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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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017402
Article Type:	Research
Date Submitted by the Author:	21-Apr-2017
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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Health economics, Public health, Intensive care, Health policy
Keywords:	Infection control < INFECTIOUS DISEASES, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Cost-effectiveness

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Manuscripts

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3 1 Intended category: Research
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6 2 **Universal or targeted approach to prevent the transmission of**
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9 3 **extended-spectrum beta-lactamase–producing *Enterobacteriaceae* in**
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12 4 **intensive care units? A cost-effectiveness analysis**
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22 ABSTRACT

23 Objective

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

29 Design

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

32 Patients and setting

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

34 Interventions

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

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

41 Results

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

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3 44 outcomes and reduced costs associated with ESBL-PE infections. The overall costs (cost of
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5 45 intervention and infections) were the lowest for HH compliance improvement to 80%/80%.
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8 46 Two strategies required higher investments than the HH programme, but also improved health
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10 47 benefits; 1) HH improvement to 80%/80% combined with antibiotic stewardship and 2) screening
11
12 48 and cohorting strategy combined with antibiotic stewardship.
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15 **Conclusions**

16
17 50 Improved compliance with HH was the most cost-saving strategy to prevent the transmission of
18
19 51 ESBL-PE. Adding antibiotic restriction to HH or screening and cohorting slightly improved their
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21 52 effectiveness and may be worthy of consideration by decision-makers'.
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26 54 **Strength and limitations of this study**

- 27 55 ▪ We used a dynamic transmission model to take into account that the risk of colonization
28
29 56 in the ICU depends on the number of ESBL-PE carriers and could change over time.
- 30
31 57 ▪ Parameters used in the model were derived from recent multicentre studies.
- 32
33 58 ▪ We undertook sensitivity analyses to show the impact of uncertainty in parameter
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35 59 estimation and the impact of model assumptions on the conclusions.
- 36
37 60 ▪ Direct HCW-to-HCW transmissions as well as environmental contamination were not
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39 61 included in the model.
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48 63 **INTRODUCTION**

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50 64 The incidence of infection and colonization with extended-spectrum beta-lactamase-producing
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52 65 *Enterobacteriaceae* (ESBL-PE) has increased worldwide. In Europe, in 2014, the percentage of
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54 66 *Escherichia coli* and *Klebsiella pneumoniae* resistant to 3rd generation cephalosporins in invasive
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3 67 isolates was 12% and 23%, respectively¹. A similar trend was observed in the United States,
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5 68 although with large variations between states².

6 69 In hospital settings, ESBL-PE acquisition is mainly due to indirect transmission between patients
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8 70 with the hands of healthcare workers (HCWs) as vectors. Increased prevalence of colonization
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10 71 augments the risk of acquiring ESBL-PE infection³. Such infections represent a serious socio-
11
12 72 economic burden and are associated with a raised mortality, a longer hospitalization, and
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14 73 additional costs⁴.

15 74 Many interventions have been proposed to limit the transmission of multidrug-resistant
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17 75 organisms (MDROs) in hospitals. They can be classified as either 1) a 'universal' or 'horizontal'
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19 76 approach, applied to all patients e.g. improvement of hand hygiene (HH) among HCWs or
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21 77 antibiotic stewardship or 2) a 'targeted' or 'vertical' approach, e.g. screening and isolation of
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23 78 asymptomatic carriers in addition to infected patients, with the aim of identifying carriers and
24
25 79 implementing measures to prevent the transmission from carriers to other patients⁵.

26
27 80 There is general agreement that HH reduces the transmission of MDROs, especially MRSA³.
28
29 81 However, few studies have evaluated the impact of HH on the prevention of ESBL-PE
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31 82 dissemination and, so far, most of those studies have not provided evidence of HH benefit⁶, with
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33 83 the exception of one recently published study⁷. The effectiveness of targeted measures in
34
35 84 controlling the spread of MDROs, and especially ESBL-PE, remains controversial. This approach
36
37 85 is mainly recommended in high-risk units, e.g. intensive care units (ICUs)⁸.

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39 86 The implementation of interventions with demonstrated effectiveness in reducing ESBL-PE
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41 87 infections is associated with costs that are generally supported by hospitals. However, when
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43 88 evaluating implementation of an infection prevention programme, one should also take into
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45 89 account savings associated with these interventions, but this has been largely ignored in previous
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47 90 studies.

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3 91 In this study, we used a mathematical model to evaluate the effectiveness and cost-effectiveness
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5 92 of universal and targeted control strategies for the prevention of ESBL-PE transmission in an
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8 93 ICU in a high-income country.
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13 95 **METHODS**

16 96 The model

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18 97 We extended a previously described stochastic, compartmental and dynamic model of ESBL-PE
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21 98 transmission⁹ to assess the economic impact of infection control strategies implemented in a
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23 99 hypothetical, ICU setting over a one-year time horizon.

