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Effectiveness of national and sub-national infection prevention and control interventions in high and upper-middle income countries: outcomes of a systematic literature review

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Summary

Evidence-based guidance for national infection prevention and control (IPC) programmes is needed to support national and global capacity building to reduce healthcare-associated infection and antimicrobial resistance. This systematic review evaluated the evidence on the effectiveness of IPC interventions implemented at national or sub-national level to inform the development of World Health Organization's guidelines on the core components of national IPC programmes. CENTRAL, CINAHL, EMBASE, MEDLINE, and WHO IRIS were searched from January 1, 2000 to April 19, 2017. Twenty-nine studies meeting the eligibility criteria were categorised according to intervention type: multimodal; care bundles; policies; and surveillance, monitoring, and feedback. There was evidence of effectiveness in all categories but the best quality evidence was on multimodal interventions and surveillance, monitoring, and feedback. We call for improvements in study design, reporting of research and robust evidence, in particular from low income countries, to strengthen the uptake and international relevance of IPC interventions.

Panel: Recommendations and future research

- This review of the effectiveness of IPC interventions based on international, national, state or collaborative guidelines and implemented countrywide, region wide or across countries, regions or collaborations was undertaken to inform the development of international guidance on national IPC programmes.
- Surveillance with active feedback tended to report positive effects, as did the majority of multimodal interventions.
- There is some evidence of effectiveness for two other interventions, namely, care bundles and policies.
- No evidence meeting the review selection criteria was found for other core components of IPC programmes, until this evidence becomes available, these other components continue to be considered “best practice” based on expert opinion alone.
- Recommendations are made for improvement in future research design to ensure such studies develop a viable evidence base.
- There is a need for improved research design, with cluster randomised trials (CRT), better designed epidemiology studies including rigorous time series analysis, and the consistent use of standardised outcomes to inform the future evidence base for IPC.
- In addition, it is important to measure both outcomes and processes, particularly if an experimental design is not possible.
- With regard to the reporting of studies, care should be taken to report the intervention content, how it was implemented, and its hypothesised mechanisms of action.
- Studies also need to specify any theoretical underpinning and consider wider use of theory.

Introduction

Healthcare-associated infection (HAI) is a major global health problem. It affects millions of patients worldwide every year.^{1,2} HAI has serious implications for patients and health care systems.¹ A large burden of HAI exists worldwide, despite a call to action over the last decade to make care safer.³ Estimates suggest 80,000 patients/per day have at least one HAI on any given day in Europe, corresponding to a prevalence of 5·7% of hospitalized patients (95% confidence interval (CI): 4·5% to 7·4%) suffering from HAI.⁴ The estimated HAI prevalence in low-income countries ranges from 5·7% to 19·1%.¹

The contribution of antimicrobial resistance (AMR) to HAI at a global level is not well described. However, it is known that wide national variations in multidrug resistance exist, with low resistance rates in some countries, particularly in Northern Europe, and alarming prevalence in others. Extended-Spectrum β -Lactamase-producing *Escherichia coli* and *Klebsiella spp* range in terms of the proportion of isolates which are resistant, from 11·8% to 58·5% and from 35·1% to 57·3%, respectively, and for Methicillin-Resistant *Staphylococcus aureus* (MRSA) from 27·7% to 44·4%.⁵ Since AMR moves freely across national borders, co-ordinated global action is needed to maximise prevention of HAI and containment of AMR. Infection Prevention and Control (IPC) is recognised as a key strategy in this regard,⁶ with the focus being on what are the core components that should be part of any IPC programme, resulting in repeated international calls for evidence-based guidelines for core national interventions.^{1,7}

A recent systematic review of IPC programmes, organisation, management, and structure identified ten core components to reduce HAI at a hospital level,⁸ but no review exists on the components required for effective national IPC interventions. Previous World Health Organization (WHO) guidance on national IPC core components⁹ was based only on expert opinion. New evidence-based guidelines, including recommendations for core components of effective IPC programmes at the national and healthcare facility level have been developed by a panel of international experts to support the global prevention of HAI and reduce the burden of AMR. These guidelines were based on the available evidence and its quality, the

balance between benefits and harms, cost and resource implications, acceptability and feasibility, and user and patient values and preferences.¹⁰⁻¹¹ Where studies not meeting our inclusion criteria were not available, the panel of international experts deemed it crucial to make best practice statements on key core components to be recommended at the national level. In this systematic review, as part of the guideline development, we aimed to evaluate the evidence on the effectiveness of IPC interventions at the national level.

Methods

This systematic review was conducted according to a protocol (appendix, page 3) and is reported according to the PRISMA guidelines.¹²

Search strategy and study selection

Inclusion criteria: studies were included in the review if they were published from 2000 to 2016; reported in English, French, or Spanish with an English title or abstract; a population of healthcare workers; and an IPC intervention, based on international, national, state or guidelines from a collaboration/network of hospitals, and implemented in healthcare settings country-wide, region-wide or across a country, region or collaboration/network of hospitals. Primary outcomes were HAI rates, including those caused by antibiotic-resistant microorganisms, mortality, quality adjusted life years (QALY), disability adjusted life years, length of stay, or economic costs associated with HAI. Secondary outcomes included use of alcohol-based hand rub (ABHR), compliance with IPC practices (e.g. hand hygiene (HH)) and policies (e.g. mandatory reporting of HAI), knowledge, or attitudes. Only studies meeting EPOC study design criteria were included.¹³⁻¹⁵ These included full or partial economic evaluations, cluster randomised trials (CRT), non-randomised trials, (NRT), controlled before and after (CBA) studies, and interrupted time series (ITS) studies.

Exclusion criteria were: locally led hospital-level interventions; interventions for the prevention of HAI in the context of occupational health and antibiotic stewardship; non-controlled before and after studies; cohort studies; cross sectional surveys; reviews; letters; notes; conference proceedings; theses; and opinion articles.

Databases searched included: CENTRAL, CINAHL (via EBSCO), EMBASE (via Ovid), MEDLINE (via EBSCO), and the WHO IRIS. In addition, manual searching of the reference lists of the included studies was conducted. Consistent with the principle of using current evidence to inform practice and taking cognisance of the evolving nature of IPC practice, the search to inform the WHO guideline development included studies published from January 1, 2000 to December 31, 2016. The search was re-run prior to the manuscript submission and included studies up until April 19, 2017. This additional search added four more studies to the review. Delimiters were population (human only) and publication type (CINAHL and MEDLINE - journal article; EMBASE - article; WHO IRIS - analytic, e-journal, periodical). The database-specific search strategy comprised both index terms and free text words; details of which are available in the appendix, page 8.

