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Universal or targeted approach to prevent the transmission of extended-spectrum beta-lactamase–producing *Enterobacteriaceae* in intensive care units? A cost-effectiveness analysis

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ABSTRACT

Objective

Several control strategies have been used to limit the transmission of multidrug-resistant organisms in hospitals. However, their implementation is expensive and effectiveness of interventions for the control of extended-spectrum beta-lactamase–producing Enterobacteriaceae (ESBL-PE) spread is controversial. Here we aim to assess the cost-effectiveness of hospital-based strategies to prevent ESBL-PE transmission and infections.

Design

Cost-effectiveness analysis based on dynamic, stochastic transmission model over a one-year time horizon.

Patients and setting

Patients hospitalized in a hypothetical 10- bed intensive care unit (ICU).

Interventions

Base case scenario compared to 1) universal strategies (e.g. improvement of hand hygiene (HH) among healthcare workers (HCWs), antibiotic stewardship), 2) targeted strategies (e.g. screening of patient for ESBL-PE at ICU admission and contact precautions or cohorting of carriers) and 3) mixed strategies (e.g. targeted approaches combined with antibiotic stewardship).

Main Outcomes and Measures: Cases of ESBL-PE transmission, infections, cost of intervention, cost of infections, incremental cost per infection avoided.

Results

In the base case scenario, 15 transmissions and 5 infections due to ESBL-PE occurred per 100 ICU admissions, representing a mean cost of €94 792. All control strategies improved health

outcomes and reduced costs associated with ESBL-PE infections. The overall costs (cost of intervention and infections) were the lowest for HH compliance improvement to 80%/80%. Two strategies required higher investments than the HH programme, but also improved health benefits; 1) HH improvement to 80%/80% combined with antibiotic stewardship and 2) screening and cohorting strategy combined with antibiotic stewardship.

Conclusions

Improved compliance with HH was the most cost-saving strategy to prevent the transmission of ESBL-PE. Adding antibiotic restriction to HH or screening and cohorting slightly improved their effectiveness and may be worthy of consideration by decision-makers'.

Strength and limitations of this study

- We used a dynamic transmission model to take into account that the risk of colonization in the ICU depends on the number of ESBL-PE carriers and could change over time.
- Parameters used in the model were derived from recent multicentre studies.
- We undertook sensitivity analyses to show the impact of uncertainty in parameter estimation and the impact of model assumptions on the conclusions.
- Direct HCW-to-HCW transmissions as well as environmental contamination were not included in the model.

INTRODUCTION

The incidence of infection and colonization with extended-spectrum beta-lactamase–producing *Enterobacteriaceae* (ESBL-PE) has increased worldwide. In Europe, in 2014, the percentage of *Escherichia coli* and *Klebsiella pneumoniae* resistant to 3rd generation cephalosporins in invasive

isolates was 12% and 23%, respectively[1]. A similar trend was observed in the United States, although with large variations between states[2].

In hospital settings, ESBL-PE acquisition is mainly due to indirect transmission between patients with the hands of healthcare workers (HCWs) as vectors. Increased prevalence of colonization augments the risk of acquiring ESBL-PE infection[3]. Such infections represent a serious socio-economic burden and are associated with a raised mortality, a longer hospitalization, and additional costs[4].

Many interventions have been proposed to limit the transmission of multidrug-resistant organisms (MDROs) in hospitals. They can be classified as either 1) a 'universal' or 'horizontal' approach, applied to all patients e.g. improvement of hand hygiene (HH) among HCWs or antibiotic stewardship or 2) a 'targeted' or 'vertical' approach, e.g. screening and isolation of asymptomatic carriers in addition to infected patients, with the aim of identifying carriers and implementing measures to prevent the transmission from carriers to other patients[5].

There is general agreement that HH reduces the transmission of MDROs, especially MRSA[3]. However, few studies have evaluated the impact of HH on the prevention of ESBP-PE dissemination and, so far, most of those studies have not provided evidence of HH benefit[6], with the exception of one recently published study[7]. The effectiveness of targeted measures in controlling the spread of MDROs, and especially ESBL-PE, remains controversial. This approach is mainly recommended in high-risk units, e.g. intensive care units (ICUs)[8].

The implementation of interventions with demonstrated effectiveness in reducing ESBL-PE infections is associated with costs that are generally supported by hospitals. However, when evaluating implementation of an infection prevention programme, one should also take into account savings associated with these interventions, but this has been largely ignored in previous studies.

In this study, we used a mathematical model to evaluate the effectiveness and cost-effectiveness of universal and targeted control strategies for the prevention of ESBL-PE transmission in an ICU in a high-income country.

METHODS

The model

We extended a previously described stochastic, compartmental and dynamic model of ESBL-PE transmission[9] to assess the economic impact of infection control strategies implemented in a hypothetical, ICU setting over a one-year time horizon.

The model simulated the spread of ESBL-PE among patients through contacts with HCWs in an ICU, taking into account hospital admissions and discharges of patients, antibiotic exposure, and control interventions (**Figure 1**).

The **Supplementary Text S1** provides details of the model and its assumptions.

Model simulations and outcomes

Simulations of the model were performed using Gillespie's method and programmed in C++ language. The outcomes (cases of ESBL-PE transmission, infections, cost of intervention, cost of infections) were calculated after a period of 1 year and averaged over the 1,000 Monte Carlo simulations. Cost-effectiveness analysis and graphics were performed in R[10].

Base case scenario

In the base case scenario, with no control intervention, we considered that compliance with hand hygiene before/after contact with a patient was 55%/60% respectively[11] and 56% of patients received antibiotics at ICU admission[12].

Infection control strategies

Universal approaches

We evaluated control strategies implemented in all patients (independently of their colonization status), that comprised one or both of the following interventions: 1) improved compliance with HH, and 2) antibiotic stewardship. For HH, we considered different levels of compliance. First, compliance with HH before/after contact with a patient was improved from 55%/60% at baseline to 55%/80% or 80%/80%. Second, antibiotic stewardship resulted in halving the proportion of patients on antibiotics at ICU admission and in reducing by 25% the duration of antibiotic treatment.

Targeted approaches

We evaluated 2 strategies that combined screening of patients for ESBL-PE at ICU admission and one of the following interventions implemented: 1) contact precautions (improved compliance with HH before/after contact with carriers to 80%/80%); or 2) cohorting of ESBL-PE carriers with dedicated HCWs. HH compliance for other patients was maintained at baseline level.

Mixed approaches

We evaluated two strategies combining the targeted approaches with antibiotic stewardship.

Model parameters

Model parameters and their values are presented in **Supplementary Table 1**.

Based on recent French data, we assumed that 15% of patients were colonized with ESBL-PE at ICU admission[13].

Infection status was not included in the model, so we estimated the number of infections by multiplying the cumulated number of colonized patients after one year by the probability of developing an infection during an ICU stay, set at 16.4%[14]. Even though this value came from a recent large multicentre study, we also considered the impact of lower (8%) and higher (30%) probability of infection in alternative analyses.

Costs

The analysis was performed from a public hospital perspective. Cost estimates are based on values reported in Euros from 2015 (1 € = US $0.94). We considered the following costs in the model: 1) costs of intervention (material resources and personnel costs), 2) costs of ESBL-PE infections. The cost of an ESBL-PE infection was estimated using the ESBL-PE-attributable LOS and the cost of a hospital bed-day for infected patients[13,15,16]. See **Table 1** for cost parameters and **Supplementary Text 1** for more details.

Cost-effectiveness evaluation

To conduct the cost-effectiveness[17], we estimated the costs associated with each intervention implemented, and the health benefits were related to the number of avoided cases of ESBL-PE infections. First, we determined whether any strategy was dominated by another in terms of costs and health benefits. Second, we determined whether any strategy was dominated through principles of extended dominance (i.e. whether the incremental cost-effectiveness ratios [ICERs]decrease as the strategies increases in cost[17,18]). Finally, for the non-dominated strategies,

we calculated the incremental cost per case of infection avoided, which is the ratio of the difference in costs between two strategies to the difference in health benefits. This process produces an "efficient frontier" indicating more costly, but more effective strategies.

Sensitivity analysis

We performed supplementary analyses to assess the impact of parameter uncertainty on the model's predictions. We first ran a univariate sensitivity analysis to evaluate the cost-effectiveness of strategies in settings with either low or high prevalence of patients colonized at admission (from 5% to 50%). We also considered the impact of a lower (8%) and a higher (30%) probability of infection in colonized patients. We then investigated the model assuming 1) a lower baseline compliance with HH and 2) a lower sensitivity of the screening method used to detect ESBL-PE carriers at ICU admission.

We also performed an analysis to explore the uncertainty in human time required in an HH programme and its potential effects. In this analysis, we varied the time an infection control nurse works on the programme (quarter-time, half-time or full-time) simultaneously with the level of HH compliance achieved (from 55%/60% to 80%/80% before after contact).

Finally, we performed a probabilistic sensitivity analysis to explore the effect of joint uncertainty across parameters on the cost-effectiveness of universal vs targeted strategies. We varied the following parameters concurrently: 1) number of HCW contacts with patients, 2) transmission parameters, 3) length of stay of ICU patients, 4) natural decontamination rate for HCW, 5) antibiotic initiation rate, 6) prevalence of ESBL-PE carriage among patients admitted to the ICU,

7) death rate of patients, 8) probability of infection in colonized patients and 9) cost parameters. We randomly sampled values from each of the parameter distributions and calculated the mean costs and mean number of infections for each strategy (averaged over 1,000 simulations).

RESULTS

In the absence of control interventions (base case strategy), 15 new acquisitions (i.e. transmissions) and 5 new infections due to ESBL-PE occurred per 100 admissions. Compared to the base case (Strategy 1), all strategies reduced ESBL-PE acquisition and infections within one year (**Figure 2**).

Among universal strategies, HH compliance improvement to 80%/80% (Strategy 2) was the most effective, resulting in a mean reduction to 2.9 acquired infections per 100 admissions. Among targeted strategies, screening of patients on admission and cohorting of carriers (Strategy 6) was the most effective strategy and resulted in a mean reduction to 2.8 infections per 100 admissions. Screening followed by contact precautions (Strategy 5) was the least effective in comparison with all other options. Adding antibiotic stewardship to HH or targeted strategies only slightly improved their effectiveness.

Cost-saving analysis

In **Table 2** we present the estimated costs and outcomes over one year for all strategies. The mean total cost associated with the base case strategy was estimated at €105 344/100 admissions, €94 792 of which was related to infections and €10 552 to interventions. Investments in infection prevention was always cost-saving because they avoided cases of ESBL-PE infections and thus costs associated with these infections. For instance, when HH compliance was improved to

80%/80%, the mean cost of the strategy implementation increased to €25 639/100 admissions, but the costs related to infections decreased to €54 916, resulting in an overall monetary benefit of €24 788/100 admissions in comparison with the base case. This strategy was associated with the highest savings within all evaluated strategies.

Cost-effectiveness analysis

HH compliance improvement to 80%/80% was the least expensive strategy. However, two strategies required higher investments than the HH programme, but also improved health benefits. To help choose between strategies we calculated the incremental cost-effectiveness ratio (**Figure 3)**. The ICER of HH improvement to 80%/80% and antibiotic stewardship (Strategy 7) vs. HH compliance improvement to 80%/80% was estimated at €49 025/avoided infection (**Table 2**). The ICER of screening, cohorting and antibiotic stewardship (Strategy 10) vs. HH improvement to 80%/80% and antibiotic stewardship was estimated at €62 005/avoided infection. Other strategies were dominated (more expensive and less effective).

Sensitivity analysis

Findings from sensitivity analysis showed the robustness of predictions to: 1) the lower/higher prevalence of ESBL-PE carriage on ICU admission,2) the lower/higher probability of infections in colonized patients,3) the baseline compliance with HH lower than in our core analysis (20%/40%), and 4) the lower sensitivity to detect ESBL-PE carriers at ICU admission. Results of this analysis are shown in **Supplementary Text 2** (Figure S1 and Table S1, Table S2 A and B, Table S3, and Figure S2).

In a second sensitivity analysis, we focused on human time and performance to improve HH compliance. If an infection control nurse was assumed to work quarter-time, half-time or full-time on the programme, the HH compliance had to increase by at least 5%, 7.5% or 15%, respectively, to make the programme cost saving compared to the base case (**Supplementary Table S4A**).

In comparison with the screening and cohorting strategy, the HH improvement was cost-saving when an infection control nurse worked quarter-time or half-time on the programme, and HH compliance increased by at least 12.5% or 17.5%, respectively. The screening and cohorting strategy dominated the HH improvement programme when an infection control nurse was working full-time on the programme (**Supplementary Table S4B**).

Finally, the probabilistic sensitivity analysis showed that improvement of HH to 80%/80% (Strategy 2) was less expensive than the screening and cohorting intervention (Strategy 6) in 91% of simulations. Among them, in 42% of simulations, the HH strategy was less expensive but more effective (dominated the Strategy 6), and in 49% of runs the screening and cohorting was more effective and more expensive (**Supplementary Figure S3**). Screening and contact precautions (Strategy 5) were always less effective than improvement of HH to 80%/80% (Strategy 2) (**Supplementary Figure S4**).

DISCUSSION

The impact of infection control strategies for preventing ESBL-PE transmission is controversial because clinical studies cannot account for the multiple confounding factors, notably both infection control measures and antibioc stewardship. Despite several recent high-level

interventional studies (Climo et al.[19]; Derde et al.[6]; Huang et al.[20]), the most effective and cost-effective interventions for controlling MDROs are still debated. Since the spread of ESBL-PE between patients is a dynamic and complex process, modelling can help for understanding the transmission mechanisms and deciding which intervention are to be preferred (Doan et al.[21]; Grundmann et al.[22]).

Our model estimated the annual burden of ESBL-PE infections in a French ICU at €94 792 per 100 admissions in the base case strategy. Several prior studies have reported the cost of infections due to multidrug resistant organisms in the ICU[23–26]. However, even though all authors underlined the high costs of infections, comparison between studies remains difficult. Estimated costs varied according to the country, but also to the population studied, e.g. patients with site-specific or microorganism-specific infections. Moreover, the methods used to estimate the costs were not similar in all publications.

Implementation of infection control programmes may reduce the high cost of healthcare-associated infections. However, when evaluating the cost-effectiveness and benefits of such programmes, it is crucial to consider their cost.

In recent years, mathematical models have increasingly been used to study the cost-effectiveness of control strategies. For example, Robotham et al.[27]compared a wide range of strategies to control MRSA transmission in ICUs and found that universal decolonization was the most cost-effective option. In another study, Gidengil et al.[28]compared hospital strategies to prevent MRSA transmission and infections in an ICU. They confirmed that universal decolonization was the most cost-saving strategy.

Our study is the first to compare the effectiveness and the costs of universal and targeted control strategies in the context of the spread of ESBL-PE in ICUs. Our model predicted that improving HH to 80%/80% in contacts with all patients would prevent 83% of ESBL-PE acquisitions and avoid at least two out of five infections per 100 admissions. This strategy represented the most cost-saving, with a monetary benefit of €24 788 per 100 admissions.

The association between HH and reduction of MDROs infections has long been known and HH has been accepted as a crucial component of infection prevention. HH has in addition the benefit of being effective for reducing transmission of many resistant or susceptible bacteria. A recent publication reported that a programme designed to control MRSA by implementing universal components in addition to screening and contact precautions for MRSA carriers also effectively reduced the incidence of resistant gram-negative bacteria, the most likely being ESBL-PE[7]. Thus, the overall economic benefit of an HH programme for the hospital might be greater than reported in our study.

Despite the confirmed effectiveness of HH and national and international recommendations, compliance with HH remains low and is often lower than values used in our base case analysis[29,30].However, we showed in a sensitivity analysis that improving HH remained the most cost-saving strategy even in a low baseline compliance scenario.

Different strategies have been suggested to improve HH in hospitals[31], but the evidence-based approach is still lacking. Recently, a revue [32] concluded that a multimodal strategy proposed by the WHO and consisting of five components: 1) system change, 2) training and education, 3) observation and feedback, 4) reminders in the hospital, and 5) a hospital safety climate, was effective at increasing HH among HCWs. Moreover, the authors underlined that additional

measures (e.g. reward incentives for reaching a certain level of compliance) could lead to further improvements. In our study, we assumed that a key component of an HH programme was a dedicated staff working on the programme (i.e. HH education, observation and feedback). We hypothesized, for example, that to improve HH compliance an infection control nurse working half-time would be sufficient. However, to explore the uncertainty of the required time dedicated to the HH programme and its expected effects, we performed a sensitivity analysis.

Screening strategies have been used to prevent transmission of MDROs, however their effectiveness and cost-effectiveness have been largely debated. In this study, we showed, that in endemic settings, screening and cohorting strategy had comparable efficacy as HH but was more expensive and dominated by other control options. We can hypothesize that in the case of highly resistant bacteria (e.g. Carbapenem-resistant *Enterobacteriaceae*) where there is a highest clinical impact on the outcomes of infected patients, given the lack of therapeutic options, a rapid identification and cohorting of carriers may be more beneficial from the hospital but also societal perspective.

While antibiotic use is the major driver for the selection of antibiotic-resistant bacteria, there is no clear evidence of the effectiveness of antimicrobial restriction policies on resistance[33]. We assumed in the model that a reduction in antibiotic use acted in 2 ways: it decreased the colonization probability of uncolonized patients and the probability of transmission from colonized patients to HCWs. However, we found that reducing antibiotic use was less effective than HH or a screening and cohorting strategy. Under the hypotheses used in our model, we also demonstrated in a previous study through sensitivity analyses that antibiotic parameters did not significantly influence the effectiveness of interventions[9].

However, adding antibiotic stewardship to an HH strategy slightly improved its effectiveness and may be worthy of consideration if the decision-makers are willing to pay at least €49 025per infection avoided (we calculated that it would be equivalent to €5 562 per life-year gained (LYG)). Combining antibiotic stewardship with screening and cohorting was even more effective than combining HH and antibiotic stewardship, but with an additional cost of €62 005 per infection avoided (or €7 030/LYG).

Our study has several strengths. Firstly, we used a dynamic model to represent interactions between patients and HCWs and to take into account that the risk of colonization in the ICU depends on the number of ESBL carriers and could change over time. Moreover, our model incorporated the key elements of ESBL-PE transmission, such as the impact of prevalence at admission or antibiotic treatment. Secondly, we used input parameters derived from recent multicentre studies. Thirdly, we estimated the cost of HCW according to the time they spend working on the programme based on the best evidence from the literature and expert opinion. Finally, we assessed the impact of uncertainty in parameter estimation and the impact of model assumptions on the model's predictions by performing multiple sensitivity analyses.

Our study also has several limitations. Firstly, ICU parameters and costs were based mostly on French data, and ESB L-PE infections, prevalence, compliance with control measures and costs may be different in other countries. Secondly, we modelled an ICU as a single-room unit where transmission among patients results via contacts with HCWs. In the absence of detailed information on transmission of ESBL-PE in hospital wards, we ignored direct HCW-to-HCW transmissions as well as environmental contamination. Finally, ESBL-PE acquisition in the ICU can lead to transmission from an ICU-acquired case and infection in downstream units, thus increasing costs of hospitalization. Our cost evaluation was therefore conservative, since

transmission and infection after ICU discharge were not added to the global costs of infections. A ward-based model, including other hospital units, should be tested.

CONCLUSION

Our study suggests that a universal approach with improved compliance with HH was the most cost-saving strategy to prevent the transmission of ESBL-PE in an ICU setting. Screening and cohorting of carriers had comparable effectiveness to HH improvement, but was more expensive. Adding antibiotic restriction to the HH or the screening and cohorting strategies slightly improved their effectiveness and may be worthy of consideration by decision-makers.

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FOOTNOTES

Contributors: YY, JCL, CP and LKS designed the study. YY, JCL, PYB, AA, CP and LKS contributed to the development of the model. CP, AP, GB, ER and LKS collected the data. CP and LKS wrote the code. LKS conducted computer simulations and result analysis. LKS, JCL and YY drafted the manuscript. All authors read and critically revised the manuscript.

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FIGURE LEGENDS

Figure 1. Model of transmission of ESBL-PE between patients through contacts with health-care workers (HCWs) and impact of infection control measures in the transmission process. Solid lines represent the transitions between population groups and dashed lines represent the transmission between patients and HCWs.

A. Impact of universal (horizontal) control measures: 1) hand hygiene (reduces the transmission among patients and HCWs); 2) antibiotic restriction (reduces the risk of transmission from colonized patients receiving antibiotics to HCWs or from contaminated HCWs to uncolonized patients receiving antibiotics).

B. Impact of targeted (vertical) control measures: screening of patients on ICU admission and identification of patients who had positive screening results (patients surrounded be a shaded box). Implementation of: 1) contact precautions (hand hygiene reduces the transmission from identified ESBL-PE carriers to HCWs); 2) cohorting of identified ESBL-PE carriers and attribution of a dedicated HCW (prevents the transmission from cohorted patients to other HCWs and patients). Note that we included two categories of colonized patients: 1) who had false negative admission screening results; 2) who had positive admission screening results (patients surrounded by a shaded box).

Figure 2. Patient outcomes after one year under the different control strategies tested. (A) New acquisitions (transmissions) of ESBL-PE per 100 admissions, (B) Total number of ESBL-PE infections per 100 admissions in patients who: 1) acquired colonization in the ICU, and 2) those who were already colonized at ICU admission.

Strategies are: (1) Base case (reference strategy with no control intervention and hand hygiene compliance of 55%/60% before/after patient contact); (2) Hand hygiene improvement to 80%/80%; (3) Hand hygiene improvement to 55%/80%; (4) Antibiotic reduction; (5) Screening of all admissions and contact precautions for identified carriers; (6) Screening of all admissions and cohorting of identified carriers; (7) Hand hygiene improvement to 80%/80% and antibiotic reduction; (8) Hand hygiene improvement to 55%/80% and antibiotic reduction; (9) Screening of all admissions, contact precautions with identified carriers and antibiotic reduction; (10) Screening of all admissions, cohorting of identified carriers and antibiotic reduction.

Figure 3. Cost-effectiveness plane showing the incremental health benefits (infections avoided) and costs relative to the least expensive strategy (Strategy 2). Strategies 1, 3, 4, 5, 8, 9 are dominated as they have both a worse outcome and a higher cost. The efficiency frontier (grey line), joins Strategy 2 with more expensive and more efficient strategies (7 and 10). Strategy 6 is extended to this frontier and excluded by the principle of extended dominance. The slope of the efficiency frontier represents the incremental cost-effectiveness.

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TABLES

Table 1. Cost parameters, their sources and ranges for sensitivity analyses.

Costs of control strategies were based on material and personnel. For example, the cost of the HH improvement strategy included the cost of HH (hand-rub and HCWs' time) and the cost of an infection control nurse working on the programme, i.e. HH education, observation and feedback.

	Resource	Cost (€[a]) mean	Cost (€[a]) SD	Source	Distribution
	ICU bed-day	1,583	226	AP-HP [b]	Gamma
Universal strategies					
Hand hygiene	Alcohol-based hand rub	0.011	0.0055	[34,35]	Gamma
	HCW's time per hand hygiene	0.143	0.0714		Gamma
	Infection control nurse at half-time/month	2,048[c]	164	AP-HP [b]	Gamma
Antibiotic stewardship	Infectious disease physician at half-time/month	5,500[c]	273	AP-HP [b]	Gamma
Targeted strategies					
Screening	Screening test + laboratory costs	40	20	[35–37]	Gamma
Contact precautions (= hand hygiene at 80%/80% with identified ESBL-PE patients)	Alcohol-based hand rub	0.011	0.0055	[34,35]	Gamma
	HCW's time per hand hygiene	0.143	0.0714		Gamma

Cohorting (additional HCW + contact precautions)	Additional full-time HCW/month	3,598[c]	642	AP-HP [b]	Gamma
	Alcohol-based hand rub	0.011	0.0055	[34,35]	Gamma
	HCW's time per hand hygiene	0.143	0.0714		Gamma

[a] 1€ = US $0.94

[b] AP-HP: The Assistance publique – Hôpitaux de Paris

[c] Cost of staff from a hospital perspective (salary + employer contributions)

536 **Table 2.** Results of cost-effectiveness analysis.