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25
26 100 The model simulated the spread of ESBL-PE among patients through contacts with HCWs in an
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28 101 ICU, taking into account hospital admissions and discharges of patients, antibiotic exposure, and
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30 102 control interventions (**Figure 1**).

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33 103 The **Supplementary Text S1** provides details of the model and its assumptions.

35 104 **Model simulations and outcomes**

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37 105 Simulations of the model were performed using Gillespie's method and programmed in C++
38
39 106 language. The outcomes (cases of ESBL-PE transmission, infections, cost of intervention, cost of
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41 107 infections) were calculated after a period of 1 year and averaged over the 1,000 Monte Carlo
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43 108 simulations. Cost-effectiveness analysis and graphics were performed in R¹⁰.
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50 110 Base case scenario

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52 111 In the base case scenario, with no control intervention, we considered that compliance with hand
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54 112 hygiene before/after contact with a patient was 55%/60% respectively¹¹ and 56% of patients
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56 113 received antibiotics at ICU admission¹².
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3 114 Infection control strategies
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6 115 **Universal approaches**
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8 116 We evaluated control strategies implemented in all patients (independently of their colonization
9 status), that comprised one or both of the following interventions: 1) improved compliance with
10 117 HH, and 2) antibiotic stewardship. For HH, we considered different levels of compliance. First,
11 118 compliance with HH before/after contact with a patient was improved from 55%/60% at baseline
12 119 to 55%/80% or 80%/80%. Second, antibiotic stewardship resulted in halving the proportion of
13 120 patients on antibiotics at ICU admission and in reducing by 25% the duration of antibiotic
14 121 treatment.
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27 124 **Targeted approaches**
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29 125 We evaluated 2 strategies that combined screening of patients for ESBL-PE at ICU admission
30 126 and one of the following interventions implemented: 1) contact precautions (improved
31 127 compliance with HH before/after contact with carriers to 80%/80%); or 2) cohorting of ESBL-PE
32 128 carriers with dedicated HCWs. HH compliance for other patients was maintained at baseline
33 129 level.
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44 131 **Mixed approaches**
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46 132 We evaluated two strategies combining the targeted approaches with antibiotic stewardship.
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51 134 Model parameters
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54 135 Model parameters and their values are presented in **Supplementary Table 1**.
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3 136 Based on recent French data, we assumed that 15% of patients were colonized with ESBL-PE at
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5 137 ICU admission¹³.
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8 138 Infection status was not included in the model, so we estimated the number of infections by
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10 139 multiplying the cumulated number of colonized patients after one year by the probability of
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12 140 developing an infection during an ICU stay, set at 16.4%¹⁴. Even though this value came from a
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14
15 141 recent large multicentre study, we also considered the impact of lower (8%) and higher (30%)
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17 142 probability of infection in alternative analyses.
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21 22 144 Costs

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24 145 The analysis was performed from a public hospital perspective. Cost estimates are based on
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26 146 values reported in Euros from 2015 (1 € = US \$0.94). We considered the following costs in the
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28 147 model: 1) costs of intervention (material resources and personnel costs), 2) costs of ESBL-PE
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30 148 infections. The cost of an ESBL-PE infection was estimated using the ESBL-PE-attributable LOS
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32 149 and the cost of a hospital bed-day for infected patients^{13,15,16}. See **Table 1** for cost parameters and
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35 150 **Supplementary Text 1** for more details.
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39 40 41 152 Cost-effectiveness evaluation

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43 153 To conduct the cost-effectiveness¹⁷, we estimated the costs associated with each intervention
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45 154 implemented, and the health benefits were related to the number of avoided cases of ESBL-PE
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47 155 infections. First, we determined whether any strategy was dominated by another in terms of costs
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49 156 and health benefits. Second, we determined whether any strategy was dominated through
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51 157 principles of extended dominance (i.e. whether the incremental cost-effectiveness ratios
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53 158 [ICERs] decrease as the strategies increases in cost^{17,18}). Finally, for the non-dominated strategies,
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3 159 we calculated the incremental cost per case of infection avoided, which is the ratio of the
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5 160 difference in costs between two strategies to the difference in health benefits. This process
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8 161 produces an “efficient frontier” indicating more costly, but more effective strategies.
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12 13 Sensitivity analysis