Studies were selected in the following manner: Titles and abstracts of papers were individually screened against eligibility criteria by one of a team of reviewers, with 30% of these independently screened by a second reviewer (LP, JM, LM, DW). Full text review was conducted on papers by one reviewer (LP), with checking by a second reviewer (JM). Disagreement between reviewers was resolved by discussion or by a third reviewer (JR).

Data analysis

Data were extracted: (appendix, page 23) by two independent reviewers for 30% of the studies. The remaining studies were data extracted by one reviewer and checked by a second reviewer (LP, EC, KC, PF, TH, JM, LM, VN, JR). Disagreement between reviewers was resolved by discussion or by a third reviewer (LP, JM).

Quality assessment: Risk of bias of individual CRT, NRT, CBA studies, and ITS studies were assessed using standard EPOC risk of bias criteria,¹⁶ resulting in a summary assessment of overall high, low or unclear risk of bias.¹⁷ Risk of bias assessments were conducted by two independent reviewers for 20% of the studies and by one reviewer, checked by a second reviewer, for the remainder of the studies (LP, JM, TH, PF, KC, EC, VN, JR). Disagreement

between reviewers was resolved by discussion or by a third reviewer (LP, JM). The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system^{18–20} was used to grade the quality of the body of evidence, where one existed (LP, JM). Two independent reviewers (SM, AM, JR) used the Phillips’ checklist²¹ to critically appraise the methodological quality of each economic study.²² Disagreement between reviewers was resolved by discussion or by a third reviewer (LP). A narrative summary was produced in line with Cochrane recommendations (LP, JM, SM).²³

Studies were considered for meta-analysis; however, due to heterogeneity in interventions and primary outcomes, no meta-analysis was conducted as it was considered statistically inappropriate. Therefore, results were synthesised in a narrative form according to the type of IPC intervention being evaluated.

Results

The database searches identified 9,960 studies. A further 139 studies were identified by manually searching the reference lists of included studies, resulting in 9,777 studies after removing duplicates, all of which were screened against the eligibility criteria. The majority of these (9,422) were excluded at the title/abstract screening stage, with a further 326 excluded at full-text review. Twenty-nine studies^{24–53} meeting the inclusion criteria were included in the systematic review (figure 1, table 1).

Studies were from the USA (18),^{26–29,32,36–38,40–47,49,50,53} England (3),^{24,34,51} Australia (2),^{35,39} Hong Kong (2),^{25,30} Brazil (1),³¹ Israel (1),⁴⁸ England and Wales (1),⁵² and Germany (1).³³ These included nine ITS studies,^{32–34,42–48} nine CRT,^{25–31,52,53} five CBA studies,^{38–41,49} one NRT,²⁴ and five economic evaluations.^{35–37,50,51} Two studies utilised international guidelines from the World Health Organization^{25,30} and 23 national^{24,27–29,31,33–38,40,42–53} three collaborative^{26,32,41} and one state³⁹ guidelines. Nine of the studies implemented the intervention country-wide^{24,35,37,41,45,47–48,50,51,52}, three region- or state-wide^{34,38,39}, seven across countries^{25,30,31,33,36,46,49}, five across collaborations of hospitals^{27,32,42–44,53} and four across states.^{26,28,29,40} Even though time limits for inclusion were 2000–2017, the majority of

the studies were recent, with 26 published between 2009 and 2017. There were several possible ways of categorising the studies for analysis. These included per type of infection, organism, or intervention. Not all studies fitted into one category so a combination of approaches was used. Since the findings were to be used to inform guidance on the core components of national IPC programmes, type of intervention was the main category with sub-categories according to organism or type of infection where possible.

The 29 included studies were categorised into four groups: multimodal IPC interventions (n = 18 studies, 418 intensive care units (ICUs), 337 hospitals, 50 long term care facilities (LTCFs), and 18 area health services)^{24–41}; IPC care bundles (n = 3 studies, 32 paediatric units, 29 ICUs and 20 hospitals)^{42–45}; IPC policies (n = 6 studies, 2,444 hospitals)^{46–51}; and IPC surveillance, monitoring and feedback (n = 2 studies, 16 area health services and eight hospitals).^{52–53} Multimodal interventions aim to improve an outcome and change behaviour through implementation of several elements, most commonly system change, staff education, monitoring and feedback, reminders, and culture change.⁵⁴ Implementation uses an integrated and multidisciplinary approach and can be supported by practical tools, including care bundles and checklists. Care bundles comprise a small, straightforward set of evidence-based patient focused practices (generally three to five) that improve patient outcomes when performed collectively and reliably.⁵⁴ Care bundles were differentiated from multimodal interventions as they are an implementation tool to guide the delivery of a specific aspect of a patient's care, whereas multimodal interventions generally operate at the level of the organisation to change healthcare workers behaviour through implementation of the abovementioned elements and may include the use of care bundles.⁵⁴ This categorisation is used to structure the results and discussion.

Of the 18 studies investigating multimodal IPC strategies, there was one NRT,²⁴ seven CRT,^{25–31} three ITS studies,^{32–34} three economic evaluations,^{35–37} and four CBA studies.^{38–41} Most of the studies were conducted in acute hospital settings, but four were in LTCFs (table 1).^{25,26,28,30}

The multimodal interventions in this review varied in terms of number (ranging from two to eight) and type of components included (appendix, page 24), but were reported by authors as a collective whole with no attempts to distinguish the relative effect of the different elements. The most frequently cited elements were the implementation of a care bundle (11/18), with provision of training (12/18) and posters/campaign materials (6/18) to support the intervention. The target of these interventions also varied, with some aiming at preventing specific types of HAI, others HAIs in general,^{26,41} and others focusing on hand hygiene (HH).^{25,29,30,35,39} The specific infections addressed were MRSA,^{32,34} central line associated blood stream infection (CLABSI),^{24,27,33,36} surgical site infection (SSI),⁴⁰ *Clostridium difficile* infection (CDI),³⁷ catheter-associated urinary tract infection (CAUTI) and multidrug resistant organisms.²⁸ Two studies^{31,38} targeted both CLABSI and ventilated-associated pneumonia (VAP). Outcomes were measures of infection, cost effectiveness, or compliance with infection control practices. All multimodal intervention studies except three^{26,31,40} showed a significant effect on at least one outcome measure. The economic evaluations of multimodal interventions demonstrated cost savings or cost effectiveness (table 2).³⁵⁻³⁷

Only four studies within the multimodal IPC interventions category measured the same outcome; CLABSI incidence rates per 1,000 patient or central line-days (CL-days).^{24,27,31,33} They all used Centers for Disease Control definitions, although one of these²⁴ also used 'refined' European Centre for Disease Prevention and Control definitions, therefore affecting case ascertainment, but not internal consistency. The other 14 studies reported a range of outcome measures, preventing direct comparison.

