: Studies implementing an intervention to improve hand-hygiene compliance amongst healthcare workers in hospital settings and measuring hand-hygiene compliance or appropriate proxies that met the Cochrane Effective Practice and Organisation of Care Group (EPOC) quality inclusion criteria were included. Where studies had not used appropriate analytical methods, we re-analysed primary data.

Results: Of 3,633 studies retrieved, 36 met the inclusion criteria (6 randomized controlled trials (RCTs), 26 interrupted time-series (ITSs), 2 controlled trials, and 2 controlled before-and-after studies). Meta-analysis of two RCTs showed the addition of goal-setting to WHO-5 was associated with improved compliance (pooled odds ratio [OR] = 1.39, 95% confidence interval 1.15 to 1.67; I^2= 80.0%). Of the 13 ITS pairwise comparisons, 12 showed stepwise increases in hand-hygiene compliance and all but three showed a post-intervention trend for increasing hand-hygiene compliance. Network meta-analysis indicated considerable uncertainty in the relative efficacy of interventions, but nonetheless provided evidence that WHO-5 is effective, and that compliance can be further improved by adding interventions including goal-setting, reward

incentives and accountability. The reported cost of interventions ranged from $US 225 to 4,669 per 1,000 bed-days.

3.2 Introduction

More than 1.4 million patients around the world suffer from healthcare associated infections (HAIs) at any point in time.[1] HAI causes excess morbidity and is associated with increased mortality.[2 3] Direct patient contact with healthcare workers (HCWs) who are transiently contaminated with nosocomial pathogens is believed to be the primary route of transmission for several organisms and can lead to patients becoming colonised or infected. Although hand hygiene is widely thought to be the most important activity for the prevention of nosocomial infections, a review of hand hygiene studies by the World Health Organization (WHO) found that baseline hand hygiene compliance among HCWs was on average only 38.7% (range: 5% to 89%).[4]

In 2005, the WHO World Alliance for Patient Safety launched a campaign, the First Global Patient Safety Challenge, "Clean Care is Safer Care" aiming to improve hand hygiene in healthcare.[4] This campaign promotes a multimodal strategy (WHO-5) consisting of five components: system change; training and education; observation and feedback; reminders in the hospital; and a hospital safety climate. More recently, additional strategies for improving hand hygiene have been evaluated, including those based on behavioural theory.

Evaluating the evidence for the efficacy of different interventions is complicated by three factors: first, most evaluations of hand hygiene promotion interventions use non-randomized study designs, and in many cases the reported analysis is inappropriate or methodological quality is too low to allow meaningful conclusions to be drawn;[5-7] second, there is wide variation between studies in the hand-hygiene promotion activities used in the comparison group; third, direct head-to-head comparisons of most interventions are lacking.[8]

In this review and meta-analysis we aimed to overcome these problems by: i) restricting attention to randomized trials and high quality non-randomized studies, re-analysing data where necessary; ii) explicitly accounting for hand hygiene promotion activities in the comparison group in each study; iii) using a network meta-analysis to allow indirect comparison between interventions.

Information on resources used in different interventions is essential for those wishing to implement such interventions or evaluate their cost-effectiveness.[9 10] A secondary aim was therefore to document information on resources used in hand-hygiene promotion interventions.

3.3 Methods

A protocol was developed and systematic methods were used to identify relevant studies, screen study eligibility, and assess study quality. This review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11]

Search strategy

A two-stage search strategy was used. First, all studies included in two previous reviews (covering the period up to November 2009) were obtained.[5 6] Second, we extended the search from these studies from December 2009 to February 2014. The following electronic databases was searched: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health (CINAHL), Database of Abstracts of Reviews of Effects (DARE), National Health Service Economic Evaluation Database (NHS-EED), National Health Service Centre for Reviews and Dissemination (NHS-CRD) and British Nursing Index (BNI), Cochrane Library (Cochrane database of systematic reviews, Cochrane central register of controlled trials, Cochrane methodology register, Database of abstracts of reviews of effects, Health Technology assessment database), Clinical Trial.gov, Current Clinical Control trial, EPOC register, ACP journal, and Evidence-based medicine reviews. Results were limited to peer-reviewed publications. The complete search strategy is provided in Appendix A1.

Inclusion and Exclusion

A study was considered to meet initial inclusion criteria if

i) it evaluated one or more interventions intended to improve hand hygiene compliance among HCWs in a hospital setting

AND

ii) it measured hand hygiene compliance either using opportunities with pre-specified indications or using proxies linked to compliance (eg soap and alcohol hand rub consumption).

AND

iii) it was either a randomized controlled trial (RCT), controlled clinical trial (CCT), controlled before and after study (CBA), or used an interrupted time series (ITS) design.

No restrictions were placed on hand hygiene promotion in the comparison group. Studies were excluded if they were retrospective, not reported in peer-reviewed publications or not written in English.

We then applied a methodological filter by excluding studies that failed meet minimal quality criteria specified by the Cochrane Effectiveness Practice and Organisation of Care Group (EPOC).[12]

Data extraction and Quality assessment

Two reviewers (NL and BSC) independently screened the titles and abstracts of the citations obtained from the search to assess the eligibility. Consensus was reached by discussion if initial assessments differed. Evaluation of the full-text and data abstraction was conducted by NL and checked by BSC.

The reviewers abstracted data on study design, population, interventions, comparisons, outcomes, and settings. Interventions implemented in each study were extracted and classified according to WHO guidelines on hand hygiene in healthcare.[4] Results and raw compliance data from each study were extracted for further re-analyses. In addition, cost of hand hygiene interventions or resource use data (materials and time spent on interventions) were extracted where appropriate. Additional information was obtained from the authors if it was not clear from the manuscript. For all included studies we recorded the level of information (high, moderate, or low) about resources used for hand hygiene promotion using pre-specified definitions (Appendix A2).

Assessment of risk of bias in included studies

Risk of bias was assessed using the Cochrane Collaboration's tool,[13] Nine standard criteria for RCTs, CCTs, and CBAs, and seven standard criteria for ITS studies were applied and used to classify each study's risk of bias as low, high or not clear.

Data synthesis and Statistical analysis

Measurement of intervention effect

Data synthesis was performed separately for different study designs. The primary evidence synthesis was based on studies measuring hand hygiene compliance (HHC%) by direct observation. We restricted our analysis to this outcome because it reflects the opportunities for hand hygiene.

For RCTs, the natural logarithm of the odds ratio and associated variance were calculated and used to estimate the pooled odds ratio with a random effects model,[14] using Cochrane Review Manager (RevMan) version 5.1. The same method was applied to CCTs and CBAs if applicable.

For ITS studies, a two-step approach was used.[15] First, we used a generalized linear segmented regression analysis to estimate the stepwise change in level and change in trend associated with the intervention. This approach is similar to that proposed by Ramsey et al. and Vidanapathirana et al. except that it accounts for the binomial nature of the data, appropriately weighting each data point by the number of observations.[16 17] If there was evidence of autocorrelation, we accounted for this by using Newey-West standard errors.[18] Analysis was performed with STATA 13 (Statacorp LP, College Station, TX, USA). In addition, we estimated two summary measures that combined both effects. First, we calculated the mean natural logarithm of the odds ratio for hand hygiene associated with the intervention, a measure of relative improvement.

Second, we calculated the mean percentage change in hand hygiene compliance in the post-intervention period (compared to that expected if there had been no intervention), an absolute measure of improvement in hand hygiene compliance. Standard errors were derived using the delta method using the *emdbook* package in R (Bolker, 2008).[19 20] See Appendix A3 for details.

Network meta-analysis

Network meta-analysis aims to combine all of the evidence, both direct and indirect, in order to estimate the comparative efficacy of all the interventions.[21] Each intervention strategy is represented by a node in the network. If a study directly compares two interventions they are directly connected by a link on the network and a direct comparison is possible. If two interventions are connected indirectly (for example, if there are studies comparing each with a third intervention), then indirect comparison is possible. Studies permitting a segmented regression analysis and with a clearly-defined baseline intervention and directly observed hand hygiene compliance were included in the network meta-analysis.[22 23] Intervention activities were grouped into eight components: 1) system change, 2) education, 3) feedback, 4) reminders, 5) safety climate, 6) incentives, 7) goal-setting, and 8) accountability (Table 3.1). This gave 12 hand hygiene strategies (T1-T12) (Table 3.2).

The mean of the natural logarithm of the odds ratio for the hand hygiene intervention was estimated using the segmented regression model. The weighted and pooled effect sizes obtained from each direct comparison were estimated and combined to perform a network meta-analysis using a random effects model.[15] The mean difference of pooled effect sizes estimated from direct evidence was used to estimate indirect effect sizes when head to head comparison was lacking. Intervention rankings and associated credible intervals were obtained. Model-fitting was carried out within a Bayesian framework using WinBUGS.[24] Inconsistency checks were performed for closed loops in the network.[25] Full model details are provided in Appendix A4.

We performed a sensitivity analysis by excluding studies that implemented multicomponent strategies in a stepwise manner without sufficient data to evaluate individual components. This led to the exclusion of four studies.[26-29]

3.4 Results

Overall description

A summary of the review process is shown in Figure 3.1. Of 3,633 studies screened, 136 studies met initial inclusion criteria and 36 of these met EPOC criteria. Amongst these 36 studies, six were RCTs (including four cluster RCTs),[30-35] 26 were ITSs,[26-29 36-57] two were CCTs[58 59] and two were CBAs.[60 61] Reasons for exclusions are provided in Appendix A5.

15 studies applied interventions to the whole hospital while 17 studies enrolled hospital wards. Four studies recruited the HCWs as the participant units.[30 32 35 61] 25 studies were conducted in either a hospital-wide setting or combined ICU and general wards, while 11 were conducted in ICU or general wards alone. Of eight studies conducted in more than one hospital, three studies included two or more countries.[40 46 48] Only six of the 36 studies were conducted in low or middle income countries.[32 35 44 47 49 62]

Study periods ranged between 4 months and 6 years. In nine studies the period was ≤1 year; in 16 studies it was >1 year and ≤3 years; and in 11 it was >3 years. Amongst the 26 ITS studies, only eight were longer than 12 months.

In 30 studies hand hygiene was observed in all HCW types with patient contact while four studies considered only hand hygiene in nurses and/or nursing assistants.[33 35 58 61] One study recruited only nursing students as participants.[52] Patients' relatives were also included in one study.[38]

In six studies a single-faceted intervention was employed: four implemented education alone[32 44 52 61] and two applied system change or reminders.[38 42] 14 studies employed interventions equivalent to WHO-5 and six of these added supplemental interventions including goal-setting, incentives, and accountability.[26 33 39 43 54 59] 16 studies implemented two to four-modal interventions; four of these applied components not in WHO-5 including goal-setting and incentives.[27 31 35 58]

25 studies (4 RCTs, 19 ITS, and 2 CCTs) measured hand hygiene compliance with direct observation. Two of these used a combination of video recorders and external observers.[36 37] Proxy measures were assessed in 16 studies including the rate of hand hygiene events, consumption of hand hygiene products (alcohol hand rub or soap), and a hand hygiene score checklist (2 RCTs, 12 ITSs, and 2 CBAs). Finally, HAI or device-associated HAI rate were measured as one of the outcomes in 10 studies.[26 28 34 45 47 49 53-55 57] Study characteristics including study design, setting, intervention and comparison groups are reported in Table 3.3.

Quality assessment

10 studies were considered to have a high risk of bias. 26 studies had either low or unclear risk. High risk of bias was present in all of four CCTs or CBAs, but only in six out of 26 ITS designs. No RCTs or CRCTs were thought to have a high risk of bias (Figure 3.2).

The two CBAs[60 61] had high risks for inadequate allocation sequence and concealment, while both CCTs[58 59] had high risks of dissimilarity in baseline outcome between experimental and control groups.

14 studies (39%) had a low risk of bias due to the knowledge of allocated intervention, as these studies either measured objective outcomes (eg. alcohol consumption or output from electronic counting devices) or stated that the observers were blinded to the intervention. The rest of the studies had unclear risk as they did not report whether the observers were blinded.

Risk of selective outcome reporting was unclear in 33 studies as pre-specified protocols were reported only in three RCTs.[31 33 34] Two of the ITS studies had a high risk of selective outcome reporting as they reported on a non-periodical basis.[26 57] Amongst the ITS studies, five had a high risk that outcomes were affected by other interventions such as a universal chlorhexidine body-washing program,[40] reinforcement of standard precautions,[40] screening and decolonization for multidrug-resistant micro-organisms,[46] quality improvement program,[44 57] and antibiotic use and HAI control policy implemented at the same time.[55]

Level of information on resource use

Reporting of cost and resource use information was limited with 3, 25 and 8 studies classified as having high, moderate and low information respectively (Appendix A6 in supplement). Three studies reported costs associated with both materials and person time;[33 50 59] in two cases these reports were in separate papers.[63 64] The estimated cost of interventions ranged from $US 225 to 4,669 per 1,000 bed-day (Table 3.4).

Meta analysis/Data synthesis

RCTs

Four of six RCTs measured hand hygiene compliance by direct observation with indications similar to WHO-5.[31-34] In two of these studies, WHO-5 was compared with WHO-5 with goal-setting.[31 33] Meta-analysis showed this additional intervention to be associated with improved hand hygiene compliance. The pooled odds ratio (OR) was 1.35 (95% confidence interval 1.04 to 1.75; I^2= 81%) (Figure 3.3). The other two studies also showed significant improvement in hand hygiene compliance after implementing a bundle of education, performance feedback, and visual reminders,[34] and an education program.[32]

Fisher et al. randomized individuals to either a control group where hand hygiene was not actively promoted, or an intervention arm which used audio reminders and individual feedback. Compliance was assessed using an automated system at entry to and exit from patients' rooms. The intervention was associated with a 6.8% (95% confidence interval 2.5 to 11.1) improvement in compliance.[30] Salmanti et al. randomized nursing personnel to either a *Motivational Interviewing* intervention (a behaviour-modification approach initially developed to treat patients with alcoholism) or a control group. Both arms also received an educational intervention. The outcome measure was a composite hand hygiene score, which was found to increase significantly in the intervention arm. The scoring details, however, are unclear.[35]

Interrupted Time Series Studies (ITSs)

Of 26 ITS studies, 19 measured hand hygiene compliance. However, only 15 studies with direct observation reported the number of observations at each time point making them eligible for re-analysis.[26-29 36 37 39-41 43 44 46 48 52 54] As some of these studies were conducted at multiple sites[46] or had multiple intervention phases,[54] 19 pair-wise comparisons from these 15 studies were available for re-analysis (Figure 3.4). In four studies there was evidence of positive first order autocorrelation.[36 37 39 54]

The baseline compliance ranged between 7.6% and 91.3%. 11 of 19 comparisons showed a declining trend in compliance during the pre-intervention period while 13 pair-wise contrasts showed a positive post-intervention change in trend for hand-hygiene compliance (Table 3.5). All but three contrasts showed both stepwise increases in hand hygiene compliance associated with the intervention and in increase in mean hand hygiene compliance in the post-intervention period compared to that expected in the absence of the intervention. However, the range was wide: the mean hand hygiene change attributed to the intervention varied between a decrease of 14.8% and an increase of 83.3% (Table 3.5). Two studies had an intervention period lasting at least two years; neither showed evidence for any decline in compliance over this period.[27 39] In only one study was there a net trend for decreasing hand hygiene compliance over the post-intervention period (Figure 3.4).[43]

CCTs and CBAs

Both CCT studies reported positive effects of hand hygiene interventions. Mayer et al.,[59] using an appropriate analysis, found that a bundle of interventions, WHO-5 and reward incentive compared with a combination of system change, education and feedback and a standard practice as control group were associated with improved compliance (odds ratio 1.78, 95% confidence interval 1.34 to 2.37).

Harne-Britner et al. reported that a combination of education, group incentives and goal-setting were associated with an increase in mean compliance of 21.7% while education and poster reminders were not associated with any improvement (change in mean: -1.8%).[58] Confidence intervals were not reported.

Benning et al., using a CBA design, reported an increased hospital-wide trend of soap and alcohol consumption in both intervention (package of system change, reminders, and safety climate) and control (no intervention) groups but found no evidence of an increased effect in the intervention group.[60] Gould et al. found no evidence of improvement in hand decontamination frequency in surgical ICU wards resulting from a series of educational lectures compared to no intervention (control).[61]

Network meta-analysis

Amongst 15 ITS studies, 11 had clear details about interventions and similar indications for hand hygiene compliance amongst qualified HCWs. These were eligible for network meta-analysis (see Appendix A7 for exclusion reasons). 15 direct pairwise comparisons between interventions were possible from 12 different hand hygiene intervention strategies (Figure 3.5). 10 strategies are connected in the network (Figure 3.6), making indirect comparisons possible. The comparative efficacy amongst nine of these strategies in a connected network was assessed compared with T1 (no intervention or standard practice).

The network meta-analysis showed that although there was large uncertainty in effect size amongst the pairwise comparisons, all intervention strategies were associated with an improvement in hand hygiene compliance compared with T1 (Figure 3.7). For four strategies, T7 (WHO-5), T8 (system change+education +feedback+reminders+incentive+goal-setting), T11 (WHO-5+incentive+goal-setting), and T12 (WHO-5+incentive+goal-setting+accountability), 95% credible intervals for odds ratios did not include one (Table 3.2).

Strategies T8, T9, T10, T11, and T12, which combined WHO-5 with (respectively) incentives, goal-setting, and accountability, showed additional improvement compared with T7 (WHO-5) alone. T8 (system change+education+feedback+reminders+incentive+goal-setting) had the highest probability (90%) and highest median rank of being the best strategy in improving hand hygiene compliance (Figure 3.7).

When excluding studies with multiple stepwise interventions in the sensitivity analysis there was a decrease in the effect size of T2 (system change), T6 (system change+education+feedback+reminders) and T7 (WHO-5). Other interventions were not affected. As T8 (system change+education+feedback+reminders +incentive+goal-setting) and T10 (WHO-5+goal-setting) strategies were unavailable in the network structure, T12 (WHO-5+incentive+goal-setting+accountability) became dominant with the highest probability (57%) of being the best intervention, and the highest median rank of being the most effective strategy (see Appendix A4).

Figure 3.1: Systematic review flow chart.

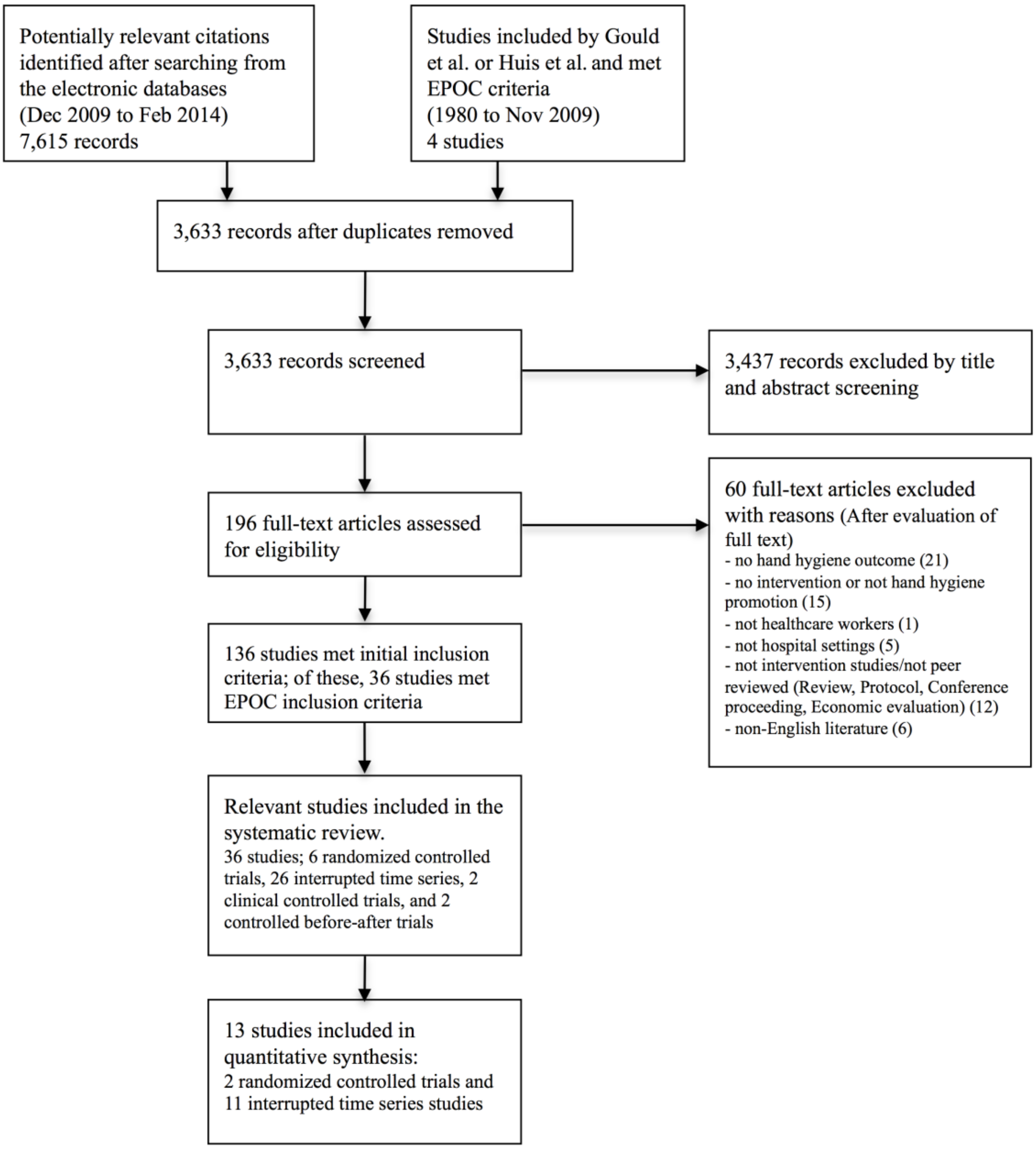

Figure 3.2: Assessment of risk of bias in included studies.

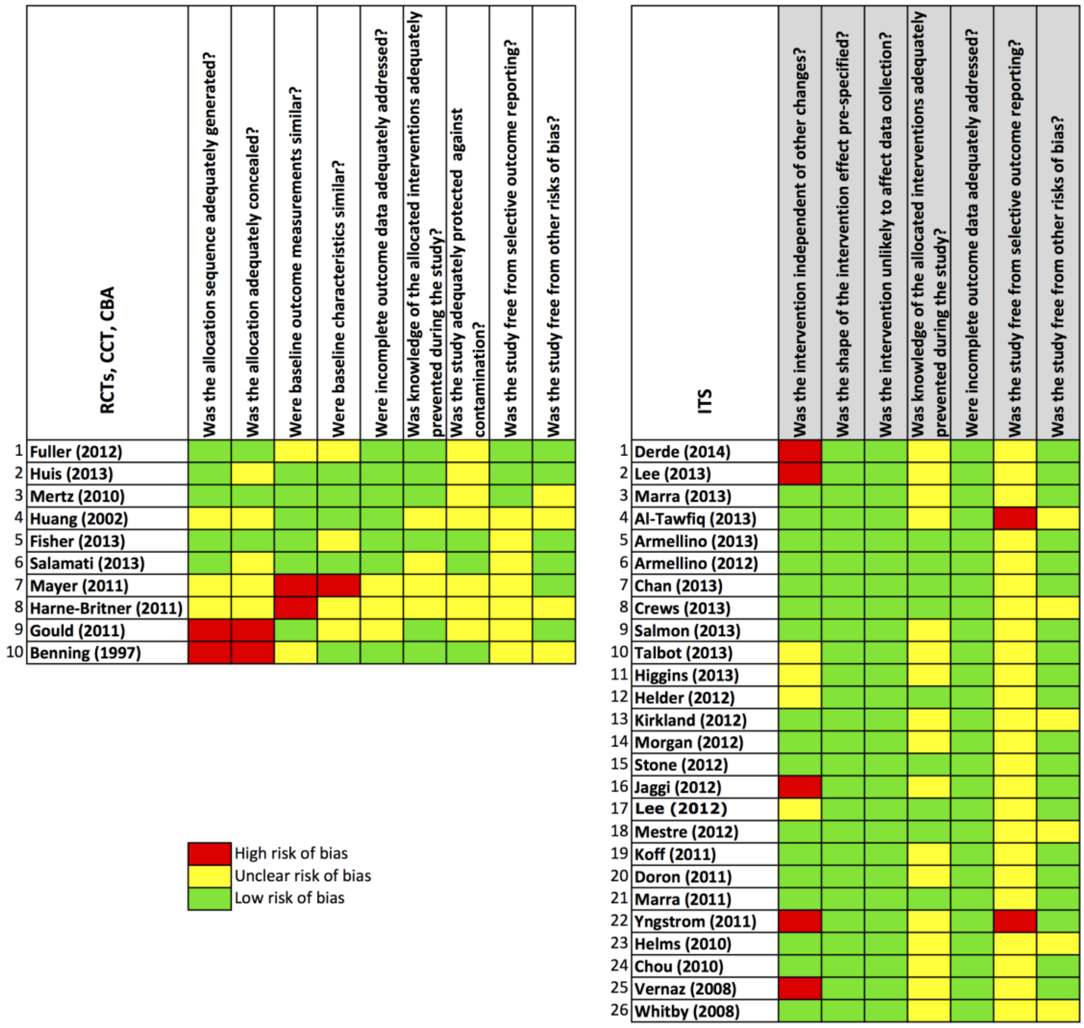

Figure 3.3: Forest plot of the associations between WHO-5 and goal setting compared with WHO-5 alone and hand hygiene compliance from RCTs using intention to treat results. Fuller 2012a refers to results from acute care of the elderly wards and Fuller 2012b to results from intensive care units.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Fuller 2012a	0.058	0.092	34.3%	1.06 [0.88, 1.27]
Fuller 2012b	0.365	0.102	33.1%	1.44 [1.18, 1.76]
Huis 2013	0.495	0.106	32.6%	1.64 [1.33, 2.02]
Total (95% CI)			**100.0%**	**1.35 [1.04, 1.76]**

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 10.63$, df = 2 (P = 0.005); $I^2 = 81\%$
Test for overall effect: Z = 2.27 (P = 0.02)

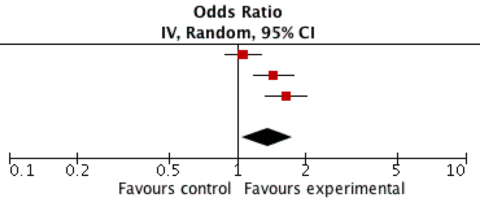

Figure 3.4: Re-analysis of studies involving interrupted time series where the outcome was hand hygiene compliance. Points represent observations, solid lines show expected values from fitted segmented regression models, and broken lines represent extrapolated pre-intervention trends.
*The last four studies (Jaggi et al., Armellino et al. (2012), Armellino et al. (2013), and Salmon et al.) were not eligible for the network meta-analysis.

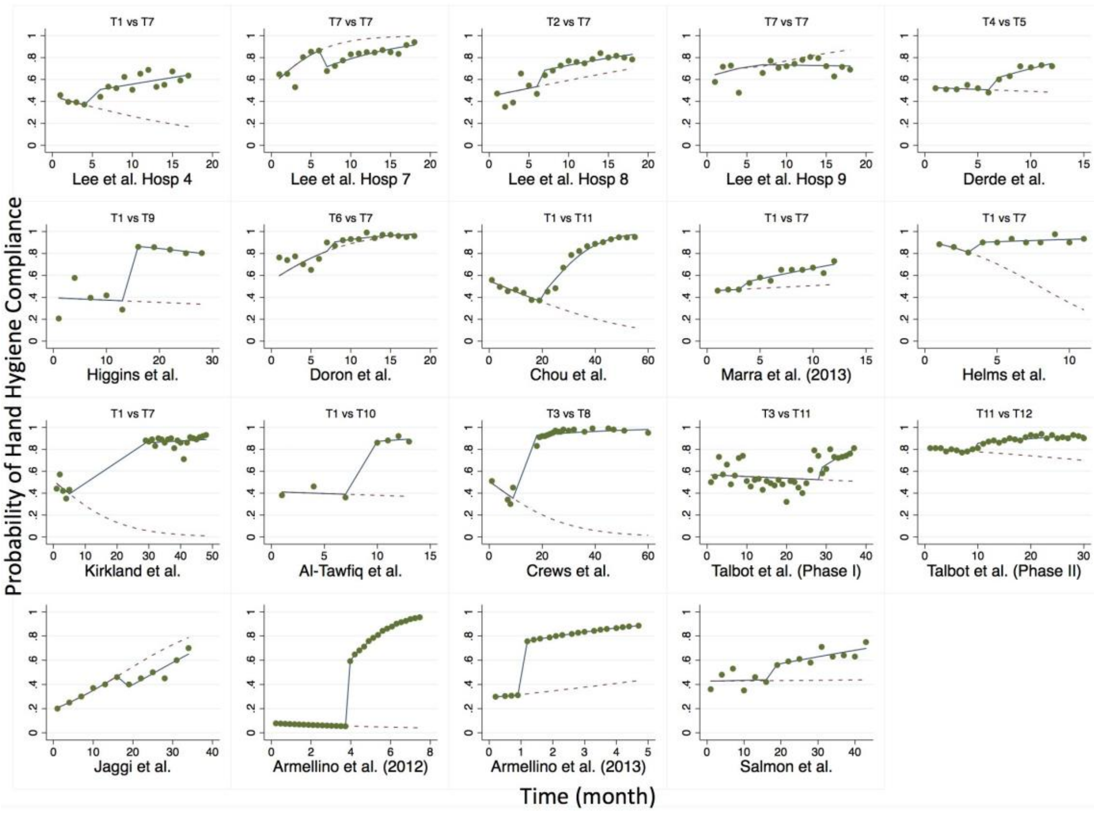

Figure 3.5: Forest plot showing the effect size as mean log odds ratios for hand hygiene compliance for all direct pair-wise comparisons from interrupted time series studies.
(Note that Lee H4, Lee H7, Lee H8, and Lee H9 all come from a multi-centre study. In two of the hosptials (H7 and H9) the baseline strategy was already equivalent to WHO-5.)

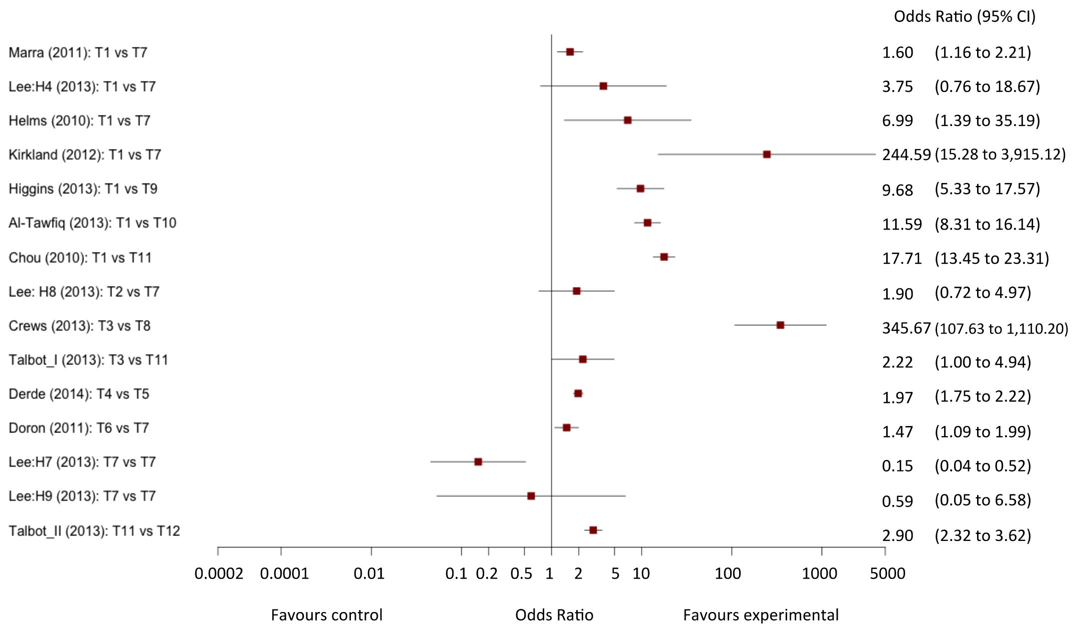

Figure 3.6: Network structure of indirect treatment comparison of 12 different hand hygiene intervention strategies from interrupted time series studies.

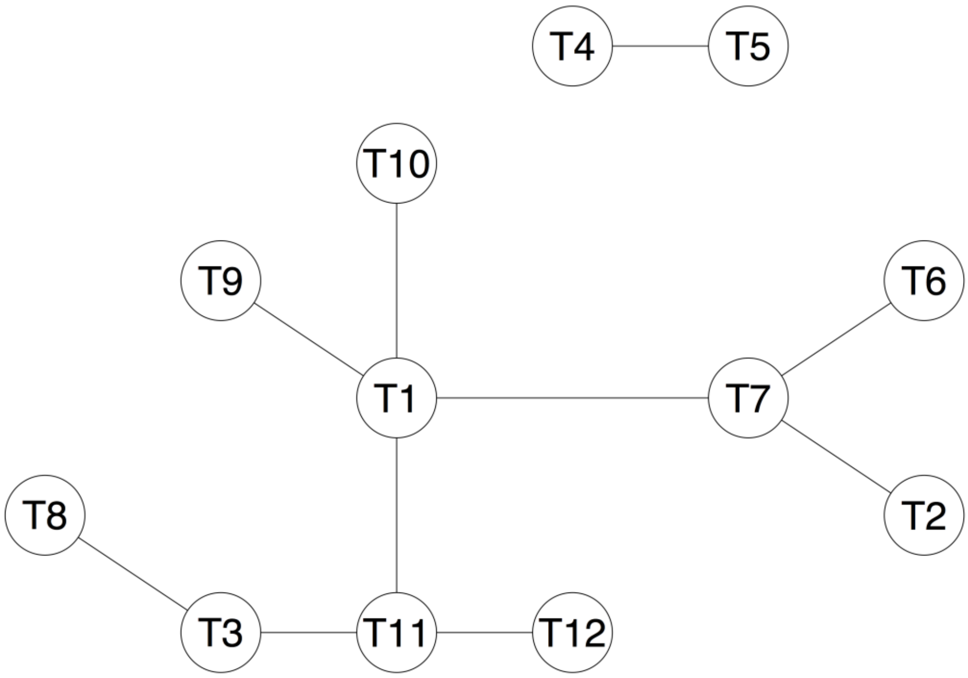

Figure 3.7: Box-and-whiskers plot showing relative efficacy of different hand hygiene intervention strategies compared with standard of care estimated by network meta-analysis from interrupted time series studies. Lower and upper edges represent 25th and 75th percentiles from the posterior distribution; the central line represents the median. Whiskers extend to the 5th and 95th percentiles. Intervention strategies were as follows: T2-System change; T3-Education; T6-System change+Education+Feedback+Reminders; T7-WHO-5; T8-System change+Education+Feedback+Incentives+Goal-setting; T9-WHO-5+Incentives; T10-WHO-5+Goal-setting; T11-Incentives+Goal-setting; T12-WHO-5+Incentives+Goal-setting+Accountability.

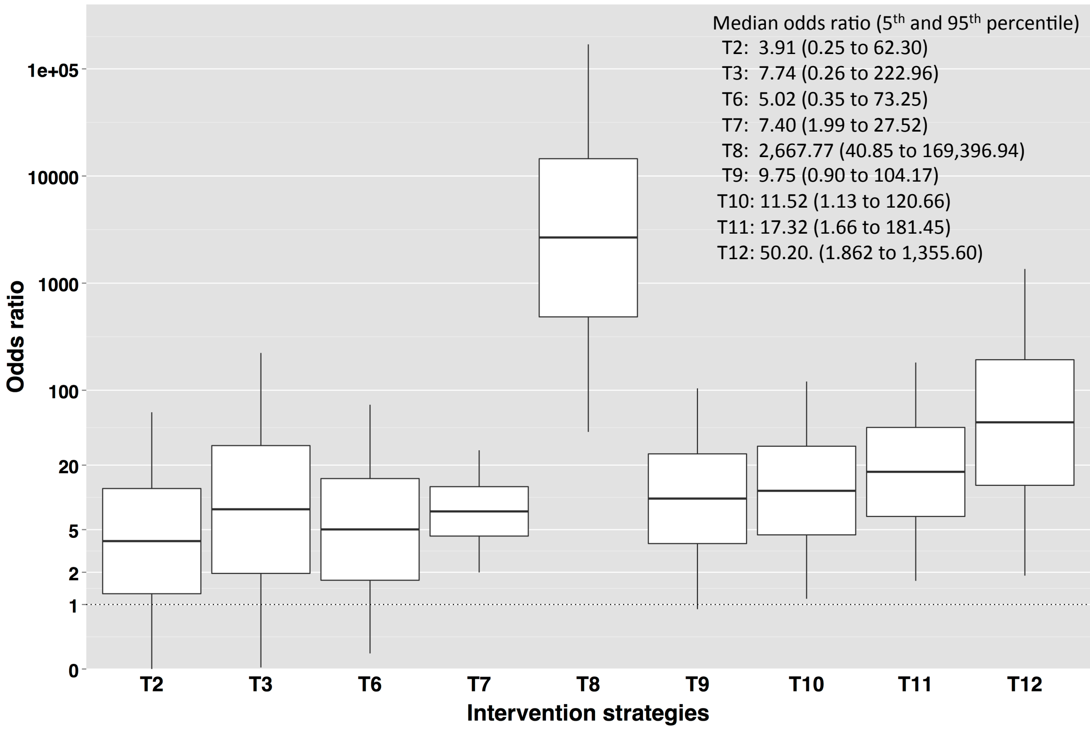

Figure 3.8: Rankograms showing the probabilities of possible rankings for each intervention strategy (rank 1=best, rank 10=worst).

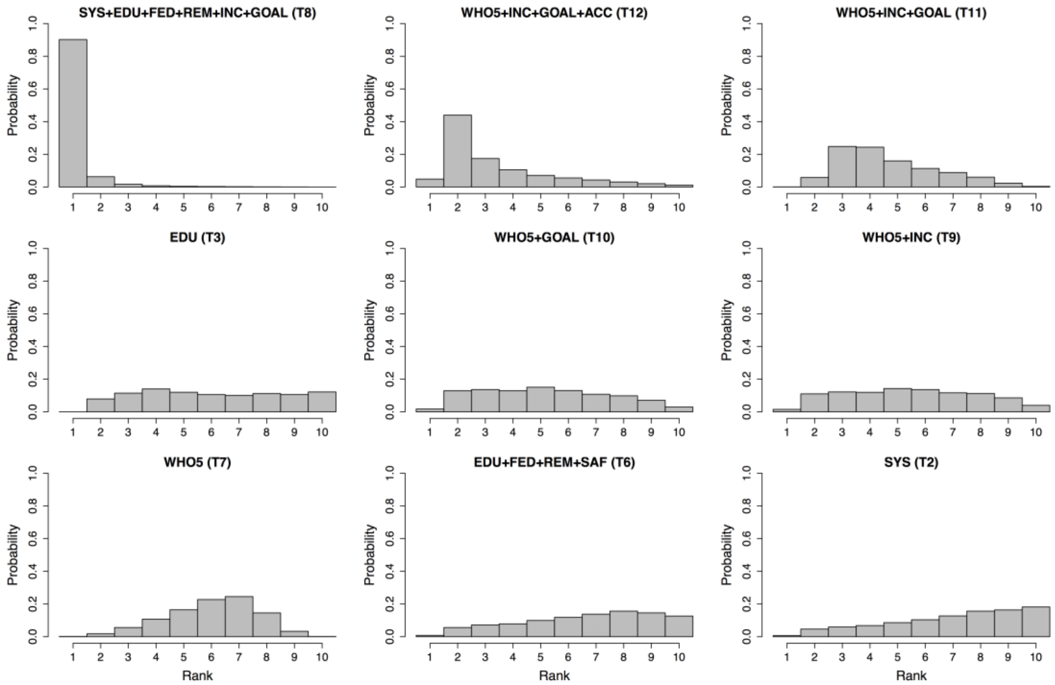

Table 3.1: Description of hand hygiene intervention components.

Type of Hand hygiene intervention component	Description
1. System change [a]	Ensuring necessary infrastructure is available including a) access to water, soap and towels and b) alcohol-based handrub at the point of care.
2. Education and Training	Providing training or educational programme on the importance of hand hygiene and the correct procedures for hand hygiene, for healthcare workers.
3. Feedback	Monitoring hand hygiene practices among healthcare workers while providing the compliance feedback to staff.
4. Reminders at workplace	Prompting healthcare workers either through printed material, verbal reminders, electronic communications or other methods, to remind them about the importance of hand hygiene and the appropriate indications and procedures.
5. Institutional safety climate	Active participation at institutional level, creating an environment allowing prioritization of hand hygiene.
6. Goal-setting	Setting of specific goals aimed at improving hand hygiene compliance, which may both apply at the individual and group level and may include healthcare associated infection rates.
7. Reward incentives	Interventions involved with providing any reward incentive for the participants once they achieve a particular task or reach a certain level of hand hygiene compliance. Both non-financial and financial rewards are included.
8. Accountability	Interventions involved with improving healthcare workers' accountability both at an individual and unit level.

[a] if the intervention period included changing the place or formulation or installing more dispensers of alcohol based handrub, the baseline intervention was counted as no intervention or standard practice (no system change component) although the alcohol-based handrub had been used during the baseline.

Table 3.2: Mean odds ratios with 95% credible intervals for hand hygiene intervention strategies. Results are from random effects network meta-analysis model.