Strategy	Number of ICU admissions	Total cost/100 admissions (€)	Cost of infections/ 100 admissions (€)	Cost of intervention/ 100 admissions (€)	Infections due to ESBL-PE/ 100 admissions	Incremental cost/100 admissions (ΔC) (€)	Incremental effect (ΔE) (infections avoided/100 admissions)	ICER (ΔC/ΔE) (€ / infection avoided)
2: HH 80%/80%	573	80 556	54 916	25 639	2.9	-	-	-
7: HH 80%/80% + ATB reduction	581	88 498	51 840	36 657	2.7	7 941[a]	0.1618[a]	49 025[a]
10: Screening + cohorting + ATB reduction	584	94 313	50 058	44 255	2.6	5 815[b]	0.0937[b]	62 005[b]
3: HH 55%/80%	548	84 751	66 773	17 978	3.5			Dominated [c]
6: Screening + cohorting	575	86 713	53 278	33 435	2.8			Dominated [d]
8: HH 55%/80% + ATB reduction	565	88 621	59 445	29 176	3.1			Dominated [c]

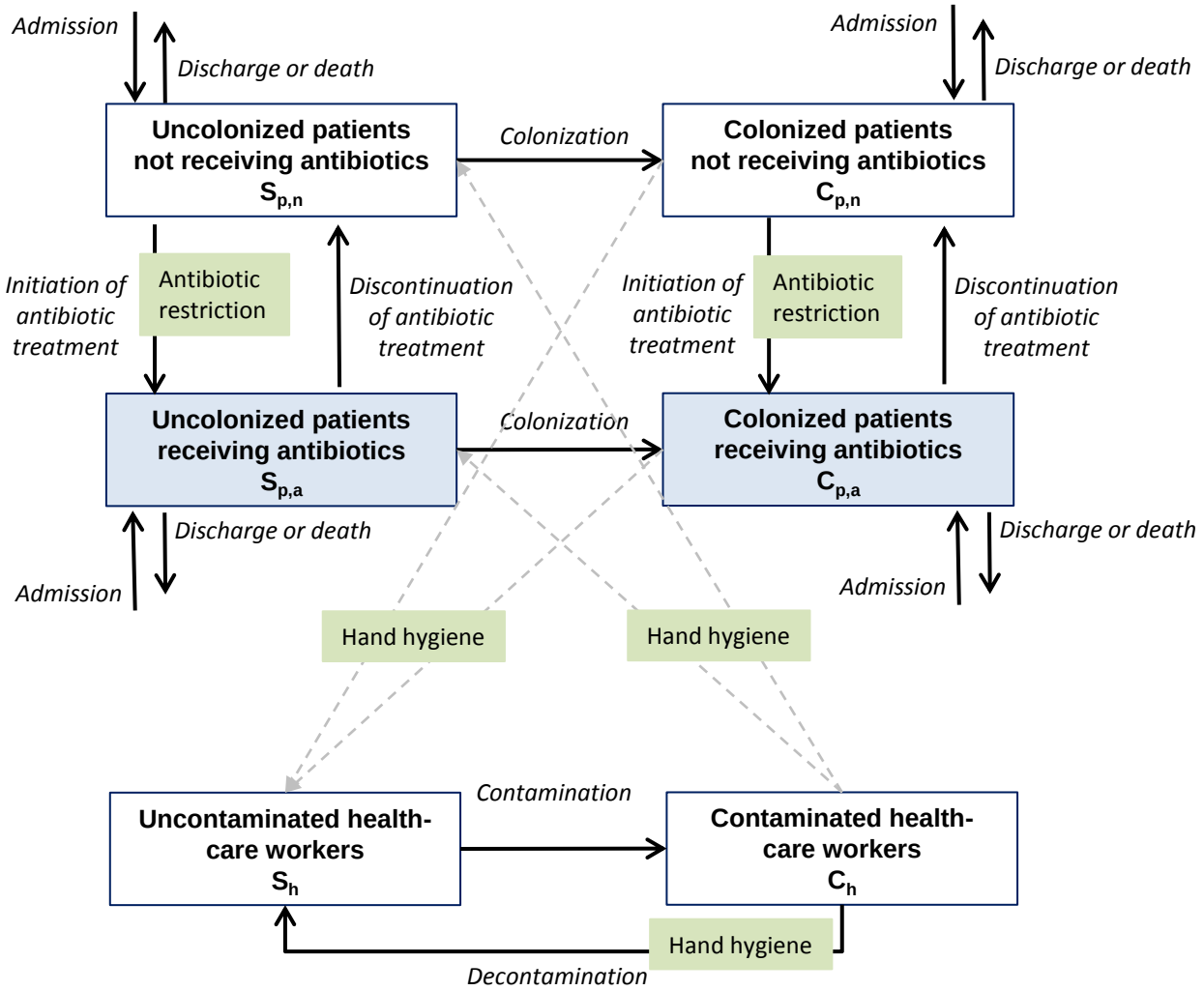
9: Screening + contact precautions + ATB reduction	546	94 309	67 560	26 749	3.6		Dominated [c]
5: Screening + contact precautions	519	96 716	81 582	15 134	4.3		Dominated [c]
4: ATB reduction	528	100 128	77 641	22 486	4.1		Dominated [c]
1: **Base case**	498	105 344	94 792	10 552	5.0		Dominated [c]

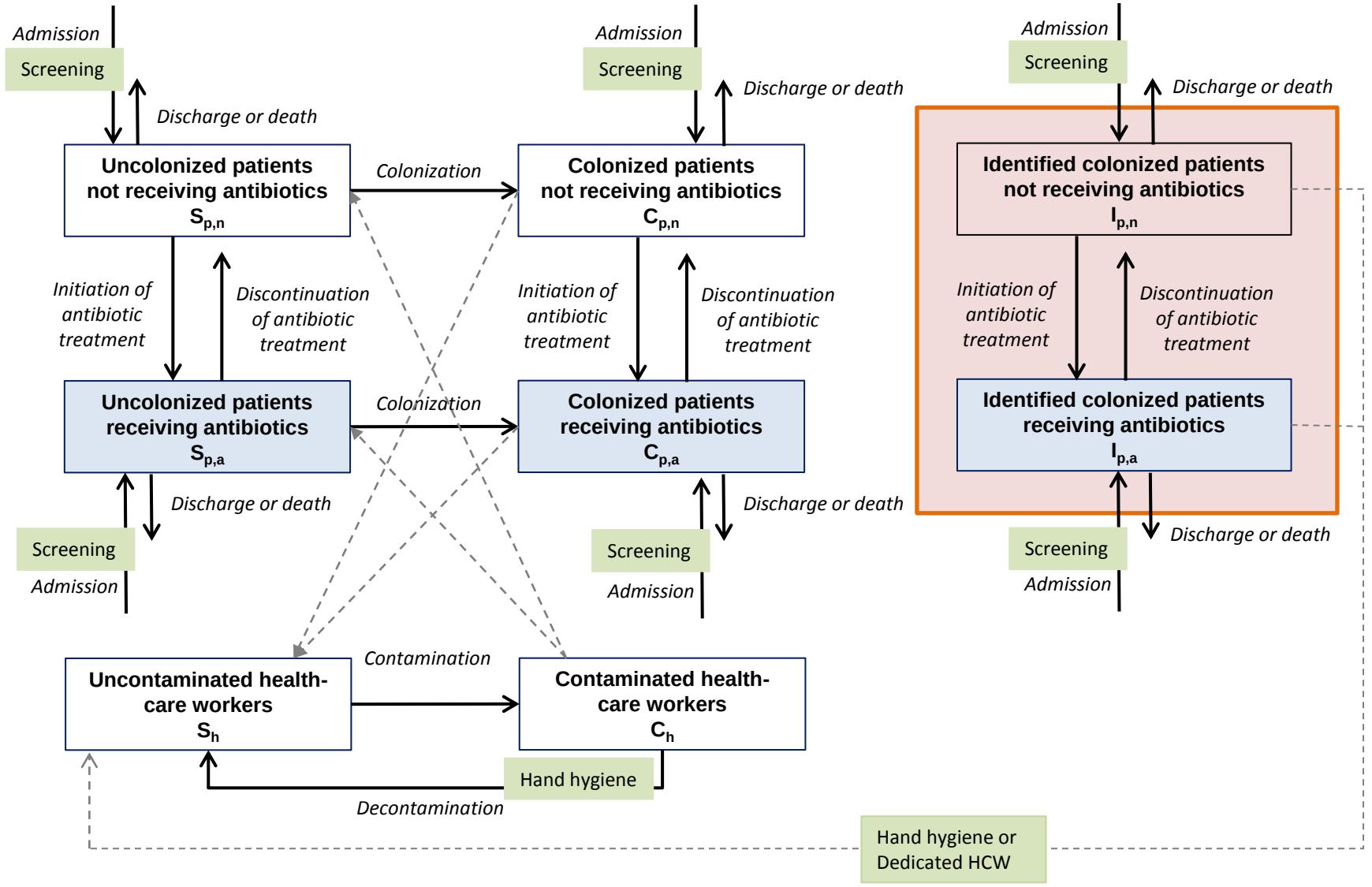
[a] Relative to strategy 2

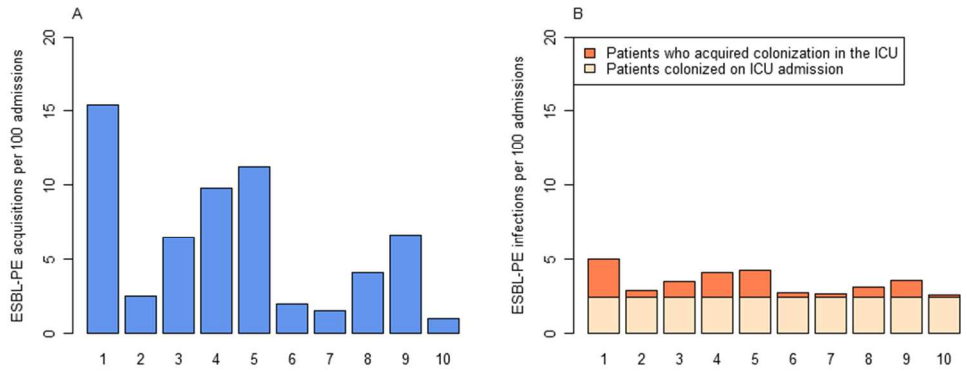
[b] Relative to strategy 7

[c] Dominated: A strategy is dominated when it has higher cost and lower health benefit than another strategy.

[d] Dominated by extended dominance: Strategy is dominated by extended dominance if the linear combination of other strategies produces greater benefit at lower cost.


Admission
Discharge or death
Uncolonized patients not receiving antibiotics $S_{p,n}$
Colonization
Colonized patients not receiving antibiotics $C_{p,n}$
Admission
Discharge or death
Initiation of antibiotic treatment
Antibiotic restriction
Discontinuation of antibiotic treatment
Initiation of antibiotic treatment
Antibiotic restriction
Discontinuation of antibiotic treatment
Uncolonized patients receiving antibiotics $S_{p,a}$
Colonization
Colonized patients receiving antibiotics $C_{p,a}$
Discharge or death
Admission
Admission
Discharge or death
Hand hygiene
Hand hygiene
Contamination
Uncontaminated health-care workers S_h
Contaminated health-care workers C_h
Hand hygiene
Decontamination


Admission
Screening
Discharge or death
Uncolonized patients not receiving antibiotics $S_{p,n}$
Colonization
Colonized patients not receiving antibiotics $C_{p,n}$
Identified colonized patients not receiving antibiotics $I_{p,n}$
Initiation of antibiotic treatment
Discontinuation of antibiotic treatment
Uncolonized patients receiving antibiotics $S_{p,a}$
Colonized patients receiving antibiotics $C_{p,a}$
Identified colonized patients receiving antibiotics $I_{p,a}$
Contamination
Uncontaminated health-care workers S_h
Contaminated health-care workers C_h
Hand hygiene
Decontamination
Hand hygiene or Dedicated HCW



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Strategies are: (1) Base case (reference strategy with no control intervention and hand hygiene compliance of 55%/60% before/after patient contact); (2) Hand hygiene improvement to 80%/80%; (3) Hand hygiene improvement to 55%/80%; (4) Antibiotic reduction; (5) Screening of all admissions and contact precautions for identified carriers; (6) Screening of all admissions and cohorting of identified carriers; (7) Hand hygiene improvement to 80%/80% and antibiotic reduction; (8) Hand hygiene improvement to 55%/80% and antibiotic reduction; (9) Screening of all admissions, contact precautions with identified carriers and antibiotic reduction; (10) Screening of all admissions, cohorting of identified carriers and antibiotic reduction.

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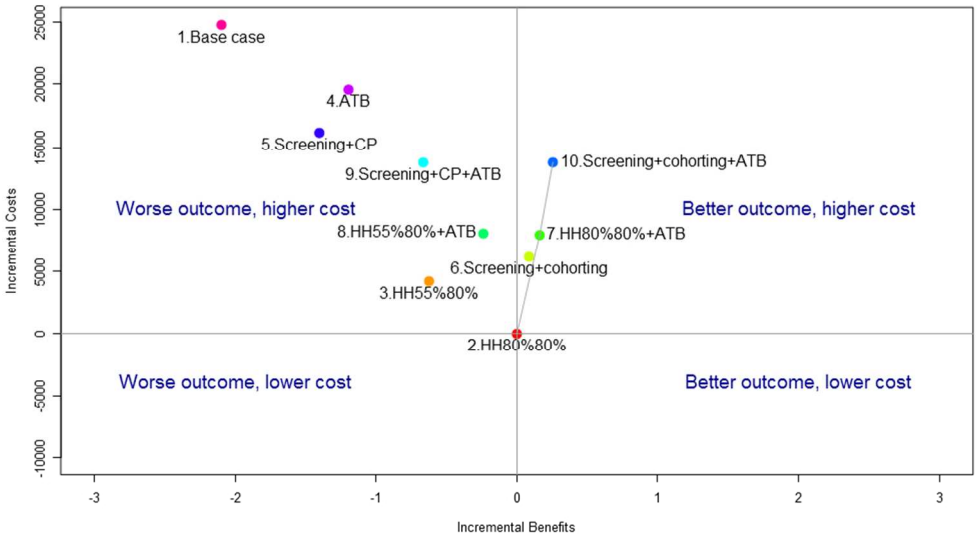

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352x211mm (72 x 72 DPI)

Supplementary material

Supplementary Text S1

Defining the objectives, scope and policy context of a model.	
Decision objective	To evaluate ESBL-PE control strategies
Policy context	This analysis was used to support decision makers in choosing the best strategy for controlling ESBL-PE
Funding source	PREPS Program*, Inserm**
Disease	ESBL-PE infections
Perspective	Hospital perspective
Target population	ICU patients
Health benefits	Reduction in ESBL-PE infections
Strategies	Universal strategies (hand hygiene improvement or antibiotic reduction) Targeted strategies (screening of patients on ICU admission and contact precaution in contact with carriers or cohorting)
Resources/costs	Staff time working on the program, materials
Time horizon	1 year
*PREPS - French government's program on Care System Performance **Inserm- National Institute for Health and Medical Research	

Transmission model

We have used an extended version of a previously developed compartmental, dynamic, stochastic model to simulate the transmission of ESBL-PE in a hypothetical ICU with 10 single-bed rooms among patients through contacts with healthcare workers (HCWs)[1].

For each simulation, we introduced a single unidentified ESBL-PE carrier receiving antibiotics within the ward and simulated the ESBL-PE dynamics for one year. In this version of the model, following the first admitted colonized patient, φ was the fraction of admitted patients assumed to be colonized with ESBL-PE. Patients are discharged at rate γ or die at rate ν but bed occupancy is assumed to be 100% (the population of patients in the ward is constant).

Patients may or may not receive antibiotics at admission; antibiotics are initiated during the patient's stay at rate τ per day and antibiotics are discontinued at rate θ per day.

In the model, all patients were classified as 1) uncolonized receiving antibiotics ($S_{p,a}$) or not ($S_{p,n}$), 2) unidentified ESBL-PE carriers receiving antibiotics ($C_{p,a}$) or not ($C_{p,n}$) (**Figure 1A**). Antibiotics in the model acted in two ways: 1) increased the risk of becoming colonized for uncolonized patients receiving antibiotics; and 2) increased the risk of transmission from colonized patients receiving antibiotics.

Initially uncontaminated HCWs (S_h) can become transiently contaminated (and go to the compartment C_h) after contact with a colonized patient ($C_{p,n}$ or $C_{p,a}$).

Transmission parameters

Exposure to antibiotics has been associated with increased probability of colonization for uncolonized patients[2,3] and of transmission from colonized patients to HCWs[4]. Thus, we hypothesized that: 1) the colonization probability after contact with a contaminated HCW was higher in patients on antibiotics than in untreated patients ($b_{p,a} > b_{p,n}$), 2) the probability of contamination of an HCW through contact with a colonized patient was higher if the patient was treated with antibiotics ($b_{h,a} > b_{h,n}$).

The model parameters and their values are presented in **Supplementary Table 1.**

Model calibration

The model was simulated stochastically. We calibrated the colonization and contamination parameters using Monte Carlo methods in order to reproduce the observed 12.9% acquisition rate in an ICU after a 6-month period[5].

Mathematical model under targeted infection control measures

The model was modified to account for the effect of targeted control measures. To detect ESBL-PE carriers, we simulated the screening of patients at ICU admission. We assumed that the screening method had 95% sensitivity and 100% specificity. Thus in the model, all patients were classified as 1) uncolonized receiving antibiotics ($S_{p,a}$) or not ($S_{p,n}$), 2) unidentified ESBL-PE carriers receiving antibiotics ($C_{p,a}$) or not ($C_{p,n}$), and 3) identified ESBL-PE carriers receiving antibiotics ($I_{p,a}$) or not ($I_{p,n}$) (**Figure 1B**).

The transmission parameter β depends on the rate of HCW visits followed by contacts with the patient (a), the probability of ESBL-PE bacteria transmission per infectious contact ($b_{..}$), and the compliance with hand hygiene (HH) (p_p and $p_{h.}$).

The risk of transmission from an unidentified ESBL-PE carrier to n HCW might differ from that of an identified ESBL-PE carrier, because of the implementation of targeted control measures. Firstly, we modelled the implementation of contact precautions (improvement of HH) in contacts with identified ESBL-PE carriers. HH for other patients was maintained at baseline level.

The transmission parameters were defined as follows:

$$\beta_{p,a} = a \cdot b_{p,a} \cdot (1 - p_p)$$
$$\beta_{p,n} = a \cdot b_{p,n} \cdot (1 - p_p)$$

Transmission from contaminated HCWs to uncolonized patients (receiving antibiotics or not)

$$\beta_{h,a} = a \cdot b_{h,a} \cdot (1 - p_h)$$
$$\beta_{h,n} = a \cdot b_{h,n} \cdot (1 - p_h)$$

Transmission from non-identified, colonized patients (receiving antibiotics or not) to HCWs

$$\beta_{h,a,I} = a \cdot b_{h,a,I} \cdot (1 - p_{h,Is})$$
$$\beta_{h,n,I} = a \cdot b_{h,n,I} \cdot (1 - p_{h,I}s)$$

Transmission from identified, colonized patients (receiving antibiotics or not) to HCWs

Secondly, we modelled the introduction of a dedicated HCW to interact only with identified, colonized patients. The transmission parameters were defined as follows:

$$\beta_{p,a} = a \cdot b_{p,a} \cdot (1 - p_p)$$
$$\beta_{p,n} = a \cdot b_{p,n} \cdot (1 - p_p)$$

Transmission from contaminated HCWs to uncolonized patients (receiving antibiotics or not)

$$\beta_{h,a} = a \cdot b_{h,a} \cdot (1 - p_h)$$
$$\beta_{h,n} = a \cdot b_{h,n} \cdot (1 - p_h)$$

Transmission from non-identified, colonized patients (receiving antibiotics or not) to HCWs

$$\beta_{h,a,I} = 0$$
$$\beta_{h,n,I} = 0$$

Transmission from identified, colonized patients (receiving antibiotics or not) to HCWs (other than the dedicated HCW)

Once colonized, patients do not clear ESBL-PE colonization before discharge. HCWs are transiently contaminated and they become decontaminated either by performing HH or after a mean waiting time of one hour.

Model parameters

The model parameters and their values are presented in **Supplementary Table 1**. Parameter values were derived from multicentre studies if available, and by default based on best evidence from the literature or expert opinion.

We modelled an ICU with 10 single-rooms with continuous presence of 6 HCWs[6]. We assumed 100% bed occupancy. Consequently, a shorter length of stay (LOS) implies a higher turnover and possible admission of colonized patients[7]. As reported recently, the ICU LOS of ESBL-PE carriers is longer (13 days) than uncolonized patients (5 days)[8]. The extended LOS in ESBL-PE carriers increases the colonization pressure in the ICU, consequently increasing the risk of cross-transmission.

When targeted control strategies were used, colonization was detected using a screening method assuming that the time between collection of specimens and reporting results to the ward was less than 1 day. We assumed that the sensitivity of the screening method was 95%[9]. Screening results had 100% specificity.

Costs of control strategies

We estimated the costs of control strategies over the one-year simulation period. See **Table 1** for details on cost parameters. The cost of the base case strategy (reference strategy) was considered

to be the cost of HH at baseline level, namely cost of the alcohol-based hand rub and costs associated with the time HCWs required for hand disinfection.

As reported recently, the highest cost of an HH program arose from the time people spent working on the program[10]. We therefore assumed that the cost of an HH improvement strategy included the cost of HH (hand-rub and HCWs' time) and the cost of an infection control nurse working on the program, i.e. HH education, observation and feedback[10,11]. We assumed that improving hand HH compliance to 55/80% and to 80/80% required respectively a quarter and a half of the working time of an infection control nurse. In accordance with staffing practices common in the European Union, we assumed that one staff position requires the recruitment of three nurses[12].

Antibiotic stewardship programs (ASPs) have proven efficient in reducing antibiotic use and antibiotic duration in hospitals[13,14]. Interventions included in ASPs require additional resources associated with higher costs[15]. One of the resources needed and associated with the highest costs is the staff time[16]. We calculated the cost of an action to reduce antibiotic use as the cost of a half-time infectious disease physician working on the ASP. The cost of antibiotics is considered to be marginal and was not considered in our study[14].

The cost of screening was first based on the cost of testing materials and on the cost of laboratory technician time. For the strategy in which screening at admission was combined with contact precautions for identified ESBL-PE carriers, we also included the cost of contact precautions such as the cost of improved HH (i.e. the cost of the alcohol-based hand rub), and the costs associated with the time HCWs required for hand disinfection. Here we did not consider the cost

of an infection control nurse. We hypothesized that knowing that the patient is an ESBL-PE carrier, HCWs would adhere more easily to HH.

For the strategy in which screening on admission was combined with cohorting of identified ESBL-PE patients, the cost of cohorting was the cost of contact precautions and the cost of additional HCWs caring for cohorted patients. For screening interventions, the cost of HH in non-carriers and unidentified carriers was considered to be identical to the costs of the baseline level.

Cost of hospital-acquired infections

The mean cost of an ICU bed-day was estimated at €1,583 (based on the average amount paid in 2015 for ICUs in Paris public hospitals (AP-HP). This amount is based on French Diagnosis-Related Groups and complementary revenues specific to ICU units and divided by the mean length of stay in ICUs in 2015[17]. Based on published reports, the cost per day of a patient with ESBL-PE infection was 50% higher than the cost of an uninfected patient [18,19]. The cost of an ESBL-PE infection was estimated using the ESBL-PE-attributable LOS and the cost of a hospital bed-day for infected patients[20,21].

Model simulations and outcomes

Simulations of the model were performed using Gillespie's method and programmed in C++ language. The outcomes were calculated after a period of 1 year and averaged over the 1,000 Monte Carlo simulations. Cost-effectiveness analysis and graphics were performed in R[22].

TABLES

Supplementary Table 1. Base case values and ranges for probabilistic sensitivity analysis of input parameters used in the compartmental model of ESBL-PE transmission.

Comment. As can be seen, for some parameters the ranges for a sensitivity analysis are omitted (e.g. $d_{ATB,S}$). This is because these parameters are specific to a strategy (e.g. Atb reduction) and must be fixed in sensitivity analysis to allow the comparison of outcomes with other strategies.