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15 164 We performed supplementary analyses to assess the impact of parameter uncertainty on the
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18 165 model’s predictions. We first ran a univariate sensitivity analysis to evaluate the cost-
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20 166 effectiveness of strategies in settings with either low or high prevalence of patients colonized at
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22 167 admission (from 5% to 50%). We also considered the impact of a lower (8%) and a higher (30%)
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24 168 probability of infection in colonized patients. We then investigated the model assuming 1) a
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26 169 lower baseline compliance with HH and 2) a lower sensitivity of the screening method used to
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29 170 detect ESBL-PE carriers at ICU admission.
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34 172 We also performed an analysis to explore the uncertainty in human time required in an HH
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36 173 programme and its potential effects. In this analysis, we varied the time an infection control nurse
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38 174 works on the programme (quarter-time, half-time or full-time) simultaneously with the level of
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40 175 HH compliance achieved (from 55%/60% to 80%/80% before after contact).
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46 177 Finally, we performed a probabilistic sensitivity analysis to explore the effect of joint uncertainty
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48 178 across parameters on the cost-effectiveness of universal vs targeted strategies. We varied the
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50 179 following parameters concurrently: 1) number of HCW contacts with patients, 2) transmission
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52 180 parameters, 3) length of stay of ICU patients, 4) natural decontamination rate for HCW, 5)
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54 181 antibiotic initiation rate, 6) prevalence of ESBL-PE carriage among patients admitted to the ICU,
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3 182 7) death rate of patients, 8) probability of infection in colonized patients and 9) cost parameters.
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5 183 We randomly sampled values from each of the parameter distributions and calculated the mean
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8 184 costs and mean number of infections for each strategy (averaged over 1,000 simulations).
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12 13 186 **RESULTS**

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15 187 In the absence of control interventions (base case strategy), 15 new acquisitions (i.e.
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17 188 transmissions) and 5 new infections due to ESBL-PE occurred per 100 admissions. Compared to
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19 189 the base case (Strategy 1), all strategies reduced ESBL-PE acquisition and infections within one
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21 190 year (**Figure 2**).

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23
24 191 Among universal strategies, HH compliance improvement to 80%/80% (Strategy 2) was the most
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26 192 effective, resulting in a mean reduction to 2.9 acquired infections per 100 admissions. Among
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28 193 targeted strategies, screening of patients on admission and cohorting of carriers (Strategy 6) was
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30 194 the most effective strategy and resulted in a mean reduction to 2.8 infections per 100 admissions.
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32 195 Screening followed by contact precautions (Strategy 5) was the least effective in comparison with
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34 196 all other options. Adding antibiotic stewardship to HH or targeted strategies only slightly
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36 197 improved their effectiveness.
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43 44 199 **Cost-saving analysis**

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46 200 In **Table 2** we present the estimated costs and outcomes over one year for all strategies. The
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48 201 mean total cost associated with the base case strategy was estimated at €105 344/100 admissions,
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50 202 €94 792 of which was related to infections and €10 552 to interventions. Investments in infection
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52 203 prevention was always cost-saving because they avoided cases of ESBL-PE infections and thus
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54 204 costs associated with these infections. For instance, when HH compliance was improved to
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3 205 80%/80%, the mean cost of the strategy implementation increased to €25 639/100 admissions,
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5 206 but the costs related to infections decreased to €54 916, resulting in an overall monetary benefit
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8 207 of €24 788/100 admissions in comparison with the base case. This strategy was associated with
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10 208 the highest savings within all evaluated strategies.
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14 210 **Cost-effectiveness analysis**

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17 211 HH compliance improvement to 80%/80% was the least expensive strategy. However, two
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19 212 strategies required higher investments than the HH programme, but also improved health
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21 213 benefits. To help choose between strategies we calculated the incremental cost-effectiveness ratio
22
23 214 (**Figure 3**). The ICER of HH improvement to 80%/80% and antibiotic stewardship (Strategy 7)
24
25 215 vs. HH compliance improvement to 80%/80% was estimated at €49 025/avoided infection (**Table**
26
27 216 **2**). The ICER of screening, cohorting and antibiotic stewardship (Strategy 10) vs. HH
28
29 217 improvement to 80%/80% and antibiotic stewardship was estimated at €62 005/avoided infection.
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32 218 Other strategies were dominated (more expensive and less effective).
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37 220 **Sensitivity analysis**

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39 221 Findings from sensitivity analysis showed the robustness of predictions to: 1) the lower/higher
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41 222 prevalence of ESBL-PE carriage on ICU admission, 2) the lower/higher probability of infections
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43 223 in colonized patients, 3) the baseline compliance with HH lower than in our core analysis
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45 224 (20%/40%), and 4) the lower sensitivity to detect ESBL-PE carriers at ICU admission. Results of
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47 225 this analysis are shown in **Supplementary Text 2** (Figure S1 and Table S1, Table S2 A and B,
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49 226 Table S3, and Figure S2).
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3 228 In a second sensitivity analysis, we focused on human time and performance to improve HH
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5 229 compliance. If an infection control nurse was assumed to work quarter-time, half-time or full-
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7 230 time on the programme, the HH compliance had to increase by at least 5%, 7.5% or 15%,
8
9 231 respectively, to make the programme cost saving compared to the base case (**Supplementary**
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11 232 **Table S4A**).