Code	Hand hygiene strategies	System change	Education	Feedback	Reminders	Safety climate	Incentives	Goal-setting	Accountability	Mean OR	95% Credible Interval	
T1	None/Current practice	×	×	×	×	×	×	×	×	Reference		
T2	System change	✓	×	×	×	×	×	×	×	3.50	0.12	100.38
T3	Education	×	✓	×	×	×	×	×	×	7.72	0.14	435.28
T4	Reminders	×	×	×	✓	×	×	×	×	Not in the network		
T5	Education+Feedback+Reminders	×	✓	✓	✓	×	×	×	×	Not in the network		
T6	System change+Education+Feedback+Reminders	✓	✓	✓	✓	×	×	×	×	4.52	0.18	112.51
T7	WHO-5 [a]	✓	✓	✓	✓	✓	×	×	×	6.65	1.33	33.41
T8	System change+Education+Feedback+Reminders +Incentives+Goal-setting	✓	✓	✓	✓	×	✓	✓	×	2,646.52	18.39	396,329.02
T9	WHO-5+Incentives	✓	✓	✓	✓	✓	✓	×	×	9.64	0.56	164.84
T10	WHO-5+Goal-setting	✓	✓	✓	✓	✓	×	✓	×	11.54	0.68	189.81
T11	WHO-5+Incentives+Goal-setting	✓	✓	✓	✓	✓	✓	✓	×	17.27	1.07	288.30
T12	WHO-5+ Incentives+ Goal-setting+Accountability	✓	✓	✓	✓	✓	✓	✓	✓	50.10	1.01	2578.60

Model fit statistic: posterior mean residual deviance= 13.82 and deviance information criterion (DIC)= 26.41

T1-T12: 12 hand hygiene intervention strategies. Refer to Table3.1 for details of components.

[a] WHO-5 strategy contained five components: System change, Education, Feedback, Reminders, and Institutional safety climate.

Table 3.3: Summary of study characteristics.

Author (year)	Study design	Study period/ duration	Settings and Details of the design	Unit of Participant	Population	Interventions	Comparison group	Methods of observation	Indication	Outcomes	Country
Fuller (2012)	CRCT (Stepped wedge)	Total: 39 months Baseline: approx. 20 months Intervention: approx. 20 months October 2006 to December 2009	60 wards from 16 hospital trusts Experimental: 33 mixed wards from 13 trusts Control: 27 mixed wards from 11 trusts	Ward	HCWs	WHO-5+GOAL+FED	WHO-5 (UK national campaign)	Direct observation by ward coordinators	Before and after patient contact	Hand hygiene compliance Soap and AHR consumption	England and Wales
Huis (2013)	CRCT	Total: 13 months Baseline: 1 month Intervention: 6 months Follow up (no intervention): 6 months September 2008 to November 2009	67 wards from 3 hospitals Experimental: 30 mixed wards Control: 37 mixed wards	Ward	Nurses	WHO-5+GOAL	WHO-5 (except SAF)	Direct observation by nursing student	Before and after patient contact, patient surroundings and use of gloves	Hand hygiene compliance	Netherlands
Mertz (2010)	CRCT	Total: 15 months Baseline: 3 months Intervention: 12 months October 2006 to December 2006 (Baseline) and June 2007 to May 2008 (Intervention)	30 wards from 3 acute care sites Experimental: 15 mixed wards Control: 15 mixed wards Randomized stratified by hospital site and type of hospital unit. (number of bed not reported)	Ward	HCWs	SYS+EDU+FED+REM	SYS (with AHR at point of care)	Direct observation by researchers	Before and after patient contact, skin wounds or mucous, insertion of an intravenous line and use of gloves	Hand hygiene compliance Incidence of hospital-acquired *MRSA* colonisation	Canada
Huang (2002)	RCT	Intervention: 4 months period (Pre and Post-test) September 2000 to January 2001	100 randomly selected nurses from a 1,300 bed hospital Experimental: 50 nurses Control: 50 nurses	Individual	Nurses	EDU	None (unclear AHR)	Direct observation by researchers	Before and after patient contact	Hand washing compliance	China
Fisher (2013)	RCT	Total: 24 weeks Baseline: 14 weeks Intervention I: 6 week Intervention II: 4 weeks Start from January 2012	233 participants from 3 wards from 2 hospitals Experimental: 119 participants Control: 114 participants	Individual	HCWs	SYS+REM+FED	SYS (with AHR at point of care)	Direct observation by trained nurses	Room entry and exit	Hand hygiene compliance AHR consumption	Singapore
Salamati (2013)	RCT	No data provided Year 2010	128 participants from a 109-bed hospital Experimental: 64 participants Control: 64 participants	Individual	Nurses, Anesthesiology, Technician, and Nurese-aid	SYS+EDU+FED	SYS+EDU	Direct observation by infection control supervisor	Unclear	Hand hygiene score with unclear details	Iran

Derde (2014)	ITS	Total: 36 months (3 years) Baseline: 6 months Intervention I: 18 months Intervention II: 12 months May 2008 to April 2011	13 European ICUs (all with least 8 beds)	Ward	HCWs	EDU+FED+REM	REM (unclear AHR use)	Direct observation by researchers	Before and after patient contact, before an aseptic task, and after contact with patients' body fluids and surroundings	Hand hygiene compliance	Multiple European countries
Lee (2013)	ITS	Total: 24 months (2 years) Baseline: 6 months Intervention: 12 months Post-Intervention (Wash out): 6 months March 2008 to July 2010	33 Surgical wards of 10 hospitals in 9 countries	Ward	HCWs	WHO-5	None (with AHR) in 1 hospital, SYS in 1 hospital and WHO-5 in 2 hospitals	Direct observation by researchers	Before and after patient contact, before an aseptic task, and after contact patients' body fluids and surroundings	Hand hygiene compliance	Multi-center 9 European countries including Germany, Israel, Serbia, Switzerland, France, Greece, Italy, Spain, Scotland
Marra (2013)	ITS	Total: 12 months Baseline: 3 months Intervention: 9 months August 2011 to July 2012	9 wards (8 ICUs and 1 general ward) from 7 tertiary hospitals in 2 countries	Ward	HCWs	WHO-5	None (with AHR)	Direct observation by trained nurses	WHO "Five Moments of Hand Hygiene"	Hand hygiene compliance	Brazil and Thailand
Al-Tawfiq (2013)	ITS	Total: 54 months (4 years 6 months) Baseline: 9 months Intervention: 42 months (implemented at multiple time points) Post-Intervention: 3 months October 2006 to December 2011	A 350-bed hospital	Hospital	HCWs	WHO-5+GOAL	None (with AHR)	Direct observation by infection control team	Before wearing gloves, after removing gloves, before and after patient contact, after leaving patient's room, before and after performing invasive procedures, and after contact with patient's body fluids.	Hand hygiene compliance AHR consumption Device-associated infection rate	Saudi Arabia
Armellino (2013)	ITS	Total: 17 months Baseline: 1 month Intervention: 16 months March 2010 to July 2011	An 18-bed surgical intensive care unit (SICU) from a 804-bed hospital	Ward	HCWs	FED + GOAL	None (unclear AHR use)	Electronic motion sensor and video recorders and sinks and dispensers. Review and audit by researchers	Room entry and exit	Hand hygiene compliance	USA
Armellino (2012)	ITS	Total: 25 months Baseline: 4 months Intervention: 4 months Maintenance: 17 months June 2008 to June 2010	A 17-bed medical intensive care unit from a 804-bed hospital	Ward	HCWs	FED + GOAL	None (unclear AHR use)	Electronic motion sensor and video recorders and sinks and dispensers. Review and audit by researchers	Room entry and exit	Hand hygiene compliance	USA

Chan (2013)	ITS	Total: 7 months Baseline: 1 month Intervention: 6 months April 2009 to October 2009	A general medical unit with 10 single rooms	Ward	HCWs and others including patients and relatives	SYS	None (with AHR)	n/a	Dispenser count	Hand hygiene event per patient-day	USA
Crews (2013)	ITS	Total: 63 months (5 years 3 months) Baseline: 9 months Intervention: 15 months (implemented at multiple time points) Post-Intervention: 39 months October 2006 to December 2011	A 46-bed children hospital	Hospital	HCWs	SYS+EDU+FED+REM+ INC+GOAL	EDU (with AHR)	Direct observationby contracted certified infection control practitioner	Before and after contact patient or environment	Hand hygiene compliance	USA
Salmon (2013)	ITS	Total: 45 months (3 years 9 months) Baseline: 18 months Intervention: 3 month Post-Intervention: 24 months January 2009 to September 2012	A 1,032-bed hospital	Hospital	Nursing students	EDU	None (unclear AHR use)	Direct observation by infection control nurses	WHO "Five Moments of Hand Hygiene"	Hand hygiene compliance	Singapore
Talbot (2013)	ITS	Total: 68 months (5 years 8 months) Baseline: 29 months Intervention phase I: 18 months Intervention phase II: 21 months January 2007 to August 2012	A university medical center (support 65,000 inpatient admission, annually)	Hospital	HCWs Settings were inpatient, outpatient clinics and procedural areas	Phase I: WHO-5 +INC+GOAL Phase II: WHO-5 +INC+GOAL+ACC	Phase I: EDU (unclear AHR use) Phase II: WHO5+INC+GOAL	Direct observation by trained healthcare workers	WHO "Five Moments of Hand Hygiene"	Hand hygiene compliance Device-associated infection rate	USA
Higgins (2013)	ITS	Total: 30 months (2 years 6 months) Baseline: 15 months Intervention: 15 months November 2009 to April 2012	A tertiary referral private hospital (acute healthcare setting) (number of bed not reported)	Hospital	HCWs	WHO-5+INC	None (with AHR)	Direct observation by trained infection prevention control nurses	WHO "Five Moments of Hand Hygiene"	Hand hygiene compliance	Ireland
Helder (2012)	ITS (for hand hygiene event) BA (for HHC% observation) not eligible as no control group and inadequate data collection point	Total: 4 months Baseline: 2 months Intervention: 2 months January 2008 to May 2008	A 27-bed Neonatal Intensive Care Unit (NICU)	Ward	HCWs	(SYS+) REM	SYS (with AHR at POC)	Electronic dispensers counting Direct observation by medical students	Before and after touching a patient, before sterile procedures, before and after the use of gloves and after contact with body fluids	Hand hygiene compliance (pre-post test) Hand hygiene event per patient-day	Netherlands

Kirkland (2012)	ITS	Total: 48 months (4 years) Baseline: 6 months Intervention: 42 months January 2006 to November 2009	A 383-bed teaching hospital	Hospital	HCWs	WHO-5	None (with AHR)	Direct observation by trained infection control staff	Before and after contact with patients or their immediate environment	Hand hygiene compliance	USA
Morgan (2012)	ITS	Total: 30 weeks Baseline: 15 weeks Intervention: 15 weeks March 2010 to October 2010	2 ITS wards; Neurological ICU and Cardiac ICU, 15 beds each	Ward	HCWs	SYS+EDU+FED+REM	None (with AHR)	Direct observation by trained researcher	Room entry and exit	Hand hygiene compliance	USA
Stone (2012)	ITS	Total: 48 months (4 years) Baseline: 5 months Intervention: 43 months July 2004 to June 2008	187 acute hospital trusts	Trust (Hospital)	HCWs	WHO-5	None (unclear AHR use)	n/a	Procurement	AHR consumption Antimicrobial consumption Incidence of hospital acquired MRSA and MSSA bacteraemia	England and Wales
Jaggi (2012)	ITS	Total: 12 months Baseline: 6 months Intervention: 6 months January 2009 to December 2009	A 215-bed tertiary-care hospital	Hospital	HCWs	Unclear	Unclear	Direct observation by staff	Unclear	Hand hygiene compliance	India
Lee (2012)	ITS	Total: 6 years Baseline: 3 years Intervention: 3 years January 2004 to December 2010	A 1162-bed tertiary-care university hospital	Hospital	HCWs	WHO-5	None (with AHR)	n/a	Procurement	AHR consumption Antimicrobial consumption Incidence of healthcare acquired infection and hospital acquired-MRSA	Taiwan
Mestre (2012)	ITS	Total: 51 months (4 years 3 months) Baseline: 27 months Intervention phase I: 12 months (2010) Intervention phase II: 12 months (2011) March 2007 to December 2011	A private 200-bed hospital	Hospital	HCWs	Phase I: WHO-5 Phase II: WHO-5 (intense) + Reinforcement	Phase I: None (with AHR) Phase II: WHO5	Direct observation by infection control and nursing supervisors	WHO "Five Moments of Hand Hygiene"	Hand hygiene compliance AHR consumption	Spain
Koff (2011)	ITS	Total: 36 months Baseline: 12 month Intervention: 12 months Post-Intervention: 12 months December 2006 to November 2009	A medical-surgical ICU (number of beds not reported)	Ward	HCWs (nursing staff, physicians, and respiratory therapists)	EDU+FED	None (with AHR)	Direct observation by infection control	Upon entering the patient care environment and after leaving	Hand hygiene compliance Hand hygiene decontamination event Ventilator associated pneumonia (VAP) rate Catheter-related bloodstream infection (CRBSI) rate	USA

Doron (2011)	ITS	Total: 18 months Baseline: 6 months Intervention: 12 months September 2007 to February 2009	A 425-bed hospital, an academic medical center	Hospital	HCWs	WHO-5	SYS+EDU+FED+REM (with AHR)	Direct observation by trained staff	Before touching the patient or an object in the patient's room and before or after the encounter with the patient	Hand hygiene compliance	USA
Marra (2010, 2011)	ITS	Total: 21 months, East Step-down Unit (SDU) Baseline: 3 months Intervention: 19 months West Step-down Unit (SDU) Baseline: 6 months Intervention: 15 months April 2008 to November 2009	Two 20-bed SDUs from a private tertiary care hospital (all had single bed rooms)	Ward	HCWs	WHO-5	None (with AHR)	n/a	Dispenser count	Hand hygiene event Alcohol gel consumption Incidence of healthcare associated infections	Brazil
Yngstrom (2011)	ITS	Total: 10 months Baseline: 3 months Intervention: 6 months September 2004 to June 2005	A 110-bed multidisciplinary district hospital	Hospital	HCWs	SYS+EDU+FED+GOAL	None (with AHR)	Direct observation by trained nurse at each ward	Use of short-sleeved uniforms, protective clothing, aprons and gloves, hand disinfection with AHR, and wearing rings and wristwatches	Basic hygiene compliance Incidence of healthcare associated infection in ventilated patients (healthcare-associated infections with regard to ventilator associated pneumonia, intubation-related infections in blood vessels and healthcare-associated urinary infections).	Sweden
Helms (2010)	ITS	Total: 12 months Baseline: 3 months Intervention: 9 months August 2007 to July 2008	A 116-bed hospital	Hospital	HCWs	WHO-5	None (with AHR)	Direct observation by selected staff members and volunteers	WHO "Five Moments of Hand Hygiene" *(Information from author contact)	Hand hygiene compliance Incidence of HAIs; urinary tract infection, ventilator associated pneumonia and central line infections	USA
Chou (2010)	ITS	Total: 57 months (4 years 9 months) Baseline: 21 months Intervention: 36 months April 2005 to December 2009	A hospital, part of a 9-hospital healthcare system	Hospital	HCWs	WHO-5+INC+GOAL	None (with AHR)	Direct observation by a staff liaison from each department	Based on opportunities	Hand hygiene compliance	USA

Vernaz (2008)	ITS	Total: 72 months (6 years) Baseline: 22 months (1 year and 10 months) Intervention: 50 months (4 years and 2 months) February 2000 to September 2006	A 2,200 bed tertiary university hospital	Hospital	HCWs	WHO-5 (Swiss national campaign)	SYS (with AHR at point of care)	n/a	Procurement	AHR consumption Antibiotics use Incidence of MRSA and *C.difficile* (number of clinical isolates per 100 patient-days)	Switzerland
Whitby (2008)	ITS	Total: 2 years Baseline: 4 to 5 months Intervention: 18 months 2004 to 2006	5 wards from a 800-bed hospital with 3 intervention groups 1) Washington campaign (1 ward) 2) Geneva campaign (2 wards) 3) AHR substitution (2 wards)	Ward	HCWs	Group I: WHO-5 Group II: SYS+EDU+REM+SAF Group III: SYS	None (with AHR)	n/a	Dispenser (liquid soap) count	Hand hygiene events per occupied bed-day	Australia
Mayer (2011)	CCT/ITS	Total: 16 months CCT step-down Baseline: 2 months Intervention phase I: varied between 2 to 7 months August 2000 to November 2001 ITS (less than 3 time points baseline); 2 years 9 months April 2003 to December 2006	3 units (6 wards) from a 450-bed hospital Intervention 2 units (4 wards) Control 1 unit (2 wards) Step-down phase 1 and 2	Ward	HCWs	Phase I: SYS+EDU+FED Phase II: WHO-5+INC	None (unclear AHR use)	Direct observation by trained part-time staff	Before, after, or before and after contact patient or patient's environment.	Hand hygiene compliance	USA
Harne-Britner (2011)	CCT	Total: 7 months Baseline: 1 month Intervention: 6 months April to October 2005	3 medical-surgical units from an urban healthcare system Intervention: 2 wards with different interventions Control: 1 ward	Ward	Nurses and patient care assistants	Phase I: EDU+REM Phase II: EDU+INC+GOAL	EDU (with AHR use)	Direct observation by trained staff	Before or after, or before and after patient contact.	Hand hygiene compliance	USA
Benning (2011)	CBA	Total: 20 months (as a second phase of a national improving the quality of healthcare program) March 2007 to September 2008	Total 18 hospitals Intervention: 9 hospitals Control: 9 matched hospitals by size and geographic area	Hospital	HCWs	SYS+REM+SAF	None (with AHR)	n/a	Procurement	Soap and AHR consumption	England and Wales
Gould (1997)	CBA	Total: 3 months intervention period Data on date is not available	Total 4 surgical wards from a teaching hospital Intervention: 2 surgical wards Control: 2 surgical wards	Ward/Individual	Nurses	EDU	None (unclear AHR use)	Direct observation by researchers	Frequency, appropriateness and duration of hand decontamination compliance and the use of gloves	Hand decontamination compliance	UK

*SYS: system change, EDU: education, FED: feedback, REM: reminders, SAF: institutional safety climate, INC: incentives, GOAL: goal-setting, ACC: accountability, WHO-5: a combined intervention strategies including SYS, EDU,FED, REM, and SAF, AHR: alcohol based hand rub, HHC: hand hygiene compliance, HCW: healthcare worker, n/a: information is not available.

Table 3.4: Resource use extracted data

No	Author (year), Study design	Intervention	Comparison	Settings	Resource use (Material)	Resource use (Time)	Sources	Total cost ($US)	No of bed	Intervention period (day)	Cost per 1,000 bed-day ($US)	Base year
1	Huis (2013), CRCT	WHO-5 + goal-setting	WHO5 (except institutional safety climate)	Netherlands	**State of art strategies** Alcohol hand rub Material including website, leaflets, posters, newsletters, article in hospital magazines	**State of art strategies** Hand hygiene direct observation Extra time for performing hand hygiene	Separate paper [63]	320,278 ϒ (€ 246,368)	993	365	883.7	2009
					Team and leader directed strategies Same as above	**Team and leader directed strategies** Same as SAS above Coach salary Staffing costs for managers, role models and nurses in coaching session and preparation		474,068 ᵞ (€ 364,668)	1225	365	1,060.5	
2	Higgins (2013), ITS	WHO-5 + incentive	None (with AHR)	Ireland	A mobile interactive stand-alone computer using gaming technology and annual license Swab and ATP machine	Research Assistant for audit and training 1.79 full-time equivalent (287 hours) assuming salary as £2,500 per month	Author contact	42,358 ᵞ (£ 26,474)	170	450	553.7	2010
3	Armellino (2012), ITS	Feedback + goal-setting	None (unclear AHR use)	USA	21 Video cameras	n/a	Paper	50,000	17	630	4,668.5	2008
4	Morgan (2012), ITS	System change + education + feedback + reminders	None (with AHR)	USA	60 alcohol dispensers system in two wards 12 posters in total	1.46 FTE (234 hours) of research assistant (10-20 hours a week for trouble shooting, refilling, and collecting data from the devices, and 2 hours a month to design and present posters)	Author contact	6,960	27	105	2,455.0	2010

5	Mestre (2012), ITS	Phase I: WHO-5 Phase II: WHO-5 (intense) + Reinforcement	Phase I: None (with AHR) Phase II: WHO-5	Spain	Alcohol handrub solution Material for campaign including posters, pens, and candy	Hand hygiene direct observation Data analysis and interpretation	Separate Paper [64]	19,259	n/a	365	385.2	2011
6	Doron (2011), ITS	WHO-5	System change + education + feedback + reminders (with AHR)	USA	Cost for marketing consultancy	n/a	Author contact	35,000 - 50,000	425	365	225.6-322.3	2008-9
7	Mayer (2011), CCT	Phase I: System change + education + feedback Phase II: WHO-5 + incentive	None (unclear AHR use)	USA	Prizes as candy, chocolate bars, pizza and others	2.25 FTE (yearly) of Infection preventionists 0.6 FTE of Manager 0.35 FTE of Clark	Paper	165,600	450	365	1,008.2	2003-6
8	Harne-Britner (2011), ITS	Phase I: Education + reminders Phase II: Education + incentive + goal-setting	Education (with AHR use)	USA	Printing, supply for education program	Staff time for preparation of education program Attendance at education programs including data collection training, in services, review material. Investigator monitoring for study. Validation of data collection tool and analysis	Author contact	4,835	n/a	180	n/a	2005

[¥] Assumed exchange rates: € 1 Euro = $US 1.3 and £1 British pound = $US 1.6
[*] HHC: hand hygiene compliance, HCW: healthcare worker, POS: point of care service, AHR: alcohol based hand rub, CRCT: cluster randomized controlled trial, RCT: randomized controlled trial, ITS: Interrupted time series study, CCT: controlled clinical trial, CBA: controlled before and after study, WHO-5: a combined intervention including system change, education, feedback, reminders, and institution safety climate, n/a: information is not available.

Table 3.5: Results of the re-analysis of studies using interrupted time series.

Study	Comparison	Baseline Level (intercept)		Baseline trend	Change in trend	Change in level	[d] Hand Hygiene change (%HHC)		
		%HHC	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Mean	95% Confidence interval	
Lee, Hosp 4	**T1 vs T7**	44.6	-0.215 (0.30)	-0.081 (0.10)	0.130 (0.10)	0.606 (0.26)	29.9	3.5	56.4
Lee, Hosp 7	**T7 vs T7**	53.8	0.154 (0.29)	0.281 (0.07)	-0.151 (0.08)	-1.042 (0.25)	-11.5	-13.5	-9.5
Lee, Hosp 8	**T2 vs T7**	44.6	-0.215 (0.26)	0.059 (0.06)	0.014 (0.06)	0.563 (0.19)	13.3	-9.2	35.8
Lee, Hosp 9	**T7 vs T7**	62.3	0.503 (0.33)	0.088 (0.13)	-0.094 (0.13)	-0.007 (0.51)	-9.7	-63.6	44.3
Derde	**T4 vs T5**	52.8	0.112 (0.04)	-0.015 (0.01)	0.133 (0.02)	0.346 (0.05)	16.3	13.6	19.1
Higgins	**T1 vs T9**	37.2	-0.428 (0.17)	-0.009 (0.25)	-0.030 (0.03)	2.448 (0.25)	48.8	45.4	52.3
Doron	**T6 vs T7**	70.7	0.204 (0.12)	0.187 (0.10)	-0.040 (0.03)	0.586 (0.01)	4.7	2.3	7.1
[a] **Chou**	**T1 vs T11**	54.9	0.198 (0.03)	-0.039 (0.00)	0.151 (0.01)	0.453 (0.17)	56.4	53.1	59.8
Marra	**T1 vs T7**	45.7	-0.173 (0.07)	0.020 (0.06)	0.063 (0.03)	0.218 (0.06)	11.5	3.4	19.6
Helms	**T1 vs T7**	91.3	2.350 (0.42)	-0.297 (0.18)	0.354 (0.19)	0.706 (0.33)	35.9	-5.8	77.7
Kirkland	**T1 vs T7**	51.3	0.052 (0.14)	-0.097 (0.04)	0.111 (0.04)	4.443 (1.03)	83.3	77.0	89.6
Al-Tawfiq	**T1 vs T10**	41.3	-0.350 (0.09)	-0.014 (0.02)	0.081 (0.07)	2.328 (0.21)	49.9	42.8	57.0
Crews	**T3 vs T8**	50.7	0.028 (0.12)	-0.070 (0.02)	0.103 (0.02)	3.679 (0.22)	38.2	35.5	40.9
[a] **Talbot (Phase I)**	**T3 vs T11**	56.7	0.271 (0.20)	-0.006 (0.02)	0.109 (0.02)	0.363 (0.41)	18.5	-1.4	38.4
Talbot (Phase II)	**T11 vs T12**	81.1	1.455 (0.45)	-0.020 (0.01)	0.060 (0.01)	0.464 (0.05)	15.0	10.6	19.5
[b] **Jaggi**	[c]**Unclear intervention details**	19.5	-1.420 (0.26)	0.080 (0.02)	-0.006 (0.03)	-0.586 (0.34)	-14.8	-33.1	3.6
[a, b] **Armellino (2012)**	**T1 vs Feedback+Goal-setting**	7.6	-2.493 (0.15)	-0.088 (0.133)	0.849 (0.235)	3.046 (0.68)	45.4	38.5	52.3
[a, b] **Armellino (2013)**	**T1 vs Feedback+Goal-setting**	29.0	-0.895 (0.04)	0.122 (0.10)	-0.109 (0.08)	2.267 (0.14)	74.9	65.5	84.4
[b] **Salmon**	**T1 vs T3**	42.7	-0.295 (0.17)	0.003 (0.02)	0.021 (0.02)	0.485 (0.22)	17.9	-0.3	36.2

[a] Evidence of auto correlation; Newey-West standard errors are reported.
[b] Studies excluded in the network meta-analysis (see Appendix A6 for exclusion criteria).
[c] Details of intervention were not clear.
[d] The mean change in hand hygiene compliance during the post-intervention period attributed to the intervention accounting for baseline trends (see Appendix A3 for details)

3.5 Discussion

We found that a multi-faceted hand hygiene intervention, WHO-5, and single interventions including system change, training and education, or reminders alone are associated with improved hand hygiene compliance compared with standard practice. Results from both RCT and ITS designs provided consistent evidence that adding supplemental interventions including goal-setting, reward incentives, and accountability to the WHO-5 strategy led to additional improvements in compliance. Information about resources used in the interventions was not well-reported.

We are aware of four previous systematic reviews of hand-hygiene interventions in healthcare settings.[5-8] One of these found only four studies of sufficient methodological quality to reliably evaluate hand hygiene promotion interventions and was unable to reach firm conclusions.[5] Overlap between included studies in the other three and ours is small: respectively 1 (4.8%),[7] 2 (4.9%),[6] and 5 (11.1%)[8] of studies included in our review were included in previous reviews, while 20 (95.2%), 39 (95.1%), and 40 (88.9%) of the studies in these reviews failed to meet the minimum quality threshold in ours.[12] While high quality non-randomized studies can potentially play an important role in the evaluation of interventions if analysed using appropriate methods, there are many reasons for thinking that simple before-after studies (a design used by the majority of the studies included in previous reviews) do not provide a reliable basis for evaluating interventions.[65-67] In contrast to ITS studies, a strong quasi-experimental design where multiple outcome measures are taken before and after the intervention, a before-after study compares a single outcome measure pre- and post-intervention and is vulnerable to distorting effects of pre-intervention trends.

We found an increasing number of "high quality" hand hygiene intervention studies after 2009. A systematic review conducted by Gould et al.[5] examining the literature from 1980 to November 2009, found only four studies meeting the EPOC criteria (1 RCT, 2 ITSs and 1 CBA). With the same criteria, our review found 31 studies (5 RCTs, 13 ITSs, 2 CCTs and 1 CBA) published between

December 2009 and May 2014. Most of them used an ITS design, possibly reflecting logistical difficulties in conducting RCTs.

A particular strength of our study is that the network meta-analysis allows us to quantify the relative efficacy amongst a series of different intervention strategies with different baseline interventions, even where the direct head-to-head comparisons were absent.

Reporting on resource implications for interventions was generally very limited with some notable exceptions. Most included studies reported only part of the resources used and methodologies for collecting cost data were unclear. Such resource-use information is important both for those wishing to implement similar strategies and for economic evaluation of different interventions.[10 68] A good framework to collect such data has also been proposed.[69] Cost-effectiveness analysis of hand hygiene promotion is required to assess under what circumstances these initiatives represent good value for money and when resources might be better directed at supplemental interventions including care bundles,[70] ward cleaning,[71] and screening and decolonization,[72] to complement well-maintained hand hygiene compliance.

This study has several limitations. First, implementation details of intervention components may vary substantially. For example, personal feedback and group feedback were classified together but, in practice, the impacts of these strategies may vary. Moreover, different studies may implement the same program with different quality of delivery and level of adherence, so-called intervention fidelity or Type III error.[73] Both issues are common to many interventions to improve the quality of care in hospital settings and are likely to be responsible for much of the unexplained heterogeneity between studies.[74 75] Second, most direct pairwise comparisons between strategies in the network meta-analysis were based on a single study. Third, publication bias may be substantial, particularly for non-randomized studies, although a funnel plot of ITS study results did not display obvious asymmetry (Appendix A7). There might also be a low level of language bias because studies in languages other than English were excluded. However, the magnitude of such bias is likely to be small.[76 77] Finally, linking improved compliance to clinical outcomes such as number of infections prevented would provide more direct evidence about the effectiveness of interventions.[10] Such direct evidence is still limited in hospital settings, although the association is supported by a large body of indirect evidence as well as biological plausibility.[78 79]

3.6 Conclusion

While there is some evidence that uni-modal interventions led to improvements in hand hygiene, there is strong evidence that the WHO-5 intervention can lead to substantial, rapid and sustained improvements in hand hygiene compliance in HCWs. There is also evidence that goal-setting, reward incentives and accountability provided additional improvements beyond those achieved by WHO-5. Important directions for future work are to improve reporting on resource implications for interventions, increasingly focus on strong study-designs, and evaluate the long-term sustainability and cost-effectiveness of improvements in hand hygiene.

What is already known on this topic

- Hand hygiene amongst healthcare workers is widely believed to be one of the most effective measures to reduce healthcare-associated infections, but compliance remains poor in many hospital settings.
- In 2005 the World Health Organization (WHO) launched a campaign to improve hand hygiene in healthcare settings by promoting a multimodal strategy consisting of five components: system change; training and education; observation and feedback; reminders in the hospital; and a hospital safety climate.
- More recently, additional strategies for improving hand hygiene have been evaluated.

What this paper add

- These meta-analyses provide evidence that the WHO campaign is effective at increasing hand hygiene compliance in healthcare workers.
- We also found evidence that additional hand hygiene interventions (used in conjunction with the WHO campaign elements) including goal-setting, reward incentives and accountability can lead to further improvements.
- Reporting on resource implications of such interventions is limited.

Competing interests

The authors declare that they have no competing interests.

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Chapter 4: Results Paper 1

Long-term survival after intensive care unit discharge in Thailand: a retrospective study.

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Author Contribution:

NL, BSC, YL, DL, NG, and ND contributed to the study conception and design. MH, DL, SC and PT collected the data. NL and MH performed the data analysis. NL, BSC, and YL wrote the draft. DL, MH, SC, PT, NG, and ND critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethical Clearance:

This study was exempt from QUT ethical approval as this research has negligible risk and did not use patient identifiable data (in accordance with section 5.1.22 of the National Statement on Ethical Conduct in Human Research). The QUT exemption number is 1500000319 and the QV reference number is 53448.

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Contributor	Statement of contribution*
Nantasit Luangasanatip Nantasit Luangasanatip 05/03/2015	Participated in study conception and design, performed data analysis and interpretation, and drafted the manuscript.
Maliwan Hongsuwan	Helped to collect data, perform data analysis, and revising it critically for important intellectual content.
Yoel Lubell	Participated in study conception, helped to draft the manuscript and revising it critically for important intellectual content.
Direk Limmathurotsakul	Participated in study conception, helped to collect data, and revising it critically for important intellectual content.
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Nicholas PJ Day	Participated in study conception and revising it critically for important intellectual content.
Nicholas Graves	Participated in study conception and revising it critically for important intellectual content.
Ben S Cooper	Participated in study conception, helped to draft the manuscript and revising it critically for important intellectual content.

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4.1 Abstract

Introduction: Economic evaluations of interventions in the hospital setting often rely on the estimated long-term impact on patient survival. Estimates of mortality rates and long-term outcomes among patients discharged alive from the intensive care unit (ICU) are lacking from lower- and middle-income countries. This study aimed to assess the long-term survival and life expectancy (LE) amongst post-ICU patients in Thailand, a middle-income country.

Methods: In this retrospective cohort study, data from a regional tertiary hospital in northeast Thailand and the regional death registry were linked and used to assess patient survival time after ICU discharge. Adult ICU patients aged at least 15 years who had been discharged alive from an ICU between 1st January 2004 and 31st December 2005 were included in the study, and the death registry was used to determine deaths occurring in this cohort up to 31st December 2010. These data were used in conjunction with standard mortality life tables to estimate annual mortality and life expectancy.

Results: This analysis included 10,321 ICU patients. During ICU admission, 3,251 patients (31.5%) died. Of 7,070 patients discharged alive, 2,527 (35.7%) were known to have died within the five year follow-up period, a mortality rate 2.5 times higher than that in the Thai general population (age and sex matched). The mean LE was estimated as 18.3 years compared with 25.2 years in the general population.

Conclusions: Post-ICU patients experienced much higher rates of mortality than members of the general population over the five-year follow-up period, particularly in the first year after discharge. Further work assessing Health Related Quality of Life (HRQOL) in both post-ICU patients and in the general population in developing countries is needed.

4.2 Introduction

Hospital mortality amongst intensive care unit (ICU) patients is high throughout the world, typically ranging from 14 to 44% [1-6]; in Thailand the reported range is between 24 and 40% [5-7]. Interventions to improve the quality of ICU care have the potential to reduce this mortality. Examples of such interventions include development of clinical guidelines [8,9], improvements to infection control practices [10], and appropriate use of medical devices [11].

There is growing interest not just in the effectiveness of such interventions at reducing mortality, but in their cost-effectiveness, and formal economic evaluation is increasingly used to aid decisions about allocation of scarce health care resources in these settings [12]. Such analyses consider both costs of the interventions and the associated health benefits. Outcomes such as the number of life years (LYs) or quality adjusted life years (QALYs) gained or disability adjusted life years (DALYs) averted are commonly used to represent the benefit of particular interventions. However, to estimate the change in LYs caused by preventing a single ICU death, estimates of post-ICU survival are needed. A number of studies have assessed long-term survival (defined as survival for at least one year post-ICU discharge) [2,13-29]. All but one of these studies were conducted in high-income countries and high quality data are lacking from lower and middle income countries [26]. The aim of this study was to quantify the long-term survival of post-ICU patients in Thailand and to estimate life expectancy (LE) in this population.

4.3 Materials and methods

Setting and facilities

Sappasithiprasong hospital is a 1,100-bed tertiary referral hospital located in rural northeast Thailand. In 2004 and 2005, it had a catchment of 1.8 million people, predominantly rice farmers and their families. Universal health coverage has been operating in Thailand since 2002, ensuring access to this hospital for the entire population in the catchment area [30]. In 2004 Sappasithiprasong hospital had 36 general wards and 16 ICUs (4 pediatric and

12 adult), representing 6 ICU beds per 100,000 people. These wards provided care for critically ill patients and patients recovering from major surgery. Adult ICUs comprised of four medical ICUs (including one respiratory ICU), two surgical ICUs, two neurosurgical ICUs, one trauma ICU, two coronary care units, and one cardiovascular and thoracic ICU. ICUs contained a median of 8 beds (range 8 to 16) and the mean nurse-to-patient ratio was 1:1.5 (including both registered nurses and practical nurses). All of these ICUs could be defined as Level II open ICUs according to the guidelines from the American College of Critical Care Medicine [31] since there were no intensivists accredited by the Royal College of Physicians of Thailand working at Sappasithiprasong hospital in 2004. Further details about the ICUs in this hospital have been described elsewhere [32].

Data

Retrospective patient-level data from January 2004 to December 2005 were obtained from Sappasithiprasong hospital. Adult patients, aged at least 15 years who had been admitted to an adult ICU and discharged alive from the ICU between January 1st, 2004 and December 31st, 2005, were included in this retrospective cohort analysis. For patients who were subsequently readmitted to an ICU during this period, only the time since the end of the first ICU episode was considered. The regional death registry for northeast Thailand from 2004 to 2010 was obtained from the Thai Ministry of Public Health and linked to the patient data using the national identification number (ID). We verified the validity of each patient's ID number using the checksum digit and cross-checked the name and date of birth between hospital data and the regional death registry to validate the data.

Use of these data was approved by ethical committees from 1) The Faculty of Tropical Medicine, Mahidol University, 2) Sappasithiprasong hospital, Ubon Ratchatani, and 3) The Ministry of Public Health, Thailand [33]. No patient consent was required as this study was retrospective and did not use patient identifiable data.

Patients with a recorded date of death during the ICU admission period were classified as ICU deaths. It is not uncommon practice in Thailand and other Southeast Asian countries to discharge moribund patients to die at home [33]. We therefore also classified deaths occurring within two days of ICU discharge as ICU deaths. Survival time for discharged patients was assessed for five years after hospital discharge. Patients were assumed to be alive if no death was recorded within five years of ICU discharge in the death registry.

Analysis

The primary outcome was survival time after ICU discharge. A Kaplan-Meier survival curve showing the estimated proportion of post-ICU patients alive at each time point was plotted over the five year follow-up period. To quantify the potential impact of differential mortality following year five, we fitted an exponential curve to the annual risk of death from years two to five. From year eight onwards, the extrapolated post-ICU mortality differed by less than 1% from that in the general population matched for age and sex. Therefore, mortality from year eight was assumed to be equal to that in the general Thai population which we took from standard mortality life tables [34]. In the base case analysis we assumed that in years six and seven post-discharge the relative risk of death for former ICU patients compared to the general population was the same as that observed in year five (relative risk of 1.35). Since this assumption may underestimate post-ICU survival, we performed a sensitivity analysis in which we assumed that mortality rates in years six and seven post-discharge were the same as those in the general population matched for age and sex (i.e. a relative risk of one). The life expectancy (LE) amongst patients discharged from the ICU was taken as the area under the lifetime survival curve. The LE was calculated for the overall ICU population and for each age group.

Survival analysis stratified according to major diagnostic categories for ICU admission from the International Statistical Classification of Diseases, tenth revision (ICD10) [35] was also performed. The diagnostic groups were: a.) Cerebrovascular diseases (ICD10 codes: I60-I69); b.) Cardiovascular diseases except Cerebrovascular diseases (ICD10 codes: I00-I99 except I60-I69); c.)

Digestive system (ICD10 codes: K00-K93); d.) Neoplasms (ICD10 codes: C00-D48); e.) Respiratory system (ICD10 codes: J00-J99); and f.) Injury, poisoning and other external causes (ICD10 codes: S00-T98). The analysis was performed using STATA 11 (Stata Corp., College Station, Texas) and Microsoft Excel 2010, (Redmond, WA, USA).

We also performed a systematic search in order to review the related literature investigating long-term survival amongst post-ICU patients in low and middle income countries. The search strategy and inclusion criteria are provided in Appendix B.

4.4 Results

There were 11,985 adult patients admitted to an ICU in Sappasithiprasong hospital between 2004 and 2005 and discharged before 1st January 2006. After verifying the hospital dataset, 1,664 patients (13.9%) were not eligible for this analysis due to missing data, incomplete or invalid ID numbers, or coming from other countries (and therefore not recorded in the regional mortality records). As a result, 10,321 patients were included in this analysis. There were 7,223 patients who were discharged alive from the ICU; 153 of these died within two days and were counted as ICU deaths. Of these 61 (39.9%) died at the hospital and 92 (60.1%) died at home. We studied five-year survival in the remaining 7,070 patients who were discharged from the ICU alive (31.5% ICU fatality rate). Patient-flow is shown in Figure 4.1. Demographics and ICD10 codes in the group of patients who were discharged alive differed slightly from those in patients who died within the ICU (Table 4.1). In contrast, the group of post-ICU patients who died within five years of discharge tended to be older and much less likely to have ICD10 codes relating to injury, poison and other external causes than those who were alive after five years (Table 4.2). Of the 7,070 patients who were discharged alive, 79.3% survived the first year, then 74.0%, 70.3%, 66.9%, and 64.2% survived each subsequent year (Figure 4.2). Overall, within five years, 2,527 of the original 7,070 (35.7%) had died. The Kaplan-Meier survival curve indicated a greatly elevated risk of death in the first year post-ICU discharge, with 9.5% (241 of 2,527) of all deaths occurring within seven days. Of these, 67 (27.8%) died at the hospital and 174 (72.2%) died at home. Of the total 2,527 deaths over five years 21.4% (540) occurred within the first month, 35.5% (896) within 3 months, 46.0% (1,162) within 6 months, and 57.9% (1,464) within the first year. Mortality rates became close to those in the general population between years two to five after ICU discharge. The annual risks of death for each year during these periods were 0.21, 0.07, 0.05, 0.05, and 0.04, respectively. In the general population, the annual risk of death (matched for age and sex with those discharged alive from the ICU) was 0.03. Overall, half of the post-ICU patients would have been expected to die within 12.1 years of ICU discharge under base case assumptions. In a sample of the general population matched for age and sex, half would be expected to die within 21.2 years (Figure 4.3). The LE under base case assumptions and the sensitivity analysis are presented in Table 3. The overall LE amongst post-ICU patients was estimated to be 18.3 years while the LE in the general population (matched for age and sex) was estimated to be 25.2 years. The sensitivity analysis yielded estimates of LE 1.6% higher than under the base case assumption.

Survival categorised by specific diagnostic categories is presented in Figure 4.4 and Table 4.4. The lowest survival within six months of discharge was seen in patients admitted with cerebrovascular disease, though at five years post-discharge the lowest survival (33.6%) was seen in patients with neoplasms. The highest survival rates were consistently seen in those admitted due to injury, poisoning or other external causes; 86.5% of patients in this group survived at least five years.