Three studies, all with an ITS design and conducted in a hospital setting, investigated the effectiveness of patient-focused care bundles (table 1).⁴²⁻⁴⁵ The patient population for two of these studies were children, with one study^{43/44} taking place in ICUs and the other⁴² conducted in haematology/oncology inpatient units. Miller et al^{43/44} describe the same study, which involved the introduction of insertion and maintenance care bundles for CLABSI, but with one year outcomes reported in 2010 and three year outcomes reported in 2011. Bundy et al⁴² also implemented a CLABSI care bundle but the intervention in this

study was catheter maintenance only. Both studies^{42,43/44} assessed the impact on CLABSI rates per 1,000 line days and found a significant reduction. The third study⁴⁵ included a SSI care bundle for adults undergoing cardiac or orthopaedic surgery with MRSA SSI per 10,000 operations as the primary outcome. The rate of MRSA SSI significantly decreased for both orthopaedic and cardiac operations (table 2).

Six studies examined the effectiveness of a IPC policy (table 1); three used an ITS design,^{46–48} one used a CBA design,⁴⁹ and two were economic evaluations.^{50,51} The settings for all six studies^{46–51} were hospitals, although one study⁴⁹ was conducted only in ICUs. The IPC policies involved the use of financial disincentives with non-payment for preventable infection in hospitals in the USA,^{46,47} mandatory public reporting of CLABSI infection rates in some USA states,⁴⁹ estimated costs associated with HAI if health care antiseptic products were unavailable,⁵⁰ cost effectiveness of MRSA screening,⁵¹ and the instigation of a infection control task force to contain a country-wide outbreak of carbapenem-resistant *Klebsiella pneumoniae* in Israeli hospitals.⁴⁸ Neither study that evaluated non-payment for preventable infection^{46,47} showed a significant reduction in HAI, but the use of antiseptics was associated with hospital costs avoided⁵⁰ and MRSA screening for high risk specialities was shown to be cost effective in terms of QALY.⁵¹ The task force⁴⁸ and mandatory public reporting⁴⁹ studies demonstrated significant reductions in HAI (table 2).

Two CRT explored the effectiveness of implementing feedback of IPC practice (table 1).^{52,53} One⁵³ was conducted in ICUs whereas the other⁵² in acute care settings for elderly patients, general medical wards and ICUs. The former⁵³ investigated the effect of local feedback of infection rates combined with comparison to national data, versus feedback of local infection rates only; significant differences between the two groups were observed for CAUTI, CLABSI, VAP, and overall device-associated infection. The latter⁵² investigated the effect of providing feedback on HH compliance to individual healthcare workers and showed that HH compliance significantly increased (table 2).

Quality assessment of the 29 studies (appendix, pages 26 and 27) showed that five CRT were at low risk of bias,^{27,28,31} one with regard to its primary outcome⁵² and another with regard to its secondary outcome.²⁵ Three other CRT^{29,53} had an unclear risk of bias, one concerning its secondary outcome.⁵² One ITS was also at unclear risk of bias,³³ while 17 studies were at high risk of bias,^{24,26,30,32,34,38–49} one in relation to its primary outcome.²⁵ The remaining five studies were economic evaluations^{35–37,50,51}; a narrative summary of the methodological quality of these is available in the appendix, page 28.

GRADE was applicable to assess the quality of the body of evidence for studies assessing multimodal IPC interventions and IPC care bundles as these were the only types of interventions in which the same outcomes were reported in more than one study.

For multimodal IPC interventions, CLABSI incidence rate per 1,000 patient or line days was reported in four studies.^{24,27,31,33} The risk of bias for two studies^{27,31} indicated that there was an overall low risk of bias. For one study the reported confidence intervals suggested relatively precise effect estimates,²⁷ but the intervention in the second study had no effect on CLABSI.³¹ The third study²⁴ had a high risk of bias and the fourth study³³ had an unclear risk of bias. Thus, the body of evidence of multimodal IPC interventions for CLABSI incidence rates per 1,000 patient or line days may be considered low quality.

In the IPC care bundles group of interventions, two studies^{42,43/44} reported CLABSI rates per 1,000 line days. These studies used an ITS design and received a high risk of bias, so this body of evidence may also be considered low quality.

Discussion

This review of the effectiveness of IPC interventions was undertaken to inform the development of international guidance on national IPC programmes. Although a high level of heterogeneity of interventions was observed, it was possible to identify four categories of IPC intervention: multimodal IPC interventions (n = 18 studies)^{24–41}; IPC care bundles (n = 3

studies)⁴²⁻⁴⁵; IPC policies (n = 6 studies)⁴⁶⁻⁵¹; and IPC surveillance, monitoring, and feedback (n = 2 studies).^{52,53}

Evidence of effectiveness of IPC interventions, based on international, national, state or collaborative guidelines and implemented countrywide, region wide or across countries, regions or collaborations, for guideline development was limited to a small number of individual studies. Of the 29 included studies, high quality evidence with a low risk of bias was provided by four studies of multimodal interventions,^{25,27,28,31} and one study of a monitoring, surveillance, and feedback intervention.⁵² In addition, a moderate level of evidence was provided by two studies of multimodal interventions^{29,33} and a study of monitoring, surveillance and feedback interventions⁵³ with an unclear risk of bias. Another study of monitoring, surveillance and feedback interventions⁵² had both primary and secondary outcomes. It had a low risk of bias for the primary outcome and a moderate risk of bias for the secondary outcome.

Multimodal interventions were supported by the highest number of studies, with the majority demonstrating effectiveness. However, they evaluated IPC components collectively while the individual impact of each component was not identifiable, nor was which interventions collectively had the best impact on outcome, as no two studies included the same combination of interventions. This is a recurrent theme in the IPC literature, both at an organisational level and wider.^{8,9}

Surveillance with active feedback tends to report positive effects, even when it is a single intervention. Effective studies used national HH data for feedback at an individual level to drive behaviour change⁵² and national infection rates as a benchmarking tool to drive comparisons and improvement across hospitals.⁵³ Additional studies reporting a positive impact of national surveillance exist outside this review but were not included as they did not meet our inclusion criteria mainly linked to the absence of control comparators. Indeed, following introduction of national surveillance at one point in time in all hospitals, the first year is normally used as a proxy baseline and temporal trends are reported thereafter.⁵⁶⁻⁶⁰

Nonetheless there are a number of papers in the IPC literature reporting observational evidence that when national HAI surveillance is introduced there is a significant reduction in HAI seen by year 3 of the programme. This impact has been observed in Germany with SSI and MRSA,^{59,60} France with SSI and MDRB,^{56,57,61,62} Italy with SSI,⁶³ Finland with CDI,⁶⁰ and the USA with overall HAI.⁶⁴

The review identified some evidence, although subject to bias and low quality, for two other interventions, namely, care bundles and policies, including development of guidelines accompanied by related healthcare workers' education and training. Absence of evidence meeting the inclusion criteria does not of course infer absence of effect, or importance of the other key interventions required for national level IPC programmes. No study was found to evaluate the effectiveness of establishing a comprehensive national IPC programme to reduce HAI and AMR. However, the experts evaluating the evidence strongly affirmed that each country should have a stand-alone, active national IPC programme.