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15 233 In comparison with the screening and cohorting strategy, the HH improvement was cost-saving
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17 234 when an infection control nurse worked quarter-time or half-time on the programme, and HH
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19 235 compliance increased by at least 12.5% or 17.5%, respectively. The screening and cohorting
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21 236 strategy dominated the HH improvement programme when an infection control nurse was
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23 237 working full-time on the programme (**Supplementary Table S4B**).

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29 239 Finally, the probabilistic sensitivity analysis showed that improvement of HH to 80%/80%
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31 240 (Strategy 2) was less expensive than the screening and cohorting intervention (Strategy 6) in 91%
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33 241 of simulations. Among them, in 42% of simulations, the HH strategy was less expensive but
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35 242 more effective (dominated the Strategy 6), and in 49% of runs the screening and cohorting was
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37 243 more effective and more expensive (**Supplementary Figure S3**). Screening and contact
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39 244 precautions (Strategy 5) were always less effective than improvement of HH to 80%/80%
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41 245 (Strategy 2) (**Supplementary Figure S4**).

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47 48 49 247 **DISCUSSION**

50
51 248 The impact of infection control strategies for preventing ESBL-PE transmission is controversial
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53 249 because clinical studies cannot account for the multiple confounding factors, notably both
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55 250 infection control measures and antibiotic stewardship. Despite several recent high-level
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3 251 interventional studies (Climo et al.¹⁹; Derde et al.⁶; Huang et al.²⁰), the most effective and cost-
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5 252 effective interventions for controlling MDROs are still debated. Since the spread of ESBL-PE
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8 253 between patients is a dynamic and complex process, modelling can help for understanding the
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10 254 transmission mechanisms and deciding which intervention are to be preferred (Doan et al.²¹;
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12 255 Grundmann et al.²²).

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15 256 Our model estimated the annual burden of ESBL-PE infections in a French ICU at €94 792 per
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17 257 100 admissions in the base case strategy. Several prior studies have reported the cost of infections
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19 258 due to multidrug resistant organisms in the ICU²³⁻²⁶. However, even though all authors
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21 259 underlined the high costs of infections, comparison between studies remains difficult. Estimated
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23 260 costs varied according to the country, but also to the population studied, e.g. patients with site-
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25 261 specific or microorganism-specific infections. Moreover, the methods used to estimate the costs
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29 262 were not similar in all publications.

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33 263 Implementation of infection control programmes may reduce the high cost of healthcare-
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35 264 associated infections. However, when evaluating the cost-effectiveness and benefits of such
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37 265 programmes, it is crucial to consider their cost.

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40 266 In recent years, mathematical models have increasingly been used to study the cost-effectiveness
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42 267 of control strategies. For example, Robotham et al.²⁷ compared a wide range of strategies to
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44 268 control MRSA transmission in ICUs and found that universal decolonization was the most cost-
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46 269 effective option. In another study, Gidengil et al.²⁸ compared hospital strategies to prevent MRSA
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48 270 transmission and infections in an ICU. They confirmed that universal decolonization was the
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51 271 most cost-saving strategy.
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3 272 Our study is the first to compare the effectiveness and the costs of universal and targeted control
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5 273 strategies in the context of the spread of ESBL-PE in ICUs. Our model predicted that improving
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8 274 HH to 80%/80% in contacts with all patients would prevent 83% of ESBL-PE acquisitions and
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10 275 avoid at least two out of five infections per 100 admissions. This strategy represented the most
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12 276 cost-saving, with a monetary benefit of €24 788 per 100 admissions.

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15 277 The association between HH and reduction of MDROs infections has long been known and HH
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17 278 has been accepted as a crucial component of infection prevention. HH has in addition the benefit
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19 279 of being effective for reducing transmission of many resistant or susceptible bacteria. A recent
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21 280 publication reported that a programme designed to control MRSA by implementing universal
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23 281 components in addition to screening and contact precautions for MRSA carriers also effectively
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25 282 reduced the incidence of resistant gram-negative bacteria, the most likely being ESBL-PE⁷. Thus,
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27 283 the overall economic benefit of an HH programme for the hospital might be greater than reported
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29 284 in our study.

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32 285 Despite the confirmed effectiveness of HH and national and international recommendations,
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34 286 compliance with HH remains low and is often lower than values used in our base case
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36 287 analysis^{29,30}. However, we showed in a sensitivity analysis that improving HH remained the most
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38 288 cost-saving strategy even in a low baseline compliance scenario.