In the systematic search for studies of long-term survival amongst post-ICU patients studies in low and middle income countries, we found only one study evaluating post-ICU survival across all diagnostic categories [26]. This study followed up 187 post-ICU patients in Malaysia for two years. It was reported that 97 of 105 post-ICU patients (92.4%) who responded to a questionnaire survived for two years. However, the high loss to follow up in this study (43.8%, 82 from 187) makes interpretation of these findings difficult.

Figure 4.1: Patient flow from intensive care unit (ICU) admission to discharge

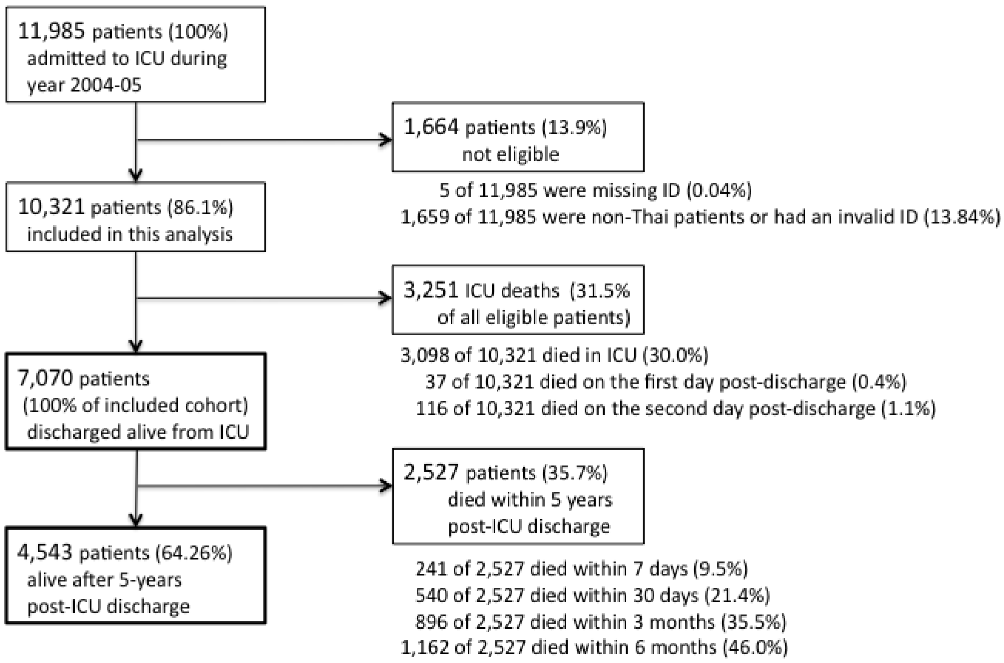

Table 4.1: Demographic data for ICU patient

	Patients dying in the ICU[1] N=3,251	Patients discharged alive from the ICU N=7,070
Age (Med [IQR])	57.6 [42.6, 71.1]	54.5 [38.2, 67.8]
Age group (number of patients)		
15-29	408 (12.6%)	1,132 (16.1%)
30-44	492 (15.1%)	1,298 (18.4%)
45-59	879 (27.0%)	1,821 (25.8%)
60-74	901 (27.7%)	1,914 (27.1%)
>75	571 (17.6%)	905 (12.8%)
Length of hospital stay (Med [IQR])	3.0 [1,7]	7.0 [3,12]
Sex (% female)	1,241 (38.2%)	2,700 (38.2%)
ICD10 (Top five, by %)		
Circulatory system (I00-I99)	1,040 (32.0%)	2,627 (37.2%)
- Cerebrovascular diseases (I60–I69)	535	404
- Other forms of heart disease (I30–I52)	179	615
- Ischemic heart diseases (I20–I25)	152	886
- Chronic rheumatic heart diseases (I05–I09)	86	441
Injury, poison and other external causes (S00-T98)	751 (23.1%)	1,598 (22.6%)
- Injury (S00–T14)	715	1,490
- Poisoning and certain other consequences of external causes (T15–T98)	36	108
Digestive system (K00-K93)	328 (10.1%)	789 (11.2%)
- Other diseases of the digestive system (K90–K93)	106	125
- Diseases of oesophagus, stomach and duodenum (K20–K31)	48	225
- Disorders of gallbladder, biliary tract and pancreas (K80–K87)	43	166
Respiratory system (J00-J99)	248 (7.6%)	376 (5.3%)
- Influenza and Pneumonia (J09–J18)	145	129
- Chronic lower respiratory diseases (J40–J47)	35	82
- Suppurative and necrotic conditions of lower respiratory tract (J85–J86)	10	61
Neoplasms (C00-D48)	186 (5.7%)	488 (6.9%)
- Malignant neoplasms (C00-C99)	160	331
- Neoplasms of uncertain or unknown behaviour (D37–D48)	22	128
- Benign neoplasms (D10–D36)	4	27
Hospital mortality (%)	N/A	139 (2.0%)
Five years mortality (%)	N/A	2,527 (35.7%)

[1]Includes patients who died within two days of ICU discharge

Table 4.2: Demographic data for post-ICU patients

	Post-ICU patients dying within 5 years of ICU discharge N=2,527	Post-ICU patients alive 5 years after ICU discharge N=4,543
Age (Med [IQR])	64.6 [52.6, 74.0]	47.46 [32.6, 62.2]
Age group (number of patients)		
15-29	127 (5.0%)	1,005 (22.1%)
30-44	256 (10.1%)	1,042 (22.9%)
45-59	618 (24.5%)	1,203 (26.5%)
60-74	949 (37.6%)	965 (21.2%)
>75	577 (22.8%)	328 (7.2%)
Length of hospital stay (Med [IQR])	8.0 [4,15]	7.0 [3,11]
Sex (% female)	1,041 (41.2%)	1,659 (36.5%)
ICD10 (Top five, by %)		
Circulatory system (I00-I99)	1,023 (40.5%)	1,604 (35.3%)
- Cerebrovascular diseases (I60–I69)	337	549
- Other forms of heart disease (I30–I52)	225	390
- Ischemic heart diseases (I20–I25)	216	188
- Chronic rheumatic heart diseases (I05–I09)	114	327
Neoplasms (C00-D48)	324 (12.8%)	164 (3.6%)
- Malignant neoplasms (C00-C99)	249	82
- Neoplasms of uncertain or unknown behaviour (D37–D48)	70	58
- Benign neoplasms (D10–D36)	5	22
Digestive system (K00-K93)	321 (12.7%)	468 (10.3%)
- Other diseases of the digestive system (K90–K93)	86	139
- Diseases of oesophagus, stomach and duodenum (K20–K31)	67	99
- Disorders of gallbladder, biliary tract and pancreas (K80–K87)	60	65
Injury, poison and other external causes (S00-T98)	215 (8.5%)	1,383 (30.4%)
- Injury (S00–T14)	182	1,308
- Poisoning and certain other consequences of external causes (T15–T98)	33	75
Respiratory system (J00-J99)	190 (7.5%)	186 (4.1%)
- Influenza and Pneumonia (J09–J18)	75	54
- Chronic lower respiratory diseases (J40–J47)	58	46
- Suppurative and necrotic conditions of lower respiratory tract (J85–J86)	15	24

Figure 4.2: Kaplan-Meier survival estimates for post-ICU patients (solid line) and age- and sex- matched survival for the general population in Thailand (broken line)

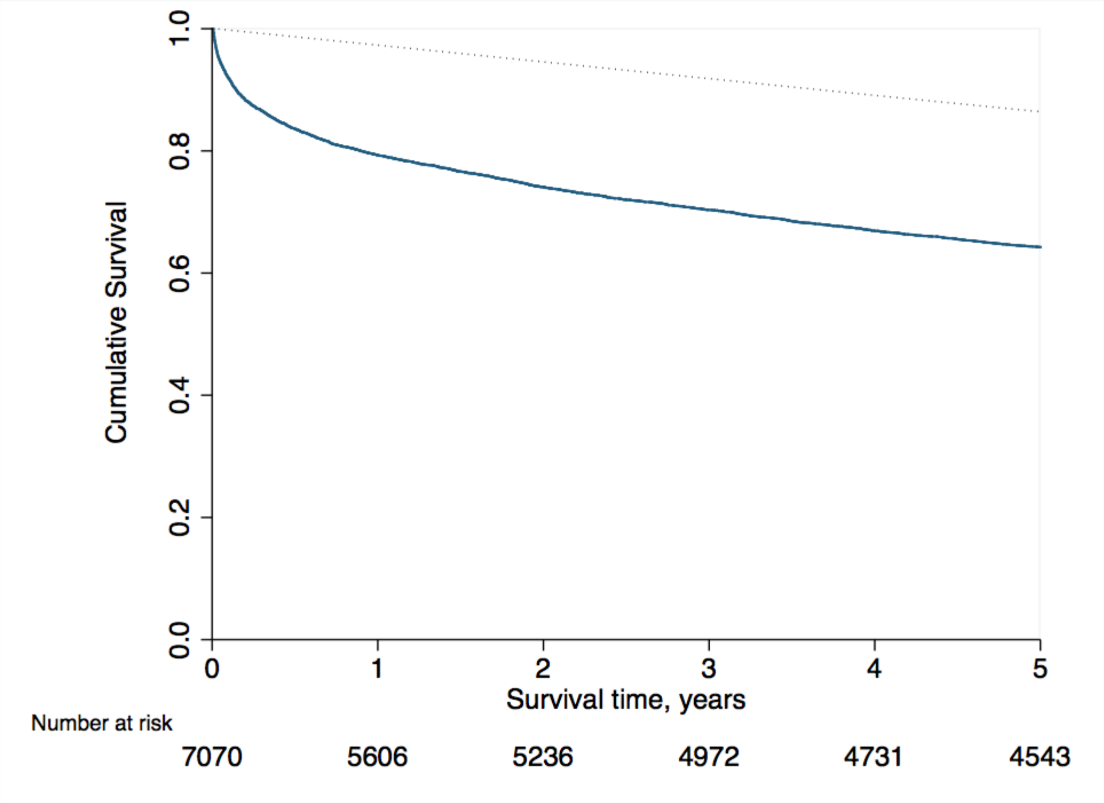

Figure 4.3: The extrapolated lifetime survival curve under base case assumptions of post-ICU patients and age- and sex- matched survival in the general population in Thailand.

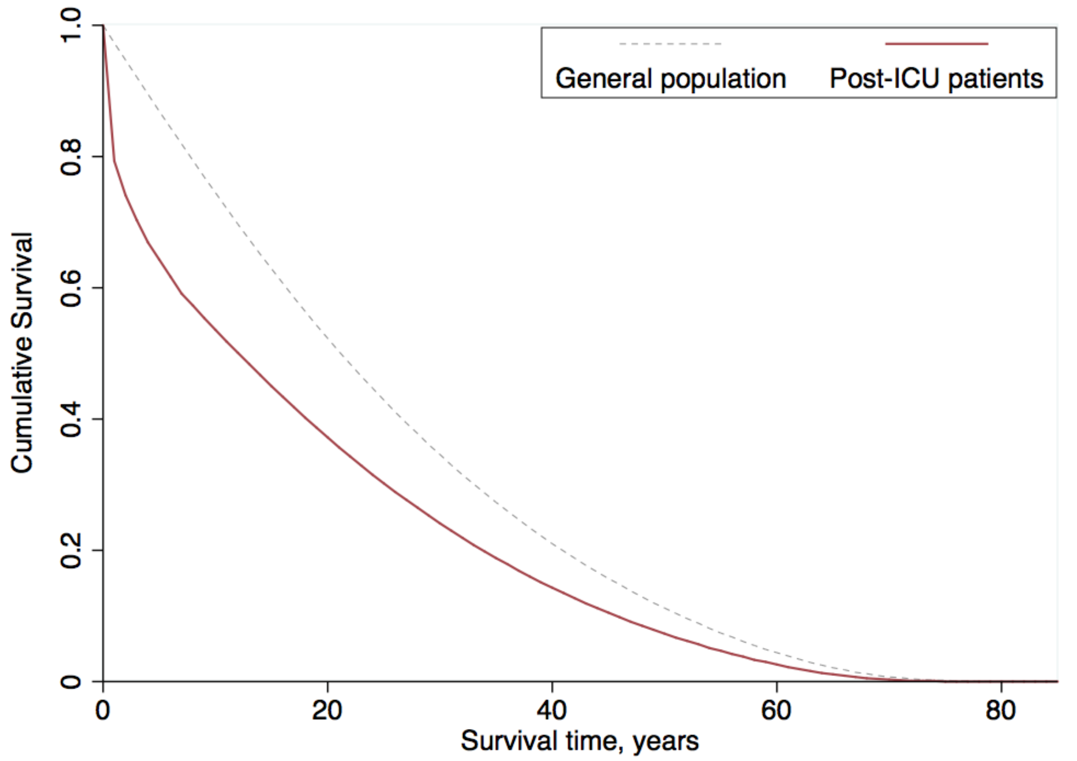

Table 4.3: Life expectancy (LE) among post-ICU patients adjusted for age and sex in the base case, sensitivity analysis and general population.

Age group (Years)	Life Expectancy (LE)		
	†Base case	*Sensitivity Analysis	◊General population
15-29	43.16	43.80	48.97
30-44	28.87	29.56	36.01
45-59	16.41	16.98	24.03
60-74	8.72	8.96	13.66
≥ 75	4.75	4.61	6.36
Overall	18.26	18.56	25.15

† Base case analysis: we assumed that from year five to seven post-discharge the relative risk of mortality amongst post-ICU patients was the same as that in year five. From year eight onwards, the relative risk was assumed to be 1.

* Sensitivity Analysis: we assumed the mortality rates among the post-ICU patients after five years post-discharge to be the same as those in the general population matched for age and sex.

◊ General population: we applied the mortality rate of the Thai general population age- and sex-matched to all post-ICU patients since ICU discharge.

Figure 4.4: Kaplan-Meier survival estimates for post-ICU patients stratified by diagnostic group.

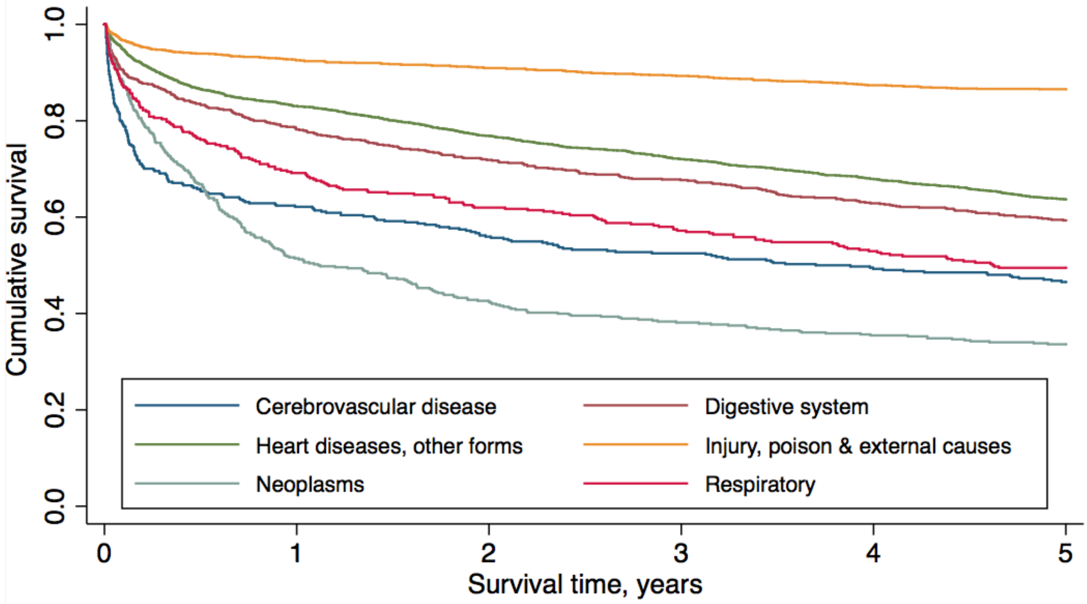

Table 4.4: Comparison of survival (%) at ICU discharge and 1, 2, 3, 4, and 5 years after ICU discharged by age and diagnostic group.

Time of follow up	At ICU discharge	1 year	2 year	3 year	4 year	5 year
Number of patients at each follow up time	7070	5606	5236	4972	4730	4543
Age (median, [IQR])	54.5[38.2, 67.8]	51.4[35.2, 65.6]	50.5[34.2, 64.8]	49.5[33.8, 63.8]	48.5[33.0, 63.0]	47.5[32.6, 62.2]
Length of hospital stay	7.0 [3,12]	7.0 [3,11]	7.0 [3,11]	7.0 [3,11]	7.0 [3,11]	7.0 [3,11]
Sex (% female)	38.2%	37.6%	37.3%	37.2%	36.7%	36.5%
Age group						
15-29	100.0%	93.0%	91.8%	90.7%	89.8%	88.8%
30-44	100.0%	88.4%	85.1%	83.1%	81.8%	80.3%
45-59	100.0%	80.2%	75.0%	71.4%	68.4%	66.1%
60-74	100.0%	70.7%	64.5%	58.9%	53.7%	50.4%
≥ 75	100.0%	65.4%	54.6%	48.5%	41.9%	36.2%
Diagnostic group						
Heart diseases, other forms (I00-I99 except I60-I69)	100.0%	83.0%	76.9%	72.0%	67.9%	63.7%
Cerebrovascular diseases (I60–I69)	100.0%	62.1%	55.9%	52.5%	49.3%	46.5%
Injury, poison and other external causes (S00-T98)	100.0%	92.6%	90.9%	89.3%	87.4%	86.5%
Digestive system (K00-K93)	100.0%	78.2%	71.9%	67.7%	62.9%	59.3%
Respiratory system (J00-J99)	100.0%	69.1%	62.0%	57.2%	52.9%	43.6%
Neoplasms (C00-D48)	100.0%	51.4%	42.4%	38.1%	35.5%	33.6%

4.5 Discussion

This study found that post-ICU patients had a substantially higher mortality rate (and substantially reduced LE) compared to the general population, with most of the difference seen in the first year post-discharge. Overall, the LE among the post-ICU patients was estimated to be seven years lower than in the general population and the number of life years gained from preventing one ICU death was found to be about two thirds that from preventing one death in the general population (matched for age and sex).

Results from this study are broadly consistent with those from previous studies conducted elsewhere in high-income countries [2,13,14,16-18,36-38]. Our estimate that cumulative mortality over the five years was 35.7% (or 2.5 times higher than in an age and sex-matched general population) is slightly higher but comparable with estimates from previous studies which found that the five years cumulative mortality rate ranged from 17.9 to 33.5% [2,13,14,16-18,36-38]. Our estimate of the risk of death in year five, 0.04, is at the upper end of the range estimated in studies conducted in high-incomes countries (0.01 to 0.04) [14,36,37]. The mortality rates among post-ICU patients in our study were high in the first 12 months, then decreased rapidly, and were projected to closely approximate those of the general population by year eight post-ICU discharge. Studies conducted in Finland, Norway, and Scotland [13,36,37] also demonstrated substantially greater risk of death during the first year, but these became similar to the general population within one to four years. On the other hand, studies conducted in the United Kingdom [16] and Australia [38] found that the mortality rate amongst former ICU patients was higher than the general population over a 5-year and 15-year follow-up period, respectively.

There are several possible reasons for differences in the time for post-ICU mortality rates to approach those in the general population. Firstly, there was considerable variation between the studies in the frequency of different diagnostic categories. Our study had a relatively high proportion of patients with ICD10 codes relating to injury, poisoning and other external causes (23% compared to a range of 7 to 15% in other studies) [18,36-38]. Conversely, there was a low proportion of patients with ICD10 codes relating to the respiratory system (5% compared with a range of 8 to 36%) [13,36,37]. Figure 4.4 suggests that these differences are likely to be associated with both a shorter period for post-ICU mortality to approach that in the general population and a relatively high five-year post-ICU survival rate.

Quality of care in different settings [39,40] is another possible factor that could impact on long-term survival rates. Higher quality of care should reduce ICU mortality, but could potentially either increase or decrease the long-term survival in patients discharged alive from ICU. The latter could occur if higher quality of care prevents ICU deaths in patients with poor long-term prognosis (where some of these patients would have died in the ICU if in lower quality of care settings). Quantifying such competing effects is challenging, but important for evaluating the cost-effectiveness of interventions to improve quality of ICU care in low and middle income countries.
Currently, however, there are few studies of long-term survival following ICU stays in lower and middle income countries. While the systematic search identified a small number of studies evaluating long-term survival following ICU discharge in specific diagnostic categories (liver transplants, myocardial infarction, metastatic solid cancer, chronic obstructive pulmonary disease) [41-45], long-term follow-up of representative ICU cohorts was lacking.

Our analysis accounted for the common practice in Southeast Asia of discharging moribund patients to die at home by classifying deaths occurring within two days of discharge as ICU deaths. The two-day cut off was chosen because post-ICU mortality showed a clear spike on day two post-discharge (with 116 deaths, or 1.12% of total ICU patients) but showed a gradual decline from day three (48 (0.47%), 46 (0.45%), 36 (0.35%), 28 (0.27%), and 29 (0.28%) for day three to seven, respectively). This resulted in only slightly higher ICU mortality than would have been obtained had we only considered deaths occurring during the admission (31.5% versus 30.0% mortality, or 153 more deaths), and consequently slightly lower cumulative five year mortality amongst the non-ICU deaths (37.1% versus 35.7%).

The mortality rates during years six and seven post-ICU discharge are likely to be somewhat lower than assumed in the base case (which assumed the same relative risk for death as in year five), but somewhat higher than assumed in the sensitivity analysis (which assumed a relative risk of one). However, these two assumptions yielded estimates of LE that differed by less than 2% (Table 4.3) indicating that improved estimates of mortality in years six and seven would have negligible impact on the results.

Interestingly, among individuals over 75 years of age, the mortality rate was higher in the post-ICU group than in the general population in the first two years, but lower in the following years, resulting in a slightly longer LE than the general population. This might be explained by the possibility that these patients are on average healthier than the general population, having survived their ICU admission.

Limitations

This study has several limitations. Data from a single regional hospital may not be representative of the national population due to differences in patient characteristics and quality of hospital care. However, similar regional hospitals provide care to most of the population in Thailand and the large population (n>7,000) and long-term follow-up strengthen our findings. Nonetheless, had resources permitted, this study could have been improved (and its external validity strengthened) by collecting data from multiple sites across Thailand. A second limitation is that this study was based on retrospective data which were inevitably incomplete. Moreover, as the regional death registry was used (not national data), it is possible that we have missed some deaths in patients who moved and died outside of the northeast region. Our analysis might therefore underestimate mortality. However, any such bias is likely to be small as the five year migration rate amongst the northeast Thai population was estimated to be 3.1% in 2000 [46]. This rate is likely to be even lower in older age groups where most of the mortality occurs. Another limitation is the lack of a standardised measure of severity of illness. A standard severity score (such as APACHE II) would have helped to inform comparisons of our findings with those from other studies, but such data is not routinely collected in ICUs in Thailand. Finally, this study would have been improved by the addition of Health Related Quality of Life (HRQOL) data to estimate the quality adjusted life expectancy (QALE) amongst the post-ICU patients. Ideally, such HRQOL information would be obtained from a long-term cohort study in the local population; resources for this were not available to us. Given the range of the HRQOL between 0.56 and 0.88 as shown in the literature [13,14,16,19] (all from high-income countries) the expected QALE of post-ICU patients would range from 10.2 to 16.1 QALYs. Prospective collection of such quality of life data is an important area for future health economic research in developing countries.

4.6 Conclusions

This study represents one of the first attempts to estimate long-term post-ICU survival in a developing country context. Post-ICU patients had higher mortality than members of the general population (matched for age and sex) over the five year follow-up period. The estimated LE is useful for economic evaluations and should support decision-makers considering potential investments in interventions that could prevent unnecessary deaths during ICU or hospital admissions.

Key messages

- Five year mortality amongst post-ICU patients in Thailand was estimated to be 35.7%. This is about 2.5 times higher than that in the general population (age and sex matched).
- The risk of death was greatly elevated in the first year after ICU discharge and approached that in the general population in subsequent years.
- The extrapolated lifetime survival indicated that post-ICU patients had 27.4% lower life expectancy than the general population (age and sex matched).
- Patients admitted to the ICU as a result of injury, poisoning or other external causes had the lowest mortality rate over the five year follow-up; patients with neoplasms had the highest.
- Estimates of the number of life years gained from interventions preventing ICU deaths will aid policy-makers considering potential investments in this area.

Abbreviations

DALY, Disability adjusted life year; HRQOL, Health-related quality of life; ICU, Intensive care unit; ID, Identification number; LE, Life expectancy; LY, Life year; QALE, Quality adjusted life expectancy; QALY, Quality adjusted life year

Competing interests

The authors declare that they have no competing interests

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Chapter 5: Result paper 2

Cost-effectiveness of interventions to improve hand hygiene in healthcare workers in middle-income hospital settings: a model-based analysis.

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NL, ML, PS, and DL were involved in data collection and NL performed the analysis. NL wrote the first draft. MH, YL, DL, PS, ND, NG, and BSC critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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5.1 Abstract

Background: Multimodal interventions are effective in increasing hand hygiene (HH) compliance amongst healthcare workers, but it is not known whether such interventions are cost-effective outside high-income countries. We developed a model-based framework to address this question and to determine whether reductions in Methicillin-resistant *Staphylococcus aureus* bloodstream infections (MRSA-BSI) alone would make HH interventions cost-effective in intensive care units (ICUs) in a middle-income country.

Method: Transmission dynamic and decision analytic models were combined to determine the expected impact of HH interventions on MRSA-BSI incidence and evaluate their cost-effectiveness. Epidemiological and economic parameters were derived using data from a tertiary hospital in North-east Thailand.

Findings: Interventions increasing HH compliance from a 10% baseline to ≥20% are likely to be cost-effective solely through reduced MRSA-BSI. Increasing compliance from 10% to 40% was estimated to cost $US 89·10 per bed-year with 4·07 QALYs gained per 10,000 bed-days in the paediatric ICU (PICU) and $US 63·34 per bed-year with 4·03 QALYs gained per 10,000 bed-days in the adult ICU. If baseline compliance is not greater than 20%, the intervention is always cost-effective even with only a 10% compliance improvement.

Interpretation: Effective multimodal HH interventions are likely to be cost-effective in ICU settings in typical middle-income countries where baseline compliance is low due to preventing MRSA-BSI alone. Where compliance is higher, the cost-effectiveness of interventions to improve it further will depend on the impact on HAIs other than MRSA-BSI.

5.2 Introduction

Hospital-acquired infections (HAIs) are a major cause of morbidity and mortality amongst hospitalised patients.[1] HAIs are also associated with a substantial economic burden due to longer hospital stays and additional antibiotic costs.[2-4] The risk of infection in developing countries is two to 20 times higher than in developed countries.[5] In Thailand, amongst hospitalized patients, the point prevalence of nosocomial infection has been estimated to be 6·5% and ~250,000 patients are believed to have an HAI each year.[6] The economic burden was estimated in 1995 to be 1·5 – 2·5 billion baht ($US 500-800 million) annually.[7]

Direct patient contact with healthcare workers (HCWs) transiently contaminated with nosocomial pathogens is believed to be the primary route of transmission for many nosocomial pathogens. Improving HCW hand hygiene compliance can minimize the impact of this transmission route and reduce the incidence of nosocomial infection.[8-10] A multimodal intervention including system change, training and education, observation and feedback, reminders, and a hospital safety climate has been developed and promoted by the World Health Organization (WHO) and this campaign (which we refer to as WHO-5) has been shown to be effective in increasing hand hygiene compliance.[11] Hand hygiene promotion is also relatively easy to implement and requires a relatively low level of investment. Nevertheless, in many healthcare settings, particularly in low and middle-income countries, compliance remains poor and reports of compliance rates of below 10% may well be typical.[12-15]

Transmission dynamic models are useful tools to help understand the likely impact of hypothetical interventions to control communicable diseases.[16] Moreover, their use in health-economic evaluations of interventions that reduce transmission is essential to fully capture the intervention benefits.[17] However, while several studies have used dynamic models to consider hospital infections,[18] economic evaluations of hand hygiene interventions have used only static models and neglected developing countries where the need for appropriate investment is greatest.[19-22]

The aims of this study are to develop a dynamic model-based framework for evaluating the cost-effectiveness of hand hygiene promotion interventions and use it to evaluate the cost-effectiveness of such interventions for reducing Methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infection (MRSA-BSI) in typical ICU settings in a middle-income country. Our model is informed by data from a typical regional hospital in Thailand, a middle-income country with a gross domestic product (GDP) per capita approximately equal to the world's median. We focus on MRSA-BSI as this is one of the most serious and best-studied types of infection in ICU patients. Moreover, there is clear evidence of frequent patient-to-patient transmission of MRSA in ICUs in Thailand,[23] and evidence that such transmission can be interrupted by improved hand hygiene.[24-26] Hand hygiene interventions should also reduce other types of MRSA infections and infections with other organisms. However, since these are harder to quantify, we take a highly conservative approach by focusing on MRSA-BSI alone and almost certainly underestimate the true health benefits of the intervention.

5.3 Methods

Overall description

Transmission dynamic and decision analytic models were combined to simulate the MRSA transmission dynamics and evaluate the impact and cost-effectiveness of hand hygiene interventions. Two ICU settings were considered: a paediatric intensive care unit (PICU) and adult intensive care unit (adult ICU). Epidemiological and economic parameters were derived from detailed local data from a typical tertiary hospital in North-east Thailand. The assumed willingness to pay for health benefits was based on that recommended in Thailand,[27] and corresponds to approximately one times GDP per capita. In addition, we also consider a cost-effective threshold of three times GDP per capita as recommended by the WHO.[28]

Transmission dynamic model

A previously-described deterministic host-vector model was constructed to simulate MRSA transmission dynamics in an ICU.[29] (Figure 5.1) Patients can be admitted to the ICU either colonised or uncolonised with MRSA. Uncolonised patients can become colonised or infected by contact with transiently-colonised HCWs. HCWs can be decolonised by performing hand hygiene. Colonized patients have a specified risk of developing MRSA-BSI. The model outputs the number of newly colonized patients, the number of MRSA-BSIs and the number of deaths over one year under different levels of hand hygiene compliance. The model was implemented in R, using the package "deSolve" to numerically solve the equations.[30,31] Model outcomes were fed into the decision analytic model. Full technical details are given in the appendix. (Appendix C)

Model parameters were obtained from a number of sources. (Table 5.1) MRSA carriage data were derived from a previous observational study in North-east Thailand which involved screening patients in a 7-bed PICU and a 10-bed adult ICU.[32,33] Estimates of the per contact transmission probability from a colonized HCW to an uncolonized patient and from a colonized patient to an uncolonized HCW were derived using these data,[33] combined with previous estimates of the probability of transmission from a colonized patient to HCW (see Appendix C).[25] The rates at which colonized patients acquired an MRSA-BSI were estimated from the average number of cases per year at each ward divided by the expected number of colonized bed-days (estimated from the carriage data). Risk of death due to MRSA-BSI was taken from an observation study in the same setting.[32] The number of beds, number of HCWs per shift, rates of ICU discharge, ward-specific contact rates, and the baseline hand hygiene compliance were directly observed from the same hospital.

Economic Evaluation

Cost-utility analysis was performed from a healthcare provider's perspective. The cost of the hand hygiene intervention was estimated over one year. Health benefits were measured with a lifetime horizon with a 3% discounting rate. Costs were adjusted to 2014 values.[34]

There were two main cost components: cost of hand hygiene promotion; and costs associated with MRSA-BSI. The latter includes costs of additional hospital stay and antibiotic treatment. (Table 5.1) The cost of the hand hygiene campaign accounted for staff time and materials used. We derived this information from a survey conducted in Australia from the national hand hygiene campaign,[35] assuming the same time per bed-day requirements but applying Thai pay-scale salaries for registered nurses with two and 10 years experience.[36] Costs of alcohol hand rub (AHR) were included in the model; other materials costs were assumed to be negligible. The intervention was assumed to increase AHR use 3·5-fold (range: 2 to 5).[37-39] Baseline AHR use was directly observed from all local paediatric and adult ICUs at baseline compliance of 10%. We found similar amount used in both type of ICUs, therefore the average AHR use estimated as 98 litres per ICU, was applied in both wards. Associated costs assumed the market price ($US 2·38 per litre) provided by the national pharmaceutical supplier in Thailand.[40] Total hand hygiene intervention costs were estimated to be $US 680 and $US 725 per ward per year in the PICU and adult ICU, respectively.

Costs associated with MRSA-BSI were estimated from additional stay and treatment. Hospitalization cost was calculated as the excess length of stay due to MRSA-BSI times cost per bed-day. Retrospective data from routine clinical and microbiological laboratory databases at the local hospital (2003-2010) were used to identify MRSA-BSI cases. Additional stay due to infection was estimated with a multi-state model accounting for time-dependent bias using the "etm" package within R.[41,42] The economic value of a bed-day should reflect the opportunity cost of an occupied bed, a value which could be quantified by asking healthcare providers for their willingness to pay (WTP) for an unoccupied bed-day.[43] This opportunity cost is typically much lower than the cost calculated with an accounting approach using the hospital budget divided by the total patient bed-days over the same period.[44] In the absence of WTP per ICU bed-day in Thailand, we estimated the accounting cost using local hospital financial data and multiplied this by the ratio of bed-day costs estimated with WTP and accounting approaches reported in a previous study.[44]

Treatment for MRSA-BSI was assumed to require a 14-day course of Vancomycin with dose regimens following treatment guidelines for hospital-acquired MRSA-BSI.[45] Drug costs were obtained from the Drug Medical Supply Information Center (DMSIC).[46]

Estimates of life expectancy amongst post-ICU patients were taken from a previous study using data from North-east Thailand.[47] Utility values for patients after ICU discharge were taken from the literature.[48-51] The median utility of 0·72 was used in the base case with a range from 0·56 to 0·88. This health utility weight was assumed constant.

Analyses

Four scenarios with different baseline versus post-intervention hand hygiene compliance values were considered: a) 10% vs 20%; b) 10% vs 40%; c) 10% vs 80%; and d) 40% vs 80%. These values were broadly consistent with results from a systematic review where odd ratios were estimated to be 7·4 and 50·1 for WHO-5 and WHO-5 plus other interventions amongst studies using an interrupted-time series design (with a baseline compliance of 10%, these would give post-intervention compliance values of 45 and 85%, respectively).[52]

In each comparison, point estimates of incremental costs (ΔC) and QALYs gained (ΔQ) due to the intervention and the incremental cost-effectiveness ratio (ICER; ΔC/ΔQ) were calculated. The threshold willingness to pay per QALY gained (λ) was taken as gross domestic product (GDP) per capita ($US 4,848),[27] and a threshold value of three times GDP per capita was considered in a scenario analysis. The latter threshold essentially corresponds to WHO criteria for a cost-effective intervention and the former to a highly cost-effective intervention.[53] Interventions with ICERs below the chosen WTP threshold are, by definition, cost-effective. Probabilistic sensitivity analyses (PSA) were undertaken to capture the effects of parameter using 10,000 Monte Carlo iterations where parameters were sampled from specified distributions. (Table 5.2) Simulation results were used to calculate the monetary net benefit (MNB), which is defined as λ*Q-C, for each level of achieved hand hygiene compliance and the distribution of incremental monetary net benefits (IMNB) for each comparison (λ*ΔQ-ΔC). In addition, the maximum level of investment in the intervention at which it would still be cost-effective was calculated as monetary incremental benefits (λ*ΔQ) plus the saving in treatment costs from averted infections.

A series of hypothetical scenarios with different assumptions about the transmissibility and prevalence of MRSA colonisation at admission were considered in order to generalize the findings. The ward reproduction number (R_A), the expected number of MRSA cross transmissions resulting from a single colonised patient during a single ward stay assuming all other patients on the ward are susceptible, was varied between 0·5 and 5 while prevalence of MRSA colonization on ICU admission was varied between 0·01 and 0·15. Changes in costs and health outcomes under different baseline compliance and improvement levels were calculated and combined to evaluate the cost-effectiveness of such interventions in terms of the IMNB. We also determined the maximum level of investment at which the intervention would still be cost-effective, the prevalence reduction and final prevalence in all scenarios.

5.4 Results

Under base case assumptions (with a pre-intervention hand hygiene compliance of 10%) a multimodal hand hygiene intervention (WHO-5) is highly likely to be cost-effective compared with the standard practice in both PICU and adult ICU settings if it increases hand hygiene compliance to 20% or more. (Table 5.2) Conversely, if the baseline compliance is 40%, the expected IMNB is likely to be negative, indicating the intervention is unlikely to be cost-effective solely as a result of reducing MRSA-BSIs. (Figure 5.2)

Risk of death due to MRSA-BSI in our study hospital was estimated to be between two and three fold higher than in high-income countries.[32,54] However, a scenario analysis showed that the intervention is still highly cost-effective if a mortality risk estimated from high-income settings is used instead. (Table 5.3) When the WTP threshold was three times GDP per capita ($US 14,545), under base case assumptions (with a pre-intervention hand hygiene compliance of 10% and post-intervention compliance of 40%), the IMNBs were $US 14,472 for PICU and $US 20,704 for adult ICU and in case of 40% compliance baseline, the IMNBs were $US 1,256 and $US 1,802, respectively.

In hypothetical scenario analyses, the hand hygiene intervention was found to be cost-effective in most scenarios, especially when there was high transmissibility and a high prevalence of MRSA colonized admission. (Figure 5.3) In the situations where the transmissibility is low (R_A=0·5), prevalence of MRSA colonization at admission is 5%, and baseline compliance is not greater than 30% in the PICU and 20% in the adult ICU, the intervention is always cost-effective even with only a 10% compliance improvement using the cost estimates in Table 5.1. When the baseline compliance is not greater than 20%, the intervention will always be cost-effective if the intervention cost per year is less than US$ 1,557 in the PICU and $US 888 in the adult ICU providing the intervention increased compliance by 10% or more.

Table 5.1: Deterministic transmission dynamic model parameters.

Parameters	Paediatric ICU			Adult ICU			Distribution	Source
	Mean	2·5th Percentile	97·5th Percentile	Mean	2·5th Percentile	97·5th Percentile		
Transmission dynamic model								
Proportion of admissions colonised with MRSA	0·063	0·029	0·108	0·087	0·038	0·139	beta	33
HCW-Patient transmission probability per contact	0·0065	0·0028	0·0105	0·0113	0·0061	0·0192	beta	25, 33
Patient-HCW transmission probability per contact	0·132	0·078	0·194	0·132	0·078	0·194	beta	25
Patient/HCW contacts per day (per patient)	8	-	-	8	-	-		Direct observation
HCW/Patient contacts per day (per HCW)	14	-	-	9	-	-		Direct observation
Infection rate from colonized (day^{-1})	0·0013	0·0007	0·0021	0·0013	0·0008	0·0020	gamma	Database
Probability of attributable death given MRSA-BSI	0·439	0·338	0·5390	0·439	0·338	0·539	beta	32
Removal rate of uncolonised patient (1/LOS) (day^{-1})	0·164	-	-	0·173	-	-		Database
Removal rate of colonised patients (1/LOS) (day^{-1})	0·164	-	-	0·173	-	-		Database
Number of beds	7	-	-	10	-	-		Direct observation
Number of HCWs (per shift)	4	-	-	9	-	-		Direct observation
Hand hygiene compliance (baseline)	0·1	-	-	0·1	-	-		Direct observation
Economic model								
Cost ($US, 2014)								
Hand hygiene intervention (per ward per year)	680·21	283·44	1076·98	724·95	307·19	1142·72	gamma	35, 36, 46
ICU bed day (days)	47·6	15·4	72·3	47·6	15·4	72·3	gamma	Database, 44
General ward bed day (days)	5·5	2·1	10·6	5·5	2·1	10·6	gamma	Database, 44
Treatment MRSA-BSI (per case)	143·8	48·2	267·3	215·7	96·3	400·9	gamma	45, 46
Excess length of stay due to MRSA-BSI (days per case)	2·2	-0·1	4·6	1·4	-1·3	4·1	normal	Database
Utility post-ICU (scale 0-1)	0·72	0·56	0·88	0·72	0·56	0·88	beta	48-51
QALYs gained per death averted (3% discounted)	17·95	10·48	24·67	10·31	7·92	12·76	gamma	Database, 47

Table 5.2: Results from economic evaluation of hand hygiene promotion in paediatric and adult ICUs (2014).

	MRSA-BSI avoided	ICU bed days released	Incremental Cost[a]	QALYs gained	ICER	Average monetary net benefits[b] (95% CI)			Average IMNB[b] (95% CI)		
Paediatric ICU											
Baseline (HHC 10%)						30,494,582	20,088,985	43,197,023			
HHC 20%	0·088	0·197	$ 640·36	0·73	874·56	30,497,252	20,090,217	43,200,550	2,670·41	142·12	7,652·58
HHC 40%	0·125	0·280	$ 623·73	1·04	600·99	30,498,651	20,090,878	43,202,378	4,068·45	515·20	11,010·90
HHC 80%	0·141	0·315	$ 616·51	1·17	526·73	30,499,257	20,091,154	43,203,201	4,674·65	700·17	12,405·28
HHC 40% vs HHC 80%	0·016	0·036	$ 673·00	0·13	5,074·55	30,499,257	20,091,154	43,203,201	-73·10	-723·99	861·37
Adult ICU											
Baseline (HHC 10%)						21,513,979	16,832,780	26,789,135			
HHC 20%	0·216	0·303	$ 659·29	1·05	626·61	21,517,994	16,836,229	26,798,861	4,015·61	963·54	9,114·78
HHC 40%	0·303	0·424	$ 633·41	1·47	431·79	21,519,897	16,838,279	26,801,443	5,918·43	1,688·61	13,072·50
HHC 80%	0·340	0·475	$ 622·61	1·64	379·66	21,520,701	16,839,232	26,801,808	6,722·64	1,982·44	14,731·19
HHC 40% vs HHC 80%	0·037	0·051	$ 714·16	0·17	4,128·75	21,520,701	16,839,232	26,801,808	77·01	-634·18	1,038·47

[a]per ward per year, [b]Monetary net benefits reported per ward (total admission) assuming a willingness to pay for a QALY of $US 4,840 (160,000 Thai baht, exchange rate; $US 1 = 33 Thai baht).
MRSA-BSI, methicillin-resistant *Staphylococcus aureus* bloodstream infection; ICU, intensive care unit; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio; IMNB, incremental monetary net benefit; HHC, hand hygiene compliance.