The strengths of this review are that it was conducted in a systematic and rigorous manner and that to the authors' knowledge this is the first systematic review evaluating IPC interventions to guide the implementation of effective national IPC programmes. The comprehensive search comprised an extensive range of appropriate index terms and free text words and spanned four major databases and one specialist repository over a wide time period (January 1, 2000 to April 19, 2017). Citation searches of included studies were also conducted. Other methodological strengths include the focus on studies meeting the EPOC design criteria¹³⁻¹⁵ and the use of design-specific quality assessment tools recommended by Cochrane and EPOC.¹⁶⁻²³ However, despite aiming to be inclusive of all countries and having the resources to translate studies in several languages, the focus on studies meeting the EPOC criteria resulted in studies from only seven high-income countries and one upper-middle income country being included. This emphasises the need to build research capability and capacity specifically to enhance the evidence base from a wider range of countries, and in particular from low- / middle-income countries.

The review describes a lack of high quality studies using comparable primary outcomes. This limits the development of evidence-based international guidance to shape policy and practice. However, clear recommendations can be made for improvement in future research design for such studies to develop a viable evidence base. Exclusion of many studies was due to their study design. The majority were cohort studies that did not meet the EPOC study design criteria. However, these studies could still provide some important and valuable evidence in the absence of studies with more rigorous study designs and can be taken into account when guidelines are being developed. As a consequence, there is a need for improved research design with CRT, better designed epidemiology studies including rigorous time series analysis,¹⁴ and the consistent use of core outcomes to inform the future evidence base for IPC. A stepped-wedge design would be ideal as it would potentially allow the evaluation of the effect of different interventions introduced in a step-wise manner in different sites. Furthermore, the use of consistent measurements for specific outcomes according to standardised definitions is crucial in order to make meta-analysis feasible and allow the assessment of impact from the body of the evidence of studies with the same outcome. In addition, it is important to measure, both outcomes and processes, in particular if an experimental design is not possible. This is crucial to demonstrate that behavioural and practice changes have occurred and can help relate the changes to the intervention in non-controlled and non-randomized studies.⁶⁵ It is recognised that such experimental approaches are challenging as national policy initiatives for IPC interventions are often implemented at pace, not designed with evaluation built in from the outset, and evaluated retrospectively, if at all.^{66,67}

In addition to the lack of studies meeting the EPOC design criteria, there were key omissions relating to the detail of reporting about the intervention content, how it was implemented, and its hypothesised mechanisms of action. These must be addressed in future IPC research as they are crucial for replicability and dissemination. The studies that evaluated the effect of a multimodal IPC intervention, for example, tended to report positive effects from the intervention whereas challenges encountered and related solutions, if any, were neglected. Furthermore, the relative contribution of individual elements was usually not identifiable,

nor was any sense of the impact of particular combinations of elements upon outcome. This is a recurrent theme in the IPC literature which seriously limits our ability to build cumulative and transferable evidence relating to intervention elements.^{8,9} In addition, studies tended not to have specified any theoretical underpinning. The use of theory provides a hypothesized mechanism of change. This can provide a rationale for the delivery of specific elements in particular combinations in specific contexts and can improve the coherence of complex interventions and limit the inclusion of extraneous intervention components.

These key omissions can be remedied by using behavioural theories and tools such as the Theory Coding Scheme⁶⁸ and the Behaviour Change Technique Taxonomy,⁶⁹ wider approaches from implementation science, and quality improvement methodologies. Together, these inform intervention development, intervention evaluation and foster reporting of key outcome measures. Culture and social context are also important in order to understand the success or failure of IPC interventions.⁷⁰ These should also be taken into account to better understand the implementation of IPC strategies.⁷¹ This is particularly true with regard to the dearth of research in low-income countries. Implementing effective interventions within the developed world alone will not help to contain HAI and AMR in the global context. Finally, studies need to be reported in such a way that they can be replicated in different contexts. There is a growing body of literature to guide authors⁷²⁻⁷⁴ that could strengthen reporting practice.

In conclusion, the best available evidence to inform international recommendations about effective IPC programmes comes from individual studies on IPC multimodal interventions and studies on surveillance, monitoring, and feedback. We call for urgent improvements in the use of more robust study designs in IPC research and research investigating the cultural and international relevance of IPC interventions. This review has made a major contribution to illustrate the state of current evidence in relation to national and sub-national IPC interventions. The findings provide direction for international guidance which will shape global action to prevent and control HAI and contain AMR.

Contributors

LP, JM, TH, JS, CK, AT, BA, and JR contributed to the design of the study and development of the protocol, with LP leading the review. LP, JM, and LM did the literature search and along with DW, performed study selection. LP, JM, LM, TH, PF, KC, EC, VN, and JR collected the data, with all, excluding LM, undertaking risk of bias assessments. AM, JR, and SM quality assessed the economic evaluations. LP, JM, and LM produced the supplementary materials. LP and JR interpreted the data. LP, JM, BA, and JR wrote the manuscript, which was finalised by LP. All authors reviewed and approved the final manuscript.

Declaration of interests

LP, JM, LM, TH, PF, KC, EC, VN, DW, AM, SM, and JR report a grant from WHO to conduct the study.