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43 290 Different strategies have been suggested to improve HH in hospitals³¹, but the evidence-based
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45 291 approach is still lacking. Recently, a revue³² concluded that a multimodal strategy proposed by
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47 292 the WHO and consisting of five components: 1) system change, 2) training and education, 3)
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49 293 observation and feedback, 4) reminders in the hospital, and 5) a hospital safety climate, was
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51 294 effective at increasing HH among HCWs. Moreover, the authors underlined that additional

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3 295 measures (e.g. reward incentives for reaching a certain level of compliance) could lead to further
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6 296 improvements. In our study, we assumed that a key component of an HH programme was a
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8 297 dedicated staff working on the programme (i.e. HH education, observation and feedback). We
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10 298 hypothesized, for example, that to improve HH compliance an infection control nurse working
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12 299 half-time would be sufficient. However, to explore the uncertainty of the required time dedicated
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14 300 to the HH programme and its expected effects, we performed a sensitivity analysis.
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20 302 Screening strategies have been used to prevent transmission of MDROs, however their
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22 303 effectiveness and cost-effectiveness have been largely debated. In this study, we showed, that in
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24 304 endemic settings, screening and cohorting strategy had comparable efficacy as HH but was more
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26 305 expensive and dominated by other control options. We can hypothesize that in the case of highly
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28 306 resistant bacteria (e.g. Carbapenem-resistant *Enterobacteriaceae*) where there is a highest clinical
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30 307 impact on the outcomes of infected patients, given the lack of therapeutic options, a rapid
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32 308 identification and cohorting of carriers may be more beneficial from the hospital but also societal
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34 309 perspective.
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39 310 While antibiotic use is the major driver for the selection of antibiotic-resistant bacteria, there is
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41 311 no clear evidence of the effectiveness of antimicrobial restriction policies on resistance³³. We
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43 312 assumed in the model that a reduction in antibiotic use acted in 2 ways: it decreased the
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45 313 colonization probability of uncolonized patients and the probability of transmission from
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47 314 colonized patients to HCWs. However, we found that reducing antibiotic use was less effective
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49 315 than HH or a screening and cohorting strategy. Under the hypotheses used in our model, we also
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51 316 demonstrated in a previous study through sensitivity analyses that antibiotic parameters did not
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53 317 significantly influence the effectiveness of interventions⁹.
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3 318 However, adding antibiotic stewardship to an HH strategy slightly improved its effectiveness and
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5 319 may be worthy of consideration if the decision-makers are willing to pay at least €49 025 per
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8 320 infection avoided (we calculated that it would be equivalent to €5 562 per life-year gained
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10 321 (LYG)). Combining antibiotic stewardship with screening and cohorting was even more effective
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12 322 than combining HH and antibiotic stewardship, but with an additional cost of €62 005 per
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14 323 infection avoided (or €7 030/LYG).

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18 324 Our study has several strengths. Firstly, we used a dynamic model to represent interactions
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20 325 between patients and HCWs and to take into account that the risk of colonization in the ICU
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22 326 depends on the number of ESBL carriers and could change over time. Moreover, our model
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24 327 incorporated the key elements of ESBL-PE transmission, such as the impact of prevalence at
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26 328 admission or antibiotic treatment. Secondly, we used input parameters derived from recent
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28 329 multicentre studies. Thirdly, we estimated the cost of HCW according to the time they spend
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30 330 working on the programme based on the best evidence from the literature and expert opinion.
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32 331 Finally, we assessed the impact of uncertainty in parameter estimation and the impact of model
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34 332 assumptions on the model's predictions by performing multiple sensitivity analyses.

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38 333 Our study also has several limitations. Firstly, ICU parameters and costs were based mostly on
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40 334 French data, and ESBL-PE infections, prevalence, compliance with control measures and costs
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42 335 may be different in other countries. Secondly, we modelled an ICU as a single-room unit where
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44 336 transmission among patients results via contacts with HCWs. In the absence of detailed
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46 337 information on transmission of ESBL-PE in hospital wards, we ignored direct HCW-to-HCW
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48 338 transmissions as well as environmental contamination. Finally, ESBL-PE acquisition in the ICU
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50 339 can lead to transmission from an ICU-acquired case and infection in downstream units, thus
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52 340 increasing costs of hospitalization. Our cost evaluation was therefore conservative, since
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3 341 transmission and infection after ICU discharge were not added to the global costs of infections. A
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5 342 ward-based model, including other hospital units, should be tested.
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10 344 **CONCLUSION**

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13 345 Our study suggests that a universal approach with improved compliance with HH was the most
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15 346 cost-saving strategy to prevent the transmission of ESBL-PE in an ICU setting. Screening and
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17 347 cohorting of carriers had comparable effectiveness to HH improvement, but was more expensive.
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19 348 Adding antibiotic restriction to the HH or the screening and cohorting strategies slightly
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21 349 improved their effectiveness and may be worthy of consideration by decision-makers.
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27 351 **ACKNOWLEDGMENTS**

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30 352 We thank Dr. Laurence Armand for useful discussion on our study.
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35 354 **FOOTNOTES**

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37
38 355 **Contributors:** YY, JCL, CP and LKS designed the study. YY, JCL, PYB, AA, CP and LKS
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40 356 contributed to the development of the model. CP, AP, GB, ER and LKS collected the data. CP
41
42 357 and LKS wrote the code. LKS conducted computer simulations and result analysis. LKS, JCL
43
44 358 and YY drafted the manuscript. All authors read and critically revised the manuscript.