Table 5.3: Scenario analysis for base case (Baseline HHC 10% vs HHC 40%)

	Incremental outcomes		ICER [a]	Average IMNB [a b]			Maximum investment [b]		
	Costs ($US)	QALYs[a]		Mean	95% Confidence Interval		Mean	95% Confidence Interval	
Paediatric ICU, per ward, per year (2014)									
Base case	624	1·04	601	4,068	515	11,011	4,748	1,240	11,683
Cost of hand hygiene intervention (5 folds increase from $US 680 to $US 3,401)	3,345	1·04	3,216	1,328	-2,908	8,632	4,736	1,228	11,678
QALY gained amongst post-ICU patients (Lower bound = 10·48 instead of 17·95)	624	0·61	1,029	2,138	36	6,113	2,819	771	6,799
No utility weights (LE = 24·93 instead of 17·95)	624	1·44	433	5,982	1,116	15,402	6,663	1,820	16,076
Low attributable mortality due to MRSA-BSI (at 20%)	624	0·47	1,319	1,526	-112	4,542	2,204	633	5,193
High attributable mortality due to MRSA -BSI (at 50%)	624	1·18	527	4,781	847	12,210	5,463	1,571	12,909
Include additional stay in general wards given BSI (12·8 days)[54]	615	1·04	592	4,134	622	11,020	4,810	1,337	11,682
Adult ICU, per ward, per year (2014)									
Base case	633	1·47	432	5,918	1,689	13,072	6,632	2,411	13,604
Cost of intervention (5 folds increase from $US 725 to $US 3,625)	3,533	1·47	2,409	3,004	-1,867	10,221	6,635	2,431	13,642
QALY gained amongst post-ICU patients (Lower bound = 7·92 instead of 10·31)	633	1·13	562	4,468	1,199	9,729	5,190	1,955	10,453
No utility weights (LE = 14·32 instead of 10·31)	633	2·04	311	8,592	2,766	17,999	9,316	3,493	18,718
Low attributable mortality due to MRSA-BSI (at 20%)	633	0·67	947	2,344	355	5,454	3,074	1,160	6,135
High attributable mortality due to MRSA -BSI (at 50%)	633	1·67	379	6,822	2,103	14,279	7,546	2,853	15,087
Include additional stay in general wards given BSI (12·8 days)[54]	610	1·47	415	5,942	1,665	13,149	6,669	2,408	13,863

[a] QALYs, quality adjusted life years; ICER, incremental cost effectiveness ratio; IMNB, incremental monetary net benefit.
[b] Incremental monetary net benefits and maximum investment at which the intervention would still be cost-effective assuming a willingness to pay for a QALY of $US 4,848 (160,000 Thai baht, exchange rate; $US 1 = 33 Thai baht).

Figure 5.1: Model structure diagram.

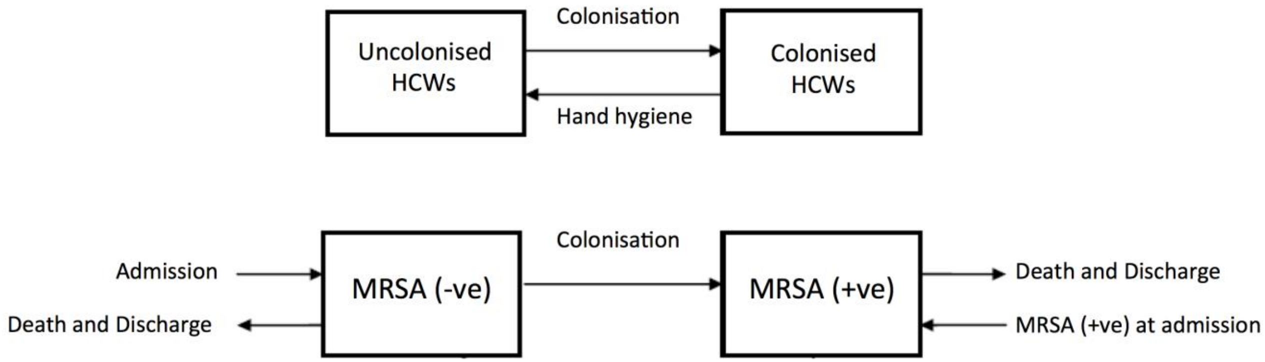
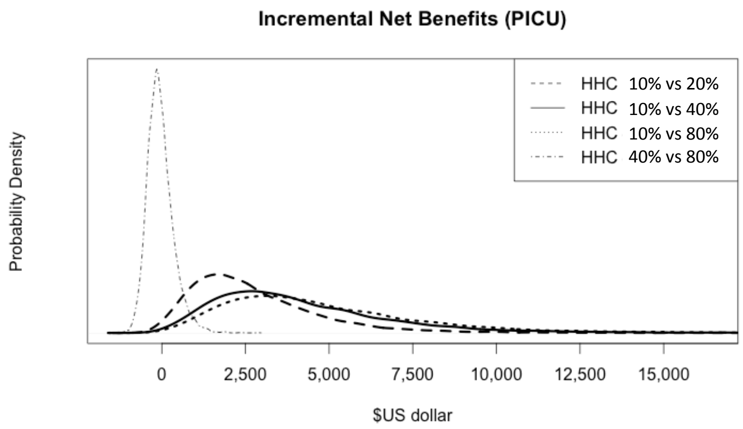


Figure 5.2: Incremental net monetary benefits.



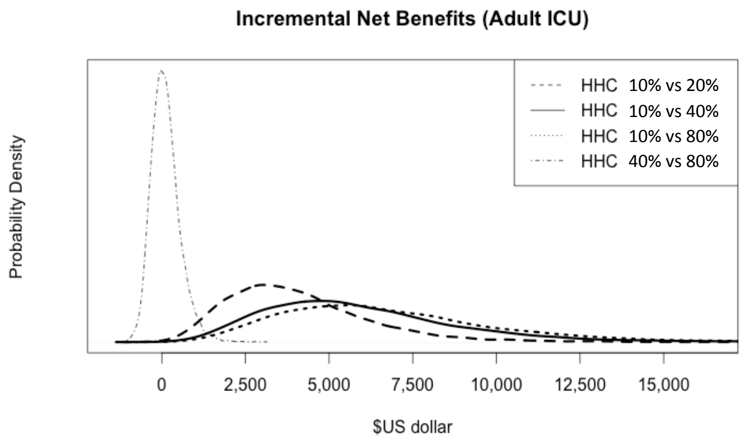


Figure 5.3: Results from hypothetical scenarios analyses for PICU (left) and adult ICU (right) at WTP per QALY gained of $US 4,848. Incremental monetary net benefit (IMNB) (top); blue for IMNB>0 and red for IMNB<0. Maximum intervention cost at which the intervention would still be cost-effective (bottom).

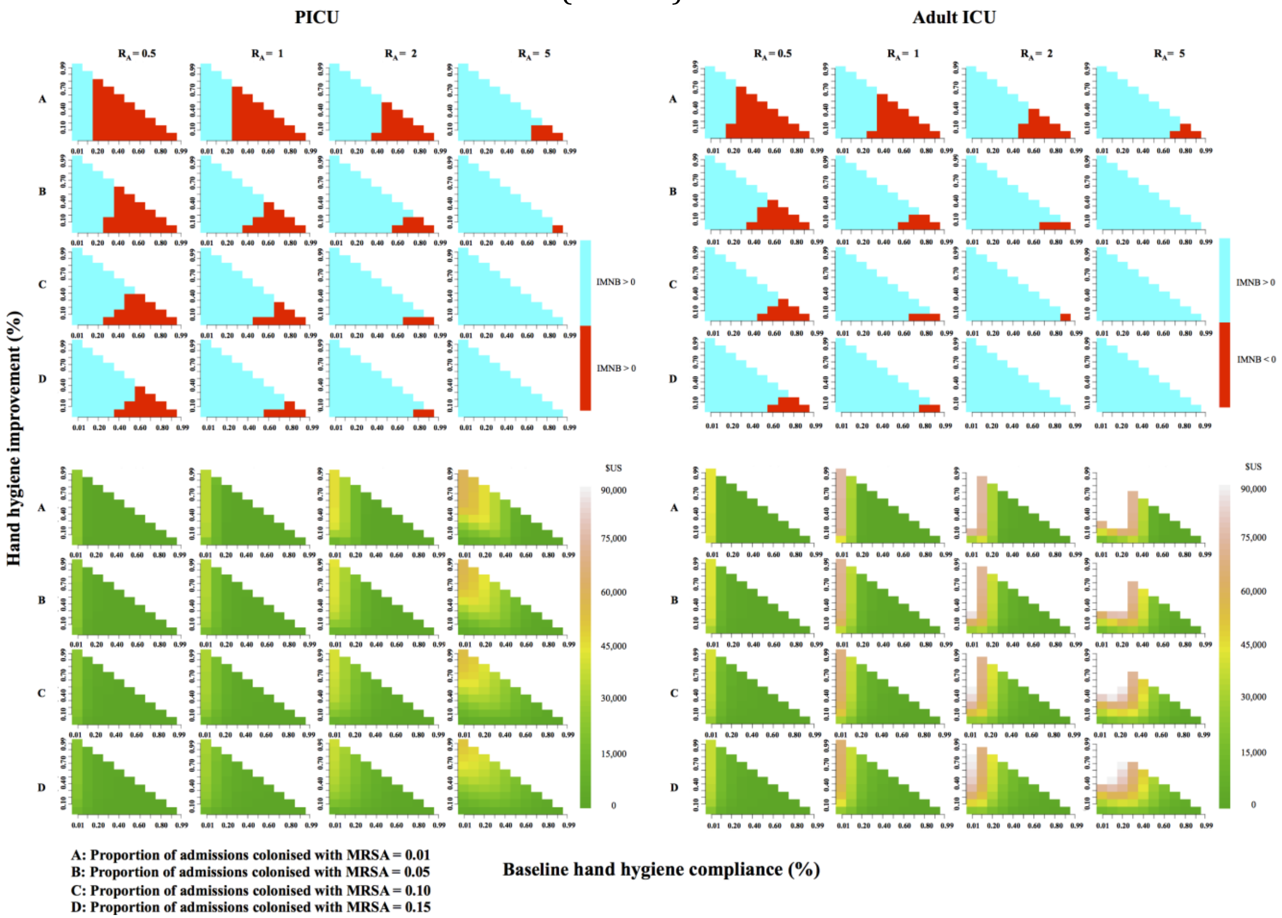
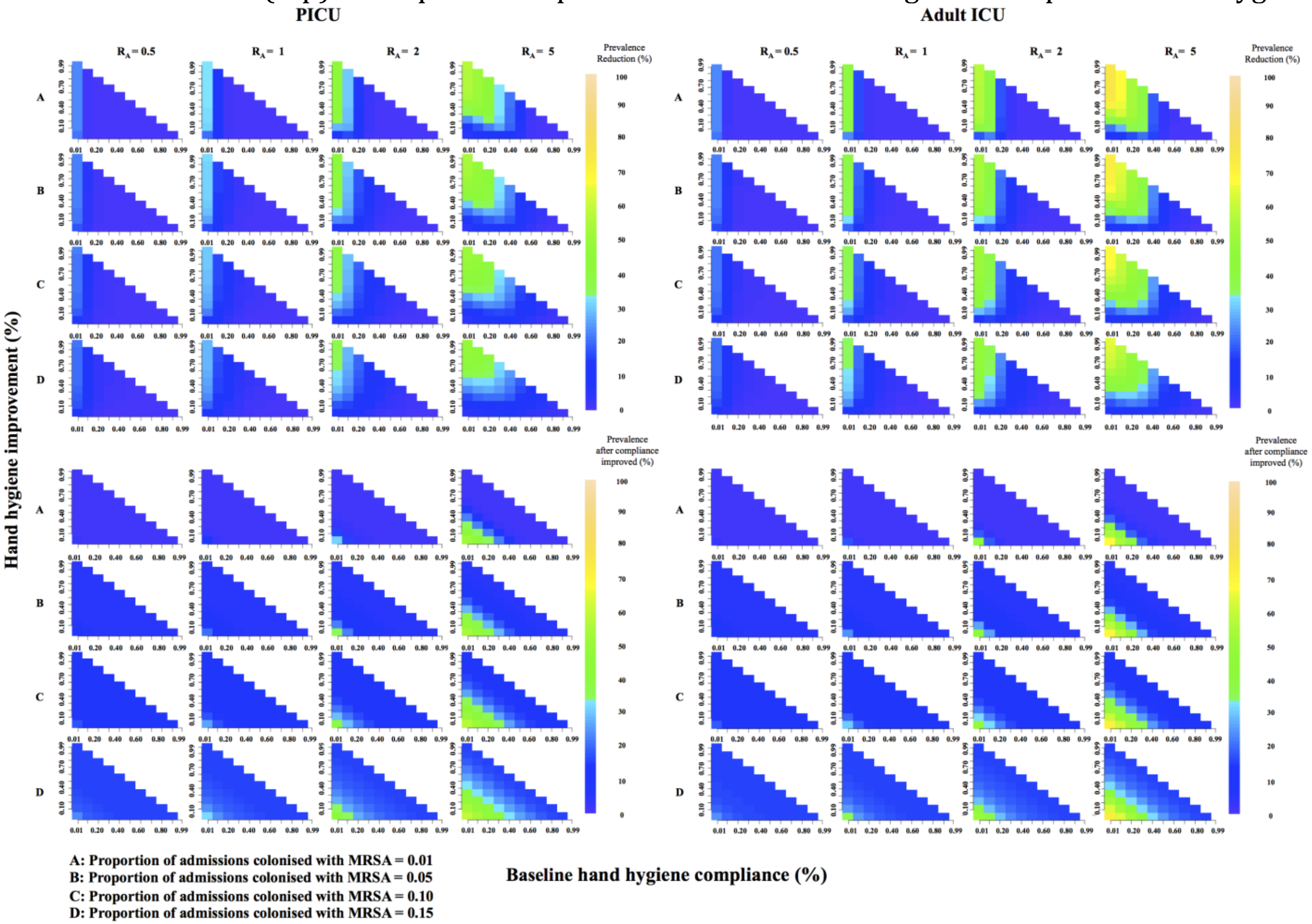


Figure 5.4: Results from hypothetical scenarios analyses for PICU (left) and adult ICU (right). Prevalence reduction of MRSA carriage due to intervention (top) and equilibrium prevalence of MRSA carriage after improved hand hygiene compliance (bottom).



5.5 Discussion

Hand hygiene promotion using the WHO's five moments campaign is likely to be highly cost-effective for ICU settings in Thailand where baseline compliance is low (≤20%) solely as a result of preventing MRSA-BSI. Factors that tended to make the intervention more cost-effective were low baseline compliance, high prevalence of colonization at admission and high transmission. With higher baseline compliance, the intervention may often still be highly cost-effective as a result of reduced MRSA-BSI alone if rates of MRSA carriage on ICU admission or ICU transmission are sufficiently high.

Because we ignored impacts of the intervention on other types of HAI (other MRSA infections and infections with other pathogens) our analysis is highly conservative and almost certainly considerably underestimates health benefits. In particular MRSA-BSIs represent only 5·1% of hospital-acquired BSIs in North-east Thailand, Gram-negatives accounting for 67·6%.[55] While the evidence linking increased hygiene with reduced infection rates is less compelling for Gram-negative organisms than it is for MRSA, there are credible reports that such an association exists.[56,57] Some of the strongest evidence is found with multi-drug-resistant *Acinetobacter spp*, where a segmented regression analysis found that a hand hygiene intervention was associated with a substantial change in incidence of infections with extensively drug-resistant *Acinetobacter spp.* in Taiwan.[20] *Acinetobacter spp.* has also been reported to be a frequent contaminant of the hands of HCWs in endemic settings in SE Asia, strengthening the evidence for a causal link between increased hand hygiene and reduced infections.[58] Since *Acinetobacter spp*. are the largest single cause of hospital-acquired BSI in North-east Thailand,[55] if infections with these organisms can be reduced substantially by improved hand hygiene the implications for our analysis could be substantial. While our work provides an analytical framework for such an evaluation, better data on the epidemiology of *Acinetobacter spp.* and the effects of hand hygiene are needed to inform it.

To the best of our knowledge, our study is the first economic evaluation of a hand hygiene intervention in a developing country and the first in any setting to make use of a dynamic model.[19-22] In previous economic evaluations in high-income countries, Pittet et al. (in Switzerland), and Chen et al. (in Taiwan) used data from observational studies to estimate reductions in infections due to hand hygiene interventions. Pittet et al. concluded that if only 1% of the observed reduction was due to the intervention it would have been cost saving. Chen et al. also concluded that their intervention was likely to be cost saving (assuming that all changes in infection rates could be attributed to the intervention). Huis et al. used data from a cluster-randomized trail of a hand hygiene intervention to inform a cost-effectiveness analysis, assuming a linear relationship between hand hygiene compliance and reduced infections (with a 1% increase in hand hygiene assumed to cause either a 0·3% or 0·15% fall in HAI rates). Under both assumptions the intervention was found likely to be cost-effective if the willingness to pay for a 1% reduction in the HAI rate was about $US 6,000. A study by the National Patient Safety Association in the United Kingdom also concluded that hand hygiene interventions were likely to be cost saving even if the reduction in rates of hospital acquired infection were as low as 0·1%. As in our study, this report explicitly calculated QALY gains (about 90% of which were due to reduced HAI mortality). However, unlike the other studies, staff time was not accounted for when costing the intervention.

Direct comparison of these findings with ours is difficult for three reasons. First, only one of the previous studies quantified benefits in terms of final health outcomes (QALYs).[19] Second, bed-day costs are much greater in high-income settings and account for most of the costs associated with HAIs. In developing country settings costs of antibiotics to treat infections are likely to be the dominant cost which overall will be much lower. Third, there are important differences in aims and methodology. We focused entirely on MRSA-BSI (where we have good data and strong evidence that it can be reduced by hand hygiene) reasoning that if the intervention is cost-effective for this outcome alone then it should certainly be cost-effective overall. We also aimed to make use of important methodological advances, accounting for the expected non-linear association between hand hygiene compliance and infection rates using a mathematical model,[17,29,59] avoiding time-dependent biases when estimating increased length of stay,[41,60,61] valuing bed-days based on opportunity cost rather than using an accounting approach,[43,44] and estimating life years gained by preventing mortality using data from a large linked-database study.[47] These approaches will tend to lead to lower estimates of cost-savings and, combined with the much lower bed-day costs, helps explain why our study estimated the cost per infection to be a few hundred dollars, while studies in high income countries estimated it to be a few thousand.[20-22]

Use of the transmission dynamic model also allowed us to generalize the analysis to scenarios with different levels of transmissibility and admission prevalence. A particular strength of our study is that we were able to make use of extensive local data including direct observations of hand hygiene compliance, historical infection surveillance data from the hospital, and prospectively collected MRSA carriage data to inform this model.

Our study has a number of limitations, the most important of which is that data are not yet available that allow us to include other pathogens in the dynamic model. A further limitation is that we evaluated the intervention over only a one-year post-intervention period. It is unclear how well improvements in hand hygiene will be sustained over a longer time frame. If substantial improvements in hand hygiene persist beyond this period we will again be likely to have substantially underestimated the health benefits of the intervention.

5.6 Conclusion

In conclusion, effective multimodal hand hygiene intervention are likely to be cost-effective in ICU settings in typical middle-income countries as a result of reduced incidence of MRSA-BSI alone under a wide range of circumstances. When this is not the case the cost-effectiveness of interventions to further improve hand hygiene will depend on the impact on other infections and other pathogens. Further work is needed to quantify this.

Panel: Research in context

Systematic review

We searched for articles describing economic evaluations of hand hygiene interventions. We combined manual searches with a search on PubMed using search terms "hand hygiene" OR "hand washing" OR "handwashing" AND "cost" AND "hospital" up to January 2015. There was no systematic review on this topic but we found four studies describing economic evaluations of hand hygiene interventions.[19-22] All concluded that the hand hygiene interventions they evaluated are likely to be cost saving. Three of these studies did not consider the intervention benefits in terms of health outcomes, such as deaths averted or quality adjusted life years gained, but focused on cost per infection averted or cost-benefit from investment in promoting hand hygiene. However, all of these were conducted in high-income settings. Little is known about the value for money of such interventions in resource-limited settings.

Interpretation

To our knowledge this is the first study combining a transmission dynamic model with an economic evaluation to assess cost-effectiveness of hand hygiene interventions in a hospital setting. We found that, provided baseline hand hygiene compliance is sufficiently low, in both paediatric and adult ICUs in a typical middle-income country implementing hand hygiene promotion interventions is likely to be cost-effective (but not cost-saving) solely as a result of prevented bloodstream infections with MRSA. This finding is likely to underestimate the benefits of hand hygiene interventions as there may be large benefits in preventing other types of infection, particularly with Gram-negative organisms, which we did not account for. Factors that made hand hygiene interventions more likely to be cost-effective were lower pre-intervention compliance, higher transmissibility, and higher carriage prevalence on admission. We suggest these findings should help encourage decision-makers to ensure more rational levels of investment in hand hygiene interventions in hospitals in developing countries.

Competing interests

The authors declare that they have no competing interests.

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Chapter 6: General Discussion and Conclusions

Chapters 3 - 5 provided the main findings, as well as discussions and conclusions for each study in turn. This chapter summarises the key findings, the strengths and limitations of this thesis and the overall conclusions. Future research recommendations are also considered.

6.1 Substantive discussion

Unlike other infection control programmes, hand hygiene promotion is relatively simple to implement and is not resource intensive. This makes it well-suited to resource-limited settings, though in practice investment in this intervention appears to have been quite limited in developing countries. This thesis evaluated the value for money of hand hygiene promotion amongst healthcare workers in intensive care units (ICUs) in Thailand and other resource-limited settings. Because MRSA-BSI is the best-studied infection and there is strong evidence that this can be reduced by hand hygiene, the analysis focused on this outcome when considering health benefits. This is the first economic evaluation of such an intervention conducted in a middle-income country and the first anywhere to make use of a transmission dynamic model.

This research required several connected components. First, in an attempt to quantify life years lost due to mortality arising from HAIs in ICU patients, life expectancy after ICU discharge was considered in Chapter 4. Deaths caused by HAIs are likely to account for a large proportion of the total health burden due to infection. Hand hygiene interventions could potentially reduce this by decreasing HAI rate and consequently preventing death. Health benefits were measured as the number of life years gained if the intervention could prevent one death in an ICU patient. To do this, a retrospective cohort study was performed using hospital data from North-east Thailand linked with the national death registry to assess patient survival time after ICU discharge. These patient-level data were obtained from the hospital electronic database while the national death registry data were obtained from the Bureau of Policy and Strategy, Ministry of Public Health, Thailand. Information in patients' charts summarised by doctors was recorded in the computer by the medical record department. Internal quality assurance was performed by routine random checks between database and patient charts for accuracy and consistency. Moreover, external audit by the Ministry of Public Health, Thailand, is routinely performed. The results from this study indicated that post-ICU patients had 27.4% lower life expectancy than the general population (age and sex matched). This estimate should also aid policy makers considering the potential health gains and cost-effectiveness of other potential investments for preventing ICU mortality. It was also found that the five-year mortality of post-ICU patients in the Thai population is slightly higher than found in other studies most of which were conducted in high-income settings (35.7% compared with a range from 17.9 to 33.5%).

The effectiveness of different hand hygiene promotion interventions, including the multimodal intervention (WHO-5) recommended by the WHO, was considered in Chapter 3. A systematic review and evidence synthesis was performed to explore all available high quality information on effectiveness of the hand hygiene intervention (for increasing hand hygiene). Costs incurred by the interventions were also summarised. Previous reviews had found only four studies using appropriate study designs, making reliable conclusions impossible and severely limiting the potential for economic evaluation.[25-28] This review made use of previously described search strategies and found 36 high quality studies according to the EPOC criteria, 32 of which were published after 2009 and therefore not included in previous reviews.[90] In total there were six RCTs, 26 interrupted time series and an additional four quasi-experimental studies (only four of these had been included in the previous Cochrane review).[25] However, only two of the RCTs and 11 of ITS studies were eligible for quantitative synthesis. Different combinations of hand hygiene intervention components were compared in different studies. Network meta-analysis accounting for both direct and indirect effects was carried out to quantify the effect size amongst different strategies where direct head to head studies are not available.[139, 140] This evidence synthesis framework is increasingly used in health technology assessment in many different areas.[141-143] Results indicated that the WHO-5 hand hygiene campaign is effective at increasing hand hygiene compliance in healthcare workers. In addition, the evidence also showed that when adding extra components including goal setting, reward incentives, and accountability, compliance is further improved. However, it was not possible to quantify the relationship between improvement in compliance and change in infection rates or mortality. In addition, it was found that information about resources used for the interventions was largely lacking. Only a few studies collected and reported such resource-use properly and, therefore, conclusions about the relationship between level of investment and improvement in compliance could not be made.

In chapter 5, costs and effectiveness of hand hygiene intervention were evaluated using a transmission dynamic model and economic analysis. To account for the dynamics of nosocomial organisms and the impact of hand hygiene interventions in hospital wards, a host-vector model was developed (where HCWs correspond to the vector) and parameterized using data from two ICU wards, paediatric and adult ICUs. MRSA carriage data from a previous study conducted at the same hospital and other useful parameters from the same source were used to simulate the situation in those settings. Unlike a static model, a dynamic mechanistic model aims to capture the interaction between patients and HCWs to reflect mechanisms of cross contamination.[38] In the model the force of infection (the rate at which a susceptible patient becomes infected) was dependent on the level of contamination on HCWs' hands which in turn depended on the level of colonization pressure (point prevalence of colonization amongst patients) at the wards.[38, 130, 144] Increasing hand hygiene compliance would tend to interrupt this chain.[20, 23, 145] As a result, a relationship between the level of hand hygiene compliance and the infection rates could be derived from the model. A non-linear relationship was found between the increased compliance and reduction of infection rate. Results indicated that at low pre-intervention hand hygiene compliance the intervention will be very effective but that there will be diminishing marginal returns as the baseline hand hygiene compliance increases. For example, in the adult ICU, when the hand hygiene increases from 10% to 20%, the number of

MRSA-BSI avoided is 0.59 cases per 10,000 bed-day while when the compliance increases from 20% to 40% and 40% to 80%, 0.23 and 0.10 cases of MRSA-BSI per 10,000 bed-day are avoided, respectively. The benefits of hand hygiene for reducing infections also increased with higher transmissibility and higher prevalence of colonization of patients at admission. One of the benefits of using such a model-based analysis is that it allows such scenario analyses.

The main outputs from the transmission dynamic model, including the number of infections and deaths averted due to the hand hygiene intervention were used in the decision analytic model. Cost-utility analysis was performed using economic data, evidence on effectiveness and health benefits from Chapter 3 and Chapter 4 as parameter inputs. As there was a wide range of uncertainty in the effectiveness of the intervention, outcomes were compared for different levels of achieved hand hygiene compliance with a fixed observed baseline compliance of 10% (based on ward observations). The findings showed that a hand hygiene intervention is likely to be cost-effective in ICU settings in Thailand where the baseline hand hygiene compliance is low (less than 20%) solely as a result of preventing MRSA-BSI.[93, 146] In the hypothetical scenario analyses, the results indicated that the intervention is very important in settings where the transmission is high (with high colonization pressure) as an improvement in compliance provides large benefits. However, as the baseline hand hygiene increases, the likelihood of the hand hygiene intervention being cost-effective decreases.

Although performing expected value of perfect information (EVPI) analysis could be very useful to explore the potential benefit of collecting more information in order to reduce uncertainty, results from the probabilistic sensitivity analysis (PSA) showed a low level of uncertainty about whether the intervention was cost-effective when the baseline compliance was at 10%. This suggests that funding for further research on effectiveness of hand hygiene promotion should focus on areas other than the immediate effectiveness of hand hygiene interventions, for example by considering how improvements in hand hygiene could be best sustained.

In the model, the improved hand hygiene compliance was assumed to be constant over one year of the intervention period. This analysis did not incorporate uncertainty of the improved hand hygiene compliance in the PSA or enable the improved compliance to change over time in the dynamic model. However, deterministic analyses with lower and upper values from the confidence interval of the odds ratios when implementing WHO-5 obtained from Chapter 3 was performed and showed robust results.

If the actual ceiling threshold is less than the figure commonly used in Thailand (~ 1 gross domestic product (GDP) per capita) by 50% or approximately $US 2,500 per QALY gained, the costs per QALY gained would still be far below the threshold when the compliance baseline is 10%.[147] However, with a fixed healthcare budget, adopting an intervention that would be classed as cost-effective according to the standard ceiling threshold might still cause an opportunity loss if the healthcare budget is not sufficient to fund interventions with lower cost per QALY gained. In general, therefore, interventions with lower cost per QALY gain should be prioritised. The work in this thesis has shown that under plausible assumptions, the cost per QALY gained with a hand hygiene promotion intervention is likely to be far below the ceiling threshold suggesting that it should be highly prioritised, at least in ICU settings in Thailand.

6.2 Implications of the research findings

These findings provide the first evidence that investments in hand hygiene campaigns in hospitals in middle-income countries are likely to represent good value for money. The also call attention for the need for appropriately resourced national campaigns in developing countries. Because only the health benefits obtained by preventing MRSA-BSI in ICU wards were considered, the analysis is likely to be very conservative: real health benefits are likely to be greater than estimated. The findings suggest that policy decision makers in Thailand and other countries where hand hygiene compliance is low should consider prioritising patient safety concerns by investing more resources in evidence-based hand hygiene promotion interventions. There is a high chance this would lead to substantial improvements in hand hygiene compliance and, as a result, HAI rate reduction.

In Thailand, were this intervention to be implemented at all ICU wards across the country, the total budget was estimated to be $US 336,631 with a minimum of 727.97 QALYs gained annually. This calculation assumes a total of 5,080 ICU beds owned by the government across the country with 80% of these for adults.[148] This figure is relevant to the Ministry of Public Health, who are responsible for most healthcare services for the population. As a centralised healthcare financing system, the government could consider efficiently allocating the budget to improve the national healthcare service.

The research findings are also relevant for other tertiary referral or teaching hospitals providing intensive care services in Thailand.[93, 146] Local hospital management could encourage their HCWs to improve compliance by adding goal-setting, reward incentives, accountability strategies in additional to WHO-5 as the evidence from meta-analysis showed further improvement. This could be initially focused on ICUs where patients are more likely to acquire HAI and more likely to die as a result. Hospital-wide programs could then be performed at a later stage.

Finally, the findings are likely to generalize to other low-middle income countries. As resources in these settings are limited, other interventions could be considered as additional options complementary to well-maintained hand hygiene compliance.

There are a number of difficulties in determining the implications of these research findings for non-ICU settings. In most cases, the burden of HAI is lower in non-ICU wards as patients are usually less severely ill and therefore less susceptible to HAI. This suggests that health benefits obtained from the improved compliance would be lower than that seen in ICU settings. However, the cost of intervention would also be lower as staff to patient ratios are lower in non-ICU settings and therefore proportionately less staff time would be spent for hand hygiene training, promotion and implementation activities.

Conclusions about the value for money of this intervention in non-ICU settings would also require setting-specific data about transmission dynamics and other parameters to be used in the analysis.

6.3 Limitations of this thesis

6.3.1 Limited to ICU settings

The scope of the analysis is limited to ICU settings. Due to the fact that all available carriage data came from ICU settings, the analysis could not be extended to cover general ward settings without a large amount of guesswork. Although implementing the intervention at non-ICU settings would also obtain benefits, the magnitude is still unknown. Such information and more complex transmission models capturing patients' movement between wards would allow a hospital wide analysis. This would provide useful information for policy decision makers.[134, 149]

6.3.2 Failure to capture all costs and benefits

In addition, the analysis did not capture all costs and benefits arising from the HAIs. Other cost components such as extra laboratory tests and healthcare services apart from the treatment and bed-day costs as well as other possible indirect costs including patients' productivity loss were neglected. Further analysis would be required to justify this. A consequence of this is that the results may underestimate the magnitude of cost reduction due to the decreased HAI cases. In addition, the impacts of the intervention on other types of HAI (other MRSA infection and infections with other pathogens) were ignored. Because of both of these factors, this analysis is highly conservative and likely to considerably underestimate the benefits of the interventions.

6.3.3 Using non-local data

A number of parameters in this model-based evaluation were not derived from local data. Resource use incurred by the intervention and utility weights amongst post-ICU patients were derived from the literature. These parameters may therefore be different from those directly collected from local data due to differences in the settings. However, scenario analyses were performed to investigate uncertainty of these parameters. It was found that the results were robust; even the cost of the intervention increased five-fold or if utility weights at the low value of the plausible range were used, the general conclusions did not change.

6.3.4 Short time horizon

A further limitation is that the intervention was evaluated over only a one-year time horizon. It is unclear how well improvements in hand-hygiene will be sustained over a longer timeframe. If substantial improvements in hand hygiene persist beyond this period the analysis will again be likely to have substantially underestimated the health benefits of the intervention.

6.4 Strengths of this thesis

The evidence synthesis of hand hygiene interventions overcame key limitations of previous reviews. [25-28] First, a much greater number of relatively high quality studies were found when compared with reviews including only papers published before 2009. Also, by using a network-meta analysis within a Bayesian framework amongst interrupted time series designs, it was possible to estimate the pooled effect size of different interventions even when direct head-to-head comparisons were absent. This made it possible to quantify relative efficacy of a series of different intervention strategies with different baseline interventions.[140] These findings are useful in determination of effectiveness of different hand hygiene promotion interventions.

This thesis also contains one of the first attempts to estimate long-term post-ICU survival conducted in a developing country context. It makes use of data in routinely collected databases combining hospital patient-level data and the national death registry. These findings are not only valuable for measuring the final health benefits from an infection control intervention but are also likely to be useful for quantifying health benefits from other quality improvement programs in hospital settings that could prevent unnecessary death in the ICU.

A particular strength of this research is that it made use of extensive local data including direct observations of hand hygiene compliance, historical infection surveillance data from the hospital, and prospectively collected MRSA carriage data to inform the model. Use of the transmission dynamic model also made it possible to generalize the analysis to scenarios with different levels of transmissibility and admission prevalence.

Importantly, this study is the first economic evaluation of a hand hygiene intervention conducted in a resource-limited setting where improving hand hygiene is most needed. Previous studies were all conducted in high-income settings.[40-43] In addition, this study contains a number of methodological advances. For example, estimates of the excess LOS were made using an approach that avoids time dependent bias;[69, 71] values of bed days were adjusted to reflect opportunity cost (not based on the accounting approach alone); [72] and use of the dynamic model made it possible to account for the expected non-linear association between hand hygiene compliance and infection rates.[129, 130] The findings should not only be relevant for Thai settings, but are also likely to generalize to other similar settings.

6.5 Future research directions

The limitations arising from this work presented in Section 6.3 are evident areas for further examination. Parameters that derived from literature could be prospectively collected from local settings. It is not uncommon in economic evaluation to adopt some parameters from non-local settings. However, setting-specific estimates would be preferable. Two of the potential parameters are the cost of hand hygiene intervention and the economic value of WTP per bed day by health care providers. A survey of resource use, HCWs' time and materials, alongside a well-design intervention trial could be performed to obtain the cost of hand hygiene intervention while an interview session asking hospital management for their WTP for an unoccupied bed-day would therefore be of value.[11]

Collecting more data on other HAIs should also be ranked as a high priority. This economic evaluation represents a very conservative analysis as it accounted for the benefits of preventing MRSA-BSI alone. More information on incidence of other types of MRSA infections and other pathogens will give more realistic estimate of the value of hand hygiene interventions. In the Thai context, potential future research could prioritise the prospective collection of *Acinetobacter spp.* data as this has been recently found to be the largest single cause of hospital-acquired BSI in North-east Thailand.[150] However, better information on the effects of hand hygiene on the epidemiology of *Acinetobacter spp.* are also needed to inform such an analysis.

In addition, a well-structured surveillance system in hospital care would be of value. The poor quality of many reporting systems is an urgent issue in developing countries,[48] and is probably a cause of under-reporting of the incidence of HAI and therefore underestimating the burden of HAI. Closely monitoring the medical chart and making use of laboratory data could lead to better HAI case detection. An improved system with better data would not only enable more accurate estimates of the burden of HAI for the national healthcare monitoring system but would also will provide good information to accurately quantify the benefits of a particular infection control interventions.

An expanded dynamic model to include non-ICU settings should also be considered. Although this research showed hand hygiene interventions are likely to be cost-effective in ICU settings, this might not be the case in general wards. There might be several differences between these two settings and it is probable that general wards have a lower burden of disease due to HAIs than ICUs as patients tend to have better health and are less susceptible to nosocomial infection. However, more research in this area is required. In addition, carriage data of other pathogens is also needed and a more complex mathematical model capturing patients' ward movement would allow a more comprehensive analysis.

Other infection control interventions could also be considered as complementary measures. Interventions with relatively low resource intensivity such as ward cleaning, universal decolonization, and care bundles are areas that should be considered for prioritization for future cost-effectiveness analyses. High resource intensive interventions such as isolation precautions and screening and decolonization could be included in the later stage.

6.6 Conclusions

This thesis highlights the importance of hand hygiene promotion as follows.

Multimodal hand hygiene intervention (WHO-5) is effective at increasing hand hygiene compliance in healthcare workers. There is evidence that adding goal-setting, reward incentives and accountability strategies can lead to greater improvements. Reporting of resources required for such intervention remains inadequate.

Effective multimodal hand hygiene interventions are likely to be very cost-effective in ICU settings in typical middle-income countries as a result of reduced incidence of MRSA-BSI alone under a wide range of circumstances. When this is not the case the cost-effectiveness of interventions to further improve hand hygiene will depend on the impact on other infections and other pathogens. Further work is needed to quantify this.

This economic evaluation of hand hygiene promotion assessed under what circumstances these initiatives represent good value for money. However, when an acceptable and stable level of hand hygiene compliance has been achieved, other supplementary interventions including care bundles, ward cleaning, and screening and decolonization may be considered to complement the hand hygiene promotion. Such interventions represent important subjects for future research.

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Appendices

Appendix A: Chapter 3 Supplementary

Appendix A1: Electronic search strategy

Databases	Adapted from Gould et al.	Adapted from Huis et al.
MEDLINE	1 Handwashing/ 2 (hand antisepsis or handwash$ or hand wash$ or hand disinfection or hand hygiene or surgical scrub$).tw. 3 1 or 2 4 exp Hand/ 5 exp Sterilization/ 6 4 and 5 7 3 or 6 8 randomized controlled trial.pt. 9 controlled clinical trial.pt. 10 intervention studies/ 11 experiment$.tw. 12 (time adj series).tw. 13 (pre test or pretest or (posttest or post test)).tw. 14 random allocation/ 15 impact.tw. 16 intervention?.tw. 17 chang$.tw. 18 evaluation studies/ 19 evaluat$.tw. 20 effect?.tw. 21 comparative study/ 22 animal/ 23 human/ 24 22 not 23 25 or/8-21 26 25 not 24 27 7 and 26 28 limit 27 to yr="2009 -Current" 29 exp hospitals/ 30 hospital$.tw. 31 exp inpatients/ 32 inpatient$.tw. 33 exp health care/ 34 health care$.tw. 35 healthcare$.tw. 36 infirmary$.tw. 37 nosocomial$.tw. 38 intensive care unit$.tw. 39 ward$.tw. 40 OR/29-39 41 28 and 40	1 Randomized controlled trial/ 2 random$.tw. 3 experiment$.tw. 4 (time adj series).tw. 5 (pre test or pretest or post test or posttest).tw. 6 impact.tw. 7 intervention$.tw. 8 chang$.tw. 9 evaluat$.tw. 10 effect?.tw. 11 compar$.tw. 12 control$.tw. 13 or/1-12 14 limit 13 to humans 15 (hand washing or handwashing or hand hygiene) 16 14 and 15 17 limit 16 to yr="2009 - Current" 18 exp hospitals/ 19 hospital$.tw. 20 exp inpatients/ 21 inpatient$.tw. 22 exp health care/ 23 health care$.tw. 24 healthcare$.tw. 25 infirmary$.tw. 26 nosocomial$.tw. 27 intensive care unit$.tw. 28 ward$.tw. 29 OR/18-28 30 17 and 29 *EPOC Methodological filter Randomized Controlled Trial [publication type] OR Controlled Clinical Trial [publication type] OR Comparative Study OR Evaluation Studies OR 'comparative study' OR 'effects' OR 'effect' OR 'evaluations' OR 'evaluating' OR 'evaluation' OR 'evaluates' OR 'changing' OR 'changes' OR 'change' OR 'interventions' OR 'intervention' OR 'impact' OR 'random allocation' OR 'post test' OR 'posttest' OR 'pre test' OR 'pretest' OR 'time series' OR 'experimental' OR 'experiments' OR 'experiment' OR 'intervention studies' OR 'intervention study' OR 'controlled clinical trial' OR 'randomised controlled trial' OR 'randomized controlled trial'
EMBASE	1 Handwashing/ 2 (hand antisepsis or handwash$ or hand wash$ or hand disinfection or hand hygiene or surgical scrub$).tw. 3 1 or 2 4 exp Hand/ 5 exp Sterilization/	1 Randomized controlled trial/ 2 random$.tw. 3 experiment$.tw. 4 (time adj series).tw. 5 (pre test or pretest or post test or posttest).tw. 6 impact.tw.