				Sensitivity analysis	
Parameter	**Description**	**Value**	**Source**	**Range**	**Distribution**
N_p	Number of beds	10	[23]		
N_h	Number of HCWs	6	[24]		
c_p	Number of HCW visits associated with at least one aseptic contact per patient per day	81	[25–27]	13.8 [28] - 160 [25,29,30]	triangular (peak at 81)
a	Number of HCW visits associated with at least one aseptic contact per HCW per day	13.5	c_p/N_h		
$b_{p,n}$	Colonization probability for patients not receiving antibiotics	0.0127	Calibrated, consistent with data from [5]	0-0.1	triangular (peak at 0.0127)
$b_{p,a}$	Colonization probability for patients receiving antibiotics	0.0530		$b_{p,n}$-0.5	uniform

$b_{h,n}$	Probability of contamination of an HCW with ESBL-PE during a contact with a colonized patient not receiving antibiotics	0.0379	Calibrated, consistent with data from[5]	0-0.6	triangular (peak at 0.0379)
$b_{h,a}$	Probability of contamination of an HCW during a contact with a colonized patient receiving antibiotics	0.3198	Calibrated, consistent with data from[5]	$b_{h,n}$-0.8	uniform
d_S	Mean length of stay of uncolonized patients (days)	5	[8]	3-9 [8]	triangular (peak at 5)
d_C	Mean length of stay of colonized patients (days)	13	[8]	6-26 [8]	triangular (peak at 13)
d_{Is}	Mean length of stay of isolated patients (days)	13	[8]	6-26[8]	triangular (peak at 13)
γ_S	Discharge rate of uncolonized patients (/day)	0.2	$1/d_S$		
γ_C	Discharge rate of colonized patients (/day)	0.0154	$1/d_C$		
ν	Death rate of patients (/day)	0.0027	[8]	0.00135-0.0054	triangular (peak at 0.0027)

μ_0	Natural decontamination rate for HCW (i.e. not by hand hygiene) (/day)	24	[28,31]	12-48	triangular (peak at 24)
ψ	Prevalence of antibiotic therapy among admitted patients	0.56	[32,33]	0.2-0.9	triangular (peak at 0.56)
τ	Antibiotic initiation rate (/day)	0.1	assumed	0.05-0.2	triangular (peak at 0.1)
$d_{ATB,S}$	Antibiotic therapy duration for uncolonized patients (days)	8	[33]		
$d_{ATB,C}$	Antibiotic therapy duration for colonized patients (days)	18	[33]		
θ_S	Antibiotic therapy discontinuation rate for uncolonized patients (/day)	0.125	$1/dATB_S$		
θ_C	Antibiotic therapy discontinuation rate for colonized patients (/day)	0.05556	$1/dATB_C$		
p_p	Probability of hand hygiene before contact with patient (uncolonized or colonized	0.55	[34]		

	unidentified)				
p_h	Probability of hand hygiene after contact with patient(uncolonized or colonized unidentified)	0.6	[34]		
p_{pls}	Probability of hand hygiene before contact with isolated patient	0.8	assumed		
p_{hls}	Probability of hand hygiene after contact with isolated patient	0.8	assumed		
φ	Prevalence of ESBL-PE carriage among admitted patients	0.15	[20]	0.07-0.3	triangular (peak at 0.15)
p_I	Probability of infection in colonized patient	0.164	[8]	0.08- 0.32	triangular (peak at 0.164)
d_I	Mean length of stay of infected patients (days)	13	[8]	6-29 [12]	triangular (peak at 13)
s_b	Sensitivity of the screening method (%)	95	[9]		
s_p	Specificity of the screening method (%)	100	assumed		

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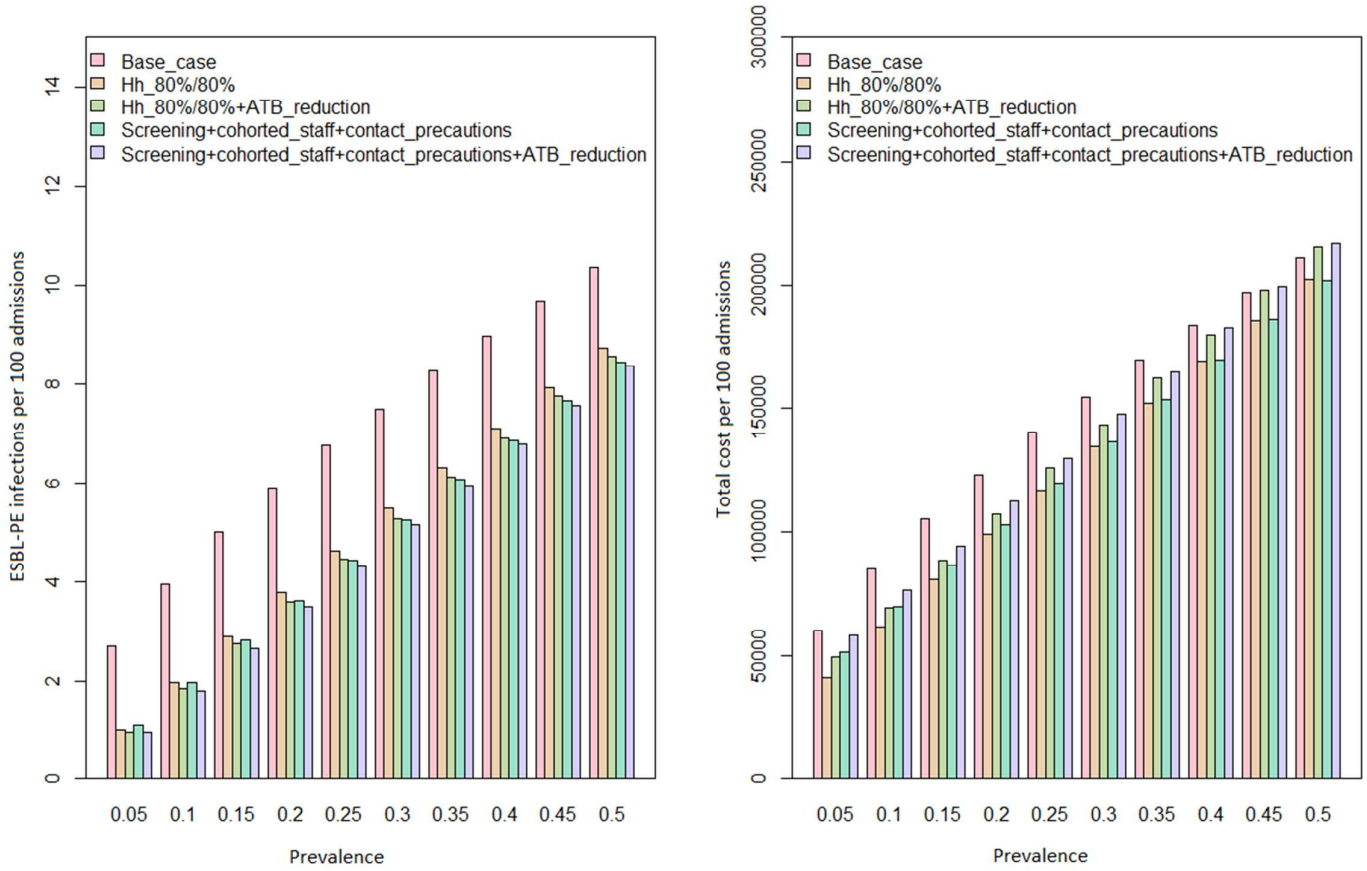
Supplementary material

Supplementary Text S2- Sensitivity analyses

1. Impact of prevalence on admission on health outcomes and costs

The prevalence of ESBL-PE carriage on ICU admission highly influenced health outcomes and costs (**Supplementary Figure S1**) as well as the ranking of the strategies (**Supplementary Table S1).** However, improvement of HH to 80%/80% (Strategy 2) remained the most cost saving strategy, if the prevalence on admission was from 5% to 50%. If 50% of patients carried ESBL-PE on ICU admission, Strategy 2 was dominated by screening + cohorting (Strategy 6).

Figure S1 Impact of prevalence on admission on the number of ESBL-PE infections and total cost of strategies for: (1) Base Case (reference strategy with no control intervention and hand hygiene compliance of 55%/60% before/after patient contact); (2) Hand hygiene improvement to 80%/80%; (6) Screening of all admissions and cohorting of identified carriers; (7) Hand hygiene improvement to 80%/80% and Antibiotic reduction; (10) Screening of all admissions, cohorting of identified carriers and Antibiotic reduction.



When the prevalence on admission was less than 15%, the improvement of hand hygiene to 80%/80% (Strategy 2) was the most cost-saving strategy. The second strategy on the efficiency frontier was the combination of hand hygiene 80%/80% with antibiotic reduction (Strategy 7). When the prevalence was 15%, the Strategy 10 (Screening + cohorting + ATB reduction) joined the efficiency frontier too. When the prevalence varied from 20% to 45%, Hand hygiene 80%/80% was always on the top of the ranking, followed by Screening + cohorting (Strategy 6) and Screening + cohorting + ATB reduction (Strategy 10). Finally, when 50% of patients carried ESBL-PE on ICU admission, hand hygiene was dominated by screening + cohorting (Strategy6).

Supplementary Table S1. Results of sensitivity analysis. Cost-effectiveness of strategies under **different levels of ESBL-PE carriage on admission**. The prevalence on admission varied from 0.05 to 0.5.

Strategy	Prevalence on admission	Total cost/ 100 admissions (€)	Infections/ 100 admissions	Incremental cost/100 admissions (ΔC) (€)	Incremental effect (ΔE) (infections avoided/100 admissions)	ICER (ΔC/ΔE) (€ / infection avoided)
2: Hh 80%/80%	0.05	41 225	1.01			
7: Hh 80%/80% + ATB reduction		49 639	0.94	8 414	0.07	122 909
6: Screening + cohorting		51 542	1.09			Dominated
10: Screening + cohorting + ATB reduction		58 218	0.94			Dominated by extended dominance
1: Base case		60 031	2.68			Dominated
2: Hh 80%/80%	0.15	80 556	2.89			
7: Hh 80%/80% + ATB reduction		88 498	2.73	7 942	0.16	49 055
10: Screening + cohorting + ATB reduction		94 313	2.63	5 815	0.09	62 005
6: Screening + cohorting		86 713	2.80			Dominated by extended dominance
1: Base case		105 344	4.99			Dominated

2: Hh 80%/80%	0.2	98 843	3.77			
6: Screening + cohorting		103 075	3.61	4 232	0.16	26 631
10: Screening + cohorting + ATB reduction		112 565	3.49	9 490	0.12	77 958
7: Hh 80%/80% + ATB reduction		107 275	3.59			Dominated by extended dominance
1: Base case		123 231	5.90			Dominated
6: Screening + cohorting	0.5	201 668	8.43			
10: Screening + cohorting + ATB reduction		216 470	8.36	14 802	0.07	208 058
2: Hh 80%/80%		202 288	8.72			Dominated
1: Base case		210 957	10.35			Dominated
7: Hh 80%/80% + ATB reduction		215 102	8.54			Dominated

2. Impact of **probability of infection** in patients colonized with ESBL-PE.

Results of sensitivity analysis for a lower and higher probability of infection in colonized ESBL-PE patients versus the basecase analysis are presented in **Supplementary Table S2 A and B.** Overall main results of our analysis were robust to variation in the probability of infection of colonized patients (8% or 30% vs. 16% in our central analysis).

Supplementary Table S2A Results of sensitivity analysis. Cost-effectiveness of strategies when **the probability of infection was set at 0.08**.

Strategy	Total cost/ 100 admissions (€)	Infections/ 100 admissions	Incremental cost/100 admissions (ΔC) (€)	Incremental effect (ΔE) (infections avoided/100 admissions)	ICER (ΔC/ΔE) (€ / infection avoided)
3: Hh 55%/80%	50 550	1.71			
2: Hh 80%/80%	52 428	1.41	1 878	0.304	6 178
7: Hh 80%/80% + ATB reduction	61 945	1.33	9 517	0.079	120 468
10: Screening + cohorting + ATB reduction	68 673	1.29	6 728	0.046	146 261
5: Screening + contact precautions	54 930	2.10			Dominated
1: Base case	56 792	2.43			Dominated
8: Hh 55%/80% + ATB reduction	58 173	1.53			Dominated by extended dominance
6: Screening + cohorting	59 424	1.37			Dominated by extended dominance
9: Screening + contact precautions + ATB reduction	59 706	1.74			Dominated
4: ATB reduction	60 360	1.99			Dominated

Supplementary Table S2B Results of sensitivity analysis. Cost-effectiveness of strategies when **the probability of infection was set at 0.30**.

Strategy	Total cost/ 100 admissions (€)	Infections/ 100 admissions	Incremental cost/100 admissions (ΔC) (€)	Incremental effect (ΔE) (infections avoided/100 admissions)	ICER (ΔC/ΔE) (€ / infection avoided)
2: Hh 80%/80%	126 096	5.29			
7: Hh 80%/80% + ATB reduction	131 487	4.99	5 391	0.296	18 204
10: Screening + cohorting + ATB reduction	135 825	4.82	4 338	0.172	25 283
6: Screening + cohorting	130 896	5.13			Dominated by extended dominance
8: Hh 55%/80% + ATB reduction	137 917	5.72			Dominated
3: Hh 55%/80%	140 124	6.43			Dominated
9: Screening + contact precautions + ATB reduction	150 335	6.50			Dominated
5: Screening + contact precautions	164 370	7.85			Dominated
4: ATB reduction	164 513	7.48			Dominated
1: Base case	183 951	9.13			Dominated

3. Impact of **lower compliance with HH** than in the base case scenario.

If the baseline compliance with HH was lower than in our core analysis, e.g. 20% before and 40% after patient contact, HH improvement, e.g. to 50%/60% was confirmed to be cost-saving. Screening + cohorting was the second strategy with an ICER of €3 236/infection avoided vs. HH improvement (**Supplementary Table S3**).

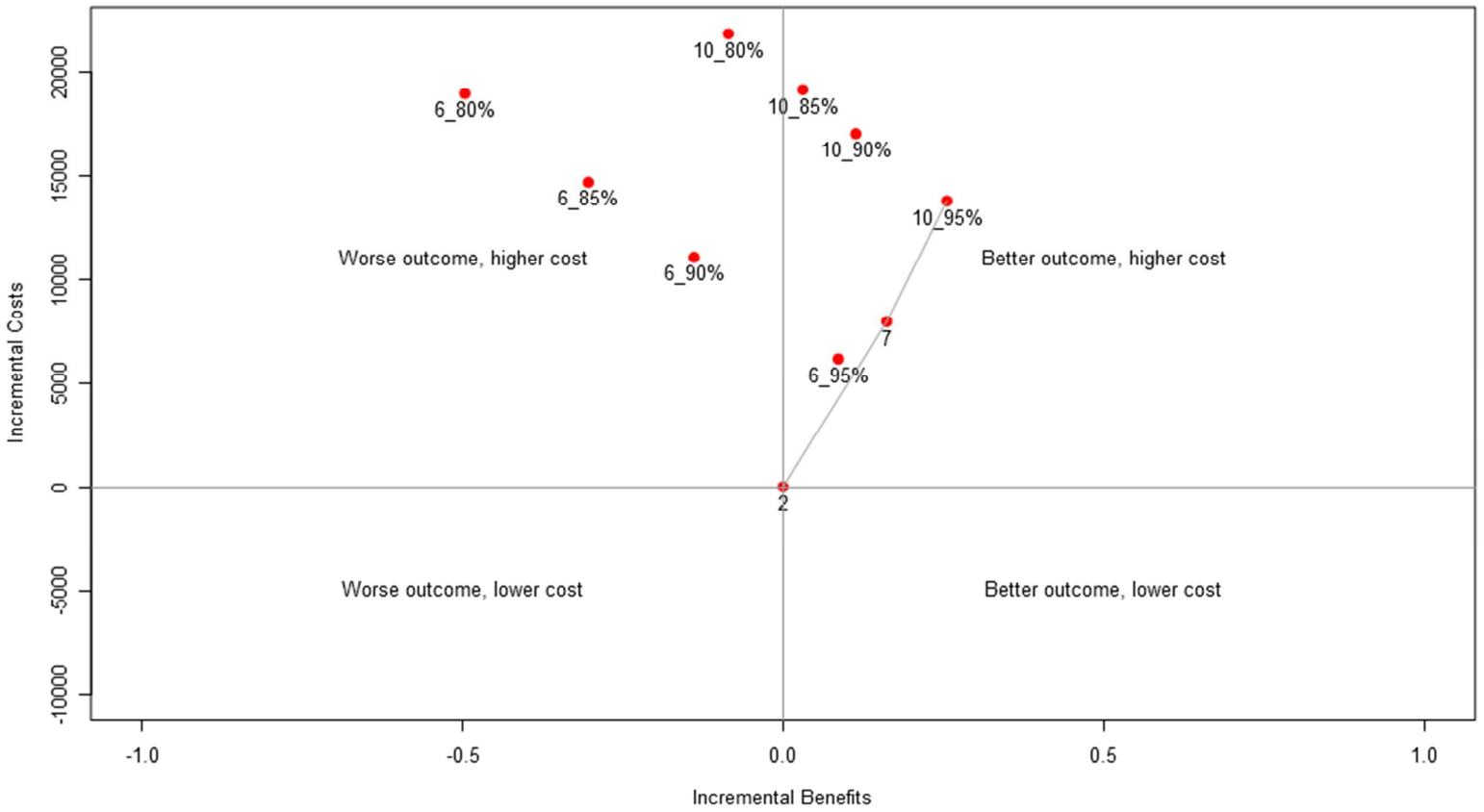
Supplementary Table S3 Results of sensitivity analysis. Cost-effectiveness of strategies when the baseline compliance with **Hand hygiene was set to 20%/40% (instead of 55%/60%).**

Strategy	Total cost/ 100 admissions (€)	Infections/ 100 admissions	Incremental cost/100 admissions (ΔC) (€)	Incremental effect (ΔE) (infections avoided/100 admissions)	ICER (ΔC/ΔE) (€ / infection avoided)
2: Hh 50%/60%	81 676	3.14			
6: Screening + cohorting	82 867	2.772	1 191	0.368	3 236
10: Screening + cohorting + ATB reduction	91 134	2.632	8 267	0.14	59 050
3: Hh 20%/60%	85 059	3.758			Dominated
8: Hh 20%/60% + ATB reduction	87 440	3.284			Dominated
7: Hh 50%/60% + ATB reduction	88 144	2.891			Dominated by extended dominance
9: Screening + contact precautions + ATB reduction	93 552	3.741			Dominated
4: ATB reduction	95 195	4.075			Dominated
5: Screening + contact precautions	97 350	4.571			Dominated
1: Base case Hh 20% 40%	100 905	5.02			Dominated

4. Impact of lower **sensitivity to detect ESBL-PE carriage** in screening strategies.

If the sensitivity to detect ESBL-PE on ICU admission was lower than in our core analysis and varied from 80% to 95%, HH 80%/80% (Strategy 2) and HH 80%/80% and antibiotic reduction (Strategy 7) always dominated the screening strategies (Strategy 6 and 10) (**Supplementary Figure S2**).

Figure S2 Cost-effectiveness plane showing the incremental health benefits (infections avoided) and costs of screening and cohorting strategies relative to the Strategy 2. The sensitivity of detection of ESBL carriers at ICU admission in screening and isolation strategies varied from 80% to 95%.
Strategies are: (2) Hand hygiene improvement to 80%/80%; (6) Screening of all admissions and cohorting of identified carriers; (7) Hand hygiene improvement to 80%/80% and Antibiotic reduction; (10) Screening of all admissions, cohorting of identified carriers and Antibiotic reduction.



Supplementary Table S4A Impact of **infection control nurse's time working on the hand hygiene program and the level of hand hygiene achieved** on model predictions compared to the Base case strategy. The cost-effective ratio (CER) was calculated when the hand hygiene strategy was more expensive but more effective that the base case.

Level of hand hygiene before contact with patient (%)	Level of hand hygiene after contact with patient (%)	Mean increase in hand hygiene from baseline (%)	Number of infections /100 admissions	Total cost /100 admissions (€)	CER (vs base case)
Base case					
55	60	-	4.99	105 344	-
ICN working on Hh program at 1/4 time					
55	60	0.0	4.99	112 783	Hh strategy dominated by the Base case
60	60	2.5	4.65	106 497	3 433
55	65	2.5	4.64	106 366	2 965
60	65	**5.0**	4.29	99 722	Base case dominated by the Hh strategy
⋮	⋮	⋮	⋮	⋮	Base case dominated by the Hh strategy
80	80	22.5	2.89	74 103	Base case dominated by the Hh strategy
ICN working on Hh strategy at 1/2 time					
55	60	0.0	4.99	120 222	Hh strategy dominated by the Base case
60	60	2.5	4.65	113 789	25 146
55	65	2.5	4.64	113 675	24 160
60	65	5.0	4.29	106 861	2 182
65	65	**7.5**	4.02	101 484	Base case dominated by the Hh strategy
⋮	⋮	⋮	⋮	⋮	Base case dominated by the Hh strategy
80	80	22.5	2.89	80 556	Base case dominated by the Hh strategy
ICN working on Hh strategy at full time					
55	60	0.0	4.99	135 100	Hh strategy dominated by the Base case
60	60	2.5	4.65	128 375	68 573
55	65	2.5	4.64	128 292	66 551

60	65	5.0	4.29	121 137	22 712
65	65	7.5	4.02	115 442	10 397
55	70	5.0	4.22	119 423	18 278
60	70	7.5	3.98	114 488	9 029
65	70	10.0	3.75	110 092	3 823
70	70	12.5	3.53	105 942	411
55	75	7.5	3.85	111 932	5 806
60	75	10.0	3.68	108 574	2 468
65	75	12.5	3.51	105 357	9
70	75	**15.0**	3.32	101 754	Base case dominated by the Hh strategy
⋮	⋮	⋮	⋮	⋮	Base case dominated by the Hh strategy
80	80	22.5	2.89	93 462	Base case dominated by the Hh strategy

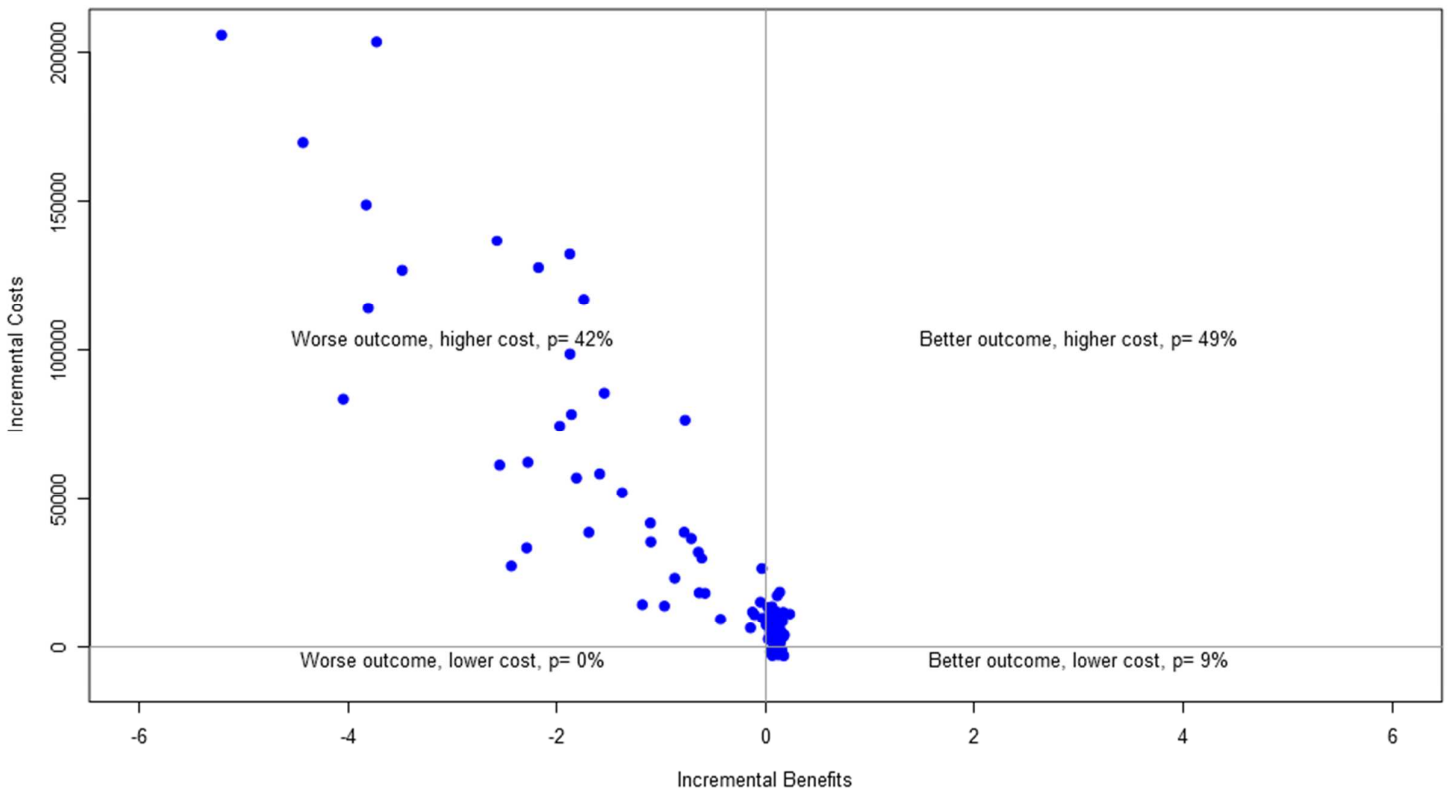
Supplementary Table S4B Impact of **infection control nurse's time working on the hand hygiene strategy and the level of hand hygiene achieved** on model predictions compared to the Screenig and cohorting strategy. The cost-effective ratio (CER) was calculated when the screening and cohorting strategy was more expensive but more effective that the hand hygiene.