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46
47 359 **Funding:** This work was supported by the French government (PREPS program [grant number
48
49 360 13-0693]) and by the National Institute for Health and Medical Research (INSERM).
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52 361 **Competing interests:** None declared.
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55 362 **Data sharing statement:** Details of the computer code for the model are available from the
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57 363 corresponding author.
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3 477 **FIGURE LEGENDS**

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5 478 **Figure 1.** Model of transmission of ESBL-PE between patients through contacts with health-care
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8 479 workers (HCWs) and impact of infection control measures in the transmission process. Solid
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10 480 lines represent the transitions between population groups and dashed lines represent the
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12 481 transmission between patients and HCWs.

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15 482**A.** Impact of universal (horizontal) control measures: 1) hand hygiene (reduces the transmission
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17 483 among patients and HCWs); 2) antibiotic restriction (reduces the risk of transmission from
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19 484 colonized patients receiving antibiotics to HCWs or from contaminated HCWs to uncolonized
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21 485 patients receiving antibiotics).
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27 487**B.** Impact of targeted (vertical) control measures: screening of patients on ICU admission and
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29 488 identification of patients who had positive screening results (patients surrounded by a shaded
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31 489 box). Implementation of: 1) contact precautions (hand hygiene reduces the transmission from
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33 490 identified ESBL-PE carriers to HCWs); 2) cohorting of identified ESBL-PE carriers and
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35 491 attribution of a dedicated HCW (prevents the transmission from cohorted patients to other HCWs
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37 492 and patients). Note that we included two categories of colonized patients: 1) who had false
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39 493 negative admission screening results; 2) who had positive admission screening results (patients
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41 494 surrounded by a shaded box).
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48 496 **Figure 2.** Patient outcomes after one year under the different control strategies tested. (A) New
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50 497 acquisitions (transmissions) of ESBL-PE per 100 admissions, (B) Total number of ESBL-PE
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52 498 infections per 100 admissions in patients who: 1) acquired colonization in the ICU, and 2) those
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3 500 Strategies are: (1) Base case (reference strategy with no control intervention and hand hygiene
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5 501 compliance of 55%/60% before/after patient contact); (2) Hand hygiene improvement to
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7 502 80%/80%; (3) Hand hygiene improvement to 55%/80%; (4) Antibiotic reduction; (5) Screening
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9 503 of all admissions and contact precautions for identified carriers; (6) Screening of all admissions
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11 504 and cohorting of identified carriers; (7) Hand hygiene improvement to 80%/80% and antibiotic
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13 505 reduction; (8) Hand hygiene improvement to 55%/80% and antibiotic reduction; (9) Screening of
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15 506 all admissions, contact precautions with identified carriers and antibiotic reduction; (10)
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17 507 Screening of all admissions, cohorting of identified carriers and antibiotic reduction.
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25 **Figure 3.** Cost-effectiveness plane showing the incremental health benefits (infections avoided)
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27 509 and costs relative to the least expensive strategy (Strategy 2). Strategies 1, 3, 4, 5, 8, 9 are
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29 510 dominated as they have both a worse outcome and a higher cost. The efficiency frontier (grey
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31 511 line), joins Strategy 2 with more expensive and more efficient strategies (7 and 10). Strategy 6 is
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33 512 extended to this frontier and excluded by the principle of extended dominance. The slope of the
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35 513 efficiency frontier represents the incremental cost-effectiveness.
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39 514 Strategies are: (1) Base case (reference strategy with no control intervention and hand hygiene
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41 515 compliance of 55%/60% before/after patient contact); (2) Hand hygiene improvement to
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47 518 and cohorting of identified carriers; (7) Hand hygiene improvement to 80%/80% and antibiotic
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49 519 reduction; (8) Hand hygiene improvement to 55%/80% and antibiotic reduction; (9) Screening of
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524 **TABLES**525 **Table 1. Cost parameters, their sources and ranges for sensitivity analyses.**

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

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	<u>Resource</u>	<u>Cost (€^a)</u>		<u>Source</u>	<u>Distribution</u>
		<u>mean</u>	<u>SD</u>		
	ICU bed-day	1,583	226	AP-HP ^b	Gamma
<u>Universal strategies</u>					
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
<u>Targeted strategies</u>					
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

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3	Cohorting	Additional full-time HCW/month	3,598 ^c	642	AP-HP ^b	Gamma
4	(additional HCW +					
5	contact precautions)					
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10		Alcohol-based hand rub	0.011	0.0055	34,35	Gamma
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15		HCW's time per hand hygiene	0.143	0.0714		Gamma
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17 530 ^a 1€ = US \$0.94