	6 4 and 5 7 3 or 6 8 randomized controlled trial/ 9 randomi$.tw. 10 exp controlled clinical trial/ 11 controlled clinical trial$.tw. 12 intervention studies/ 13 experiment$.tw. 14 (time adj series).tw. 15 (pre test or pretest or (posttest or post test)).tw. 16 random allocation/ 17 impact.tw. 18 intervention?.tw. 19 chang$.tw. 20 evaluation studies/ 21 evaluat$.tw. 22 effect?.tw. 23 comparative study/ 24 animal/ 25 human/ 26 24 not 25 27 or/8-23 28 27 not 26 29 7 and 28 30 limit 29 to yr="2009 -Current" 31 exp hospitals/ 32 hospital$.tw. 33 exp hospital patient/ 34 inpatient$.tw. 35 exp health care/ 36 health care$.tw. 37 healthcare$.tw. 38 infirmary$.tw. 39 nosocomial$.tw. 40 intensive care unit$.tw. 41 ward$.tw. 42 or/31-41 43 30 and 42	7 intervention$.tw. 8 chang$.tw. 9 evaluat$.tw. 10 effect?.tw. 11 compar$.tw. 12 control$.tw. 13 or/1-12 14 limit 13 to humans 15 (hand washing or handwashing or hand hygiene). 16 14 and 15 17 limit 16 to yr="2009 - Current" 18 exp hospital/ 19 hospital$.tw. 20 exp hospital patient/ 21 inpatient$.tw. 22 exp health care/ 23 health care$.tw. 24 healthcare$.tw. 25 infirmary$.tw. 26 nosocomial$.tw. 27 intensive care unit$.tw. 28. ward$.tw. 29 or/18-28 30 17 and 29
CINAHL	1 (MH "Handwashing+") 2 (hand antisepsis OR handwash* OR hand wash* OR hand disinfection OR hand hygiene OR surgical scrub*) 3 1 OR 2 4 Hand* 5 Sterilization* 6 4 AND 5 7 3 OR 6 8 (MH "Clinical Trials+") 9 clinical trial* 10 randomi* 11 controlled clinical trial* 12 intervention studies* 13 experiment* 14 "time series" 15 (MH "Pretest-Posttest Design+") 16 random allocation* 17 impact* 18. intervention? 19. chang*	1(MH "Clinical Trials+") 2 clinical trial* 3 "comparative studies" 4 "experimental studies" 5 "time series" 6 impact* 7 evaluat* 8 effect* 9 (MH "Pretest-Posttest Design+") 10 (MH "Quasi-Experimental Studies+") 11 or/1-10 12 (MH "Handwashing+") 13 (handwashing OR hand hygiene) 14 or/12-13 15 11 and 14 16 limit 15 to yr="2009 - Current" 17 (MH "Hospitals+") 18 (MH "Hospital Units+") 19 Intensive Care Units 20 (MH "Inpatients") 21 (MH "Child, Hospitalized") 22 (MH "Adolescent, Hospitalized")

	20. (MH "Evaluation Research+") 21. evaluat* 22. effect? 23. comparative study* 24.(MH "Animals+") 25.(MH "Human+") 26. 24 NOT 25 27. OR/8-23 28. 27 NOT 26 29. 7 and 28 30. limit 29 to yr="2009 -Current" 31 (MH "Hospitals+") 32 (MH "Hospital Units+") 33 hospital* 34 Intensive Care Units 35 (MH "Inpatients") 36 (MH "Child, Hospitalized") 37 (MH "Adolescent, Hospitalized") 38 (MH "Aged, Hospitalized") 39 (hospitalized OR hospitalised) 40 (health care OR healthcare) 24 healthcare$.tw. 25 infirmary$.tw. 26 nosocomial$.tw. 27 intensive care unit$.tw. 28. ward$.tw. 41 or/31-40 42 30 AND 41	23 (MH "Aged, Hospitalized") 24 (hospitalized OR hospitalised) 25 (health care OR healthcare) 24 healthcare$.tw. 25 infirmary$.tw. 26 nosocomial$.tw. 27 intensive care unit$.tw. 28. ward$.tw. 26 or/17-25 27 16 AND 26
BNI	1 handwash* (137) 2 hand wash* (170) 3 hand antisep* (22) 4 hand disinfection (39) 5 hand hygiene (369) 6 hand decontamination (43) 7 hand cleansing (29) 8 hand cleaning (27) 9 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 (599) 10 hand (1438) 11 strilization (106) 12 9 OR 11 (702) 13 limit 12 to “2009 to Current”	n/a
CRD Database	n/a	1 MeSH DESCRIPTOR Clinical Trial EXPLODE ALL TREES 2 Clinical Trial* 3 control* 4 random* 5 comparative stud* 6 experimental stud* 7 time series* 8 impact* 9 intervention* 10 evaluat* 11 effect* 12 Chang* 13 Compar* 14 Experiment* 15 (pretest OR pre test OR posttest OR post test) 16 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 17 MeSH DESCRIPTOR Handwashing EXPLODE ALL TREES

		18 (hand washing OR handwashing OR hand hygiene) 19 #17 OR #18 20 #15 AND #19 21 (#20) FROM 2009 TO 2013 22 MeSH DESCRIPTOR Hospitals EXPLODE ALL TREES (MH 23 MeSH DESCRIPTOR Hospital Units EXPLODE ALL TREES (MH 24 hospital* 25 Intensive Care Unit* 26 MeSH DESCRIPTOR Inpatients EXPLODE ALL TREES 27 MeSH DESCRIPTOR Adolescent, Hospitalized EXPLODE ALL TREES 28 MeSH DESCRIPTOR Adolescent, Institutionalized EXPLODE ALL TREES 29 MeSH DESCRIPTOR Child, Hospitalized EXPLODE ALL TREES 30 MeSH DESCRIPTOR Child, Institutionalized EXPLODE ALL TREES 31 (hospitalised OR hospitalized OR healthcare OR health care) 32 #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 33 #21 AND #32
Cochrane Library	1 MeSH descriptor: [Hand hygiene] explode all trees 2 (hand antisepsis OR handwash* OR hand wash* OR hand disinfection OR hand hygiene OR surgical scrub*) 3 1 OR 2 4 Hand* 5 Sterilization* 6 4 AND 5 7 3 OR 6 8 MeSH descriptor: [Clinical Trial] explode all trees 9 clinical trial* 10 randomi* 11 controlled clinical trial* 12 intervention studies* 13 experiment* 14 time series* 15 (pretest OR pre test OR posttest OR post test) 16 random allocation* 17 impact* 18 intervention? 19 chang* 20 evaluat* 21 effect* 22 comparative study* 23 OR/8-22 24 7 and 23 25 limit 24 to yr="2009 -Current" 26. MeSH descriptor: [Hospitals] explode all trees 27 MeSH descriptor: [Hospital Units] explode all trees 28 hospital* 29 Intensive Care Unit* 30 MeSH descriptor: [Inpatients] explode all trees	1 MeSH descriptor: [Clinical Trial] explode all trees 2 Clinical Trial* 3 control* 4 random* 5 comparative stud* 6 experimental stud* 7 time series* 8 impact* 9 intervention* 10 evaluat* 11 effect* 12 Chang* 13 Compar* 14 Experiment* 15 (pretest OR pre test OR posttest OR post test) 16 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 17 MeSH descriptor: [Hand hygiene] explode all trees 18 (hand washing OR handwashing OR hand hygiene) 19 #17 OR #18 20 #16 AND #19 21 (#20) FROM 2009 TO 2013 22 MeSH descriptor: [Hospitals] explode all trees 23 MeSH descriptor: [Hospital Units] explode all trees 24 hospital* 25 Intensive Care Unit* 26 MeSH descriptor: [Inpatients] explode all trees 27 MeSH descriptor: [Adolescent, Hospitalized] explode all trees 28 MeSH descriptor: [Adolescent,

	31 MeSH descriptor: [Adolescent, Hospitalized] explode all trees 32 MeSH descriptor: [Adolescent, Institutionalized] explode all trees 33 MeSH descriptor: [Child, Hospitalized] explode all trees 34 MeSH descriptor: [Child, Institutionalized] explode all trees 35 (hospitalised OR hospitalized OR healthcare OR health care) 36 #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 37 #25 AND #36	Institutionalized] explode all trees 29 MeSH descriptor: [Child, Hospitalized] explode all trees 30 MeSH descriptor: [Child, Institutionalized] explode all trees 31 (hospitalised OR hospitalized OR healthcare OR health care) 32 #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 32 #21 AND #32
Current Clinical Control Trial	n/a	("hand hygiene" OR "hand washing" OR "handwashing" OR "hand sanitizer" OR "hand rubbing" OR "hand rubs") AND ("hospital" OR "healthcare" OR "inpatients" OR "intensive care unit" OR "hospitalised" OR "hospitalized" OR “nosocomial”)
ACP journal	("hand hygiene" OR "hand washing" OR "handwashing" OR "hand sanitizer" OR "hand rubbing" OR "hand rubs") AND ("hospital" OR "healthcare" OR "inpatients" OR "intensive care unit" OR "hospitalised" OR "hospitalized" OR “nosocomial”)	n/a
Evidence-Based Medicine Reviews	1 handwashing.sh. 2 handwash$.tx. 3 hand wash$.tx. 4 hand disinfection.tx. 5 hand hygiene.tx. 6 surgical scrub$.tx. 7 hand decontamination.mp. [mp=ti, to, ab, tx, kw, ct, sh, hw] 8 hand cleansing.mp. [mp=ti, to, ab, tx, kw, ct, sh, hw] 9 hand cleaning.mp. [mp=ti, to, ab, tx, kw, ct, sh, hw] 10 1or2or3or4or5or6or7or8or9 11 from 10 keep 1-249 12 10 13 limit 12 to yr=”2005 Current”	n/a

Appendix A2: Classification for level of information on resources use

Level of information on resources use for interventions

High: Stated clearly what the interventions were and how they were implemented and described clearly what materials were used and how much time for each person was spent as well as the duration of the implementation period.

Moderate: Stated what the interventions were and how they were implemented but lacking a clear description of materials used and person-time involved as well as time spent for each intervention.

Low: Stated only what the interventions were and how they were implemented. Largely lacking any details on materials used, person involved as well as the time spent.

Appendix A3: Analysis of interrupted time series data

Data from interrupted time series were re-analysed when data on the number of opportunities and hand hygiene compliance at different time points could be obtained.

If $n(t)$ represents the number of hand hygiene opportunities in a study at time t and $y(t)$ represents the number of occasions where compliance was observed, then we used the following generalized linear model to evaluate the effect of the intervention:

$$y(t) \sim \text{binomial}(\pi(t), n(t)) \qquad [1]$$

$$\ln(\pi(t)/(1-\pi(t)) = a + b \times t + c \times \mathbf{1}_{t \geq t.int} + d \times \mathbf{1}_{t \geq t.int} \times (t - t.int) \qquad [2]$$

where $\pi(t)$ is the probability of hand hygiene at time t, $t.int$ is the time of the intervention, $\mathbf{1}_{t \geq t.int}$ is a function of t taking the value 1 if $t \geq t.int$ and zero otherwise. In this expression the parameter a measures baseline compliance, b the initial pre-intervention trend, c the step (level) change associated with the intervention, and d corresponds to the change in trend associated with the intervention. These parameters were estimated for each study that was re-analysed. In this model an intervention can increase hand hygiene either through a step increase in compliance at the time of the intervention ($c > 0$) or through a trend for increased compliance ($d > 0$).

It is also useful to obtain a statistic that summarizes the effectiveness of the intervention, accounting for both changes in trend and level. There are several possibilities and we consider two: the mean percentage change in hand hygiene compliance in the post-intervention period attributed to the intervention (an absolute measure of change in compliance) and the mean log odds ratio of hand hygiene associated with the intervention (a relative measure).

The first statistic, the mean percentage change in hand hygiene compliance, is given by 100 times the mean difference between the value of $\pi(t)$ predicted by equation [2] and the value of $\pi(t)$ that would be expected if the terms c and d were set to zero (i.e. the expected compliance probability if the intervention had not occurred), where the mean is taken over the post-intervention interval [$t.int$, $t.end$], where $t.end$ is the time of the end of post-intervention period. This is equivalent to $100/(t.end - t.int)$ multiplied by the area between the following two curves (representing the hand hygiene compliance probability given the intervention and the hand hygiene compliance probability that would be expected without the intervention, respectively) for $t.int \leq t \leq t.end$:

$$\pi_1(t) = \frac{exp(a+bt+c1_{t \geq t.int}+d1_{t \geq t.int}(t-t.int))}{1+a+bt+c1_{t \geq t.int}+d1_{t \geq t.int}(t-t.int))} \qquad [3]$$

$$\pi_0(t) = \frac{exp(a+bt)}{1+exp(a+bt)} \qquad [4]$$

This is given by $100 \times \frac{A_1 - A_0}{t.end - t.int}$ where the areas A_1 and A_2 are found by integrating [3] and [4] over this range:

$$A_1 = \int_{t.int}^{t.end} \pi_1(t)dt \qquad A_0 = \int_{t.int}^{t.end} \pi_0(t)dt$$

which gives

$$A_1 = \frac{\ln(1+\exp(a+b\times t.end+c+d\times(t.end-t.int))}{(b+d)(1+\exp(a+b\times t.int+c))}$$

$$A_0 = \frac{\ln(1+\exp(a+b\times t.end))}{b(1+\exp(a+b\times t.int))}.$$

An associated standard error was obtained using the delta method making use of the covariance matrix obtained by fitting the full generalized linear model described by equations [1] and [2].

The relative measure of hand hygiene change associated with the intervention is the mean log odds ratio for hand hygiene. This is defined as the mean value of the logarithm of ratio of the odds of hand hygiene compliance in the post-intervention period given by equation [2] to the odds of hand hygiene given by equation [2] but setting term c and d to zero. This is given by

$$c + d \times (t.end - t.int)/2$$

and the associated variance is given by

$$\text{var}(c) + \text{var}(d) \times ((t.end - t.int)/2)^2 + 2 \times \text{cov}(c, d) \times (t.end - t.int)/2.$$

Appendix A4: WINBUGs code for network meta-analysis

a) Base case analysis

Trial-level data given as treatment differences
Random effects model

```
model{                                  # *** PROGRAM STARTS
  for(i in 1:ns) {                      # LOOP THROUGH STUDIES
    y[i] ~ dnorm(delta[i],prec[i])      # normal likelihood for trials
    var[i] <- pow(se[i],2)               # calculate variances
    prec[i] <- 1/var[i]                  # set precisions
    #Trial-specific mean diff distributions
    delta[i] ~ dnorm(md[i],bytau.sq[c[i]])
    #Mean of random effects distributions
    md[i] <-  d[t[i,2]] - d[t[i,1]]
    #Deviance contribution
    dev[i] <- (y[i]-delta[i])*(y[i]-delta[i])*prec[i]
    #summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i])
  }
      totresdev <- sum(resdev[])     #Total Residual Deviance
      d[1]<-0        #Treatment effect is zero for reference treatment

      for (k in 2:nt){d[k] ~ dnorm(0,.0001)
    }
      for ( i in 1:nc){
       tau.sq[i]<-max(0.01,t.s[i])
       t.s[i]~dnorm(2,10)
      bytau.sq[i]<- 1/tau.sq[i]
      }
      #Ranking
      for (k in 1:10) {
      rk[k] <- 11-rank(d[],k)
      best[k] <- equals(rk[k],1)}

}                                      # *** PROGRAM ENDS

# ns= number of studies;
# nt=number of treatments;

#Data
list(ns=14, nt=10, nc=10)
c[]    t[,1]  t[,2]  y[]         se[]
1      1      5      0.4711      0.1647
2      1      8      2.4499      0.1691
3      3      6      5.8455      0.5953
4      3      9      0.7974      0.4078
5      9      10     1.0656      0.1131
6      1      7      2.2700      0.3041
1      1      5      5.4996      1.4148
8      4      5      0.3847      0.1541
1      1      5      1.9448      0.8245
9      1      9      2.8740      0.1402
1      1      5      1.3230      0.8183
10     5      5      -1.8738     0.6183
7      2      5      0.6408      0.4910
10     5      5      -0.5222     1.2273
END
```

Dbar = post.mean of -2logL; Dhat = -2LogL at post.mean of stochastic nodes

	Dbar	Dhat	pD	DIC
test	0.000	0.000	-0.000	0.000
y	13.817	1.222	12.595	26.412
total	13.817	1.222	12.595	26.412

b) Sensitivity analysis

Code and results for sensitivity analysis exclude the multiple time implementation studies including Helms et al., Kirkland et al., Al-Tawfiq et al., and Crews et al.

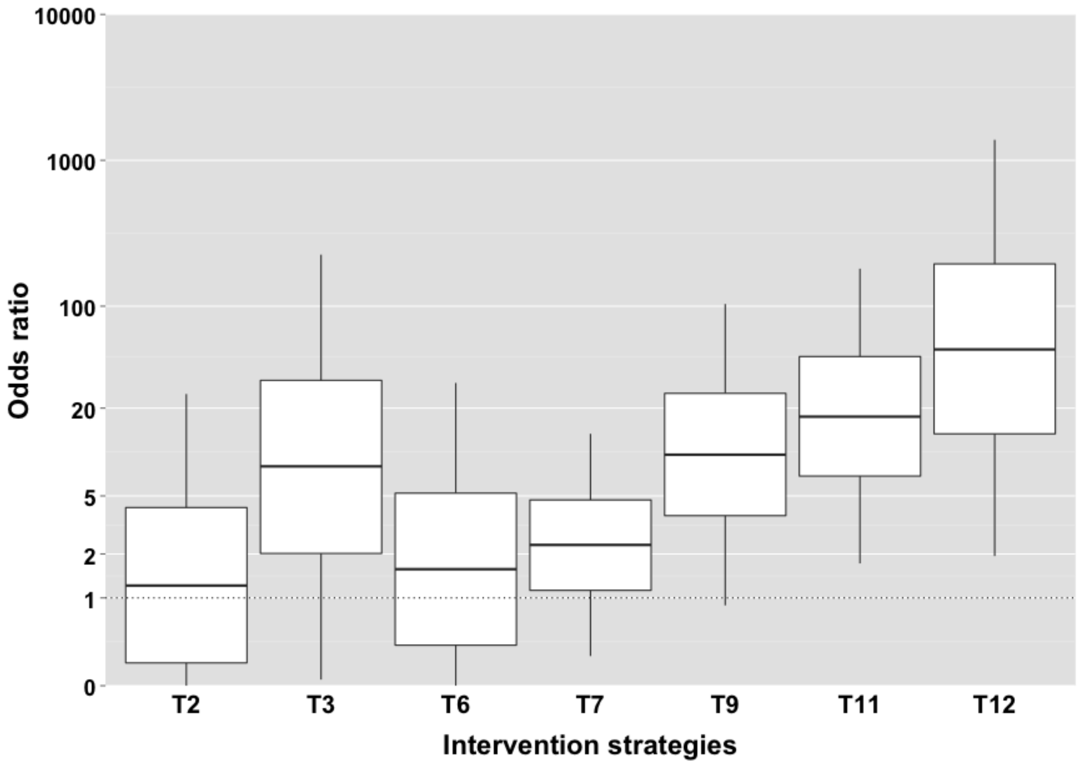
```
# Trial-level data given as treatment differences
# Random effects model
model{                              # *** PROGRAM STARTS
  for(i in 1:ns) {                   # LOOP THROUGH STUDIES
    y[i] ~ dnorm(delta[i],prec[i]) # normal likelihood for trials
    var[i] <- pow(se[i],2)   # calculate variances
    prec[i] <- 1/var[i]      # set precisions
            # trial-specific mean diff distributions
    delta[i] ~ dnorm(md[i],bytau.sq[c[i]])
            # mean of random effects distributions, with multi-arm
trial correction
    md[i] <-  d[t[i,2]] - d[t[i,1]]

    #Deviance contribution
    dev[i] <- (y[i]-delta[i])*(y[i]-delta[i])*prec[i]
    #summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i])
  }
      totresdev <- sum(resdev[])            #Total Residual Deviance
      d[1]<-0      #treatment effect is zero for reference treatment
      for (k in 2:nt){  d[k] ~ dnorm(0,.0001)
    }
     for ( i in 1:nc){
       tau.sq[i]<-max(0.01,t.s[i])
       t.s[i]~dnorm(2,10)
       bytau.sq[i]<- 1/tau.sq[i]
      }
      #Ranking
      for (k in 1:8) {
      rk[k] <- 9-rank(d[],k)
      best[k] <- equals(rk[k],1)}
}                                    # *** PROGRAM ENDS

# ns= number of studies;
# nt=number of treatments;

#Sensitivity anslysis: exclude Crews, Kirkland, Helms and Al-Tawfiq.
list(ns=10, nt=8, nc=8)
c[]   t[,1]  t[,2]  y[]         se[]
1     1      5      0.4711      0.1647
2     3      7      0.7974      0.4078
3     7      8      1.0656      0.1131
4     1      6      2.2700      0.3041
5     4      5      0.3847      0.1541
6     1      7      2.8740      0.1402
1     1      5      1.3230      0.8183
7     5      5      -1.8738     0.6183
8     2      5      0.6408      0.4910
7     5      5      -0.5222     1.2273
END
```

Dbar = post.mean of -2logL; Dhat = -2LogL at post.mean of stochastic nodes

	Dbar	Dhat	pD	DIC
test	0.000	0.000	-0.000	0.000
y	13.817	1.222	12.595	26.412
total	13.817	1.222	12.595	26.412

Results

Box-and-whiskers plot showing relative efficacy of different hand hygiene intervention strategies compared with standard of care without the multiple time implementation studies estimated by network meta-analysis from interrupted time series studies. Lower and upper edges represent 25th and 75th percentiles from the posterior distribution; the central line represents the median. Whiskers extend to the 5th and 95th percentiles. Intervention strategies were as follows: T2-System change; T3-Education; T6-System change+Education+Feedback+Reminders; T7-WHO-5; T9-WHO-5+Incentives; T11-Incentives+Goal-setting; T12-WHO-5+Incentives+Goal-setting+Accountability.



Appendix A5: Excluded studies with reason by EPOC criteria.

No.	Authors	Year	Meet inclusion criteria	Meet EPOC criteria	Reason for exclusion [a]
1	Abela	2012	Y	N	UBA with no control
2	Aboumatar	2012	Y	N	ITS with inadequate data collection points
3	Alemagno	2010	Y	N	UBA with no control
4	Allegranzi	2010	Y	N	UBA with no control
5	Allegranzi	2013	Y	N	UBA with no control
6	Ananda-Rajah	2010	Y	N	ITS with inadequate data collection points
7	Apisarnthanarak	2010	Y	N	UBA with no control
8	Apisarnthanarak	2010	Y	N	CBA with uncomparable control
9	Ardizzone	2013	Y	N	UBA with no control
10	Barahona-Guzman	2014	Y	N	ITS with inadequate data collection points
11	Barbut	2013	Y	N	UBA for AHR use/ ITS for HAI rate
12	Barrera	2011	Y	N	ITS with inadequate data collection points
13	Bessesen	2013	Y	N	UBA with no control
14	Bingham	2010	Y	N	UBA with no control
15	Biswal	2013	Y	N	UBA with no control
16	Boog	2013	Y	N	ITS with inadequate data collection points
17	Borges	2012	Y	N	UBA with no control
18	Bouadma	2010	Y	N	UBA with no control
19	Buffet-Bataillon	2010	Y	N	UBA with no control
20	Bukhari	2011	Y	N	UBA, no baseline data
21	Caniza	2009	Y	N	UBA with no control
22	Chen	2011	Y	N	UBA with no control
23	Cheng	2010	Y	N	UBA for AHR use/ ITS for HAI rate
24	Costers	2012	Y	N	UBA with no control
25	Cumbler	2013	Y	N	ITS with inadequate data collection points
26	Davis	2010	Y	N	UBA with no control
27	de Macedo	2012	Y	N	UBA with no control
28	di Martino	2011	Y	N	UBA with no control
29	DiDiodato	2013	Y	N	UBA with no control
30	Dierssen-Sotos	2010	Y	N	UBA with no control
31	Dierssen-Sotos	2010	Y	N	UBA with no control
32	Dilek	2012	Y	N	UBA with no control
33	Dos Santos	2013	Y	N	ITS with inadequate data collection points
34	El-Kafrawy	2013	Y	N	UBA with no control
35	Eveillard	2011	Y	N	UBA with no control
36	Fakhry	2012	Y	N	UBA with no control

37	Fitzpatrick	2011	Y	N	UBA with no control
38	Forrester	2010	Y	N	UBA with no control
39	Garcia-Rodriguez	2013	Y	N	UBA with no control
40	Garcia-Vazquez	2011	Y	N	UBA with no control
41	Gill	2009	Y	N	CBA with only 1 control
42	Graf	2013	Y	N	UBA with no control
43	Grant	2011	Y	N	UBA with no control
44	Grayson	2011	Y	N	ITS with inadequate data collection points
45	Helder	2010	Y	N	UBA with no control
46	Helder	2012	Y	N	UBA, no baseline data
47	Henderson	2012	Y	N	UBA with no control
48	Homa	2011	Y	N	ITS with inadequate data collection points
49	Jaggi	2013	Y	N	UBA with no control
50	Jamal	2012	Y	N	ITS with inadequate data collection points
51	Jeong	2013	Y	N	UBA with no control
52	Kanj	2013	Y	N	UBA with no control
53	KelcÃkova	2012	Y	N	UBA, no baseline data
54	Kim	2013	Y	N	UBA with no control
55	Kindness	2010	Y	N	UBA, no baseline data
56	Kowitt	2013	Y	N	ITS with inadequate data collection points
57	Langston	2011	Y	N	UBA with no control
58	Leblebicioglu	2013	Y	N	UBA with no control
59	Leblebicioglu	2013	Y	N	UBA with no control
60	Levchenko	2011	Y	N	UBA with no control
61	Linam	2011	Y	N	UBA with no control
62	Ling	2012	Y	N	UBA with no control
63	Lobo	2010	Y	N	UBA with no control
64	Marra	2013	Y	N	UBA, no baseline data
65	Mathai	2011	Y	N	UBA with no control
66	Mazi	2013	Y	N	ITS with inadequate data collection points
67	Molina-Cabrillana	2010	Y	N	UBA with no control
68	Monistrol	2012	Y	N	UBA with no control
69	Monistrol	2013	Y	N	UBA with no control
70	Mukerji	2013	Y	N	UBA with no control
71	Pontivivo	2012	Y	N	ITS with inadequate data collection points
72	Prospero	2010	Y	N	UBA with no control
73	Rahim	2009	Y	N	UBA with no control
74	Rees	2013	Y	N	ITS with inadequate data collection points
75	Reichardt	2014	Y	N	UBA with no control
76	Rello	2013	Y	N	UBA with no control
77	Roberts	2012	Y	N	ITS with inadequate data collection points
78	Rogers	2010	Y	N	UBA with no control

79	Rosenthal	2010	Y	N	UBA with no control
80	Rosenthal	2013	Y	N	UBA with no control
81	Rosenthal	2012	Y	N	UBA with no control
82	Rosenthal	2012	Y	N	UBA with no control
83	Rosenthal	2012	Y	N	UBA with no control
84	Rosenthal	2012	Y	N	UBA with no control
85	Sahud	2012	Y	N	ITS with inadequate data collection points
86	Saint	2009	Y	N	UBA with no control
87	Salama	2013	Y	N	UBA with no control
88	Santos	2013	Y	N	UBA with no control
89	Saramma	2011	Y	N	UBA with no control
90	Scheithauer	2012	Y	N	UBA, no baseline data
91	Scheithauer	2013	Y	N	UBA with no control
92	Scheithauer	2013	Y	N	UBA with no control
93	Scheithauer	2013	Y	N	UBA with no control
94	Seirafian	2013	Y	N	UBA with no control
95	Seto	2013	Y	N	ITS with inadequate data collection points
96	Simmons	2013	Y	N	UBA with no control
97	Son	2011	Y	N	UBA with no control
98	Song	2013	Y	N	ITS with inadequate data collection points
99	Tromp	2012	Y	N	UBA with no control
100	van den Hoogen	2011	Y	N	UBA with no control

[a] UBA; uncontrolled before and after study, CBA; controlled before and after study, ITS; interrupted time series study, AHR; alcohol based hand rub, and HAI; healthcare associated infection.

Appendix A6: Details of extracted intervention components and level of information on resource use.

Author (year)	Study design	1.System Change	2.Education & Training	3.Feedback	4.Reminders	5.Institutional safety climate	6.Others including Goal-setting, Incentives, and Accountability	Control/Baseline intervention	Level of information on resources use
Fuller (2012)	CRCT	Not done but available as part of the national campaign	Not done but available as part of the national campaign	Observation and feedback by "Ward Coordinator" performed one repeating 4-week cycle. The tasks were hand hygiene observation of an individual health care worker, and immediate feedback as well as preparing an action plan to feed back at a ward meeting. Training program for observers is required (Total 62 training visits, 1 to 1.5 hour)	Not done but available as part of the national campaign	Not done but available as part of the national campaign	Goal-setting: Ward coordinators were asked to fill out a form to record, observations, feedback, goals and action plans.	National "Cleanyourhands" campaign as routine practice (similar to WHO-5)	M
Huis (2013)	CRCT	Adequate product and facilities	Education for improving relevant knowledge and skills. Distribution of educational material/written information about hand hygiene Website	Feedback Bar charts of hand hygiene rates	Reminders Distribution of posters replace every 12 weeks Interviews and messages in newsletters or hospital magazines General reminders by opinion leaders/ward management	Gaining active commitment and initiative of ward manager. Modelling by informal leaders at the ward; demonstrating good hand hygiene behavior, instructing and stimulating their colleagues	Goal-setting: Setting norms and targets within the team Three interactive team sessions (1–1.5 hour each) Analysis of barriers and facilitators to determine how nurses could best adapt their behaviour in order to reach their goal Nurses address each other in case of undesirable hand hygiene behavior All managers received a 4-hr training before the start of the intervention	State of the art strategy (SAS) implemented intervention 1 to 4	H
Mertz (2010)	CRCT	Sink and AHR dispensers were available	Small group teaching seminars	Meeting of clinical manager and staff on the intervention units and the later meeting provide the specific performance feedback (biweekly meeting for 6 months)	Posters and pamphlets	Not done	Not done	System change was done Sink and AHR dispensers were available before the intervention period in both control and intervention arm	M

Huang (2002)	CRCT	Not done	Educational intervention (Universal precaution training) provided by 3 trained investigator: including a) a 2-hr lecture, b) a 1-hr demonstration, and c) 30 min discussion	Not done	Not done	Not done	Not done	No intervention but received training after the study finished	M
Fisher (2013)	RCT	AHR dispensers and basins were available at point of care	Not done	Quantified individual feedback by receiving confidential and weekly written feedback reports of hand hygiene compliance	Real-time reminders (audible beeps) using a wireless hand hygiene monitoring system	Not done	Not done	AHR dispensers and basins were available at point of care	M
Salamati (2013)	RCT	AHR dispensers and basin were available at point of care	Hand hygiene education was performed by an infection control nurse via a 2 hours lecture; the lecture session was repeated a few times in such a way as to cover all the personnel working in different shifts.	Motivational Interview; five sessions of interviewing with maximum of 15 participants for 90 minutes.	Not done	Not done	Not done	AHR dispensers were available at point of care Hand hygiene education	M
Derde (2014)	ITS	Not done	Education sessions	Direct feedback after observation and Monthly feedback of local compliance rates is provided to wards to guide the content of each local hand hygiene program.	Visual reminders (no details)	Not done	Not done	Reminder as posters	L
Lee (2013)	ITS	AHR at point of care	Training and education of healthcare worker	Observation and feedback of hand hygiene practices	Reminders in the workplace (e.g. posters)	Improving the safety climate in the institution with management support for the initiative	Not done	One unit was no intervention and another unit was system change changing AHR formulation. The other two were WHO-5.	L

Marra (2013)	ITS	Positive deviance (PD)* group incorported in changing the position of AHR dispensers, recommending a change in the pressure of the tap water and added the dispensers in the corridors. *PDs were defined as those HCWs who wanted to change, to think, to develop new ideas for improving HH and who stimulated other HCWs.	Positive Deviants (PD) meeting with all HCWs twice monthly The hospital PD coordinators provided PD training for all HCWs including nurses, physicians, physical therapists, speech pathologists, and nutritionists who used the dispensers and provided the opportunities to express feelings about hand hygiene.	PDs showed the HHC% and discussed their performance in every meeting.	Some ideas and strategies were related to the reminders such as preparing badges for doctors who perform HH and noting them as examples and preparing a short theater presentation discussing "My 5 Moments for Hand Hygiene" with their peers.	PD initiated engaging people to involve by inviting another PD in the next meeting	Not done	No intervention (but the AHR was available)	M
Al-Tawfiq (2013)	ITS	Increase availability of hand sanitizers (AHR)	Education Formation of hand hygiene compliance team Educational presentations	Feedback Posting data on intranet Compliance criteria shared with health care professionals Inclusion in dashboard with goal-setting Devotion of activity to low performing units Face-to-face feedback during weekly tracer rounds Frequent audit and feedback and discussed the feedback findings with each unit supervisor and fostering ways to improve	Promotion Flashing pins “Wash your hands stay healthy” Ask me “have you washed your hands” pins Hand hygiene banners throughout the organization Magnetic door posters promoting hand hygiene	Leadership commitment Senior leadership engagement included monthly tracking of the compliance rates and communicating to management and hospital staff during monthly meeting and through the dashboard	Goal-setting: Setting compliance goals Increased the stated goal to 75% Increased the goal to 85%	No intervention (but the AHR was available)	M
Armellino (2013)	ITS	Not done	Not done	Feedback metrics tabulated by a central server database delivered back to the HCWs through electronic light emitting diode boards, electronic mail summaries, and weekly performance reports.	Not done	Not done	24 video cameras and motion sensors at handwashing sinks and sanitizer dispensers to record hand hygiene opportunities Goal-setting: Setting the targeted compliance as >=95%	Video cameras were installed during baseline period as well but without feedback.	M

Armellino (2012)	ITS	Not done	Not done	Feedback metrics tabulated by a central server database delivered back to the HCWs through electronic light emitting diode boards, electronic mail summaries, and weekly performance reports.	Not done	Not done	24 video cameras and motion sensors at hand washing sinks and sanitizer dispensers to record hand hygiene opportunities Goal-setting: Setting the targeted compliance as >=95%	Video cameras were installed during baseline period as well but without feedback.	M
Chan (2013)	ITS	38 AHR dispensers were installed and changed the location	Not done	Not done	Not done	Not done	Not done	No intervention (but the AHR was available)	M
Crews (2013)	ITS	More than 900 wall dispensers were installed and substituted with new alcohol-based hand rubs.	Annual educational training for clinical staff including physician and hospital staff	Routine feedback to HCWs	Marketing committee launched a campaign that emphasized branding hand hygiene with a positive image. Slogan and child-friendly posters and signs with the message were displayed at strategic locations. Additional items containing the message, including pens, buttons, calendars, and coloring books, were widely distributed.	Not done	Goal-setting: Hand hygiene goal added to employee Three goals related to quality or patient safety Reward incentives: If the goals are achieved, every employee receives a financial reward.	Multiple unit-based educational initiatives and use of a gel-based alcohol hand rub	M
Salmon (2013)	ITS	Not done	Hand hygiene auditor training program based on the WHO "My 5 moments for hand hygiene" in the orientation program for final year nursing students, 1- hour session including lecture and practical auditing using WHO video tools and 398 nursing students from 3 nursing schools involved.	Not done	Not done	Not done	Not done	No intervention/routine practice	M

Talbot (2013)	ITS; Phase I	As part of the bundle of readiness assessment and planning program	Expanded HH direct observation program Observation program was expanded to include all inpatient and outpatient locations. The observers attended required training on a standardized observation methodology	Readiness assessment and planning The project bundle focused planners on addressing the following: defining the problem, ensuring project alignment with the organization's mission, securing financial support, defining performance and measurement objectives, and establishing leadership commitment.	System-wide marketing campaign Poster messaging and targeted talks aimed to increase HH awareness and its importance in preventing HAIs.	Leadership goal-setting Improved HH adherence was adopted as an institutional quality improvement goal and the performance related to the goal immediately became a factor in annual performance evaluations and incentive compensation for medical center leaders.	Goal-setting: Modest HH adherence goals were set in the first year of the program (adherence of 65% as a threshold goal, 75% as a target goal, and 85% as a reach goal) with the intent of increasing performance requirements each year. Reward incentive: Financial incentives via a self-insurance trust allocation rebate program. The component of the allocation rebate was worth up to 25% of the total rebate dollars (2.5% of yearly premiums). For example, for a physician whose yearly premium was $10,000.00, the rebate amounted to $250.00.	Phase I: Hand hygiene annual faculty and staff training	M
	Phase II	Same as Phase I above	Same as Phase I above	Same as Phase I above	Same as Phase I above	Hand Hygiene executive committee The committee consisted of key physician and nursing leaders was established to review location performance monthly and direct interventions.	Goal-setting and Reward incentive Same as Phase II above, a follow-up campaign Location-specific accountability interventions Units with low adherence were identified for interventions on the basis of a system-wide hand hygiene intervention pyramid. Structured individual accountability interventions Observers provided direct feedback when a hand hygiene opportunity was missed. System leadership monitored event reporting and acted as necessary, consistent with organizational policies concerning behaviors that undermine a culture of safety.	Phase II: Intervention Implemented in Phase I.	