Level of hand hygiene before contact with patient (%)	Level of hand hygiene after contact with patient (%)	Mean increase in hand hygiene from baseline (%)	Number of infections/100 admissions	Total cost/100 admissions (€)	CER (vs Hand hygiene strategy)
Screening and cohorting					
55 (with non cohorted patients)	60 (with non cohorted patients)		2,80	86 713	
ICN working on Hh strategy at 1/4 time					
55	60	0,0	4,99	112 783	Hh strategy dominated by Screening and cohorting
⋮	⋮	⋮	⋮	⋮	Hh strategy dominated by Screening and cohorting
70	70	12,5	3,53	85 621	1 496
55	75	7,5	3,85	91 212	Hh strategy dominated by Screening and cohorting
60	75	10,0	3,68	88 104	Hh strategy dominated by Screening and cohorting
65	75	12,5	3,51	85 102	2 283
70	75	15,0	3,32	81 748	9 554
75	75	17,5	3,15	78 568	23 561
55	80	10,0	3,51	84 751	2 763
60	80	12,5	3,38	82 408	7 507
65	80	15,0	3,24	79 993	15 442
70	80	17,5	3,12	77 946	28 012
75	80	20,0	2,99	75 742	58 203
80	80	22,5	2,89	74 103	146 278
ICN working on Hh strategy at 1/2 time					
55	60	0,0	4,99	120 222	Hh strategy dominated by Screening and cohorting
⋮	⋮	⋮	⋮	⋮	Hh strategy dominated by Screening and cohorting
75	75	17,5	3,15	85 136	4 561 €

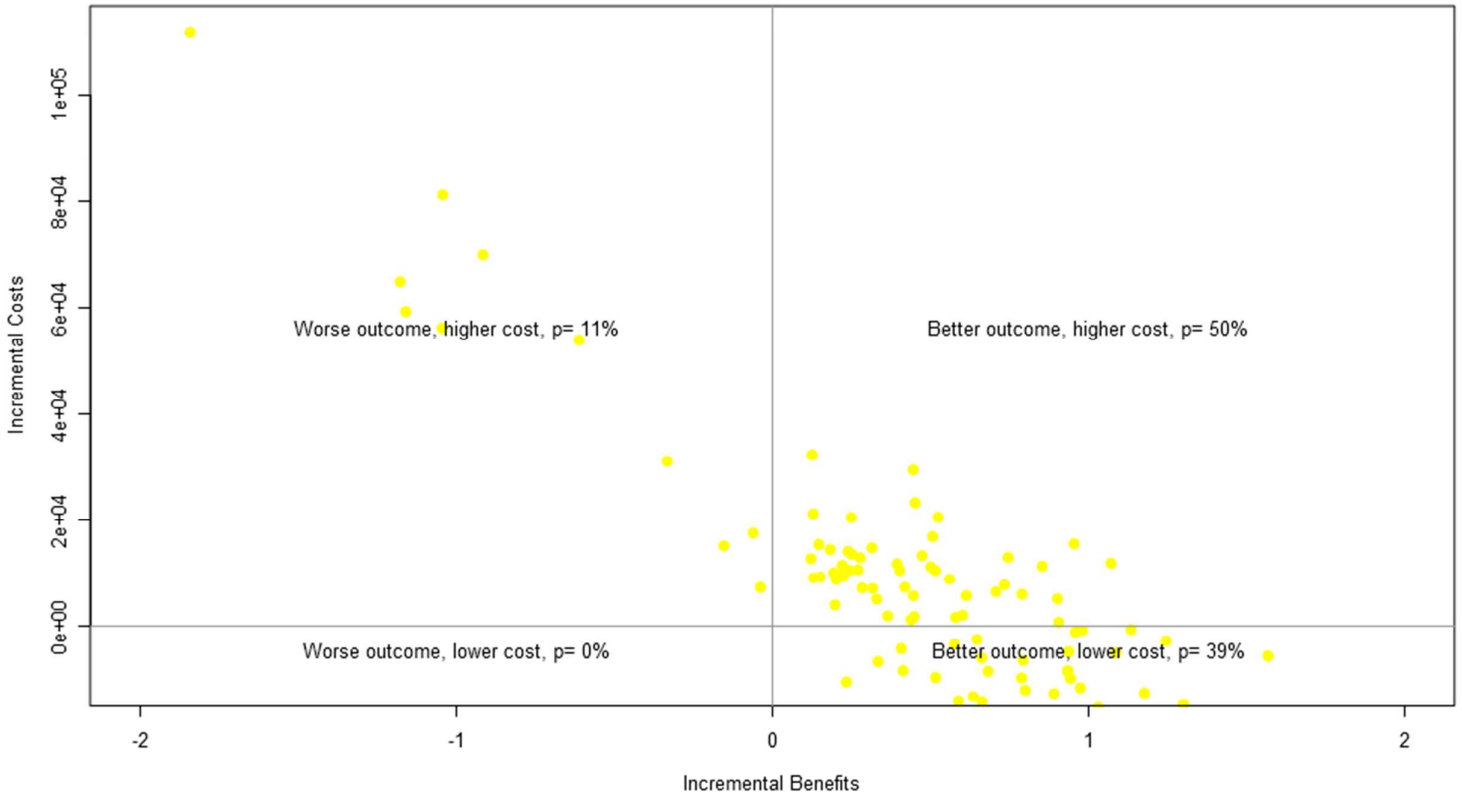
55	80	10,0	3,51	91 498	Hh strategy dominated by Screening and cohorting
60	80	12,5	3,38	89 094	Hh strategy dominated by Screening and cohorting
65	80	15,0	3,24	86 608	Hh strategy dominated by Screening and cohorting
70	80	17,5	3,12	84 516	7 023 €
75	80	20,0	2,99	82 227	23 801 €
80	80	22,5	2,89	80 556	71 424 €
ICN working on Hh strategy at full time					
55	60	0,0	4,99	135 100	Hh strategy dominated by Screening and cohorting
⋮	⋮	⋮	⋮	⋮	Hh strategy dominated by Screening and cohorting
80	80	22,5	2,89	93 462	Hh strategy dominated by Screening and cohorting

Supplementary Figure S3 Results of probabilistic sensitivity analysis. Cost-effectiveness plane shows the incremental health benefits (infections avoided) and costs for Screening and cohorting (Strategy 6), relative to horizontal strategies: A) Hand hygiene improvement to 80%/80% (Strategy 2); B) Hand hygiene improvement to 55%/80% (Strategy3); C) Antibiotic reduction (Strategy 4). The frequency that the Strategy 6 was in one of four quadrant of CE plane is represented by "**p**".

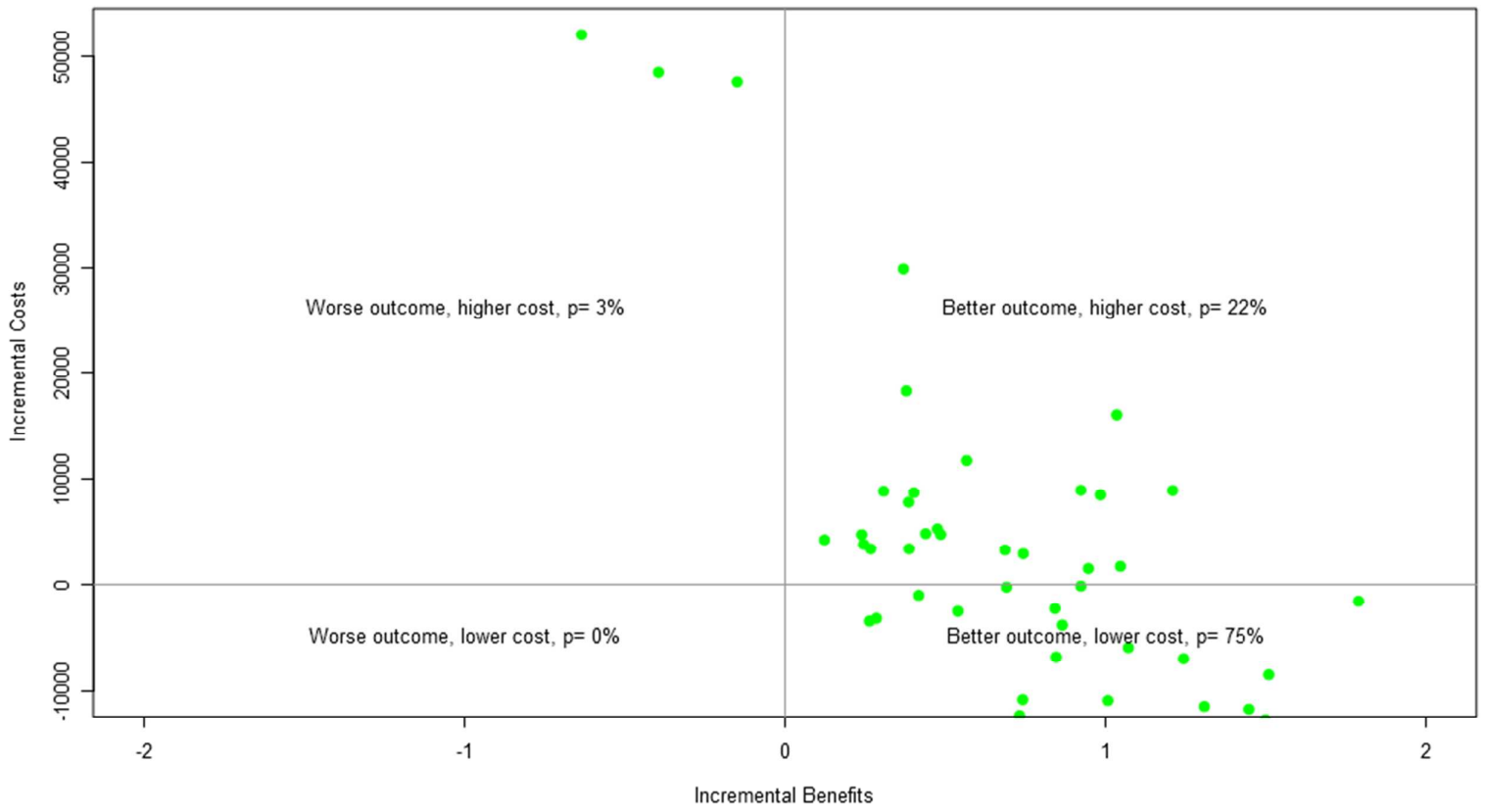
A)



B)

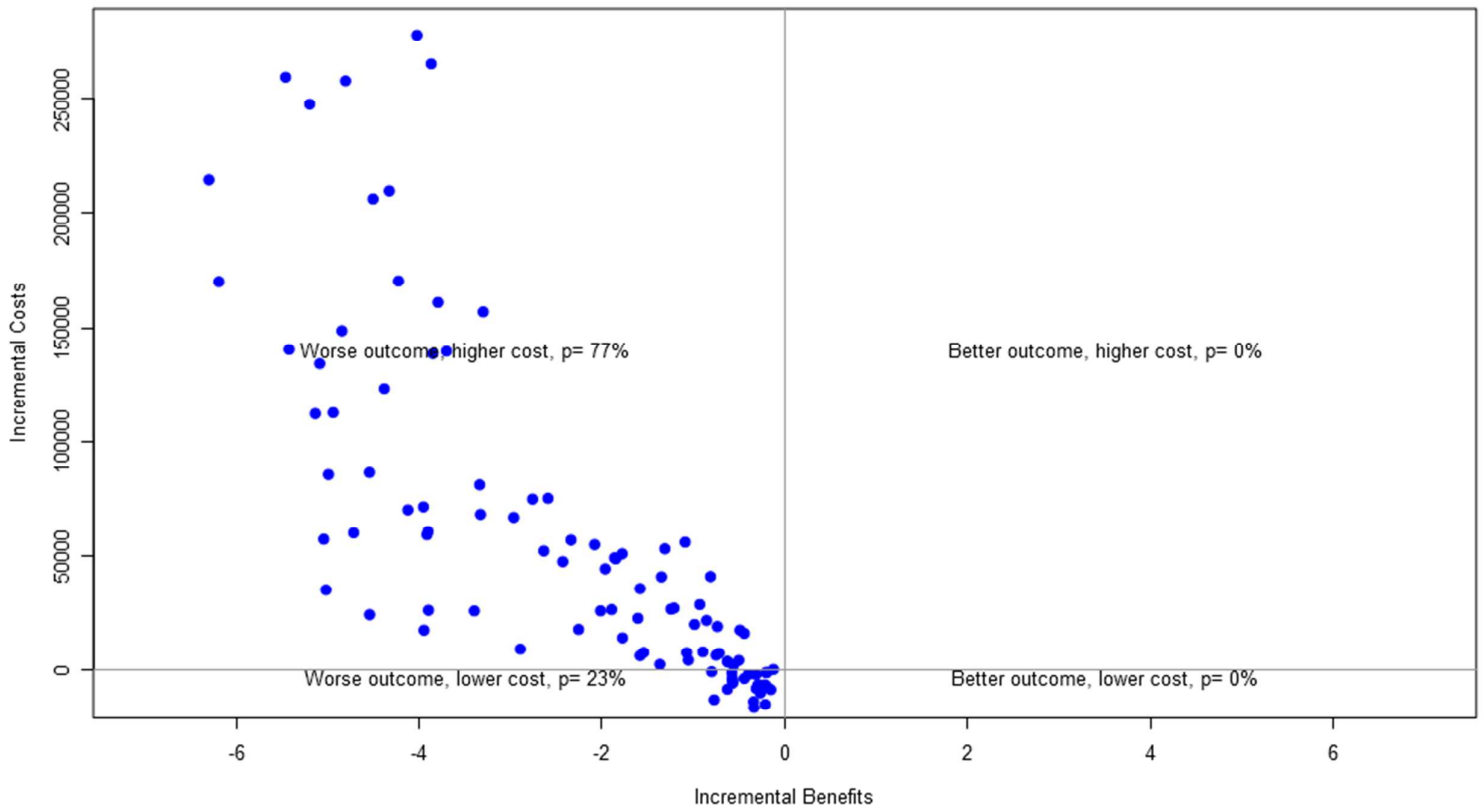

Worse outcome, higher cost, p= 11%
Better outcome, higher cost, p= 50%
Worse outcome, lower cost, p= 0%
Better outcome, lower cost, p= 39%
Incremental Costs
0e+00
2e+04
4e+04
6e+04
8e+04
1e+05
-2
-1
0
1
2
Incremental Benefits

c)

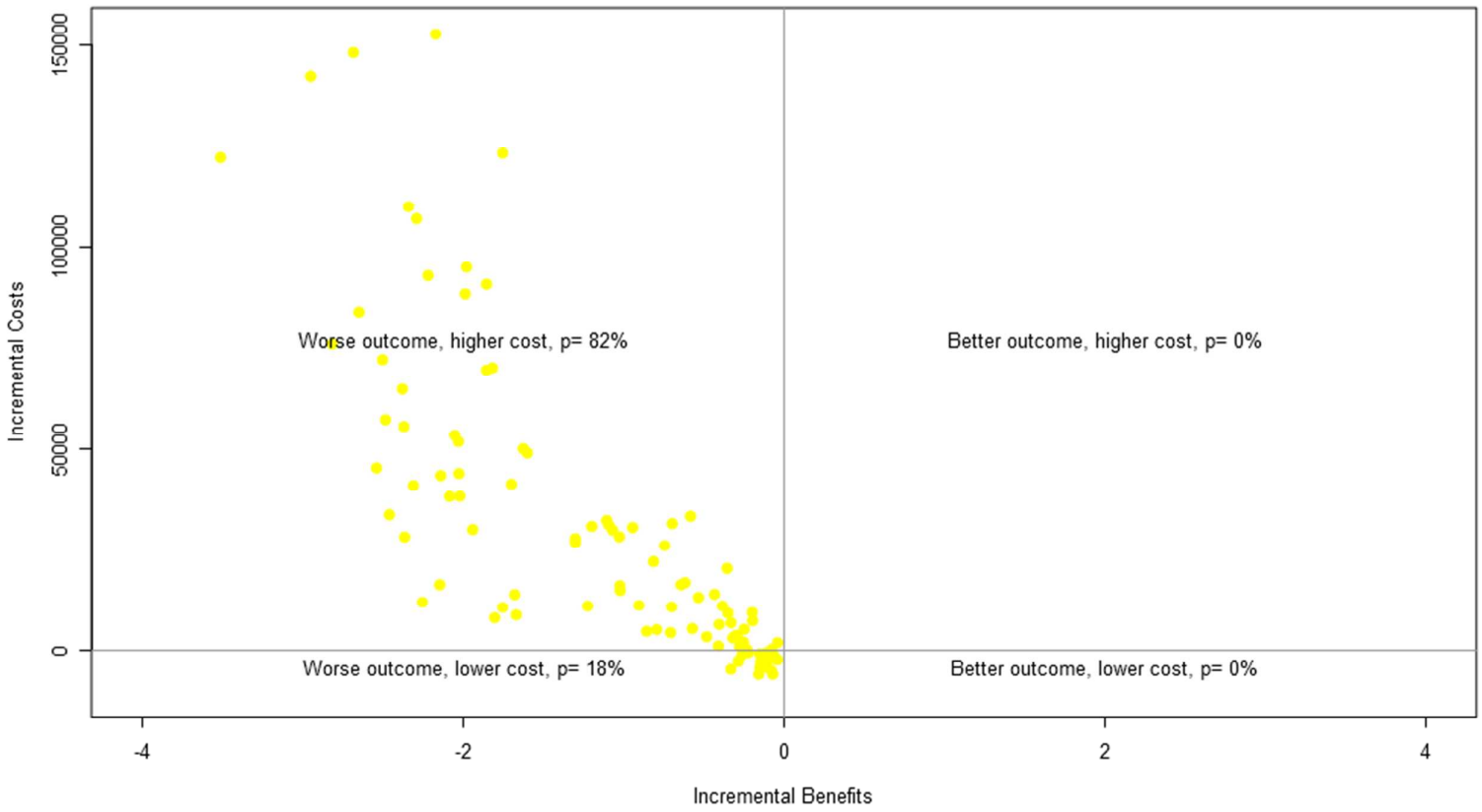

Worse outcome, higher cost, p= 3%
Better outcome, higher cost, p= 22%
Worse outcome, lower cost, p= 0%
Better outcome, lower cost, p= 75%
Incremental Costs
Incremental Benefits
50000
40000
30000
20000
10000
0
-10000
-2
-1
0
1
2

Supplementary Figure S4 Results of probabilistic sensitivity analysis. Cost-effectiveness plane shows the incremental health benefits (infections avoided) and costs for Screening and contact precautions (Strategy 5), relative to horizontal strategies: A) Hand hygiene improvement to 80%/80% (Strategy 2); B) Hand hygiene improvement to 55%/80% (Strategy3); C) Antibiotic reduction (Strategy 4). The frequency that the Strategy 6 was in one of four quadrant of CE plane is represented by "**p**".

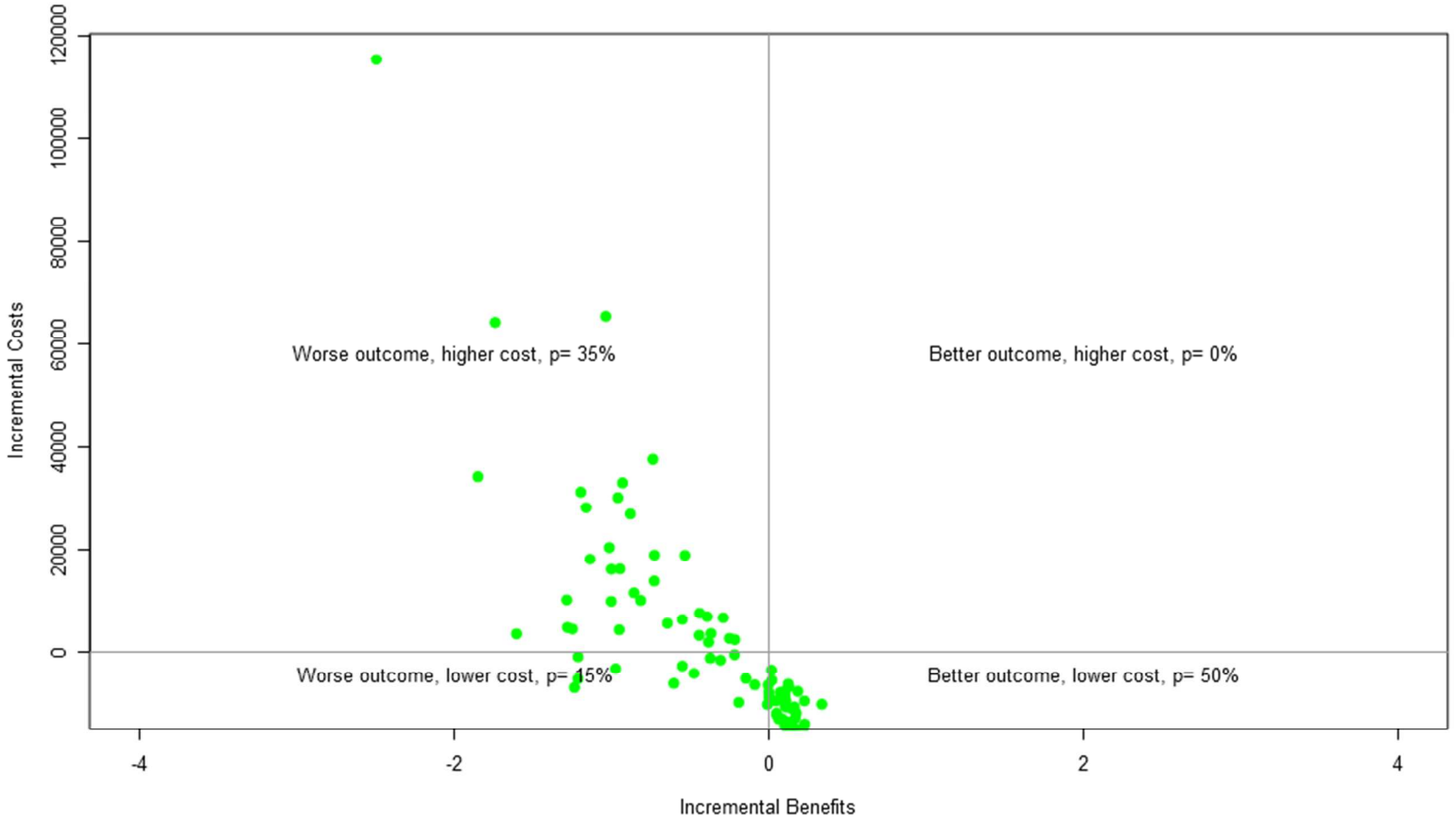
A)



B)


Incremental Costs
150000
100000
50000
0
Worse outcome, higher cost, p= 82%
Better outcome, higher cost, p= 0%
Worse outcome, lower cost, p= 18%
Better outcome, lower cost, p= 0%
-4
-2
0
2
4
Incremental Benefits

C)


Incremental Costs
120000
100000
80000
60000
40000
20000
0
Worse outcome, higher cost, p= 35%
Better outcome, higher cost, p= 0%
Worse outcome, lower cost, p= 15%
Better outcome, lower cost, p= 50%
-4
-2
0
2
4
Incremental Benefits

BMJ Open

Universal or targeted approach to prevent the transmission of extended-spectrum beta-lactamase–producing Enterobacteriaceae in intensive care units? A cost-effectiveness analysis

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Universal or targeted approach to prevent the transmission of extended-spectrum beta-lactamase–producing *Enterobacteriaceae* in intensive care units? A cost-effectiveness analysis

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ABSTRACT

Objective

Several control strategies have been used to limit the transmission of multidrug-resistant organisms in hospitals. However, their implementation is expensive and effectiveness of interventions for the control of extended-spectrum beta-lactamase–producing *Enterobacteriaceae* (ESBL-PE) spread is controversial. Here we aim to assess the cost-effectiveness of hospital-based strategies to prevent ESBL-PE transmission and infections.