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19 531 ^b AP-HP: The Assistance publique – Hôpitaux de Paris

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21 532 ^c Cost of staff from a hospital perspective (salary + employer contributions)

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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 (€)	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

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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

537 ^a Relative to strategy 2

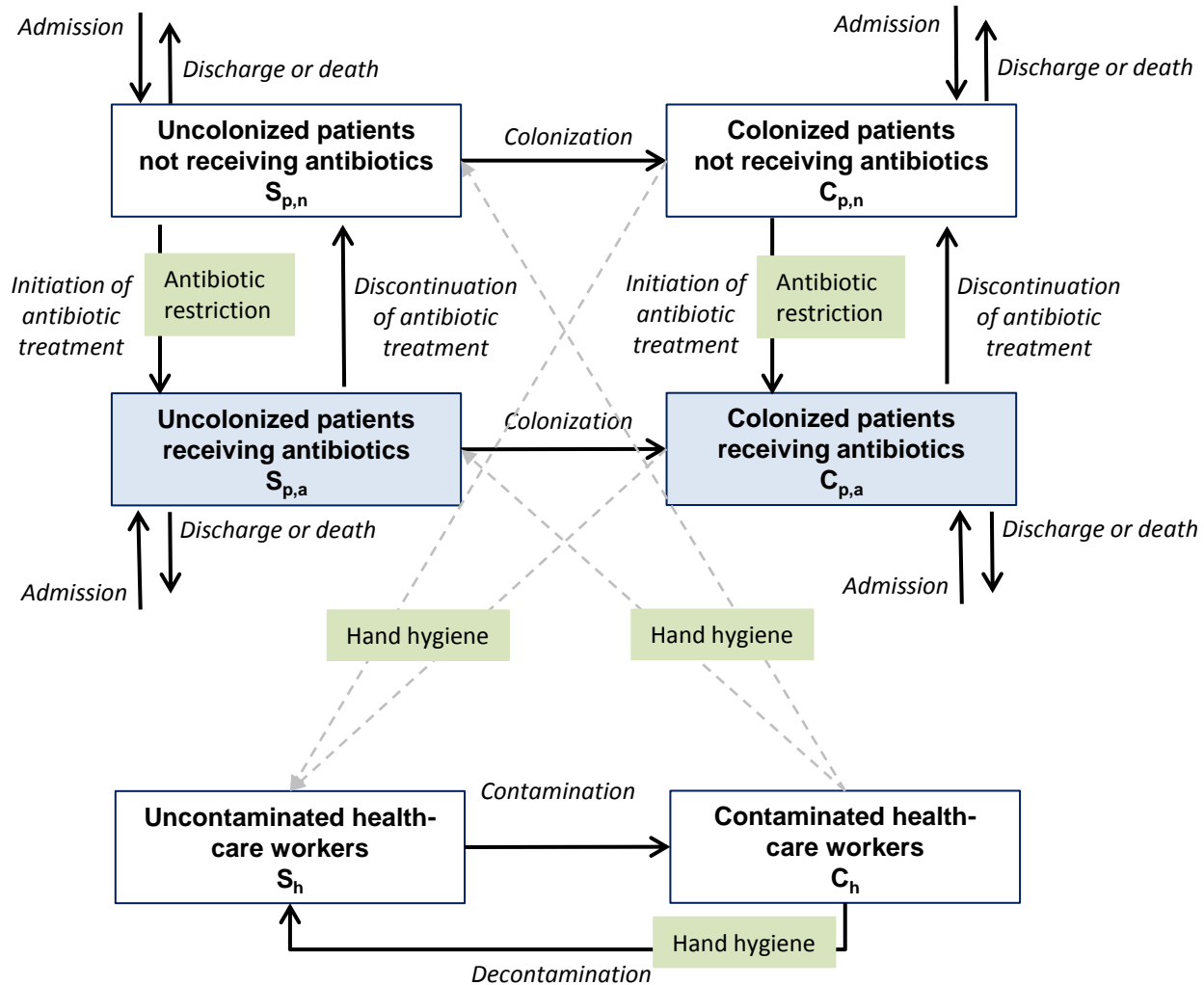
538 ^b Relative to strategy 7