Higgins (2013)	ITS	Increased supplies of hand AHR, dispenser at bedside.	Adenosine triphosphate (ATP) monitoring system, a mobile stand-alone computer system, was purchased and used in the clinical area during spot audits and also at regular intervals outside the staff canteen to measure handwashing technique. HCWs were selected at random and asked to wash their hands with soap and water. Once the hands were completely dry, the swab was rubbed against the tips of each finger, in between each finger and then in an S-shape along the palm of one hand.	Monthly hand hygiene audit and verbal feedback provided directly to staff during the audits.	Posters displaying hand hygiene technique and information of "WHO 5 moments" placed at the key area of the hospital. Advertising campaign was carried out in the hospital through e-mails and general hospital mail. An information leaflet was designed and copies were left in the canteen, at nurses' stations, in staff meeting rooms etc.	Commitment from management, hand hygiene audit results were provided to the hospital executive team and board.	Reward incentive: Fob watches were provided as spot prizes	No intervention (but the AHR was available)	M
Helder (2012)	ITS	Not done	Not done	Not done	Screen servers for 6 computer screens, 2 per unit, were involved to emphasize the need for improved adherence to hand hygiene protocols and were designed according to theoretical principles of message framing. The messages on the screen servers were replaced by a newly designed 2-screen series every 2 weeks.	Not done	Not done	AHR dispensers were available at point of care. However, five months before the study present, a multidisciplinary infection prevention education program was organized.	M
Kirkland (2012)	ITS	Optimised availability of hand sanitiser	Education and training Developed electronic learning module and training video that provided hand hygiene education for all staff. It was accessible through the hospital intranet. A 'certification' program was also available by which staff demonstrated HH competency.	Measurement and feedback Routine HH audits Monthly unit specific data published on an intranet site available to all staff, and reported to executive leadership, clinical leaders and board members	Marketing and communication Marketing staff created a series of posters and screen savers, stories in medical center publications and local news outlets, and direct communication with staff about expectations and progress towards goals.	Leadership and accountability Leadership publicly emphasised the importance of hand hygiene	Not done	No intervention (but the AHR was available)	M

Morgan (2012)	ITS	Installed multiple automated, networked, touch free AHR and soap dispensing units at the entrance to each room and the sink in each room	Infection control and research staff monthly visited each unit to present the poster, remind staff about the importance of hand hygiene, and answer any questions about the study. The WHO 5 Moments for Hand Hygiene were discussed in training.	Feedback compliance was provided for entry and exit based on human observation.	Two posters in each unit to display unit-specific monthly and quarterly hand hygiene compliance rate also included infection control reminders to link hand hygiene with infection prevention (e.g. unit infection rates, photos of unit staff performing hand hygiene, general HAI education)	Not done	Not done	No intervention (but the AHR was available)	M
Stone (2012)	ITS	Alcohol hand rub at bedside	Not done	Regular audit and feedback of compliance	Posters reminding HCWs to clean their hands	Empowering patients to remind HCWs	Not done	No intervention/routine practice	L
Jaggi (2012)	ITS	Not clear	Not clear	Not clear	Not clear	Not clear	Identify key area of improvement Training for a bundle of prevention Auditing	No intervention/routine practice	L
Lee (2012)	ITS	Dispenser installation and Pocket-sized containers provided	All HCWs received continuing education and pre-service education on hand hygiene issues by experienced infection control nurses (ICN)	Monitoring and feedback of hand hygiene compliance monthly by infection control nurses	Posters	Not done	HCWs were encouraged to educate their patients and families about proper hand hygiene.	No intervention/routine practice	L
Mestre (2012)	ITS	AHRs were placed at all bedsides on high risk areas (ER, ICUs)	Theoretical and practical workshop to all HCWs and practical sessions	Audit by a hand hygiene monitor team 8 HCWs direct observation with 2 evaluation periods and 25 days of monitoring Feedback through informal interactive session on every ward at the end of evaluation periods (2 sessions)	Posters and handout, replaced monthly	Commitment by administrative and nursing director	Not done	Phase I: No intervention/routine practice Promotion of hand hygiene such as staff education, reminders, and six months hand hygiene audit was performed during baseline period but it was neither structured nor sustained on time.	H

		AHRs were placed at all bedsides in conventional wards while maintaining those at corridors.	Maintain as above	Audit by a hand hygiene monitor team 8 HCWs carried out direct observation with 17 evaluation periods and 51 days of monitoring. 3 randomized days every 3 weeks ("3/3 strategy") Feedback using control charts on every ward at institutional and individual level.	Maintain as above	Maintain as above Corrective actions: Modification of incorrect HH habits, clarification of doubts and positive reinforcement were conducted	Not done	Phase II: Intervention Implemented in Phase I.	
Koff (2011)	ITS	Not done	A personalized hand hygiene device was worn by HCWs used for recording the frequency of hand disinfection event.	Feedback was provided to both individuals and the entire group.	Not done	Not done	Not done	Wall-mounted dispensers were installed	M
Doron (2011)	ITS	Hand-sanitizer dispensers provided in all public non-patient care areas	Educational program; online teaching, grand rounds lectures and nurses	Close observation with feedback	Promoting campaign by email to introduce the campaign to employees Posters; large size to introduce to patients and families, small size for the walls in various places) Handout for new patients Stickers and pins with positive and humorous messages A private advertising firm was contracted to develop a professional marketing campaign for the hospital.	Leadership commitment Chief medical officer and CEO spoke about HH at every given opportunity Heads of department and ICU directors were asked to make hand hygiene an educational priority and to personally carry out hand hygiene observation	Not done	During 2007 to July 2008 (baseline period), intervention component 1 to 4, including placement of hand sanitizers, reminder signs, education, and feedback with observed compliance, was implemented but reinforced with a new strategy together with component 5 during the intervention period.	M

Marra (2010, 2011)	ITS	Changing the position of alcohol gel dispensers in the patient rooms and to put more in the corridors.	Positive deviants (PD) meeting with all SDU HCWs twice monthly, 1.5 hour each, attendance about 35-40 to discuss and provide training for all HCWs including nurses, physicians, physical therapists, speech pathologists, and nutritionists who used the dispensers and provide the opportunities to express feelings about hand hygiene.	PD showed the hand hygiene compliance and discussed their performance in every meeting.	Incorporated laminated sheets on "My Five Moments for Hand Hygiene" as the first page in all of SDU patient medical records.	PD initiated engaging people to involve by inviting another PD in the next meeting	Not done	No intervention (but the AHR was available)	M
Yngstrom (2011)	ITS	Alcohol hand disinfection at every bed together with pictures and posters, and instruction.	Meeting monthly (reporting, evaluation, feedback and discussion) and continuous education program (Department level)	Feedback of hand hygiene performance during the meeting	Not done	Not done	Goal-setting: The goal was a 40% reduction in healthcare associated infections in ventilated patients. Process objective The process objective was 100% of staff to implement basic hygiene routines.	No intervention (but the AHR was available)	L
Helms (2010)	ITS	Alcohol foam dispenser installed both inside and outside patients room. Pocket-sized container for all staff Hand sanitizing station in the main lobby, emergency lobby and waiting rooms	Aggressive education program Implementation of "You bugged me" program, staff member presenting another employee with a card if they witnessed them not washing their hand properly. The infection control coordinator attended all the staff meeting in all departments and provided educations on proper hand hygiene technique. One part of the program is the use of the fluorescent lotion to see effects of handwashing	Direct feedback when staffs forget to perform hand hygiene via "You bugged me" program.	Signs to remind the staff to wash their hands. Flyers to educate patients' visitors The patients were educated on admission to remind the staff to wash their hands.	Chief executive Officer (CEO) and Chief Nurse Officer (CNO) involved in activity for the penalty of non compliance	Not done	No intervention (but the AHR was available)	M

Chou (2010)	ITS	Adding AHR dispensers in each patient room installed in all public area including outpatient clinics	Enhanced educational material includes added interactive demonstration "fluorescent germs" and bacterial cultures of hands before and after hand hygiene to hospital-wide educational programs to impress the important of hand hygiene and posters contest	Hand hygiene liaison (at least one staff each department) responsible for review in HH policy, ensuring availability of HH product, observing HH at least 20 opp. each month) Feedback in hand hygiene compliance	Posters from the contest displayed in the key areas.	Hospital wide support; the bundle of this intervention was introduced to hospital administration for their support and approval and presented to multiple leadership committees consisting of physicians, nursing directors and managers and other leaders A violation letter was sent to managerial personnel of noncompliant individuals to take corrective action with violators.	Goal-setting and Reward incentive: Nursing units were rewarded with pizza parties if they achieved and sustained the targeted hand hygiene compliance.	No intervention (but the AHR was available)	M
Vernaz (2008)	ITS	Pocket-sized containers using AHR were available during baseline and intervention)	Not clear	Not clear	Not clear	Not clear	Spring 2003: Applying social marketing theory to promote standard precautions and isolation precautions mentioned hand hygiene as an element of standard precautions (did not target the promotion of AHR in particular) Autumn 2005: Swiss national hand hygiene promotion campaign and the global patient safety challenge entitled 'Clean your hand is safer care' with an exclusive focus on the frequent and proper of AHR.	Pocket-sized bottles for AHR were provided.	L
Whitby (2008)	ITS 1) Washington campaign	AHR placed at the end of each bed, chart trolleys and in medication preparation areas. Liquid soap provided at handwashing basin. (Pre intervention: 1 month)	Pre intervention: 4 months A series of meetings led by seniors and attended by all clinical and non-clinical staff Intervention phase 1: 2 months Informal lectures by the project nurses	Intervention phase 1: 2 months Staff developed talking-wall promotional cartoons with prizes awarded and the additional cartoons developed by an external artist.	Intervention phase 1: 2 months Information in accordance with CDC's guidelines was provided via pay slips	Intervention phase 2: 3 months "Walk-arounds" by executive medical and nursing members and photograph of senior staff with speech balloons at each ward in the last month	Large photographs of the hospital executive were positioned throughout the wards	No intervention (but the AHR was available)	M

	2) Geneva campaign	AHR placed at the end of each bed, chart trolleys and in medication preparation areas Liquid soap provided at handwashing basin. (Pre intervention: 1 month)	Pre intervention: 5 months Clinician-led meetings, semi-structured format all clinical and non-clinical staff	Not done	Intervention phase 1: 2 months Posters and Screen savers	Intervention phase 2: 5 months "Walk-arounds" by executive medical and nursing members AND Photograph of senior staff with speech balloons at each ward in the last month	Not done	No intervention (but the AHR was available)	
	3) AHR substitution	AHR placed at the end of each bed, chart trolleys and in medication preparation areas. Liquid soap provided at handwashing basin. (Pre intervention: 1 month) (Pre intervention: 4-5 months)	Not done	Not done	Not done	Not done	Not done	No intervention (but the AHR was available)	
Mayer (2011)	CCT	Positioning dispensers of alcohol sanitizer in convenient locations	Education program providing standardized unit in-service presentations prepared by infection preventionist, the hospital epidemiologist, physician groups, and infection control personnel and clinical staff.	Ongoing audit with monthly feedback by infection preventionist	Not done	Not done	Not done	No intervention/routine practice	H
	ITS	Introduce AHR and positioning the dispensers	Education program providing standardized unit in-service presentations prepared by infection preventionist, the hospital epidemiologist, physician groups, and infection control personnel and clinical staff.	Ongoing audit with monthly feedback by infection preventionist	Posters with catchy phrases were placed throughout the hospital.	Monthly meeting of a hand hygiene committee comprising infection preventionists, nurse managers, service directors and hospital epidemiologist to encourage staff involvement and to provide unit specific feedback.	Reward incentive: through “Positive reinforcement” The hand hygiene committee generated new motivational campaign themes to maintain interest. An example of a group motivator theme was the “War on Germs” to encourage unit teamwork. Publicizing that the unit with the best hand hygiene compliance would win a pizza party Individual incentives theme, in which individuals who were	No intervention/routine practice	

							caught in the act of performing hand hygiene were entered into monthly drawings to win prizes.		
Harne-Britner (2011)	CCT	Not done	Hand washing self-study module and additional education sessions about microorganisms	Not done	Posters (bugs and agar plates) placed and rotated the location	Not done	Not done	Hand washing self-study module	M
		Not done	Hand washing self-study module	Not done	Not done	Not done	Goal-setting and Reward incentive: hand hygiene adherence goal and reward with pizza party. Unit-based recognition by peers on a sticker poster and rewarding some incentives, e.g. movie ticket, gift card, unit recognition and pizza party.	Hand washing self-study module	
Benning (2011)	CBA	Make AHR available at the bedside	Not done	Not done	Posters on wards updated monthly	Encouraged patients to ask staff to clean their hands	Not done	Control: no intervention but "cleanyourhands" campaign implemented during 2004-2005 (in both groups)	L
Gould and Chamberl ain (1997)	CBA	Not done	Educational program by experienced nurse teachers with specific expertise (5 different sessions, 30 min each)	Not done	Not done	Not done	Not done	No intervention/routine practice	M

* AHR: alcohol based hand rub, CRCT: cluster randomised controlled trial, RCT: randomised controlled trial, ITS: Interrupted time series study, CCT: controlled clinical trial, CBA: controlled before and after study.

Appendix A7: Reasons for exclusion from network meta-analysis.

4 studies were excluded from the network meta-analysis. The reasons were:

i.) Conducted in only nursing students (Salmon 2013)

ii.) Hand hygiene intervention and control period unclear (Jaggi 2012)

iii.) Reporting compliance only at entry and exit from the patients room (Armellino 2012, 2013)

Salmon S, Wang XB, Seetoh T, Lee SY, Fisher DA. A novel approach to improve hand hygiene compliance of student nurses. Antimicrob Resist Infect Control 2013;2:16.

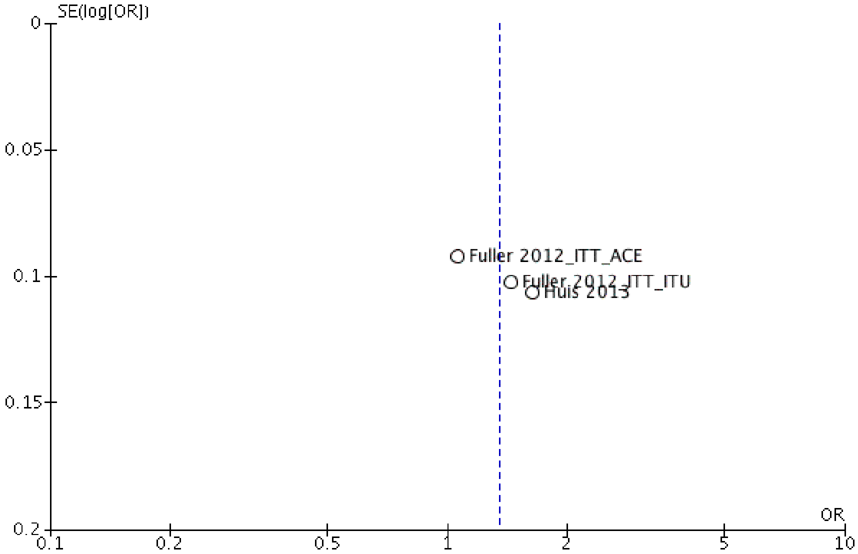
Jaggi N, Sissodia P. Multimodal supervision programme to reduce catheter associated urinary tract infections and its analysis to enable focus on labour and cost effective infection control measures in a tertiary care hospital in India. J Clin Diagn Res 2012;6:1372-76.

Armellino D, Trivedi M, Law I, Singh N, Schilling M, Hussain E, et al. Replicating changes in hand hygiene in a surgical intensive care unit with remote video auditing and feedback. Am J of Inf Control 2013;41:925-27.

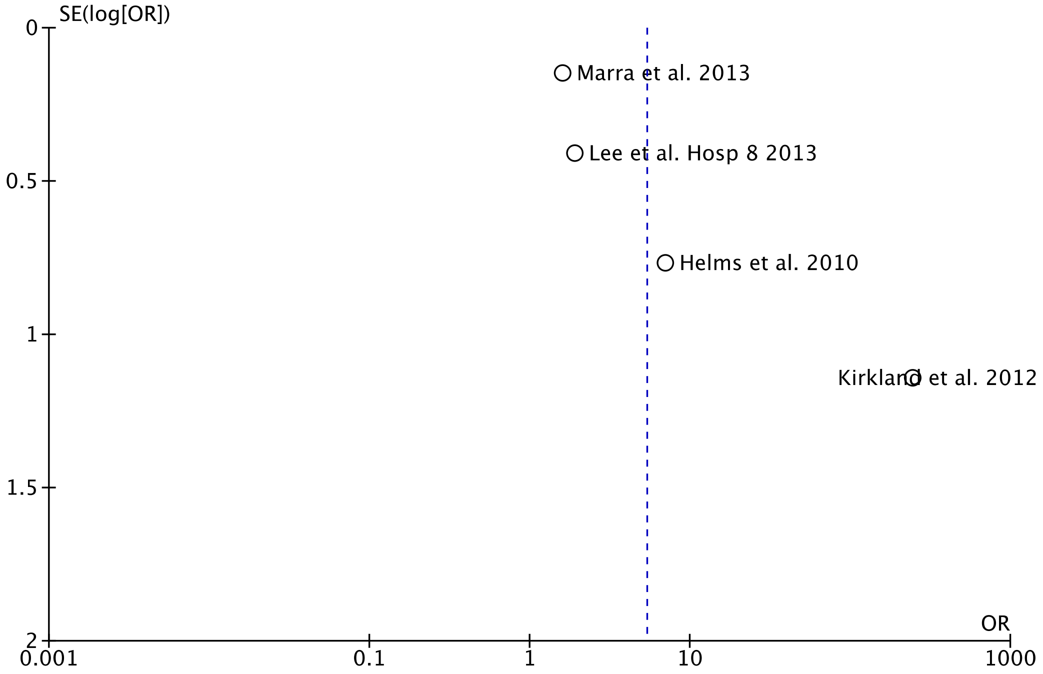
Armellino D, Hussian E, Schilling ME, Senicola W, Eichorn A, Dlugacz Y, et al. Using high-technology to enforce low-technology safety measures: the use of third-party remote video auditing and real-time feedback in healthcare. Clin Infect Dis 2012;54:1-7.

Appendix A8: Funnel plots

Funnel plots of RCT studies, WHO5 VS WHO5+GOAL
Random effects model

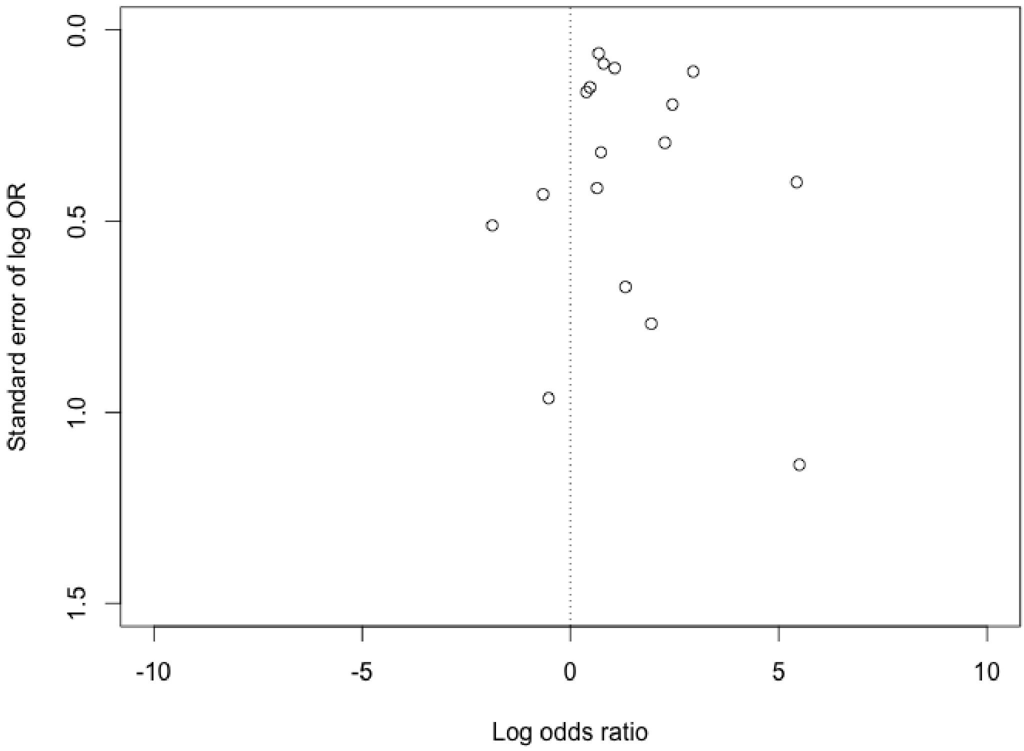


Funnel plot of ITS studies, no intervention compared to WHO5
Random effects model



Funnel plot of all ITS studies

Random effects model



Appendix B: Chapter4 Supplementary

Three main phrases used in the systematic literature search

1. Intensive care unit (ICU)
2. Long term follow up
3. Low and middle income countries

Key words:

(“intensive care unit” or “critical care unit” or “intensive therapy unit” or “intensive treatment unit”) and ("post-discharge" or "post discharge" or "post-ICU discharge" or "post ICU discharge" or "after discharge" or "long-term outcome" or "long term outcome" or "long-term follow up" or "long term follow up" or "long-term survival" or "long term survival" or "five-year survival" or "five year survival" or "five years survival" or "five years" or "two-year survival" or "two year survival" or "one-year survival" or "one year survival") and ("low income" or "developing country" or "middle income" or "low-middle" or "upper-middle-income" or "lower-middle-income" or "Afghanistan" or "Gambia" or "Mozambique" or "Bangladesh" or "Guinea" or "Myanmar" or "Benin" or "Guinea-Bisau" or "Nepal" or "Burkina Faso" or "Haiti" or "Niger" or "Burundi" or "Kenya" or "Rwanda" or "Cambodia" or "Korea, Dem Rep" or "Republic of Korea" or "Sierra Leone" or "Central African Republic" or "Kyrgyz Republic" or "Somalia" or "Chad" or "Liberia" or "Tajikistan" or "Comoros" or "Madagascar" or "Tanzania" or "Congo, Dem. Rep" or "Congo" or "Malawi" or "Togo" or "Eritrea" or "Mali" or "Uganda" or "Ethiopia" or "Mauritania" or "Zimbabwe" or "Albania" or "Indonesia" or "Samoa" or "Armenia" or "India" or "São Tomé and Principe" or "Belize" or "Iraq" or "Senegal" or "Bhutan" or "Kiribati" or "Solomon Islands" or "Bolivia" or "Kosovo" or "South Sudan" or "Cameroon" or "Lao" or "Sri Lanka" or "Cape Verde" or "Lesotho" or "Sudan" or "Congo, Rep." or "Marshall Islands" or "Swaziland" or "Côte d'Ivoire" or "Micronesia" or "Syrian" or "Djibouti" or "Moldova" or "Timor-Leste" or "Egypt" or "Mongolia" or "Tonga" or "El Salvador" or "Morocco" or "Ukraine" or "Fiji" or "Nicaragua" or "Uzbekistan" or "Georgia" or "Nigeria" or "Vanuatu" or "Ghana" or "Pakistan" or "Vietnam" or "Guatemala" or "Papua New Guinea" or "West Bank and Gaza" or "Guyana" or "Paraguay" or "Yemen" or "Honduras" or "Philippines" or "Zambia" or "Angola" or "Ecuador" or "Palau" or "Algeria" or "Gabon" or "Panama" or "American Samoa" or "Grenada" or "Peru" or "Antigua and Barbuda" or "Iran" or "Romania" or "Argentina" or "Jamaica" or "Russia" or "Azerbaijan" or "Jordan" or "Serbia" or "Belarus" or "Kazakhstan" or "Seychelles" or "Bosnia and Herzegovina" or "Latvia" or "South Africa" or "Botswana" or "Lebanon" or "St. Lucia" or "Brazil" or "Libya" or "St. Vincent and the Grenadines" or "Bulgaria" or "Lithuania" or "Suriname" or "Chile" or "Macedonia" or "Thailand" or "China" or "Malaysia" or "Tunisia" or "Colombia" or "Maldives" or "Turkey" or "Costa Rica" or "Mauritius" or "Turkmenistan" or "Cuba" or "Mexico" or "Tuvalu" or "Dominica" or "Montenegro" or "Uruguay" or "Dominican Republic" or "Namibia" or "Venezuela")

Pubmed search:

(("intensive care units"[MeSH Terms] OR ("intensive"[All Fields] AND "care"[All Fields] AND "units"[All Fields]) OR "intensive care units"[All Fields] OR ("intensive"[All Fields] AND "care"[All Fields] AND "unit"[All Fields]) OR "intensive care unit"[All Fields]) OR ("intensive care units"[MeSH Terms] OR ("intensive"[All Fields] AND "care"[All Fields] AND "units"[All Fields]) OR "intensive care units"[All Fields] OR ("critical"[All Fields] AND "care"[All Fields] AND "unit"[All Fields]) OR "critical care unit"[All Fields]) OR (intensive[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) AND unit[All Fields]) OR (intensive[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) AND unit[All Fields]))

AND

("post-discharge"[All Fields] OR "post discharge"[All Fields] OR "post-ICU discharge"[All Fields] OR "post ICU discharge"[All Fields] OR "after discharge"[All Fields] OR "long-term outcome"[All Fields] OR "long term outcome"[All Fields] OR "long-term follow up"[All Fields] OR "long term follow up"[All Fields] OR "long-term survival"[All Fields] OR "long term survival"[All Fields] OR "longterm survival"[All Fields] OR "five-year survival"[All Fields] OR "five year survival"[All Fields] OR "five years survival"[All Fields] OR "five years"[All Fields] OR "two-year survival"[All Fields] OR "two year survival"[All Fields] OR "one-year survival"[All Fields] OR "one year survival"[All Fields])

AND

("low income"[all fields] or "developing country"[all fields] or "middle income"[all fields] or "low-middle"[all fields] or "upper-middle-income"[all fields] or "lower-middle-income"[all fields] or "afghanistan"[all fields] or "gambia"[all fields] or "mozambique"[all fields] or "bangladesh"[all fields] or "guinea"[all fields] or "myanmar"[all fields] or "benin"[all fields] or "guinea-bisau"[all fields] or "nepal"[all fields] or "burkina faso"[all fields] or "haiti"[all fields] or "niger"[all fields] or "burundi"[all fields] or "kenya"[all fields] or "rwanda"[all fields] or "cambodia"[all fields] or "korea dem rep"[all fields] or "republic of korea"[all fields] or "sierra leone"[all fields] or "central african republic"[all fields] or "kyrgyz republic"[all fields] or "somalia"[all fields] or "chad"[all fields] or "liberia"[all fields] or "tajikistan"[all fields] or "comoros"[all fields] or "madagascar"[all fields] or "tanzania"[all fields] or ("congo, dem. rep"[all fields]) or "malawi"[all fields] or "togo"[all fields] or "eritrea"[all fields] or "mali"[all fields] or "uganda"[all fields] or "ethiopia"[all fields] or "mauritania"[all fields] or "zimbabwe"[all fields] or "albania"[all fields] or "indonesia"[all fields] or "samoa"[all fields] or "armenia"[all fields] or "india"[all fields] or "sao tome and principe"[all fields] or "belize"[all fields] or "iraq"[all fields] or "senegal"[all fields] or "bhutan"[all fields] or "kiribati"[all fields] or "solomon islands"[all fields] or "bolivia"[all fields] or "kosovo"[all fields] or "south sudan"[all fields] or "cameroon"[all fields] or "lao"[all fields] or "sri lanka"[all fields] or "cape verde"[all fields] or "lesotho"[all fields] or "sudan"[all fields] or "congo, rep."[all fields] or "marshall islands"[all fields] or "swaziland"[all fields] or "cote d'ivoire"[all fields] or "micronesia"[all fields] or "syrian"[all fields] or "djibouti"[all fields] or "moldova"[all fields] or "timor-leste"[all fields] or "egypt"[all fields] or "mongolia"[all fields] or "tonga"[all fields] or "el salvador"[all fields] or "morocco"[all fields] or "ukraine"[all fields] or "fiji"[all fields] or "nicaragua"[all fields] or "uzbekistan"[all fields] or "georgia"[all fields] or "nigeria"[all fields] or "vanuatu"[all fields] or "ghana"[all fields] or "pakistan"[all fields] or "vietnam"[all fields] or "guatemala"[all fields] or "papua new guinea"[all fields] or "west bank and gaza"[all fields] or "guyana"[all fields] or "paraguay"[all fields] or "yemen"[all fields] or "honduras"[all fields] or "philippines"[all fields] or "zambia"[all fields] or "angola"[all fields] or "ecuador"[all fields] or "palau"[all fields] or "algeria"[all fields] or "gabon"[all fields] or "panama"[all fields] or "american samoa"[all fields] or "grenada"[all fields] or "peru"[all fields] or "antigua and barbuda"[all fields] or "iran"[all fields] or "romania"[all fields] or "argentina"[all fields] or "jamaica"[all fields] or "russia"[all fields] or "azerbaijan"[all fields] or "jordan"[all fields] or "serbia"[all fields] or "belarus"[all fields] or "kazakhstan"[all fields] or "seychelles"[all fields] or "bosnia and herzegovina"[all fields] or "latvia"[all fields] or "south africa"[all fields] or "botswana"[all fields] or "lebanon"[all fields] or "st. lucia"[all fields] or "brazil"[all fields] or "libya"[all fields] or "st. vincent and the grenadines"[all fields] or "bulgaria"[all fields] or "lithuania"[all fields] or "suriname"[all fields] or "chile"[all fields] or "macedonia"[all fields] or "thailand"[all fields] or "china"[all fields] or "malaysia"[all fields] or "tunisia"[all fields] or "colombia"[all fields] or "maldives"[all fields] or "turkey"[all fields] or "costa rica"[all fields] or "mauritius"[all fields] or "turkmenistan"[all fields] or "cuba"[all fields] or "mexico"[all fields] or "tuvalu"[all fields] or "dominica"[all fields] or "montenegro"[all fields] or "uruguay"[all fields] or "dominican republic"[all fields] or "namibia"[all fields] or "venezuela"[all fields])

Inclusion criteria:

a). Populations are the patients who had been admitted to adults intensive care units (ICUs) including specialised ICUs; medicine/coronary care ICUs, surgical/neurosurgical ICUs, trauma ICUs, and cardiothoracic ICU. Studies confined to certain underlying or specific diseases such as sepsis, transplantations, and cardiac surgery will be excluded.

b). Follow-up period must be at least one year from ICU/hospital admission or ICU/hospital discharge.

c). No restrictions regarding language or year of publication.

Results: 201 abstracts

Accessed: 15 June 2013

Appendix C: Chapter 5 Supplementary

Appendix C1: Model description and parameter estimation

List of parameters and definition

Parameters	Definition
U_{pat}	Number of MRSA (-ve) patients on ward at one time
C_{pat}	Number of MRSA (+ve) patients on ward at one time
n_{pat}	Number of beds (U_pat+C_pat)
U_{HCW}	Number of MRSA (-ve) HCWs per shift
C_{HCW}	Number of MRSA (+ve) HCWs per shift
n_{HCW}	Number of total HCWs per shift (U_HCW+C_HCW)
μ	Removal rate of uncolonised patient (1/mean length of stay) (day^{-1})
γ	Removal rate of colonised patients (1/ mean length of stay) (day^{-1})
π	Proportion of admission with colonized
c	Patient-HCW contact per day (per patient)
P_{HP}	Transmission probability from HCW to Patient per contact
c'	HCW-patient contact per day (per HCW)
P_{PH}	Transmission probability from Patient to HCW per contact
HHC	Hand hygiene compliance
λ	Hand hygiene rate defined as $\frac{HHC*c'*n_{pat}}{(1-HHC)*n_{HCW}}$

Model equations

$$\frac{dU_{pat}}{dt} = -\mu * U_{pat} - c * P_{HP} * U_{pat} * \frac{C_{HCW}}{n_{HCW}} + (1-\pi) * (\mu * U_{pat} + \Upsilon * C_{pat}) \quad (1)$$

$$\frac{dC_{pat}}{dt} = -\Upsilon * C_{pat} + c * P_{HP} * U_{pat} * \frac{C_{HCW}}{n_{HCW}} + \pi * (\mu * U_{pat} + \Upsilon * C_{pat}) \quad (2)$$

$$\frac{dU_{HCW}}{dt} = -\left(c' * P_{PH} * C_{pat} * \frac{U_{HCW}}{n_{HCW}}\right) + \lambda * C_{HCW} \quad (3)$$

$$\frac{dC_{HCW}}{dt} = \left(c' * P_{PH} * C_{pat} * \frac{U_{HCW}}{n_{HCW}}\right) - \lambda * C_{HCW} \quad (4)$$

Estimates of transition probability from HCWs to patient (P_{HP}) and the ward reproduction number (R_A)

From Worby et al.,[1] we have an estimate from our data of the force of infection, β, arising from a single colonised patient.

Assuming the number of colonized HCWs can be approximated by the quasi-equilibrium values, we can use equation (1)-(4) to derive the expression for P_{HP} in terms of β and other parameters.

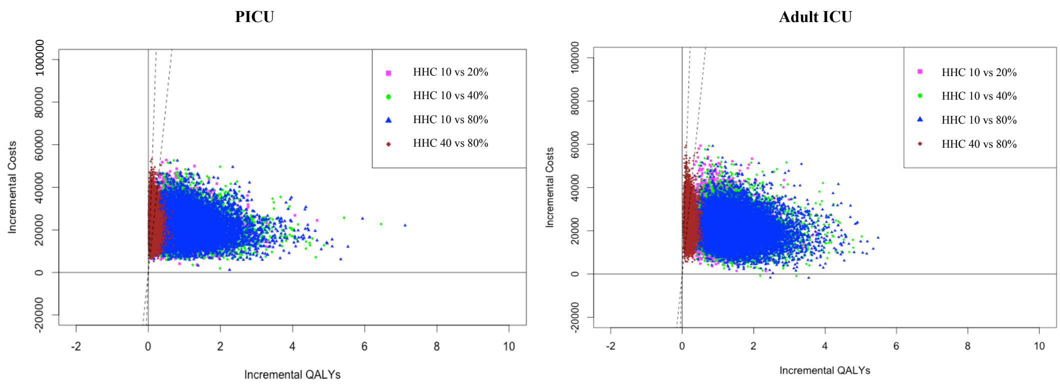
$$P_{HP} = \frac{\beta*(c'*P_{PH}+ \lambda*\text{n\_HCW})}{c*c'*P_{PH}}$$

We used directly observed values of c, c', n_{HCW}, n_{pat}, and HHC while P_{PH} was adopted from elsewhere, estimated by McBryde et al.[2]

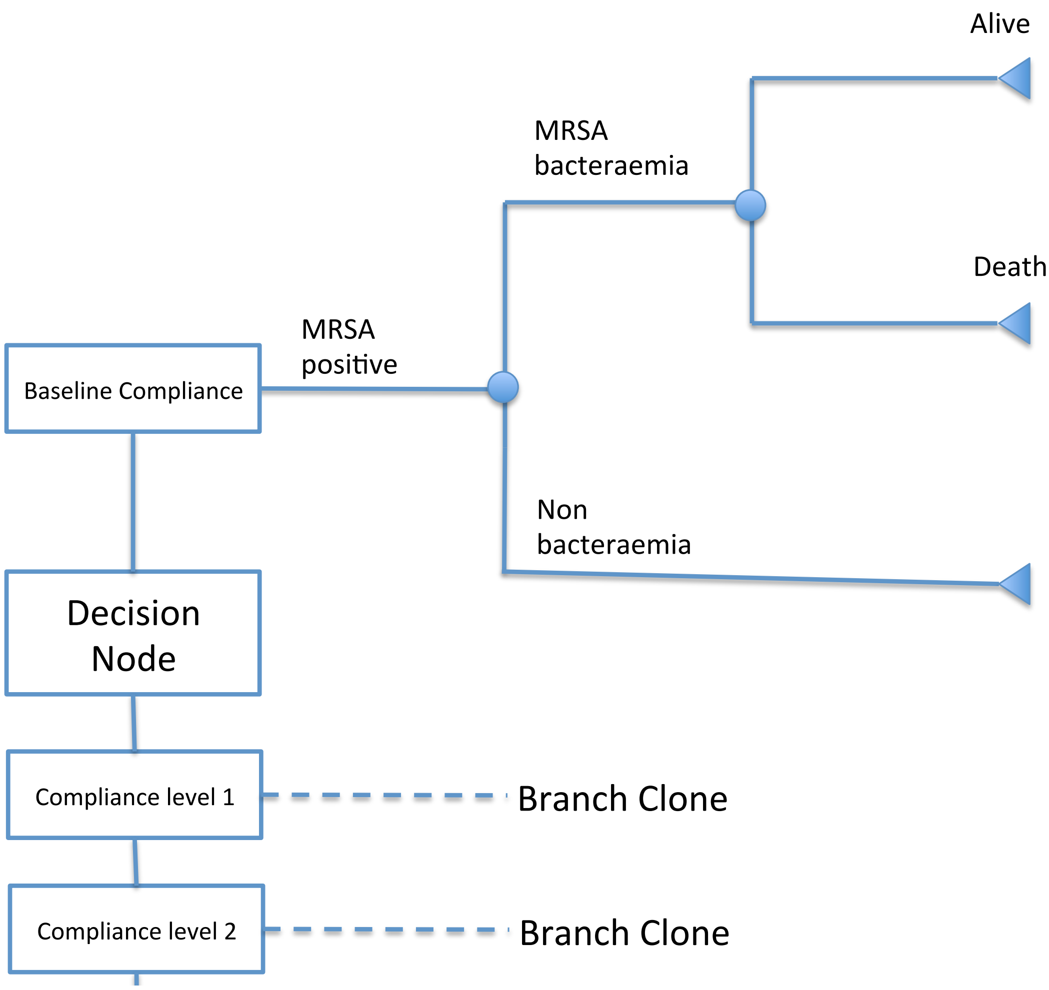
The ward reproduction number (R_A), the number of secondary cases arising from one primary case in a completely susceptible population, is given by

$$R_A = \frac{c*P_{HP}*c'*P_{PH}*(\text{n\_pat}-1)}{\gamma*(\lambda*\text{n\_HCW}+P_{PH}*c')}$$

Appendix C2: Plot of all iterations from four comparisons in probability sensitivity analysis for PICU (left) and adult ICU (right)



Appendix C3: Structure of decision analytic model



Appendix D: Peer reviewed publications arising directly from the thesis

Luangasanatip N, Hongsuwan M, Limmathurotsakul D, Lubell Y, Lee AS, Harbarth S, Day NP, Graves N, Cooper BS. Comparative efficacy of hospital hand hygiene promotion interventions: a systematic review and network meta-analysis. BMJ. 2015;351:h3728.

Luangasanatip N, Hongsuwan M, Lubell Y, Limmathurotsakul D, Teparrukkul P, Chaowarat S, Day NP, Graves N, Cooper BS. Long-term survival after intensive care unit discharge in Thailand: a retrospective study. Crit Care. 2013 Oct 3;17(5):R219.

Luangasanatip N, Hongsuwan M, Lubell Y, Limmathurotsakul D, Srisamang P, Day NP, Graves N, Cooper BS. Cost-effectiveness of hand hygiene promotion for MRSA bloodstream infection in ICU settings. (Under review)

Comparative efficacy of interventions to promote hand hygiene in hospital: systematic review and network meta-analysis

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Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmj.h3728)

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doi: 10.1136/bmj.h3728

Accepted: 22 June 2015

ABSTRACT

OBJECTIVE
To evaluate the relative efficacy of the World Health Organization 2005 campaign (WHO-5) and other interventions to promote hand hygiene among healthcare workers in hospital settings and to summarize associated information on use of resources.

DESIGN
Systematic review and network meta-analysis.

DATA SOURCES
Medline, Embase, CINAHL, NHS Economic Evaluation Database, NHS Centre for Reviews and Dissemination, Cochrane Library, and the EPOC register (December 2009 to February 2014); studies selected by the same search terms in previous systematic reviews (1980-2009).

REVIEW METHODS
Included studies were randomised controlled trials, non-randomised trials, controlled before-after trials, and interrupted time series studies implementing an intervention to improve compliance with hand hygiene among healthcare workers in hospital settings and measuring compliance or appropriate proxies that met predefined quality inclusion criteria. When studies had not used appropriate analytical methods, primary data were re-analysed. Random effects and network meta-analyses were performed on studies reporting directly observed compliance with hand hygiene when they were considered sufficiently homogeneous with regard to interventions and participants. Information on resources required for interventions was extracted and graded into three levels.

RESULTS
Of 3639 studies retrieved, 41 met the inclusion criteria (six randomised controlled trials, 32 interrupted time series, one non-randomised trial, and two controlled before-after studies). Meta-analysis of two randomised controlled trials showed the addition of goal setting to WHO-5 was associated with improved compliance (pooled odds ratio 1.35, 95% confidence interval 1.04 to 1.76; I^2=81%). Of 22 pairwise comparisons from interrupted time series, 18 showed stepwise increases in compliance with hand hygiene, and all but four showed a trend for increasing compliance after the intervention. Network meta-analysis indicated considerable uncertainty in the relative effectiveness of interventions, but nonetheless provided evidence that WHO-5 is effective and that compliance can be further improved by adding interventions including goal setting, reward incentives, and accountability. Nineteen studies reported clinical outcomes; data from these were consistent with clinically important reductions in rates of infection resulting from improved hand hygiene for some but not all important hospital pathogens. Reported costs of interventions ranged from $225 to $4669 (£146-£3035; €204-€4229) per 1000 bed days.

CONCLUSION
Promotion of hand hygiene with WHO-5 is effective at increasing compliance in healthcare workers. Addition of goal setting, reward incentives, and accountability strategies can lead to further improvements. Reporting of resources required for such interventions remains inadequate.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Hand hygiene among healthcare workers is possibly one of the most effective measures to reduce healthcare associated infections, but compliance remains poor in many hospital settings

In 2005 WHO launched a campaign to improve hand hygiene in healthcare settings by promoting a multimodal strategy consisting of five components: system change, training and education, observation and feedback, reminders in the hospital, and a hospital safety climate

WHAT THIS STUDY ADDS

These meta-analyses provide evidence that the WHO campaign is effective at increasing compliance with hand hygiene in healthcare workers

There is evidence that additional interventions (used in conjunction with the WHO campaign elements), including goal setting, reward incentive, and accountability, can lead to further improvements

Reporting on resource implications of such interventions is limited

Introduction

At any point in time more than 1.4 million patients around the world experience healthcare associated infections.[1 2] Such infections cause excess morbidity and are associated with increased mortality.[2 3] Direct contact between patients and healthcare workers who are transiently contaminated with nosocomial pathogens is believed to be the primary route of transmission for several organisms and can lead to patients becoming colonised or infected. Although hand hygiene is widely thought to be the most important activity for the prevention of nosocomial infections, a review of hand hygiene studies by the World Health Organization (WHO) found that baseline compliance with hand hygiene among healthcare workers was on average only 38.7% (range 5-89%).[4]

In 2005, the WHO World Alliance for Patient Safety launched a campaign, the First Global Patient Safety Challenge—“Clean Care is Safer Care”—aiming to improve hand hygiene in healthcare.[4] This campaign

(WHO-5) promotes a multimodal strategy consisting of five components: system change, training and education, observation and feedback, reminders in the hospital, and a hospital safety climate. More recently, additional strategies for improving hand hygiene have been evaluated, including those based on behavioural theory.

We assessed the relative effectiveness of WHO-5 and other strategies for improving compliance with hand hygiene in healthcare workers in hospital settings. Evaluation of the evidence for the effectiveness of different interventions is complicated by three factors: firstly, most evaluations of interventions to promote hand hygiene use non-randomised study designs, and in many cases the reported analysis is inappropriate or methodological quality is too low to allow meaningful conclusions to be drawn;[5-8] secondly, there is wide variation between studies in the activities to promote hand hygiene used in the comparison group; thirdly, direct head-to-head comparisons of most interventions are lacking.[7]

We aimed to overcome these problems by restricting attention to randomised trials and high quality non-randomised studies, re-analysing data when necessary; explicitly accounting for activities to promote hand hygiene in the comparison group in each study; and using network meta-analysis to allow indirect comparison between interventions.

We also summarise information on changes in clinical and microbiological outcomes associated with interventions when this was reported. Information on resources used in different interventions is essential for those wanting to implement such interventions or evaluate their cost effectiveness.[9 10] An additional aim was therefore to document information on resources used in interventions to promote hand hygiene.

Methods

We developed a protocol and used systematic methods to identify relevant studies, screen study eligibility, and assess study quality. This protocol was not registered. This review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11]

Search strategy

We used a two stage search strategy. Firstly, we obtained all studies considered in two previous reviews (covering the period up to November 2009), including those that had been reported as failing to meet inclusion criteria.[5 6] Secondly, we extended the search from these studies from December 2009 to February 2014. We searched Medline, Embase, Cumulative Index to Nursing and Allied Health (CINAHL), Database of Abstracts of Reviews of Effects (DARE), National Health Service Economic Evaluation Database (NHS-EED), National Health Service Centre for Reviews and Dissemination (NHS-CRD) and British Nursing Index (BNI), Cochrane Library (Cochrane database of systematic reviews, Cochrane central register of controlled trials, Cochrane methodology register, Health Technology assessment database), Clinical Trial.gov, Current Clinical Control trial, Cochrane Effective Practice and Organisation of Care Group (EPOC) register, American College of Physicians journal, and reviews of evidence based medicine. Results were limited to peer reviewed publications. To validate previous search results we also repeated the electronic search for three earlier years (1980, 1995, and 2009). The complete search strategy is provided in appendix 1.

Inclusion and exclusion

Studies were included if they met all the following initial criteria: they evaluated one or more interventions intended to improve hand hygiene compliance among healthcare workers in a hospital setting; they measured compliance with hand hygiene using opportunities with prespecified indications or using proxies linked to compliance (such as consumption of soap and alcohol hand rub); they were either randomised controlled trials, non-randomised trials, controlled before-after studies, or used an interrupted time series design.

We placed no restrictions on promotion of hand hygiene in the comparison group. Studies were excluded if they were not reported in peer reviewed publications or not written in English.

We applied a methodological filter by excluding studies that failed meet minimal quality criteria specified by the Cochrane Effectiveness Practice and Organisation of Care Group (EPOC). Acceptable study designs were randomised controlled trials and non-randomised trials (with at least two intervention and two control sites); controlled before-after studies (with outcome measures before and after the intervention from at least two intervention and two comparable control sites); and interrupted time series (with a clearly defined point in time for the intervention and outcome measures from at least three time points in both baseline and intervention periods).[12 13]

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in dissemination.