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Figure 1 Flow diagram of study selection

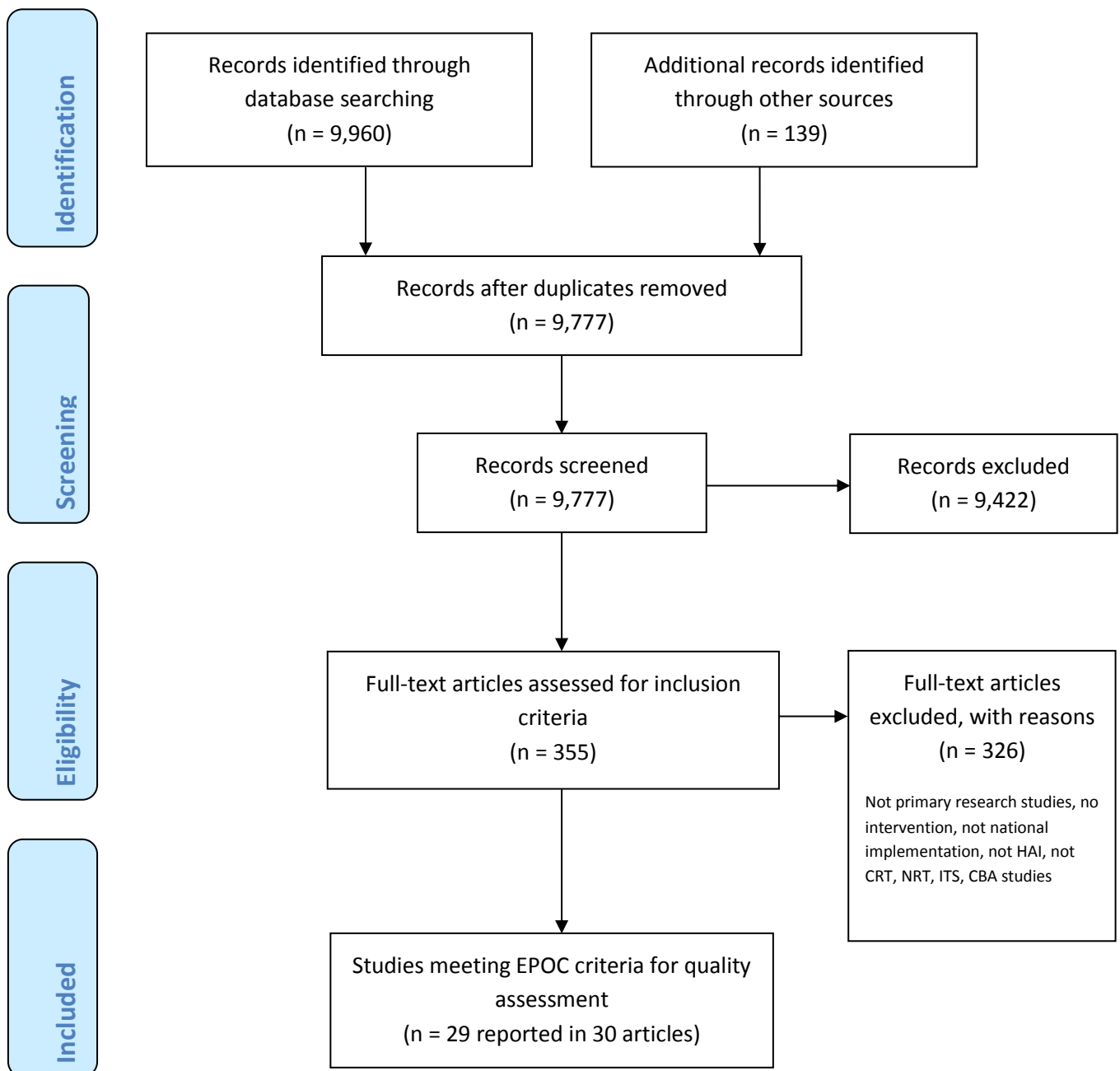


Table 1 Study characteristics and summary assessment of risk of bias

Authors	Study design	Intervention content	Intervention guidelines	Intervention implemented	Sample size	Summary assessment of risk of bias
National multimodal infection prevention and control interventions						
CLABSI						
Bion et al (2013) ²³	NRT	Care bundle, cultural change, surveillance, training, ad hoc support and guidance, teamwork and communication, and executive support	“Matching Michigan” National Patient Safety Agency central line CRBSI multimodal programme	All 139 acute hospitals in England, UK	223 ICU 438,887 patient days (adult 404,252; paediatric 34,635)	High risk
Marsteller et al (2012) ²⁶	CRT	Care bundle, cultural change, training, teamwork and communication, executive support, checklist, learning from incidents, and identified lead	Keystone ICU and Comprehensive Unit-based Safety Program	Adventist Health and Adventist Health System in West and Midwest and Southeast regions of USA	35 hospitals from 12 states 45 ICU	Low risk
Hansen et al (2014) ³²	ITS	Surveillance, care bundle, teaching materials, train the trainers, and posters/campaign materials	Krankenhaus Surveillance System (KISS) CLABSI Programme	All ICU (107) in Germany with CLABSI rates equal to or greater than the national average	32 ICU intervention group 344 ICU control groups 266,471 central line-days intervention group	Unclear risk
Herzer et al (2014) ³⁵ USA	Economic evaluation	Care bundle, cultural change, and performance feedback	On the CUSP: stop BSI national collaborative	1200 US hospitals	Hospital setting Adult ICU	NA
MRSA						
Jain et al (2011) ³¹	ITS	Care bundle, cultural change, training, train the trainers, and funding	Veterans Health Administration National MRSA Prevention Initiative	All 153 Veterans Hospitals USA	153 hospitals 624 acute care units. 1,934,598 admissions.	High risk
Newitt et al (2015) ³³	ITS	Care bundle, provision of ABHR, performance feedback, posters/campaign materials, and policy review	National and regional HAI interventions	Areas Health Services (NHS Trusts) East Midland Region, England, UK	8 Area Health Services.	High risk
Hand hygiene						
Ho et al (2012) ²⁴	CRT	Training, provision of ABHR, train the trainers, performance feedback, and posters/campaign materials. Intervention arm 1 - slightly powdered gloves, intervention arm 2 - powderless gloves	World Health Organization multimodal hand hygiene strategy	Care and attention nursing homes in Hong Kong	18 LTCFs 11,669 HH opportunities	High risk HH compliance Low risk respiratory outbreaks and MRSA infections
Stevenson et al (2014) ²⁸	CRT	Training, provision of ABHR, training materials, train the trainers, performance feedback, and posters/campaign materials	Healthcare Infection Control Practices Advisory Committee and the ICPAC/SHEA/APIC/IDSA guidelines	Community hospitals in Idaho and Utah, USA	10 hospitals 4,527 HH opportunities	Unclear risk
Yeung et al (2011) ²⁹	CRT	Training, provision of ABHR, and posters/campaign materials.	World Health Organization hand hygiene guidelines	Community-based , private or semiprivate residential long-term	6 LTCFs. 3,300 HH opportunities.	High risk