Design

Cost-effectiveness analysis based on dynamic, stochastic transmission model over a one-year time horizon.

Patients and setting

Patients hospitalized in a hypothetical 10- bed intensive care unit (ICU) in a high-income country.

Interventions

Base case scenario compared to 1) universal strategies (e.g. improvement of hand hygiene (HH) among healthcare workers (HCWs), antibiotic stewardship), 2) targeted strategies (e.g. screening of patient for ESBL-PE at ICU admission and contact precautions or cohorting of carriers) and 3) mixed strategies (e.g. targeted approaches combined with antibiotic stewardship).

Main Outcomes and Measures:

Cases of ESBL-PE transmission, infections, cost of intervention, cost of infections, incremental cost per infection avoided.

Results

In the base case scenario, 15 transmissions and 5 infections due to ESBL-PE occurred per 100 ICU admissions, representing a mean cost of €94 792. All control strategies improved health outcomes and reduced costs associated with ESBL-PE infections. The overall costs (cost of intervention and infections) were the lowest for HH compliance improvement from 55%/60% before/after contact with a patient to 80%/80%.

Two strategies required higher investments than the HH programme, but also improved health benefits; 1) HH improvement to 80%/80% combined with antibiotic stewardship and 2) screening and cohorting strategy combined with antibiotic stewardship.

Conclusions

Improved compliance with HH was the most cost-saving strategy to prevent the transmission of ESBL-PE. Antibiotic stewardship was not cost-effective. However, adding antibiotic restriction strategy to HH or screening and cohorting strategies slightly improved their effectiveness and may be worthy of consideration by decision-makers'.

Strength and limitations of this study

- We used a dynamic transmission model to take into account that the risk of colonization in the ICU depends on the number of ESBL-PE carriers and could change over time.
- Parameters used in the model were derived from recent multicentre studies.
- We undertook sensitivity analyses to show the impact of uncertainty in parameter estimation and the impact of model assumptions on the conclusions.
- Direct HCW-to-HCW transmissions as well as environmental contamination were not included in the model.

INTRODUCTION

The incidence of infection and colonization with extended-spectrum beta-lactamase–producing *Enterobacteriaceae* (ESBL-PE) has increased worldwide[1–4]. In Europe, in 2014, the percentage of *Escherichia coli* and *Klebsiella pneumoniae* resistant to 3rd generation cephalosporins in invasive isolates was 12% and 23%, respectively[1]. A similar trend was observed in the United States, although with large variations between states[2].

In hospital settings, ESBL-PE acquisition is mainly due to indirect transmission between patients with the hands of healthcare workers (HCWs) as vectors[5]. Increased prevalence of colonization augments the risk of acquiring ESBL-PE infection[6]. Such infections represent a serious socio-economic burden and are associated with a raised mortality, more frequent hospital admissions in comparison with non-carriers, and additional costs[7].

Many interventions have been proposed to limit the transmission of multidrug-resistant organisms (MDROs) in hospitals. They can be classified as either 1) a 'universal' or 'horizontal' approach, applied to all patients e.g. improvement of hand hygiene (HH) among HCWs or antibiotic stewardship or 2) a 'targeted' or 'vertical' approach, e.g. screening and isolation of asymptomatic carriers in addition to infected patients, with the aim of identifying carriers and implementing measures to prevent the transmission from carriers to other patients[8].

There is general agreement that HH reduces the transmission of MDROs, especially MRSA[6]. However, few studies have evaluated the impact of HH on the prevention of ESBL-PE dissemination and they have provided conflicting results[9,10]. The effectiveness of targeted measures in controlling the spread of MDROs, and especially ESBL-PE, remains controversial. This approach is mainly recommended in high-risk units, e.g. intensive care units (ICUs)[11].

The implementation of interventions with demonstrated effectiveness in reducing ESBL-PE infections is associated with costs that are generally supported by hospitals. However, when evaluating implementation of an infection prevention programme, one should also take into account savings associated with these interventions, but this has been largely ignored in previous studies.

In this study, we used a mathematical model to evaluate the effectiveness and cost-effectiveness of universal and targeted control strategies for the prevention of ESBL-PE transmission in an ICU in a high-income country.

METHODS

The model

We extended a previously described stochastic, compartmental and dynamic model of ESBL-PE transmission[12] to assess the economic impact of infection control strategies implemented in a hypothetical, ICU setting. We run the model over a one-year to capture all costs and health effects relevant to implemented control strategies.

The model simulated the spread of ESBL-PE among patients through contacts with HCWs in an ICU, taking into account hospital admissions and discharges of patients, antibiotic exposure, and control interventions (**Figure 1**).

The **Supplementary Text S1** provides details of the model and its assumptions.

Model simulations and outcomes

Simulations of the model were performed using Gillespie's method and programmed in C++ language. The outcomes (cases of ESBL-PE transmission, infections, cost of intervention, cost of

infections) were calculated after a period of 1 year and averaged over the 1,000 Monte Carlo simulations. Cost-effectiveness analysis and graphics were performed in R[13].

Base case scenario

In the base case scenario, with no control intervention, we considered that compliance with hand hygiene before/after contact with a patient was 55%/60% respectively[14] and 56% of patients received antibiotics at ICU admission[15].

Infection control strategies

Universal approaches

We evaluated control strategies implemented in all patients (independently of their colonization status), that comprised one or both of the following interventions: 1) improved compliance with HH, and 2) antibiotic stewardship. For HH, we considered different levels of compliance. First, compliance with HH before/after contact with a patient was improved from 55%/60% at baseline to 55%/80% or 80%/80%. Second, antibiotic stewardship resulted in halving the proportion of patients on antibiotics at ICU admission and in reducing by 25% the duration of antibiotic treatment.

Targeted approaches

We evaluated 2 strategies that combined screening of patients for ESBL-PE at ICU admission and one of the following interventions implemented: 1) contact precautions (improved compliance with HH before/after contact with carriers to 80%/80%); or 2) cohorting of ESBL-PE

carriers with dedicated HCWs. HH compliance for other patients was maintained at baseline level.

Mixed approaches

We evaluated two strategies combining the targeted approaches with antibiotic stewardship.

Model parameters

Model parameters and their values are presented in **Supplementary Table 1**.

Based on recent French data, we assumed that 15% of patients were colonized with ESBL-PE at ICU admission[16].

Infection status was not included in the model, so we estimated the number of infections by multiplying the cumulated number of colonized patients after one year by the probability of developing an infection during an ICU stay, set at 16.4%[17]. Even though this value came from a recent large multicentre study, we also considered the impact of lower (8%) and higher (30%) probability of infection in alternative analyses.

Costs

The analysis was performed from a public hospital perspective. Cost estimates are based on values reported in Euros from 2015 (1 € = US $0.94). We considered the following costs in the model: 1) costs of intervention (material resources and personnel costs), 2) costs of ESBL-PE infections. The cost of an ESBL-PE infection was estimated using the ESBL-PE-attributable LOS and the cost of a hospital bed-day for infected patients[16,18,19]. See **Table 1** for cost parameters and **Supplementary Text 1** for more details.

Cost-effectiveness evaluation

To conduct the cost-effectiveness[20], we estimated the costs associated with each intervention implemented, and the health benefits were related to the number of avoided cases of ESBL-PE infections. First, we determined whether any strategy was dominated by another in terms of costs and health benefits. Second, we determined whether any strategy was dominated through principles of extended dominance (i.e. whether the incremental cost-effectiveness ratios [ICERs]decrease as the strategies increases in cost[20,21]). Finally, for the non-dominated strategies, we calculated the incremental cost per case of infection avoided, which is the ratio of the difference in costs between two strategies to the difference in health benefits. This process produces an "efficient frontier" indicating more costly, but more effective strategies.

Sensitivity analysis

We performed supplementary analyses to assess the impact of parameter uncertainty on the model's predictions. We first ran a univariate sensitivity analysis to evaluate the cost-effectiveness of strategies in settings with either low or high prevalence of patients colonized at admission (from 5% to 50%). We also considered the impact of a lower (8%) and a higher (30%) probability of infection in colonized patients. We then investigated the model assuming 1) a lower baseline compliance with HH (20%/40% or 40%/50%), 2) a lower sensitivity of the screening method used to detect ESBL-PE carriers at ICU admission**,** and 3) a lower, 30% reduction in antibiotic prescribing.

We also performed an analysis to explore the uncertainty in human time required in an HH programme and its potential effects. In this analysis, we varied the time an infection control nurse

works on the programme (quarter-time, half-time or full-time) simultaneously with the level of HH compliance achieved (from 55%/60% to 80%/80% before after contact).

Finally, we performed a probabilistic sensitivity analysis to explore the effect of joint uncertainty across parameters on the cost-effectiveness of universal vs targeted strategies. We varied the following parameters concurrently: 1) number of HCW contacts with patients, 2) transmission parameters, 3) length of stay of ICU patients, 4) natural decontamination rate for HCW, 5) antibiotic initiation rate, 6) prevalence of ESBL-PE carriage among patients admitted to the ICU, 7) death rate of patients, 8) probability of infection in colonized patients and 9) cost parameters. We randomly sampled values from each of the parameter distributions and calculated the mean costs and mean number of infections for each strategy (averaged over 1,000 simulations).

RESULTS

In the absence of control interventions (base case strategy), 15 new acquisitions (i.e. transmissions) and 5 infections due to ESBL-PE (those from new acquisitions and in patients colonized at admission) occurred per 100 admissions**.** Compared to the base case (Strategy 1), all strategies reduced ESBL-PE acquisition and infections within one year (**Figure 2**).

Among universal strategies, HH compliance improvement to 80%/80% (Strategy 2) was the most effective, resulting in a mean reduction to 2.9 acquired infections per 100 admissions. Among targeted strategies, screening of patients on admission and cohorting of carriers (Strategy 6) was the most effective strategy and resulted in a mean reduction to 2.8 infections per 100 admissions. Screening followed by contact precautions (Strategy 5) was the least effective in comparison with

all other options. Adding antibiotic stewardship to HH or targeted strategies only slightly improved their effectiveness.

Cost-saving analysis

In **Table 2** we present the estimated costs and outcomes over one year for all strategies. The mean total cost associated with the base case strategy was estimated at €105 344/100 admissions, €94 792 of which was related to infections and €10 552 to interventions. Investments in infection prevention was always cost-saving because they avoided cases of ESBL-PE infections and thus costs associated with these infections. For instance, when HH compliance was improved to 80%/80%, the mean cost of the strategy implementation increased to €25 639/100 admissions, but the costs related to infections decreased to €54 916, resulting in an overall monetary benefit of €24 788/100 admissions in comparison with the base case. This strategy was associated with the highest savings within all evaluated strategies.

Cost-effectiveness analysis

HH compliance improvement to 80%/80% was the least expensive strategy. However, two strategies required higher investments than the HH programme, but also improved health benefits. To help choose between strategies we calculated the incremental cost-effectiveness ratio (**Figure 3)**. The ICER of HH improvement to 80%/80% and antibiotic stewardship (Strategy 7) vs. HH compliance improvement to 80%/80% was estimated at €49 055/avoided infection (**Table 2**). The ICER of screening, cohorting and antibiotic stewardship (Strategy 10) vs. HH improvement to 80%/80% and antibiotic stewardship was estimated at €61 994/avoided infection. Other strategies were dominated (more expensive and less effective).

Sensitivity analysis

Findings from sensitivity analysis showed the robustness of predictions to: 1) the lower/higher prevalence of ESBL-PE carriage on ICU admission,2) the lower/higher probability of infections in colonized patients,3) the baseline compliance with HH lower than in our core analysis (20%/40% or 40%/50%), 4) the lower sensitivity to detect ESBL-PE carriers at ICU admission, and 5) the 30% reduction in antibiotic prescribing, Results of this analysis are shown in **Supplementary Text 2** (Figure S1 and Table S1, Table S2A and B, Table S3, Figure S2 and Table S4).

In a second sensitivity analysis, we focused on human time and performance to improve HH compliance. If an infection control nurse was assumed to work quarter-time, half-time or full-time on the programme, the HH compliance had to increase by at least 5%, 7.5% or 15%, respectively, to make the programme cost saving compared to the base case (**Supplementary Table S5A**).

In comparison with the screening and cohorting strategy, the HH improvement was cost-saving when an infection control nurse worked quarter-time or half-time on the programme, and HH compliance increased by at least 12.5% or 17.5%, respectively. The screening and cohorting strategy dominated the HH improvement programme when an infection control nurse was working full-time on the programme (**Supplementary Table S5B**).

Finally, the probabilistic sensitivity analysis showed that improvement of HH to 80%/80% (Strategy 2) was less expensive than the screening and cohorting intervention (Strategy 6) in 91%

of simulations. Among them, in 42% of simulations, the HH strategy was less expensive but more effective (dominated the Strategy 6), and in 49% of runs the screening and cohorting was more effective and more expensive (**Supplementary Figure S3**). Screening and contact precautions (Strategy 5) were always less effective than improvement of HH to 80%/80% (Strategy 2) (**Supplementary Figure S4**).

DISCUSSION

The impact of infection control strategies for preventing ESBL-PE transmission is controversial because clinical studies cannot account for the multiple confounding factors, notably both infection control measures and antibiotic stewardship. Despite several recent high-level interventional studies (Climo et al.[22]; Derde et al.[9]; Huang et al.[23]), the most effective and cost-effective interventions for controlling MDROs are still debated. Since the spread of ESBL-PE between patients is a dynamic and complex process, modelling can help for understanding the transmission mechanisms and deciding which intervention are to be preferred (Doan et al.[24]; Grundmann et al.[25]).

Our model estimated the annual burden of ESBL-PE infections in a French ICU at €94 792 per 100 admissions in the base case strategy. Several prior studies have reported the cost of infections due to multidrug resistant organisms in the ICU[26–29]. However, even though all authors underlined the high costs of infections, comparison between studies remains difficult. Estimated costs varied according to the country, but also to the population studied, e.g. patients with site-specific or microorganism-specific infections. Moreover, the methods used to estimate the costs were not similar in all publications.

In recent years, mathematical models have increasingly been used to study the cost-effectiveness of control strategies. For example, Robotham et al.[30]compared a wide range of strategies to control MRSA transmission in ICUs and found that universal decolonization was the most cost-effective option. In another study, Gidengil et al.[31]compared hospital strategies to prevent MRSA transmission and infections in an ICU. They confirmed that universal decolonization was the most cost-saving.

While decolonization regimens have been indicated as cost-effective for MRSA, only a few studies have examined the effect of decolonization on ESBL-PE carriage[32,33]. These studies have shown that decolonization strategies might be efficacious only in the short-term. Moreover, they have reported the risk of emergence of resistance to antibiotics used for decolonisation, namely to colimycin, which is the last line effective therapy against carbapenemase-producing *Enterobacteriacae* [33]. Thus, decolonization was not considered in our study.

Our study is the first to compare the effectiveness and the costs of universal and targeted control strategies in the context of the spread of ESBL-PE in ICUs. Our model predicted that improving HH to 80%/80% in contacts with all patients would prevent 83% of ESBL-PE acquisitions and avoid at least two out of five infections per 100 admissions. This strategy represented the most cost-saving, with a monetary benefit of €24 788 per 100 admissions.

The association between HH and reduction of MDROs infections has long been known and HH has been accepted as a crucial component of infection prevention[34]. HH has in addition the benefit of being effective for reducing transmission of many resistant or susceptible bacteria[34]. A recent publication reported that a programme designed to control MRSA by implementing universal components in addition to screening and contact precautions for MRSA carriers also

effectively reduced the incidence of resistant gram-negative bacteria, the most likely being ESBL-PE[10]. Thus, an HH programme designed to reduce ESBL-PE transmission may have positive effects on reducing the transmission of other microorganisms, and the overall economic benefit of an HH programme for the hospital might be greater than reported in our study.

Despite the confirmed effectiveness of HH and national and international recommendations, compliance with HH remains low and is often lower than values used in our base case analysis[35,36]. Furthermore, improving HH compliance from 60% to 80% may be far more difficult and costly, challenging than improving from lower baseline level. However, we showed in a sensitivity analysis that improving HH remained the most cost-saving strategy even in a low baseline compliance scenario. Different strategies have been suggested to improve HH in hospitals[37], but the evidence-based approach is still lacking. Recently, a review [38] concluded that a multimodal strategy proposed by the WHO and consisting of five components: 1) system change, 2) training and education, 3) observation and feedback, 4) reminders in the hospital, and 5) a hospital safety climate, was effective at increasing HH among HCWs. Moreover, the authors underlined that additional measures (e.g. reward incentives for reaching a certain level of compliance) could lead to further improvements. In our study, we assumed that a key component of an HH programme was a dedicated staff working on the programme (i.e. HH education, observation and feedback). We hypothesized, for example, that to improve HH compliance an infection control nurse working half-time would be sufficient. However, this assumption was based on expert opinion; we performed a sensitivity analysis to explore the uncertainty of the required time dedicated to the HH programme and its expected effects.

Screening strategies have been used to prevent transmission of MDROs, however, in a sensitivity analysis, we showed that improvement of HH to 80%/80% was always more effective than

screening and contact precautions and mostly less expensive than the screening and cohorting intervention. However, we can hypothesize that in the case of highly resistant bacteria (e.g. Carbapenem-resistant *Enterobacteriaceae*) where there is a highest clinical impact on the outcomes of infected patients, given the lack of therapeutic options, a rapid identification and cohorting of carriers may be more beneficial from the hospital but also societal perspective.

Antibiotic use is the major driver for the selection of antibiotic-resistant bacteria[39] and many strategies have been proposed to reduce the use of antibiotics in hospitals[40]. These strategies could be implemented and associated with different efficacies and costs[41]. Here, we considered that antibiotic stewardship, based on the introduction of an infectious disease specialist to the ward, led to a 50% reduction in antibiotic use [42]. However, despite this optimistic scenario, we found that antibiotic stewardship was less effective than HH or a screening and cohorting strategy.

Under the hypotheses used in our model, we also demonstrated in a previous study through sensitivity analyses that antibiotic parameters did not significantly influence the effectiveness of interventions[12].

However, adding antibiotic stewardship to an HH strategy slightly improved its effectiveness and may be worthy of consideration if the decision-makers are willing to pay at least €49 055per infection avoided (we calculated that it would be equivalent to €5 562 per life-year gained (LYG)). Combining antibiotic stewardship with screening and cohorting was even more effective than combining HH and antibiotic stewardship, but with an additional cost of €61 994 per infection avoided (or €7 030/LYG).

Our study has several strengths. Firstly, we used a dynamic model to represent interactions between patients and HCWs and to take into account that the risk of colonization in the ICU depends on the number of ESBL carriers and could change over time. Moreover, our model incorporated the key elements of ESBL-PE transmission, such as the impact of prevalence at admission or antibiotic treatment. Secondly, we used input parameters derived from recent multicentre studies. Thirdly, we estimated the cost of HCW according to the time they spend working on the programme based on the best evidence from the literature and expert opinion. Finally, we assessed the impact of uncertainty in parameter estimation and the impact of model assumptions on the model's predictions by performing multiple sensitivity analyses.

Our study also has several limitations. ICU parameters and costs were based mostly on French data, and ESBL-PE infections, prevalence, compliance with control measures and costs may be different in other countries.

A recent multicentre cohort study[17] found no difference in LOS between infected and colonised patients. Thus, in order to simplify assumptions, the "infected" state was not included to the model. However, infected patients are potentially more contaminating HCW hands, disseminating the organism in the environment and increase the transmissibility[43]. Thus, consequently we may have underestimated the number of acquisitions in the ICU and the impact of control measures.

The epidemiologic characteristics of ESBL-PE are complex and may vary, depending on ESBL-PE species. For example, Thiébaut et al. [44] showed that *E.coli* ESBL was mainly imported (66%) and *K. Pneumoniae* ESBL was acquired (77%). Furthermore, the differential capacity of cross-transmission between ESBL *E. coli* and other *Enterobacteriaceae* has been clearly established[45]. In a previous publication from our group[12], however, we showed no difference in the effectiveness of control measures, whatever the *Enterobacteriaceae* considered, either *E. coli* or

another *Enterobacteriaceae*. We therefore decided to consider *Enterobacteriacae* globally, a situation that can be extended to carbapenemase-producing *Enterobacteriacae.*

We modelled an ICU as a single-room unit where transmission among patients results via contacts with HCWs. In the absence of detailed information on transmission of ESBL-PE in hospital wards, we ignored direct HCW-to-HCW transmissions as well as environmental contamination or excreta management.

ESBL-PE acquisition in the ICU can lead to transmission from an ICU-acquired case and infection in downstream units, thus increasing costs of hospitalization. Moreover, colonization with ESBL-PE may persist several months after hospital discharge[46], therefore increasing the risk of infection with potential subsequent treatment failure. Thus, an efficient intervention to prevent the inhospital cross-transmission may also have an impact on the prevention of post-discharge infections and the need for readmissions.

Our cost evaluation therefore underestimated health benefits and cost savings resulting from inhospital interventions to control ESBL-PE, but participate to demonstrate the usefulness of inhospital intervention to prevent further costs.

CONCLUSION

Our study suggests that a universal approach with improved compliance with HH was the most cost-saving strategy to prevent the transmission of ESBL-PE in an ICU setting. Screening and cohorting of carriers had comparable effectiveness to HH improvement, but was more expensive.

Antibiotic stewardship was not cost-effective in comparison with other options. However, adding antibiotic restriction to the HH or the screening and cohorting strategies slightly improved their effectiveness and may be worthy of consideration by decision-makers.

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FOOTNOTES

Contributors: YY, JCL, CP and LKS designed the study. YY, JCL, PYB, AA, CP and LKS contributed to the development of the model. CP, AP, GB, ER and LKS collected the data. CP and LKS wrote the code. LKS conducted computer simulations and result analysis. LKS, JCL and YY drafted the manuscript. All authors read and critically revised the manuscript.

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FIGURE LEGENDS

Figure 1. Model of transmission of ESBL-PE between patients through contacts with health-care workers (HCWs) and impact of infection control measures in the transmission process. Solid lines represent the transitions between population groups and dashed lines represent the transmission between patients and HCWs.

A. Impact of universal (horizontal) control measures: 1) hand hygiene (reduces the transmission among patients and HCWs); 2) antibiotic restriction (reduces the risk of transmission from colonized patients receiving antibiotics to HCWs or from contaminated HCWs to uncolonized patients receiving antibiotics).

B. Impact of targeted (vertical) control measures: screening of patients on ICU admission and identification of patients who had positive screening results (patients surrounded be a shaded box). Implementation of: 1) contact precautions (hand hygiene reduces the transmission from identified ESBL-PE carriers to HCWs); 2) cohorting of identified ESBL-PE carriers and attribution of a dedicated HCW (prevents the transmission from cohorted patients to other HCWs and patients). Note that we included two categories of colonized patients: 1) who had false negative admission screening results; 2) who had positive admission screening results (patients surrounded by a shaded box).

Figure 2. Patient outcomes after one year under the different control strategies tested. (A) New acquisitions (transmissions) of ESBL-PE per 100 admissions, (B) Total number of ESBL-PE infections per 100 admissions in patients who: 1) acquired colonization in the ICU, and 2) those who were already colonized at ICU admission.