Data extraction and assessment of quality

Two reviewers (NL and BSC) independently screened the titles and abstracts of the citations obtained from the search to assess the eligibility. Consensus was reached by discussion if initial assessments differed. NL evaluated the full text and abstracted data, which was checked by BSC.

The reviewers abstracted data including study design and duration, population, activities to promote hand hygiene in both intervention and comparison groups, hand hygiene outcomes, clinical and microbiological outcomes, measurement methods, and settings. When possible, we classified hand hygiene promotion activities according to WHO guidelines on hand hygiene in healthcare.[4] We grouped activities into eight components: system change, education, feedback, reminders,

Table 1 | Description of eight components of interventions to promote hand hygiene in healthcare workers

Component	Description
System change*	Ensuring necessary infrastructure is available including access to water, soap and towels and alcohol based handrub at point of care
Education and training	Providing training or educational programme on importance of hand hygiene and correct procedures for hand hygiene for healthcare workers
Feedback	Monitoring hand hygiene practices among healthcare workers while providing compliance feedback to staff
Reminders at workplace	Prompting healthcare workers either through printed material, verbal reminders, electronic communications or other methods, to remind them about importance of hand hygiene and appropriate indications and procedures
Institutional safety climate	Active participation at institutional level, creating environment allowing prioritisation of hand hygiene
Goal setting	Setting of specific goals aimed at improving compliance with hand hygiene, which can both apply at individual and group level and can include healthcare associated infection rates
Reward incentives	Interventions providing any reward incentive for participants completing a particular task or reaching a certain level of compliance. Both non-financial and financial rewards are included
Accountability	Interventions involved with improving healthcare workers' accountability both at individual and unit level

*If the intervention period included changing the location or formulation of alcohol based handrub or installing more handrub dispensers, the baseline intervention was counted as no intervention or standard practice (no system change component), even if alcohol based handrub had been used during the baseline period.

safety climate, incentives, goal setting, and accountability (table 1). Results and raw compliance data from each study were extracted for further re-analyses. In addition, we extracted the costs of hand hygiene interventions or data on use of resources (materials and time spent on interventions) when appropriate. Additional information was obtained from the authors if it was not clear from the manuscript. For all included studies we used prespecified definitions to record the level of information (high, moderate, or low) about resources used for promotion of hand hygiene (see appendix 2).

Assessment of risk of bias in included studies

We used the Cochrane Collaboration's tool to assess risk of bias.[14] Nine standard criteria for randomised controlled trials, non-randomised trials, and controlled before-after studies and seven standard criteria for interrupted time series were applied and used to classify each study's risk of bias as low, high, or unclear.

Data synthesis and statistical analysis

Data synthesis was performed separately for different study designs. The primary evidence synthesis was based on studies that used direct observation to measure compliance with hand hygiene. We restricted our analysis to this outcome because it reflects the opportunities for hand hygiene.

For randomised controlled trials, we used Cochrane Review Manager (RevMan; version 5.1) to calculate the natural logarithm of the odds ratio and associated variance to estimate the pooled odds ratio with a random effects model.[15] The same method was applied to non-randomised trials, and controlled before-after studies if applicable. Heterogeneity between studies was assessed with the I^2 statistic. Risk of publication bias was evaluated with an enhanced contour funnel plot.[16,17]

For interrupted time series, if re-analysis was required, we used a generalised linear segmented regression analysis to estimate the stepwise change in level and change in trend associated with the intervention.[18] This approach is similar to that proposed by Ramsey and colleagues[19] and Vidanapathirana and colleagues,[20] except that it accounts for the binomial nature of the data, appropriately weighting each data point by the number of observations. We accounted for any evidence of autocorrelation by using Newey-West standard errors.[21] Analysis was performed with Stata 13 (Statacorp LP, College Station, TX). We then estimated two summary measures that combined both stepwise and trend changes. Firstly, we calculated the mean natural logarithm of the odds ratio for hand hygiene associated with the intervention, a measure of relative improvement. Secondly, we calculated the mean percentage change in compliance in the period after the intervention (compared with that expected if there had been no intervention), an absolute measure of improvement in compliance. Standard errors were derived with the delta method by using the emdbook package in R.[22,23] Appendix 3 provides full details.

Network meta-analysis

Network meta-analysis aims to combine all of the evidence, both direct and indirect, to estimate the comparative efficacy of all the interventions.[24] Each intervention strategy is represented by a node in the network. If a study directly compares two interventions they are directly connected by a link on the network and a direct comparison is possible. If two interventions are connected indirectly (for example, if there are studies comparing each with a third intervention), then indirect comparison is possible.

We used network meta-analysis to compare the relative effectiveness of four different strategies: no promotion of hand hygiene, single component interventions, WHO-5, and WHO-5 and others (table 2). We included in the network meta-analysis those studies that included only these strategies and permitted a segmented regression analysis and directly observed compliance with hand hygiene.[25,26]

The effect sizes obtained from each comparison were combined in a network meta-analysis with a random effects model.[25] Effect sizes were taken as the mean of the natural logarithm of the odds ratio for the hand hygiene intervention as estimated with the segmented regression model. Intervention rankings and associated credible intervals were obtained. Model fitting for the meta-analysis was carried out within a Bayesian

Table 2 | Mean odds ratios with 95% credible intervals for interventions strategies to promote hand hygiene. Results are from random effects network meta-analysis model

Strategies*	Description	Mean OR (95% credible interval)
None/current practice	No intervention or current practice	Reference
Single intervention	Single intervention (system change or education)	4.30 (0.43 to 46.57)
WHO-5†	WHO-5 components	6.51 (1.58 to 31.91)
WHO-5* + others	WHO-5 plus incentives, goal setting, or accountability	11.83 (2.67 to 53.79)

*Model fit statistic: posterior mean residual deviance=10.40 and deviance information criterion (DIC)=23.86.
†Contained five components: system change, education, feedback, reminders, and institutional safety climate (see table 1 for details).

framework using WinBUGS.[26] Inconsistency checks were performed for closed loops in the network.[27] Full model details are provided in appendix 4.

We performed a sensitivity analysis by excluding studies that implemented multicomponent strategies in a stepwise manner without sufficient data to evaluate individual components. This led to the exclusion of three studies.[28-30]

Results

Overall description

Figure 1 shows a summary of the review process. Of 3639 studies screened, 142 studies met initial inclusion criteria and 41 of these met EPOC criteria. Among these 41 studies, six were randomised controlled trials (including three cluster randomised controlled trials),[31-36] 32 were interrupted time series,[28-30 37-65] one was a non-randomised trial,[66] and two were controlled before-after studies.[67 68] Appendix 5 give details of the reasons for exclusion. Applying our search strategy to three years covered by previous reviews did not yield any studies meeting our inclusion criteria that had not already been included.

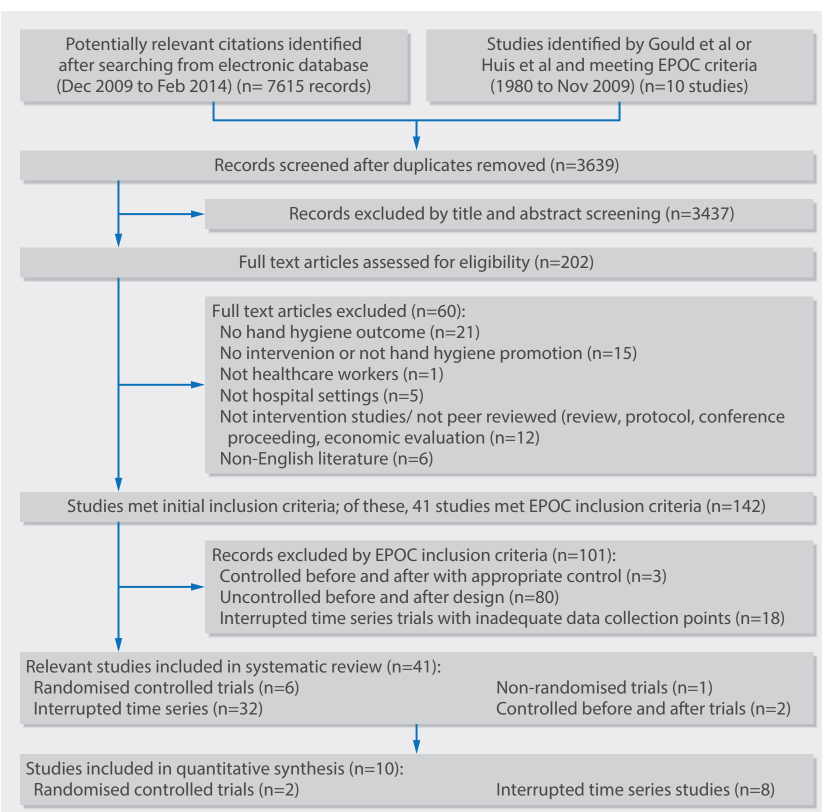

Fig 1 | Flow chart of study identification in systematic review of interventions to promote hand hygiene in healthcare workers

Seventeen studies applied interventions to the whole hospital, while 21 studies enrolled hospital wards. Three studies allocated interventions to specific healthcare workers.[31 33 36] Twenty five studies were conducted in either a hospital-wide setting or combined intensive care units and general wards, while 11 were conducted in intensive care units or general wards alone. Of 10 studies conducted in more than one hospital, three included two or more countries.[42 48 50] Only five of the 41 studies were conducted in low or middle income countries.[33 36 46 50 51]

Study periods ranged from two months to six years. In 11 studies the period was up to one year; in 17 studies it was more than a year and up to three years; and in 13 it was more than three years. Among the 32 interrupted time series, only 11 were longer than 12 months.

In 34 studies hand hygiene was observed in all types of healthcare workers with patient contact, while six studies considered only nurses and/or nursing assistants.[33 34 36 60 64 68] One study recruited only nursing students as participants.[54] One study also included patients' relatives.[39]

Six studies used a single faceted intervention: four implemented education alone[33 46 54 68] and two applied system change or reminders.[39 44] Seventeen studies used interventions equivalent to WHO-5, and six of these added supplemental interventions including goal setting, incentives, and accountability.[28 34 40 45 56 66] Nineteen studies implemented interventions with two to four components; four of these applied components not in WHO-5, including goal setting and incentives.[37 38 41 59]

Thirty studies (four randomised controlled trials, 25 interrupted time series, and one non-randomised trial) used direct observation to measure compliance with hand hygiene. Two of these used a combination of video recorders and external observers.[37 38] Proxy measures were assessed in 19 studies including the rate of hand hygiene events, consumption of hand hygiene products (alcohol hand rub or soap), and a hand hygiene score checklist (two randomised controlled trials, 15 interrupted time series, and two controlled before and after studies). Clinical outcomes were reported in 19 studies.[28-30 35 42 46-52 55-57 59 62 63 66 67 69] Appendix 6 provides full study characteristics including study design, setting, intervention, and comparison groups.

Examination of funnel plots (appendix 7) did not provide any clear evidence of publication bias, though evidence for or against such bias was limited by the fact that there were no more than four studies for any pairwise comparison of strategies.

Quality assessment

Ten studies were considered to have a high risk of bias. Thirty one had either low or unclear risk. High risk of bias was present in all three non-randomised trials or controlled before-after studies but only in seven out of

32 interrupted time series. No randomised controlled trials or cluster randomised controlled trials were thought to have a high risk of bias (fig 2).

The two controlled before-after studies[67 68] had high risks for inadequate allocation sequence and concealment, while one non-randomised trial[66] had high risk of dissimilarity in baseline outcome between experimental and control groups.

Fourteen studies (34%) had a low risk of bias due to the knowledge of allocated intervention, as these studies either measured objective outcomes (such as alcohol consumption or output from electronic counting devices) or stated that the observers were blinded to the intervention. The rest of the studies had unclear risk as they did not report whether the observers were blinded.

Risk of selective outcome reporting was unclear in 33 studies as pre-specified protocols were reported only in three randomised controlled trials.[32 34 35] Two of the interrupted time series had a high risk of selective outcome reporting as they reported on a non-periodical basis.[28 59] Among the interrupted time series, six had a high risk that outcomes were affected by other interventions such as a universal chlorhexidine body washing programme,[42 63] reinforcement of standard precautions,[42] screening and decolonisation for multidrug-resistant micro-organisms,[48] quality improvement program,[46 59] and antibiotic use and healthcare associated infections control policy implemented at the same time.[56]

RCTs, CCT, CBA	Was allocation sequence adequately generated?	Was allocation adequately concealed?	Were baseline outcome measurements similar?	Were baseline charateristics similar?	Were incomplete outcome data adequately addressed?	Was knowledge of allocated interventions adequately addressed?	Was study adequately protected against contamination?	Was study free from selective outcome reporting?	Was study free from other risks of bias?
Fuller 2012	+	+	?	?	+	+	?	+	+
Huis 2013	+	?	+	+	+	+	?	+	+
Mertz 2010	+	+	+	+	+	+	?	+	?
Huang 2002	?	?	+	+	+	?	?	?	?
Fisher 2013	+	+	+	?	+	+	+	?	+
Salamati 2013	+	?	+	+	+	?	+	?	+
Mayer 2011	?	?	−	−	?	?	?	?	+
Gould 2011	−	−	+	?	?	+	?	?	+
Benning 1997	−	−	?	+	+	+	+	?	?

ITS	Was intervention independent of other changes?	Was shape of intervention effect pre-specified?	Was intervention unlikely to affect data collection?	Was knowledge of allocated interventions adequately prevented during study?	Were incomplete outcome data adequately addressed?	Was study free from selective outcome reporting?	Was study free from other risks of bias?
Derde 2014	−	+	+	?	+	?	+
Lee 2013	−	+	+	?	+	?	+
Marra 2013	+	+	+	?	+	?	+
Al-Tawfiq 2013	+	+	+	?	+	−	?
Armellino 2013	+	+	+	+	+	?	+
Armellino 2012	+	+	+	+	+	?	+
Chan 2013	+	+	+	+	+	?	+
Crews 2013	+	+	+	+	+	?	?
Salmon 2013	+	+	+	?	+	?	+
Talbot 2013	?	+	+	?	+	?	+
Higgins 2013	?	+	+	?	+	?	+
Helder 2012	?	+	+	+	+	?	+
Kirkland 2012	+	+	+	?	+	?	?
Morgan 2012	+	+	+	?	+	?	+
Stone 2012	+	+	+	+	+	?	+
Jaggi 2012	−	+	+	?	+	?	+
Lee 2012	?	+	+	+	+	?	+
Mestre 2012	+	+	+	+	+	?	?
Koff 2011	+	+	+	?	+	?	+
Doron 2011	+	+	+	?	+	?	+
Marra 2011	+	+	+	+	+	?	+
Yngstrom 2001	−	+	+	?	+	−	+
Helms 2010	+	+	+	?	+	?	?
Chou 2010	+	+	+	?	+	?	+
Vernaz 2008	−	+	+	?	+	?	+
Whitby 2008	+	+	+	?	+	?	?
Grayson 2008	+	+	+	?	+	?	+
Eldrige 2006	+	+	+	?	+	?	+
Johnson 2005	−	+	+	?	+	?	+
Khatib 1999	+	+	+	?	+	?	+
Tibballs 1996	+	+	+	?	+	?	+
Dubbert 1990	+	+	+	?	+	?	+

+ Low risk of bias
? Unclear risk of bias
− High risk of bias

Fig 2 | **Assessment of risk of bias in included studies of interventions to promote hand hygiene in healthcare workers**

Meta-analysis/data synthesis

Randomised controlled trials

Four of six randomised controlled trials measured compliance with hand hygiene by direct observation with indications similar to WHO-5.[32-35] Two of these studies compared WHO-5 with WHO-5 combined with goal setting (WHO-5+).[32 34] Huis and colleagues performed a cluster randomised trial in 67 wards from three hospitals in the Netherlands.[34] Compliance immediately after the intervention increased from 23% to 42% in the WHO-5 arm and from 20% to 53% in the WHO-5+ arm; in both arms improvements were sustained six months later. Fuller and colleagues used a three year stepped wedge design in 16 intensive care units and 44 acute care of the elderly wards and reported an absolute increase in compliance of 13-18% and 10-13%, respectively, in implementing wards.[32] Only 33 of 60 enrolled wards, however, implemented the intervention (22 out of 44 elderly wards and 11 out of 16 intensive care units), and the intention to treat analysis did not show increased compliance in the elderly wards while compliance in intensive care units increased by 7-9%. Meta-analysis (with intention to treat results) provided evidence favouring the WHO-5+ strategy. The pooled odds ratio was 1.35 (95% confidence interval 1.04 to 1.76; I^2=81%) (fig 3). The large heterogeneity seemed to be caused by the low fidelity to intervention in acute care of the elderly wards. Per protocol analyses gave similar odds ratios for compliance to the study by Huis and colleagues (1.67 (95% confidence interval 1.28 to 2.22) for elderly wards and 2.09 (1.55 to 2.81) for intensive care units). Two other randomised controlled trials directly reported observed compliance with hand hygiene. An individually randomised trial of an education programme versus no intervention for nurses in China reported an absolute improvement in compliance of

Author	Log (odds ratio)	Standard error	Weight (%)	Mean odds ratio (95% CI)
Fuller 2012 (acute care of elderly wards)	0.058	0.092	34.3	1.06 (0.88 to 1.27)
Fuller 2012 (intensive care units)	0.365	0.102	33.1	1.44 (1.18 to 1.76)
Huis	0.495	0.106	32.6	1.64 (1.33 to 2.02)
Total (95% CI)			100.0	1.35 (1.04 to 1.76)

Test for heterogeneity: τ^2=0.04, χ^2=10.63, df=2, P=0.005, I^2=81%

Test for overall effect: z=2.27, P=0.02

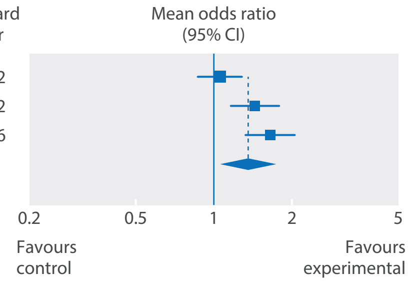

Fig 3 | **Forest plot of the associations between WHO-5 and goal setting compared with WHO-5 alone and compliance with hand hygiene from randomised controlled trials using intention to treat results**

32.7% (95% confidence interval 15.6% to 49.7%) for opportunities before contact with patients and 20.4% (5.6% to 35.2%) for opportunities after contact (baseline compliance before and after contact was about 25% and 37%, respectively, in both arms).[33] In Canada, a cluster randomised trial of a bundle of education, performance feedback, and visual reminders in 30 hospital units where alcohol hand rub was available at point of care in both arms (but with no other interventions in the control arm) reported a higher adherence after the intervention in the intervention arm (mean difference 6.3%, 95% confidence interval 4.3% to 8.4%).[35] In both arms baseline compliance was low (16%).

Fisher and colleagues randomised individuals to either a control group where hand hygiene was not actively promoted or an intervention arm that used audio reminders and individual feedback.[31] They assessed compliance using an automated system at entry to and exit from patients' rooms. The intervention was associated with a 6.8% (95% confidence interval 2.5% to 11.1%) improvement in compliance. Salamati and colleagues randomised nursing personnel to either a motivational interviewing intervention (a behaviour modification approach initially developed to treat patients with alcoholism) or a control group.[36] Both arms also received an educational intervention. The outcome measure was a composite hand hygiene score, which was found to increase in the intervention arm. The scoring details, however, were unclear.

Interrupted time series

Of 32 interrupted time series, 25 measured hand hygiene compliance. Only 18 studies with direct observation, however, reported the number of observations at each time point, making them eligible for re-analysis.[28-30 37 38 40-46 48 50 54 56 60 64 65] As some of these studies were conducted at multiple sites[48] or had multiple intervention phases,[56] 22 pairwise comparisons from these 18 studies were available for re-analysis (fig 4). In four studies there was evidence of positive first order autocorrelation.[37 38 40 56]

The baseline compliance ranged from 7.6% to 91.3%. Twelve of 22 comparisons showed a declining trend in compliance during the period before intervention; seven of these did not report any activities to promote hand hygiene before intervention, while another four used only education or reminders. Fifteen pairwise contrasts showed a positive change in trend for compliance with hand hygiene after the intervention (table 3). All but four contrasts showed both stepwise increases in compliance with hand hygiene associated with the intervention and increases in mean compliance in the period after intervention compared with that expected in the absence of the intervention. The range was wide: the mean change in hand hygiene attributed to the intervention varied between a decrease of 14.8% and an increase of 83.3% (table 3). Two studies had an intervention period lasting at least two years; neither showed evidence for any decline in compliance over this period.[40 41] In only one study was there a net trend for decreasing compliance after the intervention (fig 4).[45]

Non-randomised trials and controlled before-after studies

Mayer and colleagues compared WHO-5 and reward incentives (WHO-5+) with a combination of system change, education, and feedback using a staggered introduction of an intervention bundle, across four out of six patient units.[66] The WHO-5+ intervention was associated with improved compliance, which increased from 40% to 64% in one two-unit cohort and from 34% to 49% in the other.

Benning and colleagues reported a hospital-wide trend of increased soap and alcohol consumption in both intervention (package of system change, reminders, and safety climate) and control (no intervention) groups but found no evidence of an increased effect in the intervention group.[67] Gould and colleagues found no evidence of improvement in frequency of hand decontamination in surgical intensive care wards resulting from a series of educational lectures compared with no intervention (control).[68]

Analysis of interrupted time series and network meta-analysis

Among the 22 pairwise comparisons from interrupted time series, 18 had clear details about interventions and similar indications for compliance with hand hygiene among qualified healthcare workers. In 16 of these the intervention period included additional intervention components alongside measures to promote hand hygiene used in the baseline period, and all outcome data favoured the intervention (fig 5). In the two comparisons where there was no improvement in hand

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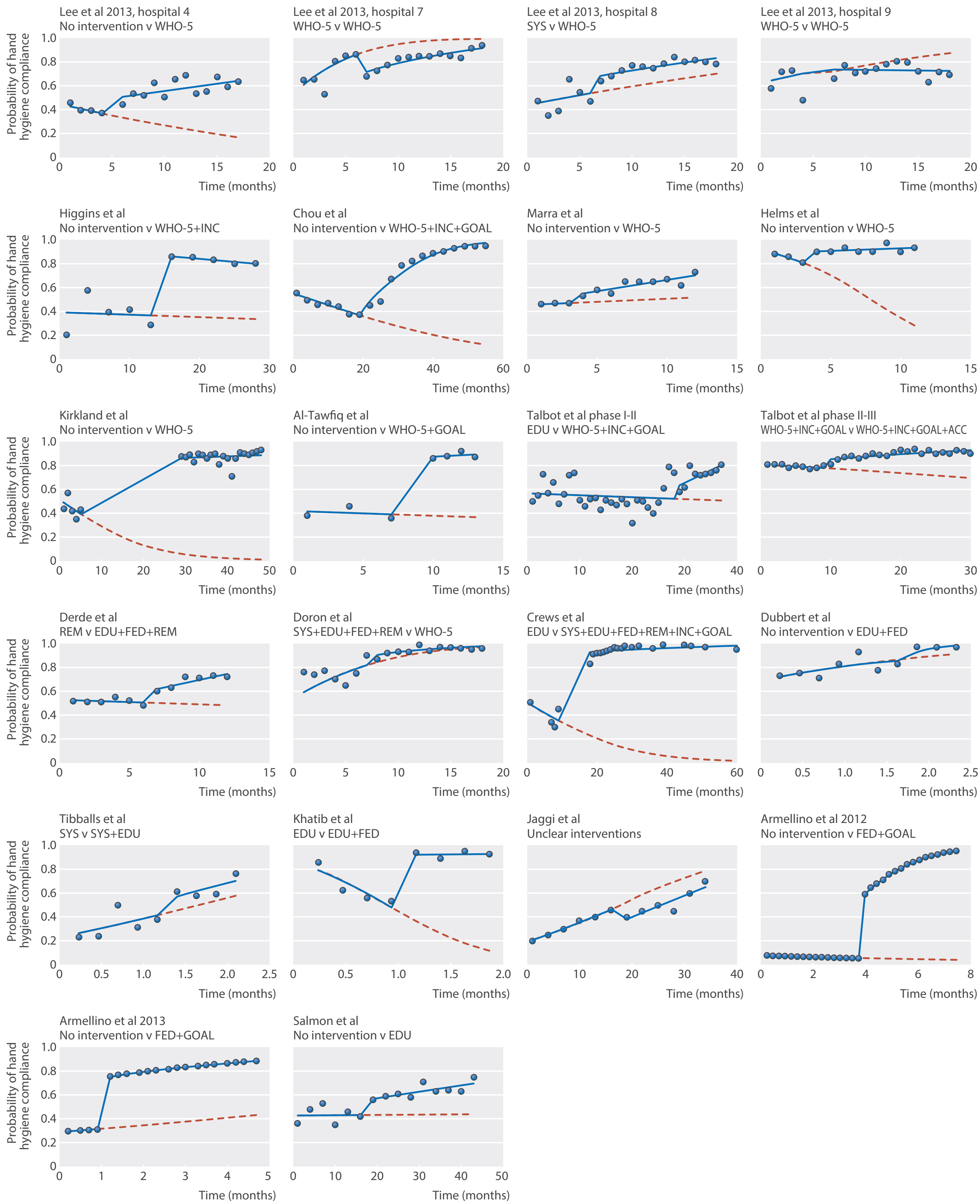

Fig 4 | Re-analysis of studies involving interrupted time series where the outcome was hand hygiene compliance. Points represent observations, solid lines show expected values from fitted segmented regression models, and broken lines represent extrapolated trends before intervention. SYS=system change; EDU=education; FED=feedback; REM=reminders; SAF=institutional safety climate; INC=incentives; GOAL=goal setting; ACC=accountability; WHO-5=combined intervention strategies including SYS, EDU, FED, REM, and SAF

Table 3 | Results of re-analysis of studies using interrupted time series to assess compliance with hand hygiene

Study	Comparison	Baseline (intercept) % compliance	Baseline (intercept) Coefficient (SE)	Coefficient (SE) for baseline trend	Coefficient (SE) for change in trend	Coefficient (SE) for change in level	Mean (95% CI)* % change in compliance
Lee[48]							
Hospital 4	No intervention *v* WHO-5	44.6	−0.215 (0.30)	−0.081 (0.10)	0.130 (0.10)	0.606 (0.26)	29.9 (3.5 to 56.4)
Hospital 7	WHO-5 *v* WHO-5	53.8	0.154 (0.29)	0.281 (0.07)	−0.151 (0.08)	−1.042 (0.25)	−11.5 (−13.5 to −9.5)
Hospital 8	SYS *v* WHO-5	44.6	−0.215 (0.26)	0.059 (0.06)	0.014 (0.06)	0.563 (0.19)	13.3 (−9.2 to 35.8)
Hospital 9	WHO-5 *v* WHO-5	62.3	0.503 (0.33)	0.088 (0.13)	−0.094 (0.13)	−0.007 (0.51)	−9.7 (−63.6 to 44.3)
Derde[42]	REM *v* EDU+FED+REM	52.8	0.112 (0.04)	−0.015 (0.01)	0.133 (0.02)	0.346 (0.05)	16.3 (13.6 to 19.1)
Higgins[45]	No intervention *v* WHO-5+INC	37.2	−0.428 (0.17)	−0.009 (0.25)	−0.030 (0.03)	2.448 (0.25)	48.8 (45.4 to 52.3)
Doron[43]	SYS+EDU+FED+REM *v* WHO-5	70.7	0.204 (0.12)	0.187 (0.10)	−0.040 (0.03)	0.586 (0.01)	4.7 (2.3 to 7.1)
Chou[40]†	No intervention *v* WHO-5+INC+GOAL	54.9	0.198 (0.03)	−0.039 (0.00)	0.151 (0.01)	0.453 (0.17)	56.4 (53.1 to 59.8)
Marra[50]	No intervention *v* WHO-5	45.7	−0.173 (0.07)	0.020 (0.06)	0.063 (0.03)	0.218 (0.06)	11.5 (3.4 to 19.6)
Helms[30]	No intervention *v* WHO-5	91.3	2.350 (0.42)	−0.297 (0.18)	0.354 (0.19)	0.706 (0.33)	35.9 (−5.8 to 77.7)
Kirkland[29]	No intervention *v* WHO-5	51.3	0.052 (0.14)	−0.097 (0.04)	0.111 (0.04)	4.443 (1.03)	83.3 (77.0 to 89.6)
Al-Tawfiq[28]	No intervention *v* WHO-5+GOAL	41.3	−0.350 (0.09)	−0.014 (0.02)	0.081 (0.07)	2.328 (0.21)	49.9 (42.8 to 57.0)
Crews[41]	EDU *v* SYS+EDU+FED+REM+INC+GOAL	50.7	0.028 (0.12)	−0.070 (0.02)	0.103 (0.02)	3.679 (0.22)	38.2 (35.5 to 40.9)
Talbot (phase I)[56]†	EDU *v* WHO-5+INC+GOAL	56.7	0.271 (0.20)	−0.006 (0.02)	0.109 (0.02)	0.363 (0.41)	18.5 (−1.4 to 38.4)
Talbot (phase II)[56]	WHO-5+INC+GOAL *v* WHO-5+INC+GOAL+ACC	81.1	1.455 (0.45)	−0.020 (0.01)	0.060 (0.01)	0.464 (0.05)	15.0 (10.6 to 19.5)
Dubbert[60]	No intervention *v* EDU+FED	69.5	0.822 (0.34)	0.636 (0.39)	2.908 (1.57)	−0.753 (0.75)	0.7 (−10.0 to 11.4)
Tibballs[65]	SYS *v* SYS+EDU	23.4	−1.186 (0.53)	0.187 (0.10)	−0.040 (0.03)	0.453 (0.57)	11.9 (−18.4 to 42.1)
Khatib[64]	EDU *v* EDU+FED	86.2	1.836 (0.17)	−2.051 (0.26)	2.185 (0.52)	2.549 (0.29)	65.8 (58.6 to 73.0)
Jaggi[46]	Unclear intervention details	19.5	−1.420 (0.26)	0.080 (0.02)	−0.006 (0.03)	−0.586 (0.34)	−14.8 (−33.1 to 3.6)
Armellino[38]†	No intervention *v* FED+GOAL	7.6	−2.493 (0.15)	−0.088 (0.133)	0.849 (0.235)	3.046 (0.68)	45.4 (38.5 to 52.3)
Armellino[37]†	No intervention *v* FED+GOAL	29.0	−0.895 (0.04)	0.122 (0.10)	−0.109 (0.08)	2.267 (0.14)	74.9 (65.5 to 84.4)
Salmon[54]‡	No intervention *v* EDU	42.7	−0.295 (0.17)	0.003 (0.02)	0.021 (0.02)	0.485 (0.22)	17.9 (−0.3 to 36.2)

SYS=system change; EDU=education; FED=feedback; REM=reminders; SAF=institutional safety climate; INC=incentives; GOAL=goal setting; ACC=accountability; WHO-5=combined intervention strategies including SYS, EDU, FED, REM, and SAF.
*Mean change in hand hygiene compliance during period after intervention period attributed to intervention accounting for baseline trends (see appendix 3 for details).
†Evidence of autocorrelation; Newey-West standard errors reported.
‡Hand hygiene compliance measured in student nurses.

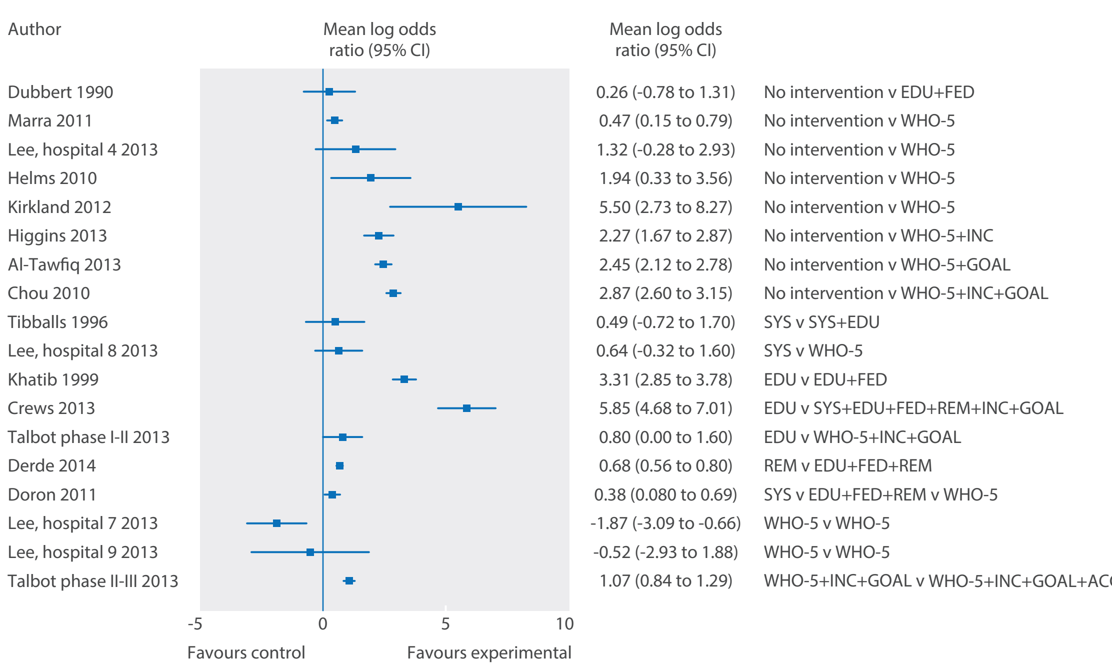

Fig 5 | Forest plot showing effect size as mean log odds ratios for hand hygiene compliance for all direct pairwise comparisons from interrupted time series studies. Lee and colleagues[48] was a multi-centre study. In hospitals 8 and 9 baseline strategy was already equivalent to WHO-5. SYS=system change; EDU=education; FED=feedback; REM=reminders; SAF=institutional safety climate; INC=incentives; GOAL=goal setting; ACC=accountability; WHO-5=combined intervention strategies including SYS, EDU, FED, REM, and SAF

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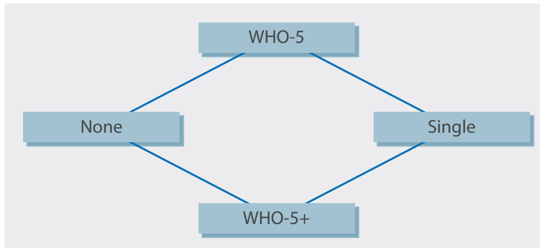

Fig 6 | Network structure for network meta-analysis of four hand hygiene intervention strategies from interrupted time series studies. Intervention strategies were: none (no intervention); single intervention; WHO-5; and WHO-5+ (WHO-5 with incentives, goal-setting, or accountability)

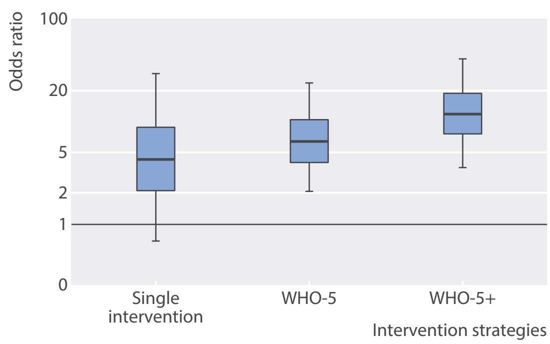

Fig 7 | Box-and-whiskers plot showing relative efficacy of different hand hygiene intervention strategies compared with standard of care estimated by network meta-analysis from interrupted time series studies. Lower and upper edges represent 25th and 75th centiles from posterior distribution; central line median. Whiskers extend to 5th and 95th centiles. Intervention strategies were single intervention; WHO-5; and WHO-5+ (WHO-5 with incentives, goal-setting, or accountability). Appendix 9 shows results from sensitivity analysis that excluded studies where interventions were implemented as multiple time points

hygiene, all components of the intervention were already in place in the baseline period.[48]

Twelve pairwise comparisons met the criteria for network meta-analysis, and included direct comparisons between all pairs of strategies except WHO-5 versus WHO-5+ and no intervention versus single intervention (fig 6). The network meta-analysis showed that although there was large uncertainty in effect sizes among the pairwise comparisons, point estimates for all intervention strategies indicated an improvement in compliance with hand hygiene compared with no intervention (fig 7). When two strategies, WHO-5 and WHO-5+, were compared with no intervention there was strong evidence that they were effective (table 2). The WHO5+ strategy also showed additional improvement compared with single intervention strategies and WHO-5 alone. For the latter comparison, which depended only on indirect comparisons, the estimated effect size was similar to that seen in the randomised controlled trials, though uncertainty was much larger (odds ratio for WHO-5 versus WHO-5+ was 1.82, 95% credible interval 0.2 to 12.2). WHO-5+ had the highest probability (67%) of being the best strategy in improving compliance (fig 8).

After we excluded studies with multiple stepwise interventions in the sensitivity analysis, there was a decrease in the effect size of all intervention strategies (appendix 4).

Clinical outcomes

Nineteen studies reported clinical or microbiological outcomes alongside hand hygiene outcomes. Six of these were multicentre studies,[35 42 48 55 62 67] and 13 were based in a single hospital.[28-30 46 47 49 52 56 57 59 63 66 69] All reported that improvements in hand hygiene were associated with reductions in at least one measure of hospital acquired infection and/or resistance rates. In most

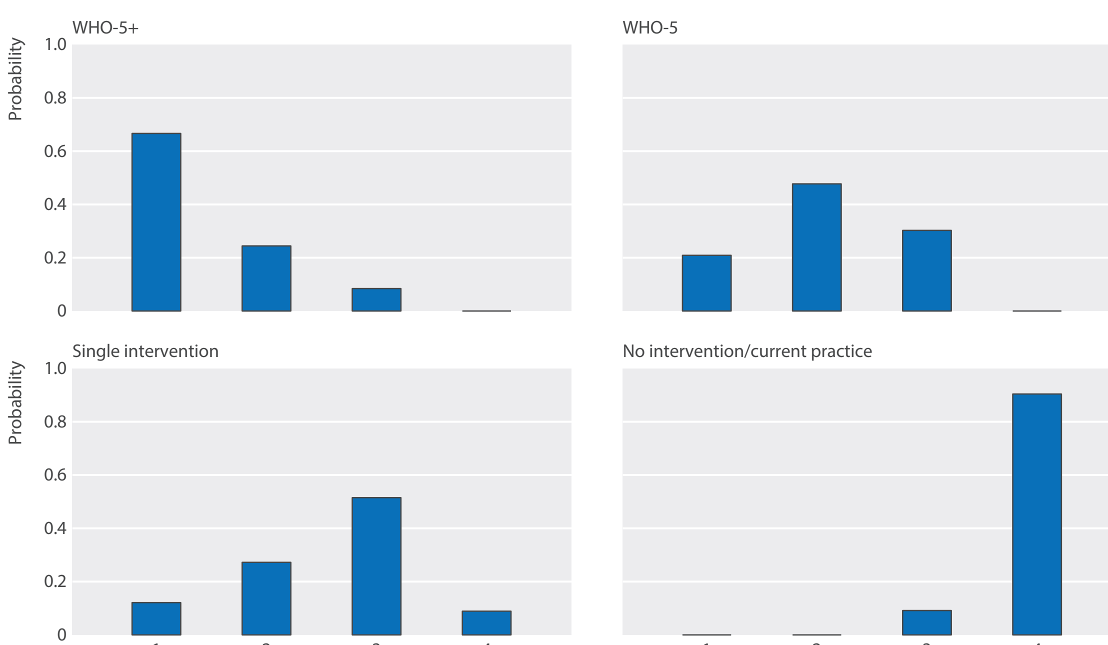

Fig 8 | Rankograms showing probabilities of possible rankings for each intervention strategy (rank 1=best, rank 4=worst) case, however, either appropriate analysis was lacking, denominators were not reported, time series data were not shown (making interrupted time series designs vulnerable to pre-existing trends), or numbers were too small to draw firm conclusions.

There were, however, three single centre studies that did not have these limitations.[49 57 63] Two of these studies, which lasted about seven years, used time series analysis to study associations between use of alcohol hand rub and clinical outcomes, with adjustment for changing patterns of antibiotic use.[49 57] Lee and colleagues found strong evidence (P<0.001) that increased use of alcohol hand rub was associated with reduced incidence of healthcare associated infection and evidence that it was associated with reduced healthcare associated methicillin resistant *Staphylococcus aureus* (MRSA) infection (P=0.02).[49] Vernaz and colleagues found strong evidence that increased use of alcohol based hand rub was associated with reduced incidence of MRSA clinical isolates per 100 patient days (P<0.001), reporting that 1L of hand rub per 100 patient days was associated with a reduction in MRSA of 0.03 isolates per 100 patient days.[57] No association was found between increased use of alcohol based hand rub and clinical isolates of *Clostridium difficile*. Johnson and colleagues reported that an intervention in an Australian teaching hospital associated with a mean improvement of compliance with hand hygiene from 21% to 42% was also associated with declining trends in clinical MRSA isolates (by 36 months after the intervention clinical isolates per discharge had fallen by 40% compared with the baseline before the intervention), declining trends in MRSA bacteraemias (57% lower than baseline after 36 months), and declining trends in clinical isolates of extended spectrum β lactamases (ESBL) producing *E coli* and *Klebsiella* (>90% below baseline 36 months after intervention), though there was no evidence of changes in patient MRSA colonisation at four or 12 months after the intervention.[63] In addition to hand hygiene, however, the intervention included patient decolonisation and ward cleaning, and the relative importance of these measures cannot be determined.