Authors	Study design	Intervention content	Intervention guidelines	Intervention implemented	Sample size	Summary assessment of risk of bias
				care facilities in different regions of Hong Kong		
Graves et al (2016) ³⁴	Economic evaluation	Cultural change, surveillance, training, teaching materials, and train the trainers	Australian National Hand Hygiene Initiative	All states and territories in Australia	50 largest acute public hospitals representative of 8 states/ territories. 1,294,656 admissions to 24,482 beds	NA
McLaws et al (2009) ³⁸	CBA	Provision of ABHR, posters/campaign materials, and identified lead	State wide Clean hands saves lives campaign	All public hospitals in New South Wales, Australia	Hospital setting 10/11 Area Health Services	High risk
Other						
Makris et al (2000) ²⁵	CRT	HAI teaching materials, visits to sites, and policy review	Medisys Infection Control Surveillance Programme mandated by the Health Care Finance Administration	LTCFs in New Jersey and Delaware, USA	8 LTCFs 900 beds	High risk
Mody et al (2015) ²⁷	CRT	Care bundle, surveillance, and training	Centers for Medicare & Medicaid Targeted Infection Program	Community-based LTCFs in Southeast Michigan, USA	12 LTCFs 418 patients 34,174 device days	Low risk
Cavalcanti et al (2016) ³⁰	CRT	Surveillance, training, ad hoc support and guidance, teamwork and communication, performance feedback, visit to sites, and check list	CDC/National Healthcare Safety Network recommendations and standards	ICU from all Brazilian regions	118 ICU (6,761 patients). 59 intervention ICU (3,327 patients). 59 control ICU (3,434 patients).	Low risk
Slayton et al (2015) ³⁶	Economic evaluation	CDI care bundle and surveillance	Society for Healthcare Epidemiology of America and the Infectious Disease Society of America CDI guidelines	USA hospitals	Hospital setting Medicare patients aged >65 years	NA
Lipitz-Snyderman et al (2011) ³⁷	CBA	CRBSI and VAP care bundle, cultural change, training, and teamwork and communication	Michigan Health n and Hospital Association Keystone ICU project	All 132 Michigan hospitals, USA	95 hospitals intervention group. 1,331,484 hospital admissions for adults aged 65 or older. 364 hospitals from 11 States control group. 1,091,547 hospital admissions.	High risk
Reames et al (2015) ³⁹	CBA	SSI care bundle, cultural change, training, teamwork and communication, executive support, checklist, and learning from incidents.	Keystone Surgery Program	101 hospitals in Michigan, USA	29 hospitals 64,891 patients	High risk
Wirtschafter et al (2011) ⁴⁰	CBA	Nosocomial infection care bundle, training, and teaching materials	California Perinatal Quality Care Collaborative program	Hospitals who are members of the California Perinatal Quality Care Collaborative USA	54 NICU 7,733 very low birth weight infants in 27 participating NICU and 4,512 very low birth weight infants in 27 non-participating NICU	High risk
National infection prevention and control care bundles						
Bundy et al	ITS	Central line maintenance care bundle	CDC recommendations and	Multicentre collaboration operated	32 paediatric haematology/ oncology	High risk

Authors	Study design	Intervention content	Intervention guidelines	Intervention implemented	Sample size	Summary assessment of risk of bias
(2014) ⁴¹			standards	by the Children's Hospital Association. Healthcare centres across the USA participated	inpatient units	
Miller et al (2010 & 2011) ^{42,43}	ITS	Insertion and maintenance CVC care bundles	CDC Insertion and Maintenance Care Bundle	65 PICU in the National Association of Children's Hospitals and Related Institutions, USA	29 paediatric ICU 501,911 central line-days	High risk
Schweizer et al (2015) ⁴⁴	ITS	SSI care bundle <i>S. aureus</i> screening, decolonisation, and antibiotic prophylaxis	American Society of Health-System Pharmacists guidelines and CDC guidelines	The Hospital Corporation of American affiliated hospitals	20 hospitals in 9 States 42,534 surgical operations	High risk
National infection prevention and control policies						
Lee et al (2012) ⁴⁵	ITS	Non-payments for preventable HAI	Centers for Medicare and Medicaid Services Non-Payment for preventable conditions	All Medicare hospitals USA but only 1166 acute hospitals eligible to participate inclusion in study as members of the National Patient Safety Network performing surveillance of HAI	Catheter-associated BSI: 398 hospitals and 4,932,056 device days CAUTI: 543 hospitals and 3,244,462 device days VAP: 548 hospitals and 2,050,996 device days	High risk
Schuller et al (2014) ⁴⁶	ITS	Non-payment policy on CAUTI	Medicare non-payment policy for CAUTI	All Medicare hospitals, USA	Hospitals in the Nationwide Inpatient Sample 1050 hospitals 8,000,000 discharges	High risk
Schwaber et al (2011) ⁴⁷	ITS	Mandatory public reporting and isolation of carbapenem-resistant enterobacteriaceae carriers. Task force visited sites, supervised adherence to guidelines, and provided feedback on performance to hospital directors	CDC guidelines	All acute hospitals in Israel	13,040 beds 27 acute care hospitals	High risk
Marsteller et al (2014) ⁴⁸	CBA	State laws mandating public reporting of CLABSI rates	State mandatory reporting of CLABSI using CDC definitions	44 states, Washington DC, and Puerto Rico, USA	Mandatory reporting in 30/47 states 36% of all hospital participated 771 hospitals	High risk
Schmier et al (2016) ⁴⁹	Economic evaluation	Health care personnel hand washes and rubs, surgical hand scrubs and rubs, and patient preoperative and preinjection skin preparations	Hospital costs of HAI if antiseptics were removed from guidance	Hospitals in the USA	US hospitals	NA
Robotham et al (2016) ⁵⁰	Economic evaluation	Screening and intervention strategies including: (1) no screening; (2) screening of all admissions; (3) screening of admissions to high-risk specialties; (4) checklist-activated screening; (5) screening of admissions to high-risk specialties plus checklist-activated screening of other admissions; (6) screening of all admissions	National universal mandatory screening for MRSA	All hospitals in England, UK	English hospitals – acute, teaching and specialist.	NA

Authors	Study design	Intervention content	Intervention guidelines	Intervention implemented	Sample size	Summary assessment of risk of bias
		plus pre-emptive isolation of individuals known to be previously MRSA positive				
National infection prevention and control surveillance, monitoring, and feedback						
Fuller et al (2012) ⁵¹	CRT	Observation, feedback, personalised action planning	National “cleanyourhands” campaign	All hospitals across England and Wales, UK	16 hospitals 16 ITU 44 wards	Low risk HH compliance Unclear risk consumption ABHR
McKinley et al (2003) ⁵²	CRT	CDC surveillance and risk-adjusted feedback on infection rates (with and without national comparative data)	National Nosocomial Infections Study System	Network of Veterans Affairs hospitals with nosocomial infections above the 90 th percentile (62)	8 hospitals in 3 different states	Unclear risk