Strategies are: (1) Base case (reference strategy with no control intervention and hand hygiene compliance of 55%/60% before/after patient contact); (2) Hand hygiene improvement to 80%/80%; (3) Hand hygiene improvement to 55%/80%; (4) Antibiotic reduction; (5) Screening of all admissions and contact precautions for identified carriers; (6) Screening of all admissions and cohorting of identified carriers; (7) Hand hygiene improvement to 80%/80% and antibiotic reduction; (8) Hand hygiene improvement to 55%/80% and antibiotic reduction; (9) Screening of all admissions, contact precautions with identified carriers and antibiotic reduction; (10) Screening of all admissions, cohorting of identified carriers and antibiotic reduction.

Figure 3. Cost-effectiveness plane showing the incremental health benefits (infections avoided) and costs relative to the least expensive strategy (Strategy 2). Strategies 1, 3, 4, 5, 8, 9 are dominated as they have both a worse outcome and a higher cost. The efficiency frontier (grey line), joins Strategy 2 with more expensive and more efficient strategies (7 and 10). Strategy 6 is extended to this frontier and excluded by the principle of extended dominance. The slope of the efficiency frontier represents the incremental cost-effectiveness.

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TABLES

Table 1. Cost parameters, their sources and ranges for sensitivity analyses.

Costs of control strategies were based on material and personnel. For example, the cost of the HH improvement strategy included the cost of HH (hand-rub and HCWs' time) and the cost of an infection control nurse working on the programme, i.e. HH education, observation and feedback.

	Resource	Cost (€*) mean	Cost (€*) SD	Source	Distribution
	ICU bed-day	1,583	226	AP-HP [a]	Gamma
Universal strategies					
Hand hygiene	Alcohol-based hand rub	0.011	0.0055	[47,48]	Gamma
	HCW's time per hand hygiene	0.143	0.0714	[47]	Gamma
	Infection control nurse at half-time/month[b]	2,048[c]	164	AP-HP [a]	Gamma
Antibiotic stewardship	Infectious disease physician at half-time/month[b]	5,500[c]	273	AP-HP [a]	Gamma
Targeted strategies					
Screening	Screening test + laboratory costs	40	20	[48–50]	Gamma
Contact precautions (= hand hygiene at 80%/80% with identified ESBL-PE patients)	Alcohol-based hand rub	0.011	0.0055	[47,48]	Gamma
	HCW's time per hand hygiene	0.143	0.0714	[47]	Gamma

Cohorting (additional HCW + contact precautions)	Additional full-time HCW/month[b]	3,598[c]	642	AP-HP [a]	Gamma
	Alcohol-based hand rub	0.011	0.0055	[47,48]	Gamma
	HCW's time per hand hygiene	0.143	0.0714	[47]	Gamma

[a] AP-HP: The Assistance Publique – Hôpitaux de Paris

[b] Assumption based on expert opinion

[c] Cost of staff from a hospital perspective (salary + employer contributions)

* 1€ = US $0.94

599 **Table 2.** Results of cost-effectiveness analysis.

Strategy	Number of ICU admissions	Total cost/100 admissions (€)	Cost of infections/ 100 admissions (€)	Cost of intervention/ 100 admissions (€)	Infections due to ESBL-PE/ 100 admissions	Incremental cost/100 admissions (ΔC) (€)	Incremental effect (ΔE) (infections avoided/100 admissions)	ICER (ΔC/ΔE) (€ / infection avoided)
2: HH 80%/80%	573	80 556	54 916	25 639	2.9	-	-	-
7: HH 80%/80% + ATB reduction	581	88 498	51 840	36 657	2.7	7 942[a]	0.1619[a]	49 055 [a]
10: Screening + cohorting + ATB reduction	584	94 313	50 058	44 255	2.6	5 815[b]	0.0938[b]	61 994[b]
3: HH 55%/80%	548	84 751	66 773	17 978	3.5			Dominated [c]
6: Screening + cohorting	575	86 713	53 278	33 435	2.8			Dominated [d]
8: HH 55%/80% + ATB reduction	565	88 621	59 445	29 176	3.1			Dominated [c]

9: Screening + contact precautions + ATB reduction	546	94 309	67 560	26 749	3.6		Dominated [c]
5: Screening + contact precautions	519	96 716	81 582	15 134	4.3		Dominated [c]
4: ATB reduction	528	100 128	77 641	22 486	4.1		Dominated [c]
1: **Base case**	498	105 344	94 792	10 552	5.0		Dominated [c]

[a] Relative to strategy 2

[b] Relative to strategy 7

[c] Dominated: A strategy is dominated when it has higher cost and lower health benefit than another strategy.

[d] Dominated by extended dominance: Strategy is dominated by extended dominance if the linear combination of other strategies produces greater benefit at lower cost.

Figure 1A

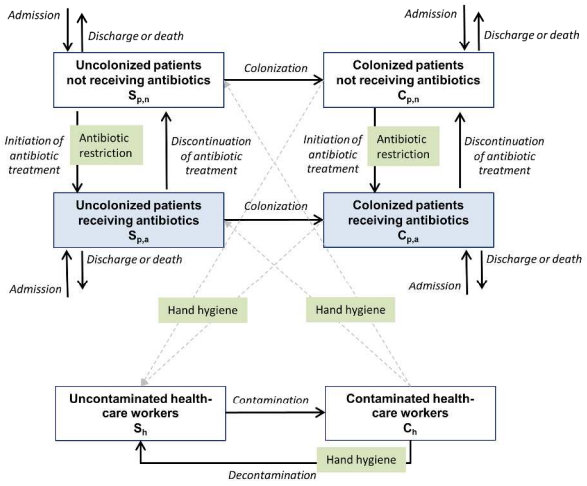
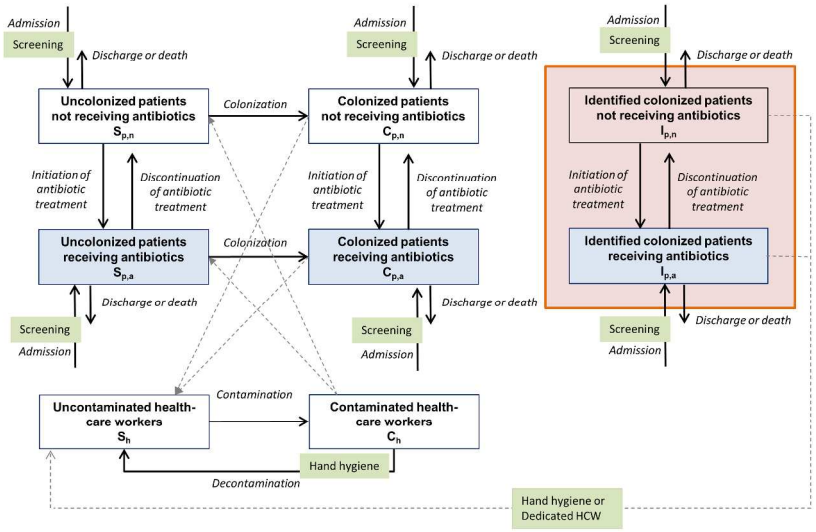


Figure 1B



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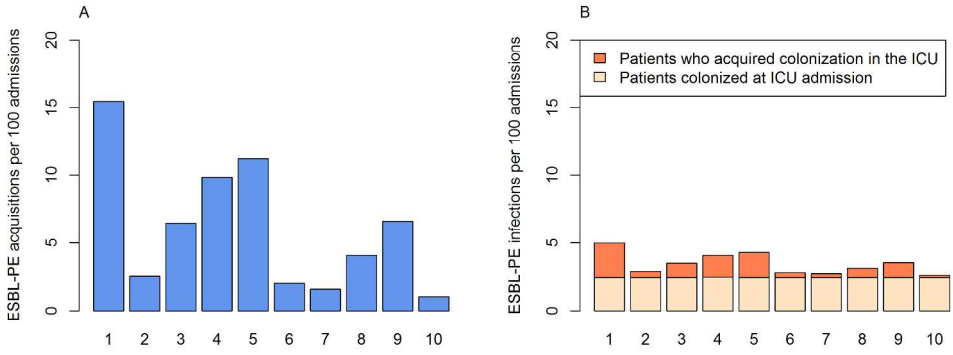

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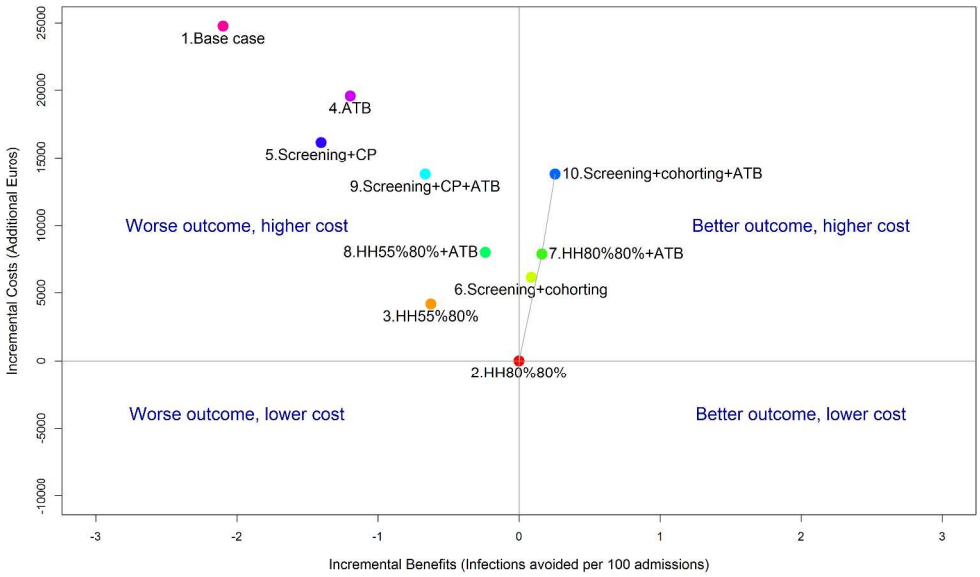

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Supplementary material

Supplementary Text S1

Defining the objectives, scope and policy context of a model.	
Decision objective	To evaluate ESBL-PE control strategies
Policy context	This analysis was used to support decision makers in choosing the best strategy for controlling ESBL-PE
Funding source	PREPS Program*, Inserm**
Disease	ESBL-PE infections
Perspective	Hospital perspective
Target population	ICU patients
Health benefits	Reduction in ESBL-PE infections
Strategies	Universal strategies (hand hygiene improvement or antibiotic reduction) Targeted strategies (screening of patients on ICU admission and contact precaution in contact with carriers or cohorting)
Resources/costs	Staff time working on the program, materials
Time horizon	1 year
*PREPS - French government's program on Care System Performance **Inserm- National Institute for Health and Medical Research	

Transmission model

We have used an extended version of a previously developed compartmental, dynamic, stochastic model to simulate the transmission of ESBL-PE in a hypothetical ICU with 10 single-bed rooms among patients through contacts with healthcare workers (HCWs)[1].

For each simulation, we introduced a single unidentified ESBL-PE carrier receiving antibiotics within the ward and simulated the ESBL-PE dynamics for one year. In this version of the model, following the first admitted colonized patient, φ was the fraction of admitted patients assumed to be colonized with ESBL-PE. Patients are discharged at rate γ or die at rate ν but bed occupancy is assumed to be 100% (the population of patients in the ward is constant).

Patients may or may not receive antibiotics at admission; antibiotics are initiated during the patient's stay at rate τ per day and antibiotics are discontinued at rate θ per day.

In the model, all patients were classified as 1) uncolonized receiving antibiotics ($S_{p,a}$) or not ($S_{p,n}$), 2) unidentified ESBL-PE carriers receiving antibiotics ($C_{p,a}$) or not ($C_{p,n}$) (**Figure 1A**). Antibiotics in the model acted in two ways: 1) increased the risk of becoming colonized for uncolonized patients receiving antibiotics; and 2) increased the risk of transmission from colonized patients receiving antibiotics.

Initially uncontaminated HCWs (S_h) can become transiently contaminated (and go to the compartment C_h) after contact with a colonized patient ($C_{p,n}$ or $C_{p,a}$).

Mathematical model under targeted infection control measures

The model was modified to account for the effect of targeted control measures. To detect ESBL-PE carriers, we simulated the screening of patients at ICU admission. We assumed that the screening method had 95% sensitivity and 100% specificity. Thus in the model, all patients were classified as 1) uncolonized receiving antibiotics ($S_{p,a}$) or not ($S_{p,n}$), 2) unidentified ESBL-PE carriers receiving antibiotics ($C_{p,a}$) or not ($C_{p,n}$), and 3) identified ESBL-PE carriers receiving antibiotics ($I_{p,a}$) or not ($I_{p,n}$) (**Figure 1B**).

Model parameters

Exposure to antibiotics has been associated with increased probability of colonization for uncolonized patients[2,3] and of transmission from colonized patients to HCWs[4–6]. Thus, we hypothesized that: 1) the colonization probability after contact with a contaminated HCW was higher in patients on antibiotics than in untreated patients ($b_{p,a} > b_{p,n}$), 2) the probability of contamination of an HCW through contact with a colonized patient was higher if the patient was treated with antibiotics ($b_{h,a} > b_{h,n}$).

The transmission parameter β depends on the rate of HCW visits followed by contacts with the patient (a), the probability of ESBL-PE bacteria transmission per infectious contact ($b_{\cdot,\cdot}$), and the compliance with hand hygiene (HH) (p_p and $p_{h\cdot}$).

The risk of transmission from an unidentified ESBL-PE carrier to n HCW might differ from that of an identified ESBL-PE carrier, because of the implementation of targeted control measures.

Firstly, we modelled the implementation of contact precautions (improvement of HH) in contacts with identified ESBL-PE carriers. HH for other patients was maintained at baseline level.

The transmission parameters were defined as follows:

$$\beta_{p,a} = a \cdot b_{p,a} \cdot (1 - p_p)$$
$$\beta_{p,n} = a \cdot b_{p,n} \cdot (1 - p_p)$$

Transmission from contaminated HCWs to uncolonized patients (receiving antibiotics or not)

$$\beta_{h,a} = a \cdot b_{h,a} \cdot (1 - p_h)$$
$$\beta_{h,n} = a \cdot b_{h,n} \cdot (1 - p_h)$$

Transmission from non-identified, colonized patients (receiving antibiotics or not) to HCWs

$$\beta_{h,a,I} = a \cdot b_{h,a,I} \cdot (1 - p_{h,Is})$$
$$\beta_{h,n,I} = a \cdot b_{h,n,I} \cdot (1 - p_{h,I}s)$$

Transmission from identified, colonized patients (receiving antibiotics or not) to HCWs

Secondly, we modelled the introduction of a dedicated HCW to interact only with identified, colonized patients. The transmission parameters were defined as follows:

$$\beta_{p,a} = a \cdot b_{p,a} \cdot (1 - p_p)$$
$$\beta_{p,n} = a \cdot b_{p,n} \cdot (1 - p_p)$$

Transmission from contaminated HCWs to uncolonized patients (receiving antibiotics or not)

$$\beta_{h,a} = a \cdot b_{h,a} \cdot (1 - p_h)$$
$$\beta_{h,n} = a \cdot b_{h,n} \cdot (1 - p_h)$$

Transmission from non-identified, colonized patients (receiving antibiotics or not) to HCWs

$$\beta_{h,a,I} = 0$$
$$\beta_{h,n,I} = 0$$

Transmission from identified, colonized patients (receiving antibiotics or not) to HCWs (other than the dedicated HCW)

Once colonized, patients do not clear ESBL-PE colonization before discharge. HCWs are transiently contaminated and they become decontaminated either by performing HH or after a mean waiting time of one hour.

The model parameters and their values are presented in **Supplementary Table 1**. Parameter values were derived from multicentre studies if available, and by default based on best evidence from the literature or expert opinion.

We modelled an ICU with 10 single-rooms with continuous presence of 6 HCWs[8]. We assumed 100% bed occupancy. Consequently, a shorter length of stay (LOS) implies a higher turnover and possible admission of colonized patients[9]. As reported recently, the ICU LOS of ESBL-PE carriers is longer (13 days) than uncolonized patients (5 days)[10]. The extended LOS in ESBL-PE carriers increases the colonization pressure in the ICU, consequently increasing the risk of cross-transmission.

When targeted control strategies were used, colonization was detected using a screening method assuming that screening results were instantaneous. We assumed that the sensitivity of the screening method was 95%[11]. Screening results had 100% specificity.

Costs of control strategies

We estimated the costs of control strategies over the one-year simulation period. See **Table 1** for details on cost parameters.

We used gamma distribution to represent uncertainty in cost parameters. Cost data are constrained to be non-negative and gamma distribution is often used in decision modelling. To estimate the parameters of the gamma distribution to cost data, we used the method of moments. When data were available from the hospital data base, e.g. cost of ICU bed-day, we performed a

goodness of fit test (Kolmogorov-Smirnov) to assure that a random sample comes from a gamma distribution. The test was performed using **R** software.

The cost of the base case strategy (reference strategy) was considered to be the cost of HH at baseline level, namely cost of the alcohol-based hand rub and costs associated with the time HCWs required for hand disinfection.

As reported recently, the highest cost of an HH program arose from the time people spent working on the program[12]. We therefore assumed that the cost of an HH improvement strategy included the cost of HH (hand-rub and HCWs' time) and the cost of an infection control nurse working on the program, i.e. HH education, observation and feedback[12,13]. We assumed (based on expert opinion) that improving hand HH compliance to 55/80% and to 80/80% required respectively a quarter and a half of the working time of an infection control nurse. In accordance with staffing practices common in the European Union, we assumed that one staff position requires the recruitment of three nurses[14].

Antibiotic stewardship programs (ASPs) have proven efficient in reducing antibiotic use and antibiotic duration in hospitals[15–17]. Interventions included in ASPs require additional resources associated with higher costs[18]. One of the resources needed and associated with the highest costs is the staff time[19]. We calculated the cost of an action to reduce antibiotic use as the cost of a half-time infectious disease physician working on the ASP. This assumption was based on expert opinion. The cost of antibiotics is considered to be marginal and was not considered in our study[17].

The cost of screening was first based on the cost of testing materials and on the cost of laboratory technician time spend on a rapid screening test (e.g. PCR).

For the strategy in which screening at admission was combined with contact precautions for identified ESBL-PE carriers, we also included the cost of contact precautions such as the cost of improved HH (i.e. the cost of the alcohol-based hand rub), and the costs associated with the time HCWs required for hand disinfection. Here we did not consider the cost of an infection control nurse. We hypothesized that knowing that the patient is an ESBL-PE carrier, HCWs would adhere more easily to HH.

For the strategy in which screening on admission was combined with cohorting of identified ESBL-PE patients, the cost of cohorting was the cost of contact precautions and the cost of additional HCWs caring for cohorted patients (based on expert opinion). For screening interventions, the cost of HH in non-carriers and unidentified carriers was considered to be identical to the costs of the baseline level.

Cost of hospital-acquired infections

The mean cost of an ICU bed-day was estimated at €1,583 (based on the average amount paid in 2015 for ICUs in Paris public hospitals (AP-HP). This amount is based on French Diagnosis-Related Groups and complementary revenues specific to ICU units and divided by the mean length of stay in ICUs in 2015[20]. Based on published reports, the cost per day of a patient with ESBL-PE infection was 50% higher than the cost of an uninfected patient [21,22]. The cost of an ESBL-PE infection was estimated using the ESBL-PE-attributable LOS and the cost of a hospital bed-day for infected patients[23,24].

Model calibration

The model was simulated stochastically. We calibrated the colonization and contamination parameters using Monte Carlo methods in order to reproduce the observed 12.9% acquisition rate in an ICU after a 6-month period[7].

Model simulations and outcomes

Simulations of the model were performed using Gillespie's method and programmed in C++ language. The outcomes were calculated after a period of 1 year and averaged over the 1,000 Monte Carlo simulations. Cost-effectiveness analysis and graphics were performed in R[25].

TABLES

Supplementary Table 1. Base case values and ranges for probabilistic sensitivity analysis of input parameters used in the compartmental model of ESBL-PE transmission.

Comment. As can be seen, for some parameters the ranges for a sensitivity analysis are omitted (e.g. $d_{ATB,S}$). This is because these parameters are specific to a strategy (e.g. Atb reduction) and must be fixed in sensitivity analysis to allow the comparison of outcomes with other strategies.

				Sensitivity analysis	
Parameter	**Description**	**Value**	**Source**	**Range**	**Distribution**
N_p	Number of beds	10	[26]		
N_h	Number of HCWs	6	[27]		
c_p	Number of HCW visits associated with at least one aseptic contact per patient	81	[28–30]	13.8 [31] - 160 [28,32,33]	triangular (peak at 81)

	per day				
a	Number of HCW visits associated with at least one aseptic contact per HCW per day	13.5	c_p/N_h		
$b_{p,n}$	Colonization probability for patients not receiving antibiotics	0.0127	Calibrated, consistent with data from[7]	0-0.1	triangular (peak at 0.0127)
$b_{p,a}$	Colonization probability for patients receiving antibiotics	0.0530		$b_{p,n}$-0.5	uniform
$b_{h,n}$	Probability of contamination of an HCW with ESBL-PE during a contact with a colonized patient not receiving antibiotics	0.0379	Calibrated, consistent with data from[7]	0-0.6	triangular (peak at 0.0379)
$b_{h,a}$	Probability of contamination of an HCW during a contact with a colonized patient receiving antibiotics	0.3198	Calibrated, consistent with data from[7]	$b_{h,n}$-0.8	uniform
d_S	Mean length of stay of uncolonized patients (days)	5	[10]	3-9 [10]	triangular (peak at 5)
d_C	Mean length of stay of colonized patients (days)	13	[10]	6-26 [10]	triangular (peak at 13)

d_{Is}	Mean length of stay of isolated patients (days)	13	[10]	6-26[10]	triangular (peak at 13)
γ_S	Discharge rate of uncolonized patients (/day)	0.2	$1/d_S$		
γ_C	Discharge rate of colonized patients (/day)	0.0154	$1/d_C$		
ν	Death rate of patients (/day)	0.0027	[10]	0.00135-0.0054	triangular (peak at 0.0027)
μ_0	Natural decontamination rate for HCW (i.e. not by hand hygiene) (/day)	24	[31,34]	12-48	triangular (peak at 24)
ψ	Prevalence of antibiotic therapy among admitted patients	0.56	[35,36]	0.2-0.9	triangular (peak at 0.56)
τ	Antibiotic initiation rate (/day)	0.1	assumed	0.05-0.2	triangular (peak at 0.1)
$d_{ATB,S}$	Antibiotic therapy duration for uncolonized patients (days)	8	[36]		
$d_{ATB,C}$	Antibiotic therapy duration	18	[36]		

	for colonized patients (days)				
θ_S	Antibiotic therapy discontinuation rate for uncolonized patients (/day)	0.125	$1/dATB_S$		
θ_C	Antibiotic therapy discontinuation rate for colonized patients (/day)	0.05556	$1/dATB_C$		
p_p	Probability of hand hygiene before contact with patient (uncolonized or colonized unidentified)	0.55	[37]		
p_h	Probability of hand hygiene after contact with patient(uncolonized or colonized unidentified)	0.6	[37]		
p_{pIs}	Probability of hand hygiene before contact with isolated patient	0.8	assumed		
p_{hIs}	Probability of hand hygiene after contact with isolated patient	0.8	assumed		
φ	Prevalence of ESBL-PE carriage among admitted patients	0.15	[23]	0.07-0.3	triangular (peak at 0.15)

p_I	Probability of infection in colonized patient	0.164	[10]	0.08- 0.32	triangular (peak at 0.164)
d_I	Mean length of stay of infected patients (days)	13	[10]	6-29 [12]	triangular (peak at 13)
s_b	Sensitivity of the screening method (%)	95	[11]		
s_p	Specificity of the screening method (%)	100	assumed		