Among the multicentre studies, Grayson and colleagues described a similar hand hygiene intervention (but without additional decolonisation or ward cleaning) initially introduced to six hospitals as a pilot study and, later, to 75 hospitals in Victoria, Australia, as part of a state-wide roll out.[62] Both the pilot and roll out were associated with large improvements in compliance (from about 20% to 50%) and similar clinically important trends after the intervention for reduced MRSA bacteraemias and MRSA clinical isolates per patient discharge (though in the state-wide roll out hospitals there was also a decline in MRSA clinical isolates before the intervention that continued after the intervention).

Roll out of a similar hand hygiene intervention (the Cleanyouhands campaign, based on WHO-5) in England and Wales was reported to be associated with reduced rates of MRSA bacteraemia (from 1.9 to 0.9 cases per 10 000 bed days) and *C difficile* infection (from 16.8 to 9.5 cases per 10 000 bed days), but no association was found with methicillin-sensitive *S aureus* (MSSA) bacteraemia.[55] This study also reported independent associations between procurement of alcohol hand rub and MRSA bacteraemias; in the last 12 months of the study, MRSA bacteraemias were estimated to have fallen by 1% (95% confidence interval 5% to 15%) for each additional mL of hand rub used per bed day (adjusted for other interventions and hospital level mupirocin use, a surrogate marker for MRSA screening and decolonisation). Similarly, each additional mL of soap used per bed day was associated with a 0.7% (0.4%, 1.0%) reduction in *C difficile* infection.

Benning and colleagues described the evaluation of a separate but contemporaneous patient safety intervention that included a hand hygiene component in nine English hospitals with nine matched controls.[67] Both intervention and control sites experienced large increases in consumption of soap and alcohol hand rub between 2004 and 2008 and substantial falls in rates of MRSA and *C difficile* infection, though in all cases (soap, hand rub, and infections) there was no evidence that differences between intervention and control sites resulted from anything other than chance.

In a two year study in 33 surgical wards in 10 European hospitals, Lee and colleagues found that, after adjustment for clustering, potential confounders, and temporal trends, enhanced hand hygiene alone was not associated with a reduction in MRSA clinical cultures and MRSA surgical site infections, and neither was a strategy of screening and decolonisation, but in wards where both interventions were combined, there was a reduction in the rate of MRSA clinical cultures of 12% per month (adjusted incidence rate ratio 0.88, 95% confidence interval 0.79 to 0.98).[48]

Among the randomised controlled trials, Mertz and colleagues found similar rates of hospital acquired MRSA colonisation in intervention and control groups (0.73 *v* 0.66 events per 1000 patient days, respectively; P=0.92), though adherence to hand hygiene was only 6% higher in the intervention arm.[35] Finally, in a study in 13 European intensive care units, Derde and colleagues reported a declining trend in acquisition of antimicrobial resistant bacteria (weekly incidence rate ratio 0.976, 95% confidence interval 0.954 to 0.999) associated with a hand hygiene intervention that increased compliance from about 50% to over 70%.[42] The decline was largely because of reduced MRSA acquisition. The intervention also included universal chlorhexidine body washing, and it is not possible to establish the relative importance of hand hygiene.

Level of information on resource use

Reporting of information on cost and resource use was limited, with 3, 26, and 12 studies classified as having high, moderate, and low information, respectively (appendix 8). Three studies reported costs associated with both materials and person time[34 52 66]; in two cases these reports were in separate papers.[70 71] Table 4 summarises the reported costs of interventions.

Table 4 | Extracted data on resource use in studies of interventions to improve hand hygiene in healthcare workers

Author (year), design	Intervention	Comparison	Settings and base year	Resource use: Materials	Resource use: Time	Sources	Total cost ($)*	No of beds	Intervention period (day)	Cost per 1000 bed day ($)
Huis (2013), CRCT	WHO-5 + goal-setting	WHO5 (except institutional safety climate)	Netherlands, 2009	State of art strategies: alcohol hand rub, website, leaflets, posters, newsletters, article in hospital magazines	State of art strategies: hand hygiene, direct observation. Extra time for performing hand hygiene	Separate paper[70]	320 278	993	365	883.7
				Team and leader directed strategies: as above	Team and leader directed strategies: as above plus coach salary, staffing costs for managers, role models and nurses in coaching session and preparation		474 068	1225	365	1060.5
Higgins (2013), ITS	WHO-5 + incentive	None (with AHR)	Ireland, 2010	Mobile interactive stand-alone computer using gaming technology and annual license. Swab and ATP machine	Research assistant for audit and training 1.79 FTE (287 hours) assuming salary as £2500 per month	Author contact	42 358	170	450	553.7
Armellino (2012), ITS	Feedback + goal-setting	None (unclear AHR use)	USA, 2008	21 video cameras	N/A	Paper	50 000	17	630	4668.5
Morgan (2012), ITS	System change + education + feedback + reminders	None (with AHR)	USA, 2010	60 alcohol dispensers system in two wards, 12 posters in total	1.46 FTE (234 hours) research assistants (10-20 hours/week for trouble shooting, refilling, and collecting data from devices, and 2 hours/month to design and present posters)	Author contact	6960	27	105	2455.0
Mestre (2012), ITS	Phase I: WHO-5. Phase II: WHO-5 (intense) + Reinforcement	Phase I: None (with AHR); phase II: WHO-5	Spain, 2011	Alcohol handrub solution. Material for campaign including posters, pens, and candy	Hand hygiene direct observation. Data analysis and interpretation	Separate paper[71]	19 259	n/a	365	385.2
Doron (2011), ITS	WHO-5	System change + education + feedback + reminders (with AHR)	USA, 2008-9	Cost for marketing consultancy	N/A	Author contact	35 000-50 000	425	365	225.6-322.3
Mayer (2011), NRT	Phase I: system change + education + feedback. Phase II: WHO-5 + incentive	None (unclear AHR use)	USA, 2003-6	Prizes as candy, chocolate bars, pizza, and others	2.25 FTE (yearly) of infection preventionists; 0.6 FTE of manager 0.35 FTE of clerk	Paper	165 600	450	365	1008.2

AHR=alcohol based hand rub, CRCT=cluster randomized controlled trial, ITS=interrupted time series, NRT= non-randomized trial, WHO-5=combined intervention including system change, education, feedback, reminders, and institution safety climate, N/A= not available, FTE=full time equivalents.
*$1=£0.65, €0.90.

Discussion

Principal findings

A multi-faceted hand hygiene intervention—WHO-5—and single interventions including system change, training and education, or reminders alone are associated with improved compliance with hand hygiene among healthcare workers in hospital compared with standard practice. Results from both randomised controlled trials and interrupted time series designs provide consistent evidence that adding supplemental interventions including goal setting, reward incentives, and accountability to the WHO-5 strategy lead to additional improvements in compliance. Information about resources used in the interventions was not well reported.

Comparison with other studies

We are aware of four previous systematic reviews of interventions for hand hygiene in healthcare settings.[5-8] One of these found only four studies of sufficient methodological quality to reliably evaluate interventions to promote hand hygiene and was unable to reach firm conclusions.[5] Overlap between included studies in the other three and our review is small: respectively four (9.8%),[8] three (7.3%),[6] and five (12.2%)[7] of studies included in our review were included in previous reviews, while 17 (80.1%), 38 (92.7%), and 40 (88.9%) of the studies in these reviews failed to meet the minimum quality threshold in ours.[12 13] While high quality non-randomised studies can potentially play an important role in the evaluation of interventions if they are analysed with appropriate methods, there are many reasons for thinking that simple before-after studies (a design used by most of the studies included in previous reviews) do not provide a reliable basis for evaluating interventions.[72-74] While an interrupted time series study (where multiple outcome measures are taken before and after the intervention) represents a strong quasi-experimental design, a before-after study compares a single outcome measure before and after the intervention and is vulnerable to distorting effects of pre-existing trends.

We found an increasing number of "high quality" studies on interventions for hand hygiene after 2009. From two previous systematic reviews[5 6] examining the literature from 1980 to November 2009, we found only 10 studies meeting the EPOC criteria (one randomised controlled trial, eight interrupted time series, and one controlled before-after study). With the same criteria, our review found 31 studies (five randomised controlled trials, 24 interrupted time series, one non-randomised trial, and one controlled before-after study) published between December 2009 and February 2014.

Reporting on resource implications for interventions was generally limited with some notable exceptions. Most included studies reported only part of the resources used, and methods for collecting cost data were unclear. Such information on resource use is important both for those wishing to implement similar strategies and for economic evaluation of different interventions.[10 75] A good framework to collect such data has also been proposed.[76] Cost effectiveness analysis of promotion of hand hygiene is required to assess under what circumstances these initiatives represent good value for money and when resources might be better directed at supplemental interventions, including care bundles,[77] ward cleaning,[78] and screening and decolonisation,[79] to complement well maintained compliance with hand hygiene.

Strengths and limitations of study

A particular strength of our study is that the network meta-analysis allowed us to quantify the relative efficacy among a series of different intervention strategies with different baseline interventions, even where the direct head-to-head comparisons were absent.

This study also has several limitations. Firstly, details on implementation of components of the intervention varied substantially. For example, personal feedback and group feedback were classified together, but, in practice, the impacts of these strategies can vary. Moreover, different studies might implement the same programme with different quality of delivery and level of adherence, so called intervention fidelity or type III error.[80] Both issues are common to many interventions to improve the quality of care in hospital settings and are likely to be responsible for much of the unexplained heterogeneity between studies.[81 82] Secondly, direct observation of compliance with hand hygiene might induce an increase in compliance unrelated to the intervention (the Hawthorne effect). Recent research suggests that such Hawthorne effects can lead to substantial overestimation of compliance.[83 84] Such effects, however, should not bias estimates of the relative efficacy of different interventions from randomised controlled trials and interrupted time series unless the effects vary between study arms/intervention periods. Thirdly, it is possible that it is the novelty of the intervention itself that leads to improvements in compliance and that any sufficiently novel intervention would do the same regardless of the components used. This clearly cannot be ruled out and is not necessarily inconsistent with our findings that interventions with more components tend to perform better. At present, however, there are too few high quality studies to evaluate whether individual components of interventions show consistent differences that cannot be explained by novelty alone. Fourth, results might be distorted by publication bias. Fifth, there might also be a low level of language bias because we excluded studies in languages other than English. The magnitude of such bias, however, is likely to be small.[85 86]

Finally, linking improved compliance to clinical outcomes such as number of infections prevented would provide more direct evidence about the value of such interventions.[10] Such direct evidence is still limited in hospital settings, although the association is supported by a growing body of indirect evidence as well as biological plausibility. Moreover, findings from studies included in our review that reported clinical or microbiological outcomes are consistent with substantial reductions in infections for some pathogens, such as MRSA, resulting from large improvements in hand hygiene.[87 88] The lack of a measureable effect of improved hand hygiene on MSSA infections might seem paradoxical but can be partly explained by the fact that MSSA infections are much more likely to be of endogenous origin, whereas MRSA is more often linked to nosocomial cross transmission. Moreover, predictions from modelling studies that hand hygiene will have a disproportionate effect on the prevalence of resistant bacteria in hospitals (provided resistance is rare in the community) seem to have been borne out in practice.[89]

Conclusions

While there is some evidence that single component interventions lead to improvements in hand hygiene, there is strong evidence that the WHO-5 intervention can lead to substantial, rapid, and sustained improvements in compliance with hand hygiene among healthcare workers in hospital settings. There is also evidence that goal setting, reward incentives, and accountability provide additional improvements beyond those achieved by WHO-5. Important directions for future work are to improve reporting on resource implications for interventions, increasingly focus on strong study designs, and evaluate the long term sustainability and cost effectiveness of improvements in hand hygiene.

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Ethical approval: Not required

Data sharing: The relevant data and code used in this study are available from the authors.

Transparency: The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Appendix 1: Complete search strategy
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RESEARCH Open Access

Long-term survival after intensive care unit discharge in Thailand: a retrospective study

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Abstract

Introduction: Economic evaluations of interventions in the hospital setting often rely on the estimated long-term impact on patient survival. Estimates of mortality rates and long-term outcomes among patients discharged alive from the intensive care unit (ICU) are lacking from lower- and middle-income countries. This study aimed to assess the long-term survival and life expectancy (LE) amongst post-ICU patients in Thailand, a middle-income country.

Methods: In this retrospective cohort study, data from a regional tertiary hospital in northeast Thailand and the regional death registry were linked and used to assess patient survival time after ICU discharge. Adult ICU patients aged at least 15 years who had been discharged alive from an ICU between 1 January 2004 and 31 December 2005 were included in the study, and the death registry was used to determine deaths occurring in this cohort up to 31st December 2010. These data were used in conjunction with standard mortality life tables to estimate annual mortality and life expectancy.

Results: This analysis included 10,321 ICU patients. During ICU admission, 3,251 patients (31.5%) died. Of 7,070 patients discharged alive, 2,527 (35.7%) were known to have died within the five-year follow-up period, a mortality rate 2.5 times higher than that in the Thai general population (age and sex matched). The mean LE was estimated as 18.3 years compared with 25.2 years in the general population.

Conclusions: Post-ICU patients experienced much higher rates of mortality than members of the general population over the five-year follow-up period, particularly in the first year after discharge. Further work assessing Health Related Quality of Life (HRQOL) in both post-ICU patients and in the general population in developing countries is needed.

Introduction

Hospital mortality amongst intensive care unit (ICU) patients is high throughout the world, typically ranging from 14 to 44% [1-6]; in Thailand the reported range is between 24 and 40% [5-7]. Interventions to improve the quality of ICU care have the potential to reduce this mortality. Examples of such interventions include development of clinical guidelines [8,9], improvements to infection control practices [10], and appropriate use of medical devices [11].

There is growing interest not just in the effectiveness of such interventions at reducing mortality, but in their cost-effectiveness, and formal economic evaluation is increasingly used to aid decisions about allocation of scarce health care resources in these settings [12]. Such analyses consider both costs of the interventions and the associated health benefits. Outcomes such as the number of life years (LYs) or quality adjusted life years (QALYs) gained or disability adjusted life years (DALYs) averted are commonly used to represent the benefit of particular interventions. However, to estimate the change in LYs caused by preventing a single ICU death, estimates of post-ICU survival are needed. A number of studies have assessed long-term survival (defined as survival for at least one year post-ICU discharge) [2,13-29]. All but one of these studies were conducted in high-income countries and high quality data are lacking from lower and middle

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income countries [26]. The aim of this study was to quantify the long-term survival of post-ICU patients in Thailand and to estimate life expectancy (LE) in this population.

Materials and methods

Setting and facilities

Sappasithiprasong Hospital is a 1,100-bed tertiary referral hospital located in rural northeast Thailand. In 2004 and 2005 it had a catchment of 1.8 million people, predominantly rice farmers and their families. Universal health coverage has been operating in Thailand since 2002, ensuring access to this hospital for the entire population in the catchment area [30]. In 2004, Sappasithiprasong Hospital had 36 general wards and 16 ICUs (4 pediatric and 12 adult), representing 6 ICU beds per 100,000 people. These wards provided care for critically ill patients and patients recovering from major surgery. Adult ICUs comprised four medical ICUs (including one respiratory ICU), two surgical ICUs, two neurosurgical ICUs, one trauma ICU, two coronary care units, and one cardiovascular and thoracic ICU. ICUs contained a median of 8 beds (range 8 to 16) and the mean nurse-to-patient ratio was 1:1.5 (including both registered nurses and practical nurses). All of these ICUs could be defined as Level II open ICUs according to the guidelines from the American College of Critical Care Medicine [31] since there were no intensivists accredited by the Royal College of Physicians of Thailand working at Sappasithiprasong Hospital in 2004. Further details about the ICUs in this hospital have been described elsewhere [32].

Data

Retrospective patient-level data from January 2004 to December 2005 were obtained from Sappasithiprasong Hospital. Adult patients, aged at least 15 years, who had been admitted to an adult ICU and discharged alive from the ICU between 1 January 2004 and 31 December 2005 were included in this retrospective cohort analysis. For patients who were subsequently readmitted to an ICU during this period, only the time since the end of the first ICU episode was considered. The regional death registry for northeast Thailand from 2004 to 2010 was obtained from the Thai Ministry of Public Health and linked to the patient data using the national identification number (ID). We verified the validity of each patient's ID number using the checksum digit and cross-checked the name and date of birth between hospital data and the regional death registry to validate the data.

Use of these data was approved by ethical committees from 1) the Faculty of Tropical Medicine, Mahidol University, 2) Sappasithiprasong Hospital, Ubon Ratchatani, and 3) the Ministry of Public Health, Thailand [33]. No patient consent was required as this study was retrospective and did not use patient identifiable data.

Patients with a recorded date of death during the ICU admission period were classified as ICU deaths. It is not uncommon practice in Thailand and other Southeast Asian countries to discharge moribund patients to die at home [33]. We, therefore, also classified deaths occurring within two days of ICU discharge as ICU deaths. Survival time for discharged patients was assessed for five years after hospital discharge. Patients were assumed

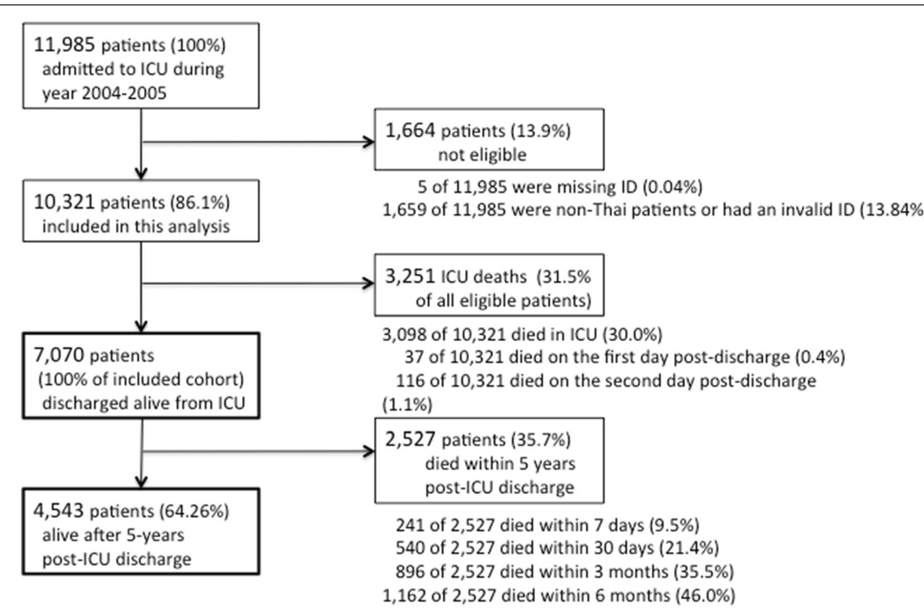

Figure 1 Patient flow from intensive care unit admission to discharge and until five-year follow-up.

Table 1 Demographic data for ICU patients

	Patients dying in the ICU[1]	Patients discharged alive from the ICU
	N = 3,251	N = 7,070
Age (Med [IQR])	57.6 [42.6, 71.1]	54.5 [38.2, 67.8]
Age group (number of patients)		
15 to 29	408 (12.6%)	1,132 (16.1%)
30 to 44	492 (15.1%)	1,298 (18.4%)
45 to 59	879 (27.0%)	1,821 (25.8%)
60 to 74	901 (27.7%)	1,914 (27.1%)
>75	571 (17.6%)	905 (12.8%)
Length of hospital stay	3.0 [1,7]	7.0 [3,12]
(Med [IQR])		
Sex (% female)	1,241 (38.2%)	2,700 (38.2%)
ICD10 (Top five, by %)		
Circulatory system (I00 to I99)	1,040 (32.0%)	2,627 (37.2%)
- Cerebrovascular diseases (I60 to I69)	535	404
- Other forms of heart disease (I30 to I52)	179	615
- Ischemic heart diseases (I20 to I25)	152	886
- Chronic rheumatic heart diseases (I05 to I09)	86	441
Injury, poison and other external causes (S00 to T98)	751 (23.1%)	1,598 (22.6%)
- Injury (S00 to T14)	715	1,490
- Poisoning and certain other consequences of external causes (T15 to T98)	36	108
Digestive system (K00 to K93)	328 (10.1%)	789 (11.2%)
- Other diseases of the digestive system (K90 to K93)	106	125
- Diseases of oesophagus, stomach and duodenum (K20 to K31)	48	225
- Disorders of gallbladder, biliary tract and pancreas (K80 to K87)	43	166
Respiratory system (J00 to J99)	248 (7.6%)	376 (5.3%)
- Influenza and pneumonia (J09 to J18)	145	129
- Chronic lower respiratory diseases (J40 to J47)	35	82
- Suppurative and necrotic conditions of lower respiratory tract (J85 to J86)	10	61
Neoplasms (C00 to D48)	186 (5.7%)	488 (6.9%)
- Malignant neoplasms (C00 to C99)	160	331
- Neoplasms of uncertain or unknown behaviour (D37 to D48)	22	128
- Benign neoplasms (D10 to D36)	4	27
Hospital mortality (%)	N/A	139 (2.0%)
Five-year mortality (%)	N/A	2,527 (35.7%)

[1]Includes patients who died within two days of ICU discharge.

to be alive if no death was recorded within five years of ICU discharge in the death registry.

Analysis

The primary outcome was survival time after ICU discharge. A Kaplan-Meier survival curve showing the estimated proportion of post-ICU patients alive at each time point was plotted over the five-year follow-up period. To quantify the potential impact of differential mortality following year five, we fitted an exponential curve to the annual risk of death from years two to five. From year eight onwards, the extrapolated post-ICU mortality differed by less than 1% from that in the general population matched for age and sex. Therefore, mortality from year eight was assumed to be equal to that in the general Thai population which we took from standard mortality life tables [34]. In the base case analysis we assumed that in years six and seven post-discharge the relative risk of death for former ICU patients compared to the general population was the same as that observed in year five (relative risk of 1.35). Since this assumption may underestimate post-ICU survival, we performed a sensitivity analysis in which we assumed that mortality rates in years six and seven post-discharge were the same as those in the general population matched for age and sex (that is, a relative risk of one). The life expectancy (LE) amongst patients discharged from the ICU was taken as the area under the lifetime survival curve. The LE was calculated for the overall ICU population and for each age group.

Survival analysis stratified according to major diagnostic categories for ICU admission from the International Statistical Classification of Diseases, 10th revision (ICD10) [35] was also performed. The diagnostic groups were: a.) Cerebrovascular diseases (ICD10 codes: I60 to I69); b.) Cardiovascular diseases except Cerebrovascular diseases (ICD10 codes: I00 to I99 except I60 to I69); c.) Digestive system (ICD10 codes: K00 to K93); d.) Neoplasms (ICD10 codes: C00 to D48); e.) Respiratory system (ICD10 codes: J00 to J99); and f.) Injury, poisoning and other external causes (ICD10 codes: S00 to T98). The analysis was performed using STATA 11 (Stata Corp., College Station, TX, USA) and Microsoft Excel 2010, (Redmond, WA, USA).

We also performed a systematic search in order to review the related literature investigating long-term survival amongst post-ICU patients in low and middle

Table 2 Demographic data for post-ICU patients

	Post-ICU patients dying within five years of ICU discharge N = 2,527	Post-ICU patients alive five years after ICU discharge N = 4,543
Age (Med [IQR])	64.6 [52.6, 74.0]	47.46 [32.6, 62.2]
Age group (number of patients)		
15 to 29	127 (5.0%)	1,005 (22.1%)
30 to 44	256 (10.1%)	1,042 (22.9%)
45 to 59	618 (24.5%)	1,203 (26.5%)
60 to 74	949 (37.6%)	965 (21.2%)
>75	577 (22.8%)	328 (7.2%)
Length of hospital stay (Med [IQR])	8.0 [4,15]	7.0 [3,11]
Sex (% female)	1,041 (41.2%)	1,659 (36.5%)
ICD10 (Top five, by %)		
Circulatory system (I00 to I99)	1,023 (40.5%)	1,604 (35.3%)
- Cerebrovascular diseases (I60 to I69)	337	549
- Other forms of heart disease (I30 to I52)	225	390
- Ischemic heart diseases (I20 to I25)	216	188
- Chronic rheumatic heart diseases (I05 to I09)	114	327
Neoplasms (C00 to D48)	324 (12.8%)	164 (3.6%)
- Malignant neoplasms (C00 to C99)	249	82
- Neoplasms of uncertain or unknown behaviour (D37 to D48)	70	58
- Benign neoplasms (D10 to D36)	5	22
Digestive system (K00 to K93)	321 (12.7%)	468 (10.3%)
- Other diseases of the digestive system (K90 to K93)	86	139
- Diseases of oesophagus, stomach and duodenum (K20 to K31)	67	99
- Disorders of gallbladder, biliary tract and pancreas (K80 to K87)	60	65
Injury, poison and other external causes (S00 to T98)	215 (8.5%)	1,383 (30.4%)
- Injury (S00 to T14)	182	1,308
- Poisoning and certain other consequences of external causes (T15 to T98)	33	75
Respiratory system (J00 to J99)	190 (7.5%)	186 (4.1%)
- Influenza and pneumonia (J09 to J18)	75	54
- Chronic lower respiratory diseases (J40 to J47)	58	46
- Suppurative and necrotic conditions of lower respiratory tract (J85 to J86)	15	24

income countries. The search strategy and inclusion criteria are provided in Additional file 1.

Results

There were 11,985 adult patients admitted to an ICU in Sappasithiprasong Hospital between 2004 and 2005 and discharged before 1 January 2006. After verifying the hospital dataset, 1,664 patients (13.9%) were not eligible for this analysis due to missing data, incomplete or invalid ID numbers, or coming from other countries (and therefore not recorded in the regional mortality records). As a result, 10,321 patients were included in this analysis. There were 7,223 patients who were discharged alive from the ICU; 153 of these died within two days and were counted as ICU deaths. Of these 61 (39.9%) died at the hospital and 92 (60.1%) died at home. We studied five-year survival in the remaining 7,070 patients who were discharged from the ICU alive (31.5% ICU fatality rate). Patient-flow is shown in Figure 1. Demographics and ICD10 codes in the group of patients who

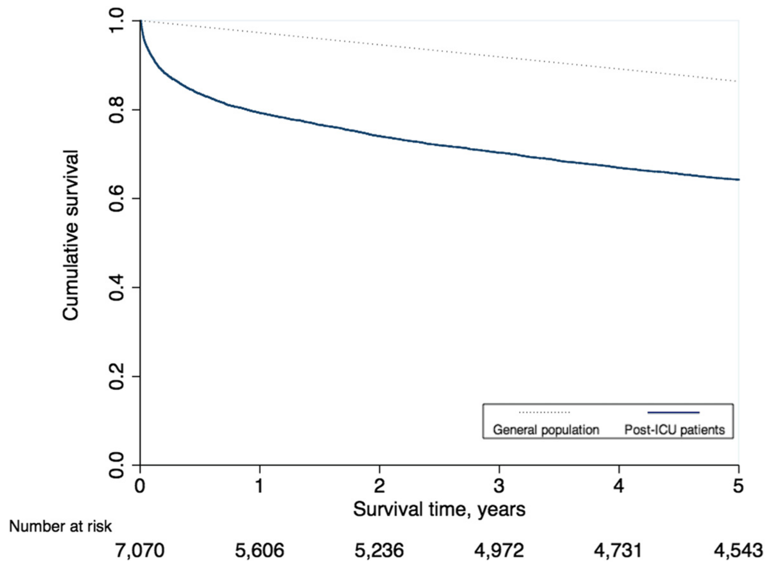

Figure 2 Kaplan-Meier survival estimates for post-ICU patients and survival for the general population in Thailand.

were discharged alive differed slightly from those in patients who died within the ICU (Table 1). In contrast, the group of post-ICU patients who died within five years of discharge tended to be older and much less likely to have ICD10 codes relating to injury, poison and other external causes than those who were alive after five years (Table 2). Of the 7,070 patients who were discharged alive, 79.3% survived the first year, then 74.0%, 70.3%, 66.9% and 64.2% survived each subsequent year (Figure 2). Overall, within five years, 2,527 of the original 7,070 (35.7%) had died. The Kaplan-Meier survival curve indicated a greatly elevated risk of death in the first year post-ICU discharge, with 9.5% (241 of 2,527) of all deaths occurring within seven days. Of these, 67 (27.8%) died at the hospital and 174 (72.2%) died at home. Of the total 2,527 deaths over five years, 21.4% (540) occurred within the first month, 35.5% (896) within three months, 46.0% (1,162) within six months, and 57.9% (1,464) within the first year. Mortality rates became close to those in the general population between years two to five after ICU discharge. The annual risks of death for each year during these periods were 0.21, 0.07, 0.05, 0.05 and 0.04, respectively. In the general population, the annual risk of death (matched for age and sex with those discharged alive from the ICU) was 0.03. Overall, half of the post-ICU patients would have

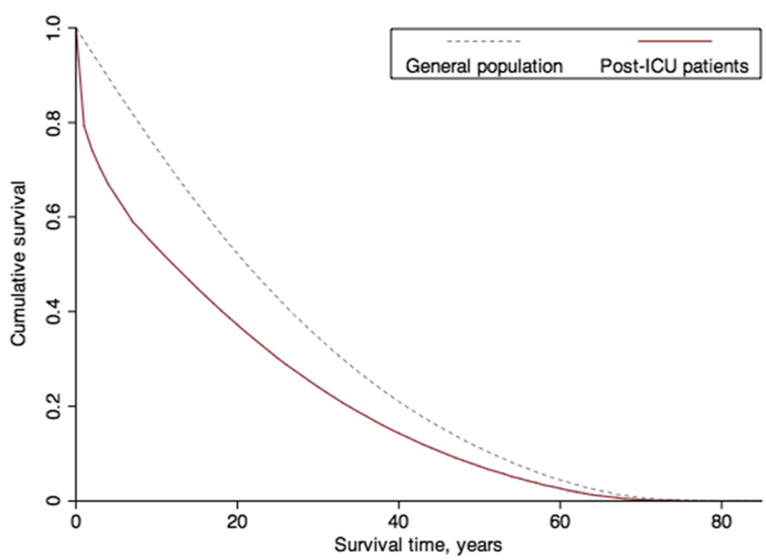

Figure 3 The extrapolated lifetime survival curve of post-ICU patients and survival for the general population.

Table 3 Life expectancy among post-ICU patients adjusted for age and sex

Age group (Years)	Life expectancy (LE)		
	†Base case	*Sensitivity analysis	◊General population
15 to 29	43.16	43.80	48.97
30 to 44	28.87	29.56	36.01
45 to 59	16.41	16.98	24.03
60 to 74	8.72	8.96	13.66
≥75	4.75	4.61	6.36
Overall	18.26	18.56	25.15

†Base case analysis: we assumed that from year five to year seven post-discharge the relative risk of mortality amongst post-ICU patients was the same as that in year five. From year eight onwards, the relative risk was assumed to be 1.
*Sensitivity analysis: we assumed the mortality rates among the post-ICU patients after five years post-discharge to be the same as those in the general population matched for age and sex.
◊General population: we applied the mortality rate of the Thai general population age- and sex-matched to all post-ICU patients since ICU discharge.

been expected to die within 12.1 years of ICU discharge under base case assumptions. In a sample of the general population matched for age and sex, half would be expected to die within 21.2 years (Figure 3). The LE under base case assumptions and the sensitivity analysis are presented in Table 3. The overall LE amongst post-ICU patients was estimated to be 18.3 years while the LE in the general population (matched for age and sex) was estimated to be 25.2 years. The sensitivity analysis yielded estimates of LE 1.6% higher than under the base case assumption.

Survival categorised by specific diagnostic categories is presented in Figure 4 and Table 4. The lowest survival within six months of discharge was seen in patients admitted with cerebrovascular disease, though at five years post-discharge the lowest survival (33.6%) was seen in patients with neoplasms. The highest survival rates were consistently seen in those admitted due to injury, poisoning or other external causes; 86.5% of patients in this group survived at least five years.

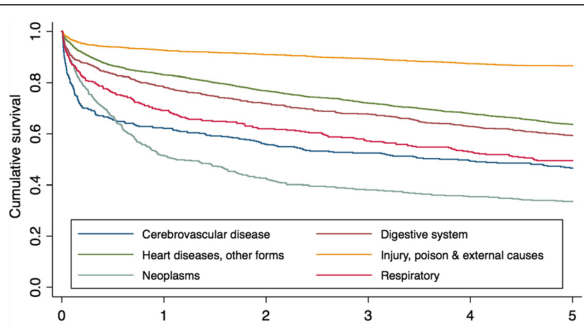

Figure 4 Kaplan-Meier survival estimates for post-ICU patients stratified by diagnostic group.

In the systematic search for studies of long-term survival amongst post-ICU patients in low and middle income countries, we found only one study evaluating post-ICU survival across all diagnostic categories [26]. This study followed up 187 post-ICU patients in Malaysia for two years. It was reported that 97 of 105 post-ICU patients (92.4%) who responded to a questionnaire survived for two years. However, the high loss to follow-up in this study (43.8%, 82 from 187) makes interpretation of these findings difficult.

Discussion

This study found that post-ICU patients had a substantially higher mortality rate (and substantially reduced LE) compared to the general population, with most of the difference seen in the first year post-discharge. Overall, the LE among the post-ICU patients was estimated to be seven years lower than in the general population and the number of life years gained from preventing one ICU death was found to be about two-thirds that from preventing one death in the general population (matched for age and sex).

Results from this study are broadly consistent with those from previous studies conducted elsewhere in high-income countries [2,13,14,16-18,36-38]. Our estimate that cumulative mortality over the five years was 35.7% (or 2.5 times higher than in an age- and sex-matched general population) is slightly higher but comparable with estimates from previous studies which found that the five years cumulative mortality rate ranged from 17.9 to 33.5% [2,13,14,16-18,36-38]. Our estimate of the risk of death in year five, 0.04, is at the upper end of the range estimated in studies conducted in high-income countries (0.01 to 0.04) [14,36,37]. The mortality rates among post-ICU patients in our study were high in the first 12 months, then decreased rapidly, and were projected to closely approximate those of the general population by year eight post-ICU discharge. Studies conducted in Finland, Norway and Scotland [13,36,37] also demonstrated substantially greater risk of death during the first year, but these became similar to the general population within one to four years. On the other hand, studies conducted in the United Kingdom [16] and Australia [38] found that the mortality rate amongst former ICU patients was higher than the general population over a 5-year and 15-year follow-up period, respectively.

There are several possible reasons for differences in the time for post-ICU mortality rates to approach those in the general population. Firstly, there was considerable variation between the studies in the frequency of different diagnostic categories. Our study had a relatively high proportion of patients with ICD10 codes relating to injury, poisoning and other external causes (23% compared

Table 4 Comparison of survival 1-5 years after ICU discharged by age and diagnostic group

Time of follow-up	At ICU discharge	1 year	2 year	3 year	4 year	5 year
Number of patients at each follow up time	7,070	5,606	5,236	4,972	4,730	4,543
Age (median, [IQR])	54.5 [38.2, 67.8]	51.4 [35.2, 65.6]	50.5 [34.2, 64.8]	49.5 [33.8, 63.8]	48.5 [33.0, 63.0]	47.5 [32.6, 62.2]
Length of hospital stay	7.0 [3,12]	7.0 [3,11]	7.0 [3,11]	7.0 [3,11]	7.0 [3,11]	7.0 [3,11]
Sex (% female)	38.2%	37.6%	37.3%	37.2%	36.7%	36.5%
Age group						
15 to 29	100.0%	93.0%	91.8%	90.7%	89.8%	88.8%
30 to 44	100.0%	88.4%	85.1%	83.1%	81.8%	80.3%
45 to 59	100.0%	80.2%	75.0%	71.4%	68.4%	66.1%
60 to 74	100.0%	70.7%	64.5%	58.9%	53.7%	50.4%
≥75	100.0%	65.4%	54.6%	48.5%	41.9%	36.2%
Diagnostic group						
Heart diseases, other forms (I00 to I99 except I60 to I69)	100.0%	83.0%	76.9%	72.0%	67.9%	63.7%
Cerebrovascular diseases (I60 to I69)	100.0%	62.1%	55.9%	52.5%	49.3%	46.5%
Injury, poison and other external causes (S00 to T98)	100.0%	92.6%	90.9%	89.3%	87.4%	86.5%
Digestive system (K00 to K93)	100.0%	78.2%	71.9%	67.7%	62.9%	59.3%
Respiratory system (J00 to J99)	100.0%	69.1%	62.0%	57.2%	52.9%	43.6%
Neoplasms (C00 to D48)	100.0%	51.4%	42.4%	38.1%	35.5%	33.6%

to a range of 7 to 15% in other studies) [18,36-38]. Conversely, there was a low proportion of patients with ICD10 codes relating to the respiratory system (5% compared with a range of 8 to 36%) [13,36,37]. Figure 4 suggests that these differences are likely to be associated with both a shorter period for post-ICU mortality to approach that in the general population and a relatively high five-year post-ICU survival rate.

Quality of care in different settings [39,40] is another possible factor that could impact on long-term survival rates. Higher quality of care should reduce ICU mortality, but could potentially either increase or decrease the long-term survival in patients discharged alive from ICU. The latter could occur if higher quality of care prevents ICU deaths in patients with poor long-term prognosis (where some of these patients would have died in the ICU if in lower quality of care settings). Quantifying such competing effects is challenging, but important for evaluating the cost-effectiveness of interventions to improve quality of ICU care in low and middle income countries.

Currently, however, there are few studies of long-term survival following ICU stays in lower and middle income countries. While the systematic search identified a small number of studies evaluating long-term survival following ICU discharge in specific diagnostic categories (liver transplants, myocardial infarction, metastatic solid cancer, chronic obstructive pulmonary disease) [41-45], long-term follow-up of representative ICU cohorts was lacking.

Our analysis accounted for the common practice in Southeast Asia of discharging moribund patients to die at home by classifying deaths occurring within two days of discharge as ICU deaths. The two-day cut-off was chosen because post-ICU mortality showed a clear spike on day two post-discharge (with 116 deaths, or 1.12% of total ICU patients) but showed a gradual decline from day three (48 (0.47%), 46 (0.45%), 36 (0.35%), 28 (0.27%) and 29 (0.28%) for days three to seven, respectively). This resulted in only slightly higher ICU mortality than would have been obtained had we only considered deaths occurring during the admission (31.5% versus 30.0% mortality, or 153 more deaths), and consequently, slightly lower cumulative five-year mortality amongst the non-ICU deaths (37.1% versus 35.7%).

The mortality rates during years six and seven post-ICU discharge are likely to be somewhat lower than assumed in the base case (which assumed the same relative risk for death as in year five), but somewhat higher than assumed in the sensitivity analysis (which assumed a relative risk of one). However, these two assumptions yielded estimates of LE that differed by less than 2% (Table 3) indicating that improved estimates of mortality in years six and seven would have negligible impact on the results.

Interestingly, among individuals over 75 years of age, the mortality rate was higher in the post-ICU group than in the general population in the first two years, but lower in the following years, resulting in a slightly longer LE than the general population. This might be explained by the possibility that these patients are on average healthier than the general population, having survived their ICU admission.

Limitations

This study has several limitations. Data from a single regional hospital may not be representative of the national population due to differences in patient characteristics and quality of hospital care. However, similar regional hospitals provide care to most of the population in Thailand and the large population (n >7,000) and long-term follow-up strengthen our findings. Nonetheless, had resources permitted, this study could have been improved (and its external validity strengthened) by collecting data from multiple sites across Thailand. A second limitation is that this study was based on retrospective data, which were inevitably incomplete. Moreover, as the regional death registry was used (not national data), it is possible that we have missed some deaths in patients who moved and died outside of the northeast region. Our analysis might, therefore, underestimate mortality. However, any such bias is likely to be small as the five-year migration rate amongst the northeast Thai population was estimated to be 3.1% in 2000 [46]. This rate is likely to be even lower in older age groups where most of the mortality occurs. Another limitation is the lack of a standardised measure of severity of illness. A standard severity score (such as Acute Physiology and Chronic Health Evaluation (APACHE) II) would have helped to inform comparisons of our findings with those from other studies, but such data are not routinely collected in ICUs in Thailand. Finally, this study would have been improved by the addition of Health Related Quality of Life (HRQOL) data to estimate the quality adjusted life expectancy (QALE) amongst the post-ICU patients. Ideally, such HRQOL information would be obtained from a long-term cohort study in the local population; resources for this were not available to us. Given the range of the HRQOL between 0.56 and 0.88 as shown in the literature [13,14,16,19] (all from high-income countries) the expected QALE of post-ICU patients would range from 10.2 to 16.1 QALYs. Prospective collection of such quality of life data is an important area for future health economic research in developing countries.

Conclusions

This study represents one of the first attempts to estimate long-term post-ICU survival in a developing country context. Post-ICU patients had higher mortality than members of the general population (matched for age and sex) over the five-year follow-up period. The estimated LE is useful for economic evaluations and should support decision-makers considering potential investments in interventions that could prevent unnecessary deaths during ICU or hospital admissions.

Key messages

- Five-year mortality amongst post-ICU patients in Thailand was estimated to be 35.7%. This is about 2.5 times higher than that in the general population (age and sex matched).
- The risk of death was greatly elevated in the first year after ICU discharge and approached that in the general population in subsequent years.
- The extrapolated lifetime survival indicated that post-ICU patients had 27.4% lower life expectancy than the general population (age and sex matched).
- Patients admitted to the ICU as a result of injury, poisoning or other external causes had the lowest mortality rate over the five-year follow-up; patients with neoplasms had the highest.
- Estimates of the number of life years gained from interventions preventing ICU deaths will aid policy-makers considering potential investments in this area.

Additional file

Additional file 1: Three main phrases used in the systematic literature search.

Abbreviations

DALY: Disability adjusted life year; HRQOL: Health-related quality of life; ICU: Intensive care unit; ID: Identification number; LE: Life expectancy; LY: Life year; QALE: Quality adjusted life expectancy; QALY: Quality adjusted life year.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

NL, BSC, YL, DL, NG and ND contributed to the study conception and design. MH, DL, SC and PT collected the data. NL and MH performed the data analysis. NL, BSC and YL wrote the draft. DL, MH, SC, PT, NG and ND critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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