ABHR – Alcohol-Based Hand Rub

BSI – Blood Stream Infection

CAUTI – Catheter Associated Urinary Tract Infection

CBA – Controlled Before and After

CDC = Centers for Disease Control and Prevention

CDI – *Clostridium difficile* Infection

CLABSI – Central-Line Associated Blood Stream Infection

CRBSI – Catheter-Related Blood Stream Infection

CRT – Cluster Randomised Trial

HAI – Healthcare Associated Infection

HH – Hand Hygiene

ICU – Intensive Care Unit

ITS – Interrupted Time Series

LTCF – Long-Term Care Facility

MRSA – Meticillin Resistant *Staphylococcus aureus*

NICU – Neonatal Intensive Care Unit

NA – Not Applicable

NRT – Non-Randomised Trial

PICU – Paediatric Intensive Care Unit

S. aureus – *Staphylococcus aureus*

SSI – Surgical Site Infection

VAP – Ventilator Associated Pneumonia

Table 2 Study outcomes

Study	Outcomes
National multimodal infection prevention and control interventions	
CLABSI	
Bion et al (2013) ²³	CVC-BSI/1,000 CVC-patient days decreased from 3.7 to 1.48 ($p < 0.0001$) for adult ICU. CVC-BSI/1,000 CVC-patient days decreased from 5.65 to 2.89 for paediatric ICU ($p = 0.625$).
Marsteller et al (2012) ²⁶	Baseline rate of CLABSI/1,000 CL-days was 4.48 and 2.71 for the intervention and control groups, respectively ($p = .28$). The CLABSI rate declined to 1.33 in the intervention group compared to 2.16 in the control group (adjusted incidence rate ratio 0.19; $p = .003$; 95% CI 0.06-0.57). The intervention group sustained CLABSI rates $<1/1,000$ CL-days at 19 months (an 81% reduction). The control group also reduced CLABSI rates to $<1/1,000$ CL-days (a 69% reduction) at 12 months.
Hansen et al (2014) ³²	At baseline, the CLABSI rate was 2.29 per 1,000 CL-days and this decreased significantly to 1.64 per 1000 CL-days in the follow-up period. Compared with baseline, the RR for CLABSI was 0.88 (95% CI 0.70-1.11) for the intervention period and 0.72 (95% CI 0.58-0.88) for the follow-up period.
Herzer et al (2014) ³⁵	Cost-effectiveness demonstrated. The quality improvement programme prevents 42 CLABSIs per 1,000 patients and averts 6 deaths per 1,000 patients at no additional cost compared to current practice.
MRSA	
Jain et al (2011) ³¹	MRSA infections decreased: ICU from 1.64 to 0.62 infections per 1,000 patient-days ($p < 0.001$) and non-ICU from 0.47 to 0.26 per 1,000 patient-days ($p < 0.001$).
Newitt et al (2015) ³³	7 of 8 Area Health Services had a significant decreasing trend for MRSA incidence rates per 100,000 bed-days during implementation and maintained in the post intervention phase ($p < 0.001$). Increasing trends in 4 hospital groups for MSSA.
Hand hygiene	
Ho et al (2012) ²⁴	HH compliance increased from 27.0% to 60.6% and from 22.2% to 48.6% in intervention arms 1 and 2, respectively, compared to controls at 21.6% compliance (both $p < 0.001$). Respiratory outbreaks (IRR 0.12; 95% CI 0.01 to 0.93; $p = 0.04$) and MRSA infections requiring hospital admission (IRR 0.61; 95% CI 0.38 to 0.97; $p = 0.04$) were reduced.
Stevenson et al (2014) ²⁸	The estimated average absolute change in "complete HH compliance" was 20.1% in intervention hospitals vs -3.1% in control hospitals ($p = 0.001$). The estimated average absolute change in "any HH compliance" was 28.4% in intervention hospitals compared to 0.7% in control hospitals ($p = 0.010$).
Yeung et al (2011) ²⁹	ABHR HH compliance improved from 5% to 15.9% ($p = 0.001$) and total HH adherence increased from 25.8% to 33.3% ($p = 0.01$); the control group showed no significant change. Incidence of infections decreased from 1.42 to 0.65 cases per 1,000 resident-days ($p = 0.002$). In the control group, it increased from 0.49 to 1.05 cases per 1,000 resident-days ($p = 0.004$).
Graves et al (2016) ³⁴	Total annual costs increased by \$2,851,475 for a return of 96 years of life giving an ICER of \$29,700 per life year gained. Probabilistic sensitivity analysis revealed a 100% chance the initiative was cost effective in the Australian Capital Territory and Queensland, with ICERs of \$1,030 and \$8,988, respectively. There was an 81% chance it was cost effective in New South Wales with an ICER of \$33,353, a 26% chance for South Australia with an ICER of \$64,729 and a 1% chance for Tasmania and Western Australia.
McLaws et al (2009) ³⁸	25% reduction in MRSA non-ICU sterile site infections, from 0.60 to 0.45/10,000 bed-days ($p = 0.027$), and a 16% reduction in ICU non-sterile site infections, from 36.4 to 30.4/10,000 bed-days ($p = 0.037$). Infection rates in ICU sterile sites (5.28 vs 4.80/10,000 bed-days, $p = 0.664$) and non-ICU non-sterile sites (5.92 vs 5.66/10,000 bed-days, $p = 0.207$) remained stable.
Other	
Makris et al (2000) ³⁵	Outcomes infections per 1,000 patient days. No significant difference between treatment vs controls in HAI ($p = 0.19$). No significant difference for types of HAI ($p = 0.06$ to $p = 0.81$).
Mody et al (2015) ²⁷	Risk of CAUTI was significantly lower in the intervention group vs the control group (hazard ratio 0.54 (95% CI 0.3 to 0.97), $p = 0.04$). 23% reduction in multi-drug resistant organism prevalence density rate (rate ratio 0.77 (95% CI 0.62 to 0.94), $p = 0.01$).
Cavalcanti et al (2016) ³⁰	No significant difference in the intervention and control group for CLABSI/1,000 patient days: RR 1.03 (95% CI 0.73 to 1.45, $p = 0.88$) nor for VAP/1,000 patient days: RR 1.04 (95% CI 0.68 to 1.58, $p = 0.87$).
Slayton et al (2015) ³⁶	CDI prevention is cost saving. Estimated that 509,000 CDI cases and 82,000 CDI-attributable deaths would be prevented over a 5-year time horizon. Nationally, the cost savings across all hospitalisations would be \$2.5 billion.
Lipitz-Snyderman et al (2011) ³⁷	Reductions in mortality were significantly greater for the study group than for the comparison group during post-implementation months 1 to 12 (OR 0.83, 95% CI 0.79 to 0.87 vs OR 0.88, 95% CI 0.85 to 0.90, $p = 0.041$) and 13 to 22 (0.76, 95% CI 0.72 to 0.81 vs 0.84, 95% CI 0.81 to 0.86, $p = 0.007$). Length of stay did not differ between groups ($p = 0.560$).
Reames et al (2015) ³⁹	No improvements in surgical outcomes during the study period. Adjusted rates of superficial SSI were 3.2% before vs 3.2% after ($p = 0.91$) and adjusted rates of 30-day mortality were 2.1% before vs 1.9% after ($p = 0.32$).
Wirtschafter et al (2011) ⁴⁰	For the entire cohort, the rate of nosocomial infection decreased from 16.9% in 2002 to 14.5% in 2006 ($p = 0.02$). For infants admitted to NICU participating in at least one quality improvement event, there was an associated decreased risk of nosocomial infection (OR 0.81, 95% CI 0.68 to 0.96) compared with those admitted to nonparticipating hospitals.
National infection prevention and control care bundles	
Bundy et al (2014) ⁴¹	Significantly lower CLABSI 28% reduction in the rate. Odds of no CLABSI in a given unit in a given month during the intervention period was 2.59 times the odds during the pre-intervention period comparing unit with similar central line day ($p = 0.001$). Changes in self-reported central line care bundle compliance were not statistically associated with changes in CLABSI rates.