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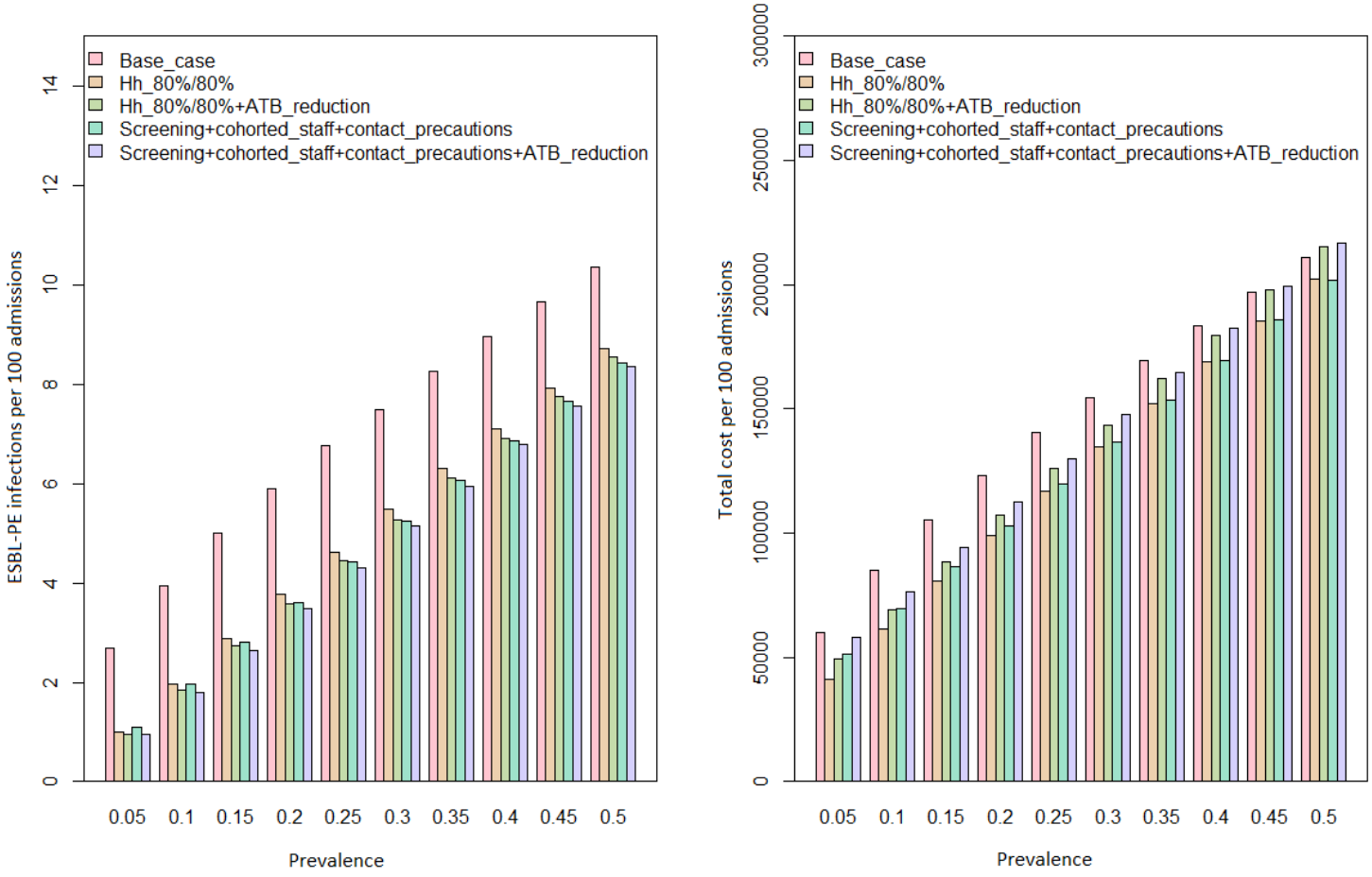
Supplementary material

Supplementary Text S2- Sensitivity analyses

1. Impact of prevalence on admission on health outcomes and costs

The prevalence of ESBL-PE carriage on ICU admission highly influenced health outcomes and costs (**Supplementary Figure S1**) as well as the ranking of the strategies (**Supplementary Table S1).** However. improvement of HH to 80%/80% (Strategy 2) remained the most cost saving strategy. if the prevalence on admission was from 5% to 50%. If 50% of patients carried ESBL-PE on ICU admission. Strategy 2 was dominated by screening + cohorting (Strategy 6).

Figure S1 Impact of prevalence on admission on the number of ESBL-PE infections and total cost of strategies for: (1) Base Case (reference strategy with no control intervention and hand hygiene compliance of 55%/60% before/after patient contact); (2) Hand hygiene improvement to 80%/80%; (6) Screening of all admissions and cohorting of identified carriers; (7) Hand hygiene improvement to 80%/80% and Antibiotic reduction; (10) Screening of all admissions. cohorting of identified carriers and Antibiotic reduction.



When the prevalence on admission was less than 15% the improvement of hand hygiene to 80%/80% (Strategy 2) was the most cost-saving strategy. The second strategy on the efficiency frontier was the combination of hand hygiene 80%/80% with antibiotic reduction (Strategy 7). When the prevalence was 15% the Strategy 10 (Screening + cohorting + ATB reduction) joined the efficiency frontier too. When the prevalence varied from 20% to 45%. Hand hygiene 80%/80% was always on the top of the ranking. followed by Screening + cohorting (Strategy 6) and Screening + cohorting + ATB reduction (Strategy 10). Finally, when 50% of patients carried ESBL-PE on ICU admission. hand hygiene was dominated by screening + cohorting (Strategy6).

Supplementary Table S1. Results of sensitivity analysis. Cost-effectiveness of strategies under **different levels of ESBL-PE carriage on admission**. The prevalence on admission varied from 0.05 to 0.5.

Strategy	Prevalence on admission	Total cost/ 100 admissions (€)	Infections/ 100 admissions	Incremental cost/100 admissions (ΔC) (€)	Incremental effect (ΔE) (infections avoided/100 admissions)	ICER (ΔC/ΔE) (€ / infection avoided)
2: Hh 80%/80%	0.05	41 225	1.01			
7: Hh 80%/80% + ATB reduction		49 639	0.94	8 414	0.07	120 200
6: Screening + cohorting		51 542	1.09			Dominated
10: Screening + cohorting + ATB reduction		58 218	0.94			Dominated by extended dominance
1: Base case		60 031	2.68			Dominated
2: Hh 80%/80%	0.15	80 556	2.89			
7: Hh 80%/80% + ATB reduction		88 498	2.73	7 942	0.16	49 638
10: Screening + cohorting + ATB reduction		94 313	2.63	5 815	0.09	64 611
6: Screening + cohorting		86 713	2.80			Dominated by extended dominance
1: Base case		105 344	4.99			Dominated

2: Hh 80%/80%	0.2	98 843	3.77			
6: Screening + cohorting		103 075	3.61	4 232	0.16	26 450
10: Screening + cohorting + ATB reduction		112 565	3.49	9 490	0.12	79 083
7: Hh 80%/80% + ATB reduction		107 275	3.59			Dominated by extended dominance
1: Base case		123 231	5.90			Dominated
6: Screening + cohorting	0.5	201 668	8.43			
10: Screening + cohorting + ATB reduction		216 470	8.36	14 802	0.07	211 457
2: Hh 80%/80%		202 288	8.72			Dominated
1: Base case		210 957	10.35			Dominated
7: Hh 80%/80% + ATB reduction		215 102	8.54			Dominated

2. Impact of **probability of infection** in patients colonized with ESBL-PE.

Results of sensitivity analysis for a lower and higher probability of infection in colonized ESBL-PE patients versus the basecase analysis are presented in **Supplementary Table S2 A and B.** Overall main results of our analysis were robust to variation in the probability of infection of colonized patients (8% or 30% vs. 16% in our central analysis).

Supplementary Table S2A Results of sensitivity analysis. Cost-effectiveness of strategies when **the probability of infection was set at 0.08**.

Strategy	Total cost/ 100 admissions (€)	Infections/ 100 admissions	Incremental cost/100 admissions (ΔC) (€)	Incremental effect (ΔE) (infections avoided/100 admissions)	ICER (ΔC/ΔE) (€ / infection avoided)
3: Hh 55%/80%	50 550	1.71			
2: Hh 80%/80%	52 428	1.41	1 878	0.304	6 178
7: Hh 80%/80% + ATB reduction	61 945	1.33	9 517	0.079	120 468
10: Screening + cohorting + ATB reduction	68 673	1.29	6 728	0.046	146 261
5: Screening + contact precautions	54 930	2.10			Dominated
1: Base case	56 792	2.43			Dominated
8: Hh 55%/80% + ATB reduction	58 173	1.53			Dominated by extended dominance
6: Screening + cohorting	59 424	1.37			Dominated by extended dominance
9: Screening + contact precautions + ATB reduction	59 706	1.74			Dominated
4: ATB reduction	60 360	1.99			Dominated

Supplementary Table S2B Results of sensitivity analysis. Cost-effectiveness of strategies when **the probability of infection was set at 0.30**.

Strategy	Total cost/ 100 admissions (€)	Infections/ 100 admissions	Incremental cost/100 admissions (ΔC) (€)	Incremental effect (ΔE) (infections avoided/100 admissions)	ICER (ΔC/ΔE) (€ / infection avoided)
2: Hh 80%/80%	126 096	5.29			
7: Hh 80%/80% + ATB reduction	131 487	4.99	5 391	0.300	17 970
10: Screening + cohorting + ATB reduction	135 825	4.82	4 338	0.170	25 518
6: Screening + cohorting	130 896	5.13			Dominated by extended dominance
8: Hh 55%/80% + ATB reduction	137 917	5.72			Dominated
3: Hh 55%/80%	140 124	6.43			Dominated
9: Screening + contact precautions + ATB reduction	150 335	6.50			Dominated
5: Screening + contact precautions	164 370	7.85			Dominated
4: ATB reduction	164 513	7.48			Dominated
1: Base case	183 951	9.13			Dominated

3. Impact of **lower compliance with HH** than in the base case scenario.

If the baseline compliance with HH was lower than in our core analysis. e.g. 20% before and 40% after patient contact. HH improvement. e.g. to 50%/60% was confirmed to be cost-saving. Screening + cohorting was the second strategy with an ICER of €3 236/infection avoided vs. HH improvement (**Supplementary Table S3A**).

Supplementary Table S3A Results of sensitivity analysis. Cost-effectiveness of strategies when the baseline compliance with **Hand hygiene was set to 20%/40% (instead of 55%/60%).**

Strategy	Total cost/ 100 admissions (€)	Infections/ 100 admissions	Incremental cost/100 admissions (ΔC) (€)	Incremental effect (ΔE) (infections avoided/100 admissions)	ICER (ΔC/ΔE) (€ / infection avoided)
2: Hh 50%/60%	81 676	3.14			
6: Screening + cohorting	82 867	2.772	1 191	0.368	3 236
10: Screening + cohorting + ATB reduction	91 134	2.632	8 267	0.14	59 050
3: Hh 20%/60%	85 059	3.758			Dominated
8: Hh 20%/60% + ATB reduction	87 440	3.284			Dominated
7: Hh 50%/60% + ATB reduction	88 144	2.891			Dominated by extended dominance
9: Screening + contact precautions + ATB reduction	93 552	3.741			Dominated
4: ATB reduction	95 195	4.075			Dominated
5: Screening + contact precautions	97 350	4.571			Dominated
1: Base case Hh 20% 40%	100 905	5.02			Dominated

If the baseline compliance with HH was 40% before and 50% after patient contact. HH improvement. e.g. to 60%/70% was confirmed to be cost-saving. Screening + cohorting was the second strategy with an ICER of €546/infection avoided vs. HH improvement (**Supplementary Table S3B**).

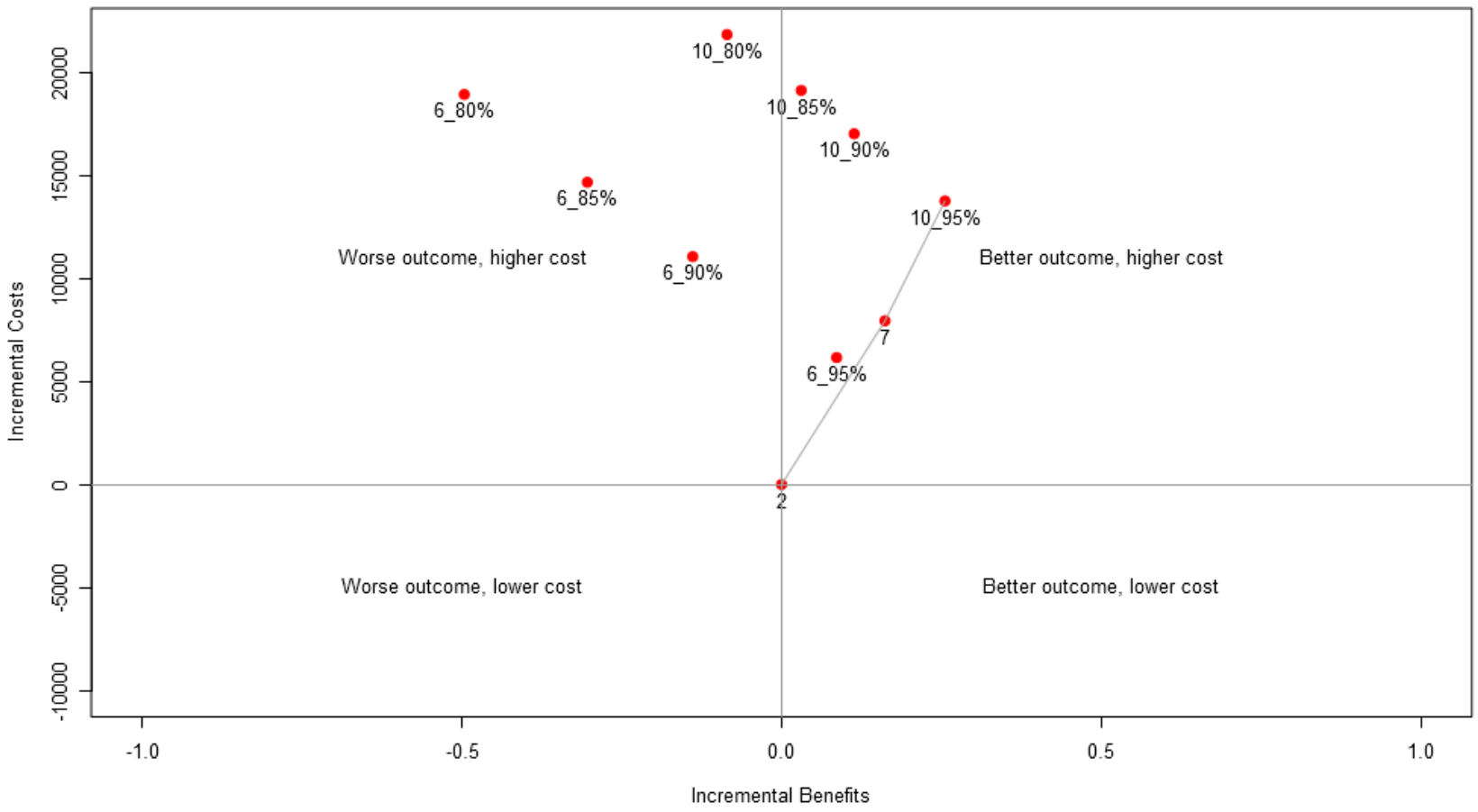
Supplementary Table S3B Results of sensitivity analysis. Cost-effectiveness of strategies when the baseline compliance with **Hand hygiene was set to 40%/50% (instead of 55%/60%).**

Strategy	Total cost/ 100 admissions (€)	Infections/ 100 admissions	Incremental cost/100 admissions (ΔC) (€)	Incremental effect (ΔE) (infections avoided/100 admissions)	ICER (ΔC/ΔE) (€ / infection avoided)
2: Hh 60%/70%	84 331	3.191			
6: Screening + cohorted staff + contact precautions	84 561	2.77	230	0.421	546
10: Screening + cohorted staff + contact precautions + ATB reduction	92 803	2.629	8 242	0.141	58 454
3: Hh 40%/70%	86 359	3.698	0	0	Dominated
8: Hh 40%/70% + ATB reduction	89 451	3.26	0	0	Dominated
7: Hh 60%/70% + ATB reduction	91 171	2.96	0	0	Dominated by extended dominance
9: Screening + contact precautions + ATB reduction	96 676	3.78	0	0	Dominated
4: ATB reduction	98 264	4.099	0	0	Dominated
5: Screening + contact precautions	98 308	4.495	0	0	Dominated
1: Base case Hh 40%/50%	102 292	4.949	0	0	Dominated

4. Impact of lower **sensitivity to detect ESBL-PE carriage** in screening strategies.

If the sensitivity to detect ESBL-PE on ICU admission was lower than in our core analysis and varied from 80% to 95%. HH 80%/80% (Strategy 2) and HH 80%/80% and antibiotic reduction (Strategy 7) always dominated the screening strategies (Strategy 6 and 10) (**Supplementary Figure S2**).

Figure S2 Cost-effectiveness plane showing the incremental health benefits (infections avoided) and costs of screening and cohorting strategies relative to the Strategy 2. The sensitivity of detection of ESBL carriers at ICU admission in screening and isolation strategies varied from 80% to 95%.
Strategies are: (2) Hand hygiene improvement to 80%/80%; (6) Screening of all admissions and cohorting of identified carriers; (7) Hand hygiene improvement to 80%/80% and Antibiotic reduction; (10) Screening of all admissions. cohorting of identified carriers and Antibiotic reduction.



Supplementary Table S4 Impact of a lower, 30% reduction in antibiotic prescribing.

Strategy	Total cost/ 100 admissions (€)	Infections/ 100 admissions	Incremental cost/100 admissions (ΔC) (€)	Incremental effect (ΔE) (infections avoided/100 admissions)	ICER (ΔC/ΔE) (€ / infection avoided)
2: Hh 80%/80%	80 556	2.890	0		
7: Hh 80%/80% + ATB reduction 30%	89 254	2.761	8 698	0.129	67 426
10: Screening + cohorted staff + contact precautions + ATB reduction 30%	95 343	2.680	6 089	0.081	75 173
3: Hh 55%/80%	84 751	3.514	0		
6: Screening + cohorted staff + contact precautions	86 713	2.804	0		
8: Hh 55%/80% + ATB reduction 30%	91 059	3.242	0		
5: Screening + contact precautions	96 716	4.294	0		
9: Screening + contact precautions + ATB reduction 30%	97 620	3.720	0		
4: ATB reduction 30%	104 271	4.285	0		
1: Base case	105 344	4.989	0		

Supplementary Table S5A Impact of **infection control nurse's time working on the hand hygiene program and the level of hand hygiene achieved** on model predictions compared to the Base case strategy. The cost-effective ratio (CER) was calculated when the hand hygiene strategy was more expensive but more effective that the base case.

Level of hand hygiene before contact with patient (%)	Level of hand hygiene after contact with patient (%)	Mean increase in hand hygiene from baseline (%)	Number of infections /100 admissions	Total cost /100 admissions (€)	CER (vs base case)
Base case					
55	60	-	4.99	105 344	-
ICN working on Hh program at 1/4 time					
55	60	0.0	4.99	112 783	Hh strategy dominated by the Base case
60	60	2.5	4.65	106 497	3 433
55	65	2.5	4.64	106 366	2 965
60	65	**5.0**	4.29	99 722	Base case dominated by the Hh strategy
⋮	⋮	⋮	⋮	⋮	Base case dominated by the Hh strategy
80	80	22.5	2.89	74 103	Base case dominated by the Hh strategy
ICN working on Hh strategy at 1/2 time					
55	60	0.0	4.99	120 222	Hh strategy dominated by the Base case
60	60	2.5	4.65	113 789	25 146
55	65	2.5	4.64	113 675	24 160
60	65	5.0	4.29	106 861	2 182
65	65	**7.5**	4.02	101 484	Base case dominated by the Hh strategy
⋮	⋮	⋮	⋮	⋮	Base case dominated by the Hh strategy
80	80	22.5	2.89	80 556	Base case dominated by the Hh strategy
ICN working on Hh strategy at full time					
55	60	0.0	4.99	135 100	Hh strategy dominated by the Base case
60	60	2.5	4.65	128 375	68 573
55	65	2.5	4.64	128 292	66 551
60	65	5.0	4.29	121 137	22 712
65	65	7.5	4.02	115 442	10 397

55	70	5.0	4.22	119 423	18 278
60	70	7.5	3.98	114 488	9 029
65	70	10.0	3.75	110 092	3 823
70	70	12.5	3.53	105 942	411
55	75	7.5	3.85	111 932	5 806
60	75	10.0	3.68	108 574	2 468
65	75	12.5	3.51	105 357	9
70	75	**15.0**	3.32	101 754	Base case dominated by the Hh strategy
⋮	⋮	⋮	⋮	⋮	Base case dominated by the Hh strategy
80	80	22.5	2.89	93 462	Base case dominated by the Hh strategy

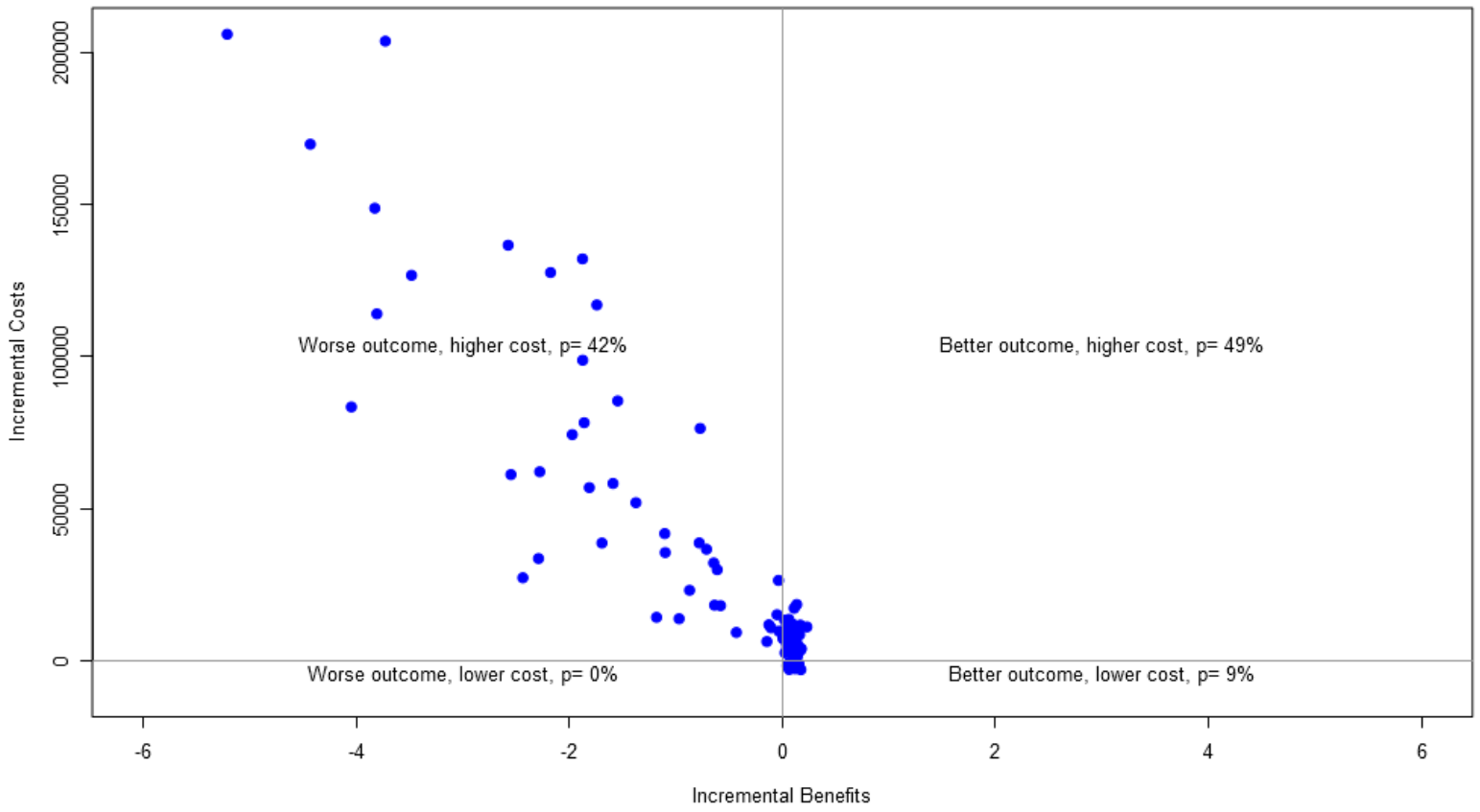
Supplementary Table S5B Impact of **infection control nurse's time working on the hand hygiene strategy and the level of hand hygiene achieved** on model predictions compared to the Screenig and cohorting strategy. The cost-effective ratio (CER) was calculated when the screening and cohorting strategy was more expensive but more effective that the hand hygiene.

Level of hand hygiene before contact with patient (%)	Level of hand hygiene after contact with patient (%)	Mean increase in hand hygiene from baseline (%)	Number of infections/100 admissions	Total cost/100 admissions (€)	CER (vs Hand hygiene strategy)
Screening and cohorting					
55 (with non cohorted patients)	60 (with non cohorted patients)		2.80	86 713	
ICN working on Hh strategy at 1/4 time					
55	60	0.0	4.99	112 783	Hh strategy dominated by Screening and cohorting
⋮	⋮	⋮	⋮	⋮	Hh strategy dominated by Screening and cohorting
70	70	12.5	3.53	85 621	1 496
55	75	7.5	3.85	91 212	Hh strategy dominated by Screening and cohorting
60	75	10.0	3.68	88 104	Hh strategy dominated by Screening and cohorting
65	75	12.5	3.51	85 102	2 283
70	75	15.0	3.32	81 748	9 554
75	75	17.5	3.15	78 568	23 561
55	80	10.0	3.51	84 751	2 763
60	80	12.5	3.38	82 408	7 507
65	80	15.0	3.24	79 993	15 442
70	80	17.5	3.12	77 946	28 012
75	80	20.0	2.99	75 742	58 203
80	80	22.5	2.89	74 103	146 278
ICN working on Hh strategy at 1/2 time					
55	60	0.0	4.99	120 222	Hh strategy dominated by Screening and cohorting
⋮	⋮	⋮	⋮	⋮	Hh strategy dominated by Screening and cohorting
75	75	17.5	3.15	85 136	4 561 €

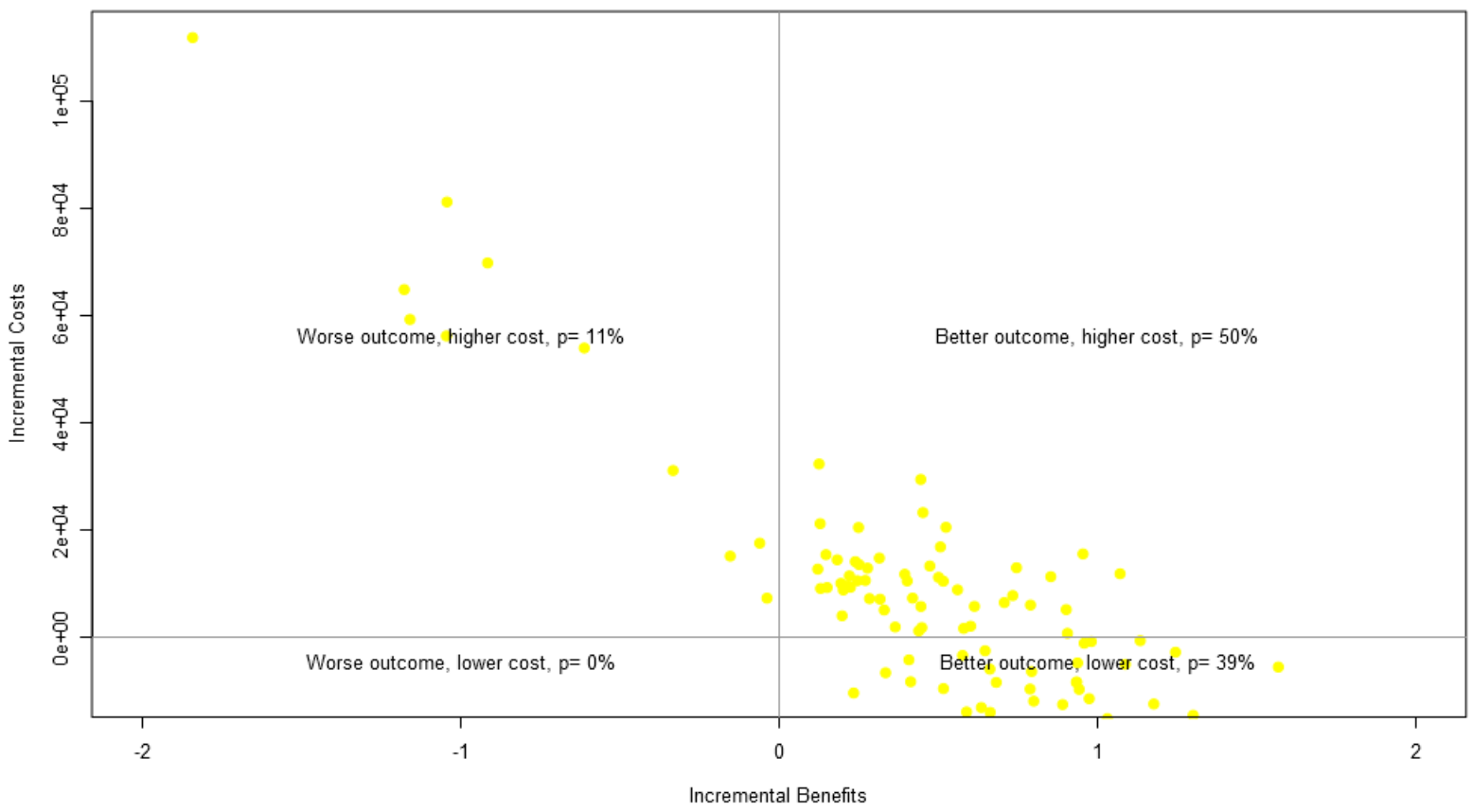
55	80	10.0	3.51	91 498	Hh strategy dominated by Screening and cohorting
60	80	12.5	3.38	89 094	Hh strategy dominated by Screening and cohorting
65	80	15.0	3.24	86 608	Hh strategy dominated by Screening and cohorting
70	80	17.5	3.12	84 516	7 023 €
75	80	20.0	2.99	82 227	23 801 €
80	80	22.5	2.89	80 556	71 424 €
ICN working on Hh strategy at full time					
55	60	0.0	4.99	135 100	Hh strategy dominated by Screening and cohorting
⋮	⋮	⋮	⋮	⋮	Hh strategy dominated by Screening and cohorting
80	80	22.5	2.89	93 462	Hh strategy dominated by Screening and cohorting

Supplementary Figure S3 Results of probabilistic sensitivity analysis. Cost-effectiveness plane shows the incremental health benefits (infections avoided) and costs for Screening and cohorting (Strategy 6). relative to horizontal strategies: A) Hand hygiene improvement to 80%/80% (Strategy 2); B) Hand hygiene improvement to 55%/80% (Strategy3); C) Antibiotic reduction (Strategy 4). The frequency that the Strategy 6 was in one of four quadrant of CE plane is represented by "**p**".

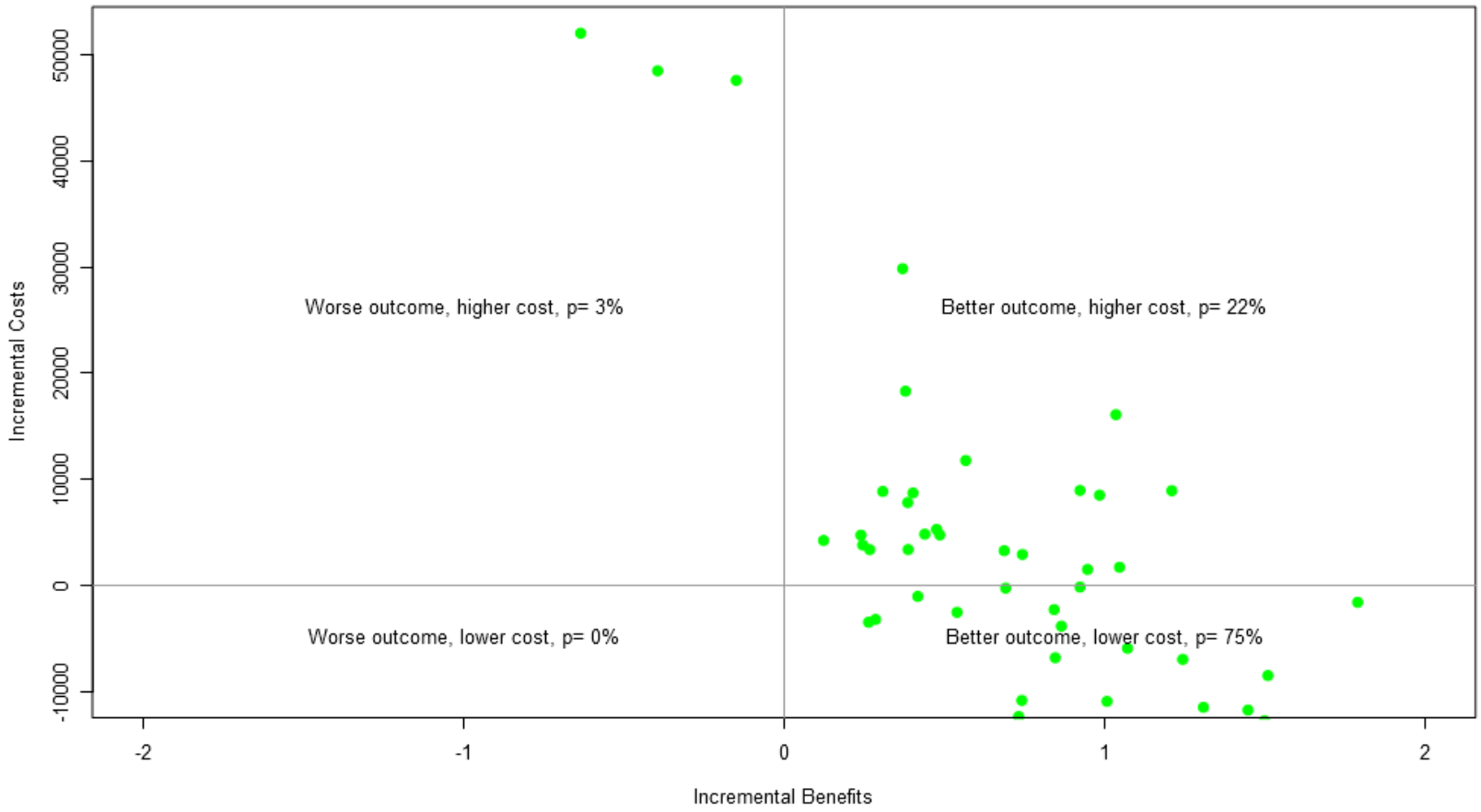
A)



B)

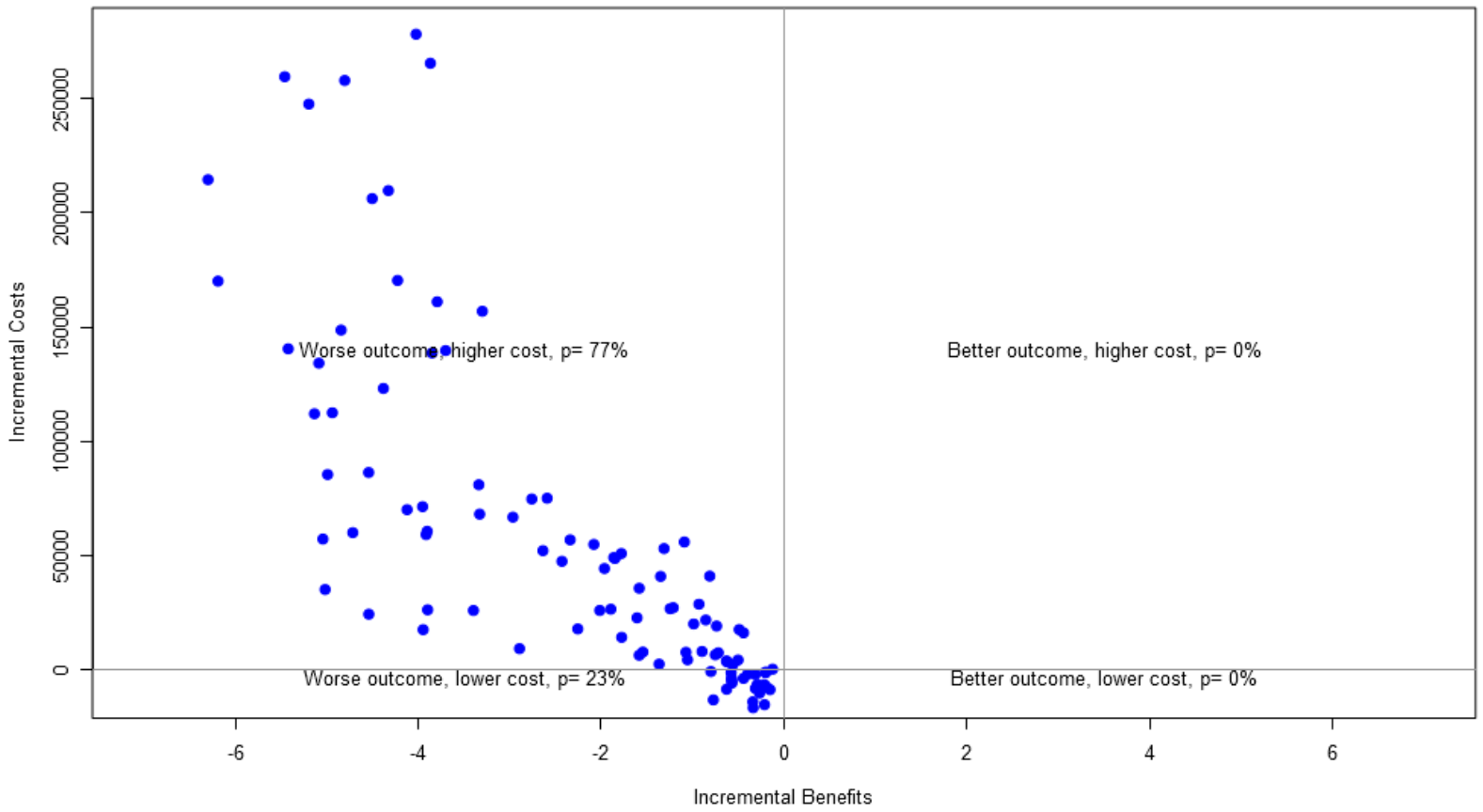

Incremental Costs
0e+00
2e+04
4e+04
6e+04
8e+04
1e+05
Worse outcome, higher cost, p= 11%
Better outcome, higher cost, p= 50%
Worse outcome, lower cost, p= 0%
Better outcome, lower cost, p= 39%
-2
-1
0
1
2
Incremental Benefits

C)

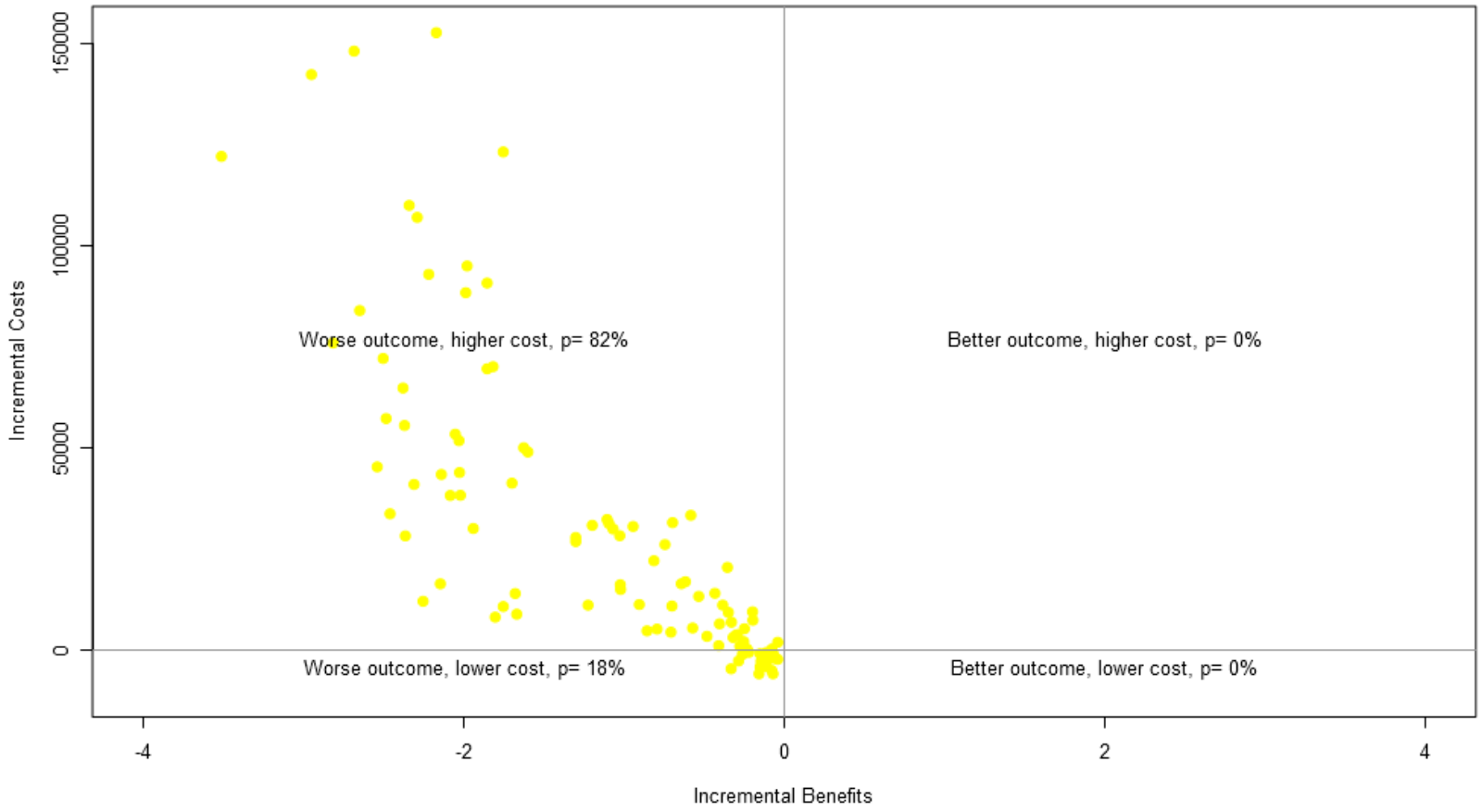

Worse outcome, higher cost, p= 3%
Better outcome, higher cost, p= 22%
Worse outcome, lower cost, p= 0%
Better outcome, lower cost, p= 75%
Incremental Costs
Incremental Benefits
50000
40000
30000
20000
10000
0
-10000
-2
-1
0
1
2

Supplementary Figure S4 Results of probabilistic sensitivity analysis. Cost-effectiveness plane shows the incremental health benefits (infections avoided) and costs for Screening and contact precautions (Strategy 5). relative to horizontal strategies: A) Hand hygiene improvement to 80%/80% (Strategy 2); B) Hand hygiene improvement to 55%/80% (Strategy3); C) Antibiotic reduction (Strategy 4). The frequency that the Strategy 6 was in one of four quadrant of CE plane is represented by "**p**".

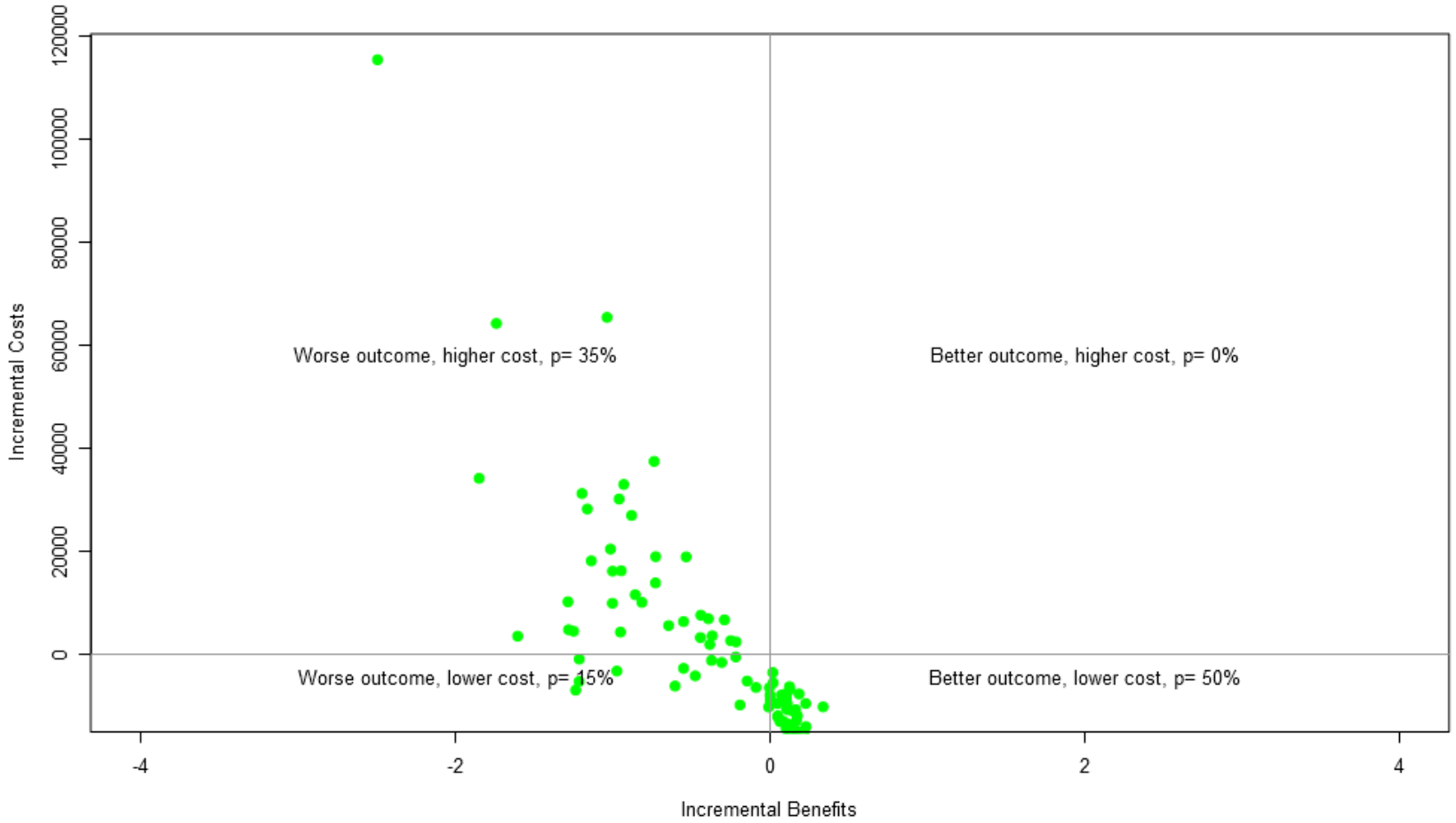
A)



B)


Incremental Costs
150000
100000
50000
0
Worse outcome, higher cost, p= 82%
Better outcome, higher cost, p= 0%
Worse outcome, lower cost, p= 18%
Better outcome, lower cost, p= 0%
-4
-2
0
2
4
Incremental Benefits

C)


Incremental Costs
120000
100000
80000
60000
40000
20000
0
Worse outcome, higher cost, p= 35%
Better outcome, higher cost, p= 0%
Worse outcome, lower cost, p= 15%
Better outcome, lower cost, p= 50%
-4
-2
0
2
4
Incremental Benefits

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Page 4-5
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 5 and Supplementary Text S1
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 7- "Costs" section
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 6"Inf.control strategies" section
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 5- "The model" section.
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Not applicabe-one-year time horizon
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 5-"The model" section and Supp.Text S1
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	---
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Supp.Text S1
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	---
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	---
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 7- "Costs" section and Supplementary Text S1-page 7
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 7- "Costs" section, Table 1 and Suppl.Text S1, p.5
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 5- The model section, Figure 1 and Suppl.Text S1
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Suppl.Text S1
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Page 8- "Sensitivity analysis" section and Suppl.Text S1- Table 1
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 1 and Suppl.Text S1- Table 1
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 2
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	---

		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Page 11 and Suppl.Text S2
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	---
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Pages 12-17
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 18
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 18

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

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