Study	Outcomes
Miller et al (2010 & 2011) ^{42,43}	Paediatric ICU CLABSI rate decreased 56% over 36 months from 5.2 to 2.3 CLABSI per 1,000 line-days (rate ratio 0.44, 95% CI 0.37 to 0.53, $p < 0.0001$). Increase in insertion and maintenance bundle compliance rates over time period, Oct 2006-Sept 2009 (no data provided)
Schweizer et al (2015) ⁴⁴	Reduced mean SSI rate 36 vs 21 per 10,000 operations, difference -15 (95% CI -35 to -2; rate ratio 0.58, 95% CI 0.37 to 0.92). Bundle adherence remained constant at 83% (full adherence, 39%; partial adherence, 44%). The complex <i>S aureus</i> SSI rates decreased significantly (rate ratio 0.26, 95% CI 0.10 to 0.69), but rates did not decrease significantly in the partially adherent or non-adherent group (rate ratio 0.80; 95% CI 0.49 to 1.31).
National infection prevention and control policies	
Lee et al (2012) ⁴⁵	Outcomes were defined as the quarterly rate of each HAI per 1,000 device-days exposed. No impact of policy implementation on catheter-associated BSI (IRR 1.00, $p = 0.97$), CAUTI (IRR 1.03, $p = 0.08$), or VAP (IRR 0.99, $p = 0.52$).
Schuller et al (2014) ⁴⁶	Outcome CAUTIs per 1,000 patient discharges. No significant rate of change with CAUTI after the policy change ($p = 0.3577$).
Schwaber et al (2011) ⁴⁷	Reduction in the incidence of carbapenem-resistant enterobacteriaceae 55.5 vs 11.7 cases per 100,000 patient-days ($p < 0.001$). Correlation between compliance with isolation guidelines and success in containment of transmission ($p = 0.02$). Compliance neutralised the effect of carrier prevalence on new incidence ($p = 0.03$).
Marsteller et al (2014) ⁴⁸	All groups had a reduction in CLABSI rates. Groups with new mandates had greater reduction in the first 6 months (voluntary: IRR = 0.73, 95% CI 0.56 to 0.94; older mandates: IRR = 0.83, 95% CI 0.70 to 0.99). Trend toward greater reduction in CLABSI after 1-year of programme implementation (new mandate: IRR 0.56, 95% CI 0.31 to 1.01; older mandate: IRR 0.83, 95% CI 0.68 to 1.01).
Schmier et al (2016) ⁴⁹	Low- and high-end estimates of national, annual HAs in hospitals avoided through use of health care antiseptics are 12,100 and 223,000, respectively, with associated hospital costs avoided of US\$142 million and US\$4.25 billion, respectively.
Robotham et al (2016) ⁵⁰	Screening all admissions was unlikely to be cost effective. Switching from screening all admissions to only high-risk specialty admissions was likely to represent better resource use with a mean reduction in total costs per year (not considering uncertainty) of £2.7 million per acute hospital, £2.9 million per teaching, and £474,000 per specialist hospital for a minimum rise in infections (about one infection per year per hospital).
National infection prevention and control surveillance, monitoring, and feedback	
Fuller et al (2012) ⁵¹	Significant sustained improvement in HH compliance on intention-to-treat for ICU OR 1.44 (95% CI 1.18 to 1.76) $p < 0.001$ and per-protocol analysis for acute care of the elderly or medical wards (OR 1.67, 95% CI 1.28 to 2.22, $p < 0.001$) and ICU (OR 2.09, 95% CI 1.55 to 2.81, $p < 0.001$). Absolute difference in HH compliance 13% to 18% on ICU, and 10% to 13% on acute care of the elderly or medical wards. Sustained effect. In the intention-to-treat analysis there was no evidence of a rise in ABHR procurement with the estimated relative change (95%CI) post-randomisation of 1.064 (0.933 to 1.214); $p = 0.4$ in ICU and 1.027 (0.919–1.148); $p = 0.6$ in ACE wards. Per-protocol analysis showed no increase in ABHR procurement for the wards with the estimated relative change post implementation being 1.183 (0.989 to 1.416) for acute care of the elderly or medical wards and 1.098 (0.904 to 1.333) for ICU.
McKinley et al (2003) ⁵²	A significant difference between the control and experimental group for CAUTI ($p = 0.012$), CLABSI ($p = 0.006$), VAP ($p = 0.0025$), and overall device-associated infection ($p < 0.001$).

ABHR – Alcohol-Based Hand Rub
 CDI – *Clostridium difficile* Infection
 CVC – Central Venous Catheter
 BSI – Blood Stream Infection
 CAUTI – Catheter Associated Urinary Tract Infection
 CI – Confidence Interval
 CL – Central Line
 CLABSI – Central-Line Associated Blood Stream Infection
 HAI – Healthcare Associated Infection
 HH – Hand Hygiene
 ICER – Incremental Cost-Effectiveness Ratio
 ICU – Intensive Care Unit
 IRR – Incidence Rate Ratio
 MRSA – Meticillin Resistant *Staphylococcus aureus*
 MSSA – Meticillin Sensitive *Staphylococcus aureus*
 NICU – Neonatal Intensive Care Unit
 OR – Odds Ratio
 RR – Relative Risk
S. aureus – *Staphylococcus aureus*
 SSI – Surgical Site Infection
 VAP – Ventilator Associated Pneumonia