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

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

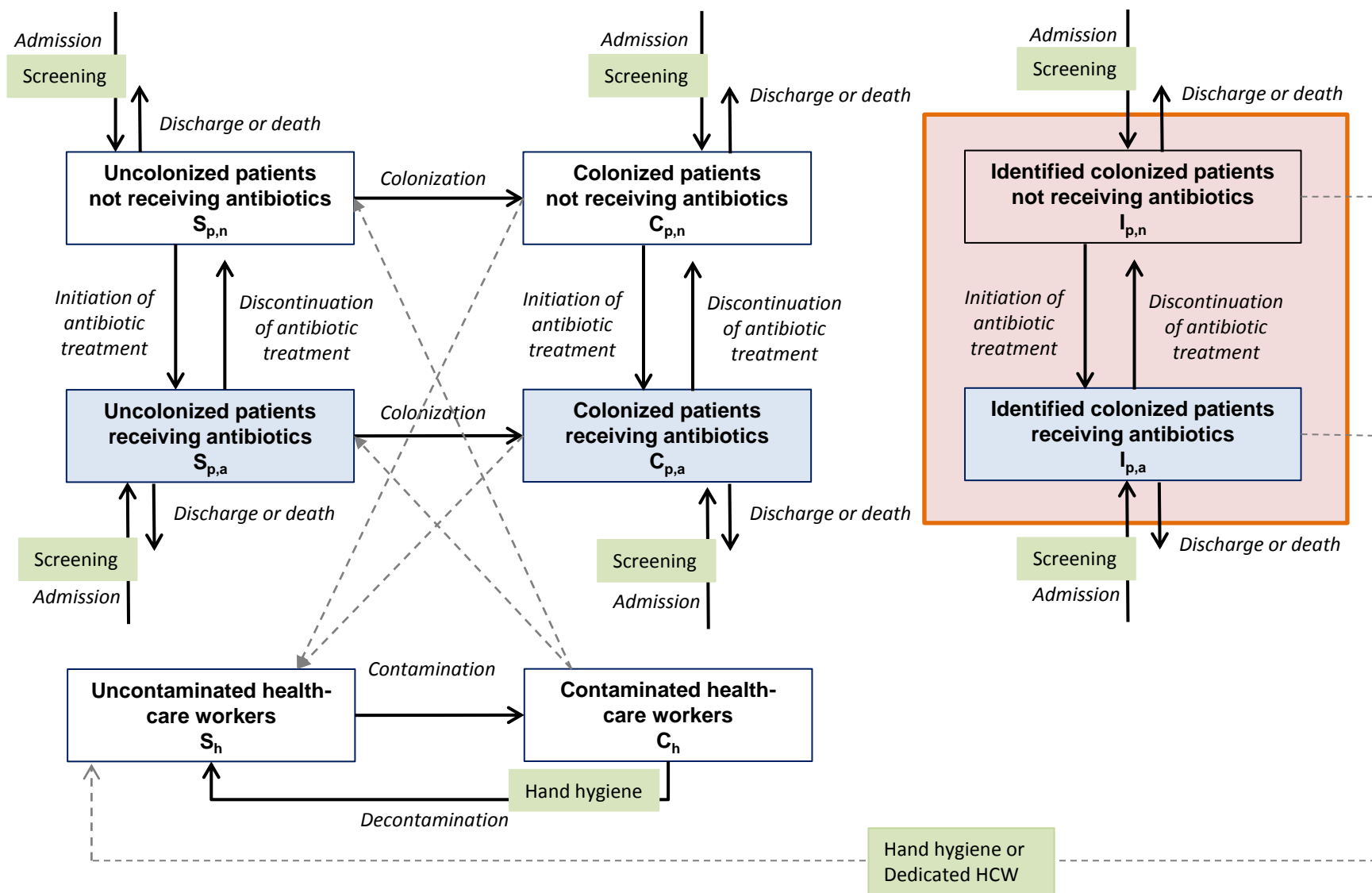
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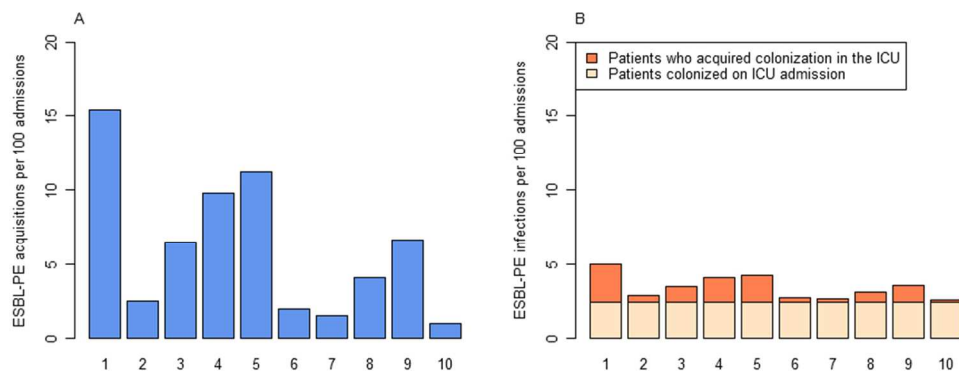


Figure 2. Patient outcomes after one year under the different control strategies tested. (A) New acquisitions (transmissions) of ESBL-PE per 100 admissions, (B) Total number of ESBL-PE infections per 100 admissions in patients who: 1) acquired colonization in the ICU, and 2) those who were already colonized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

317x141mm (72 x 72 DPI)

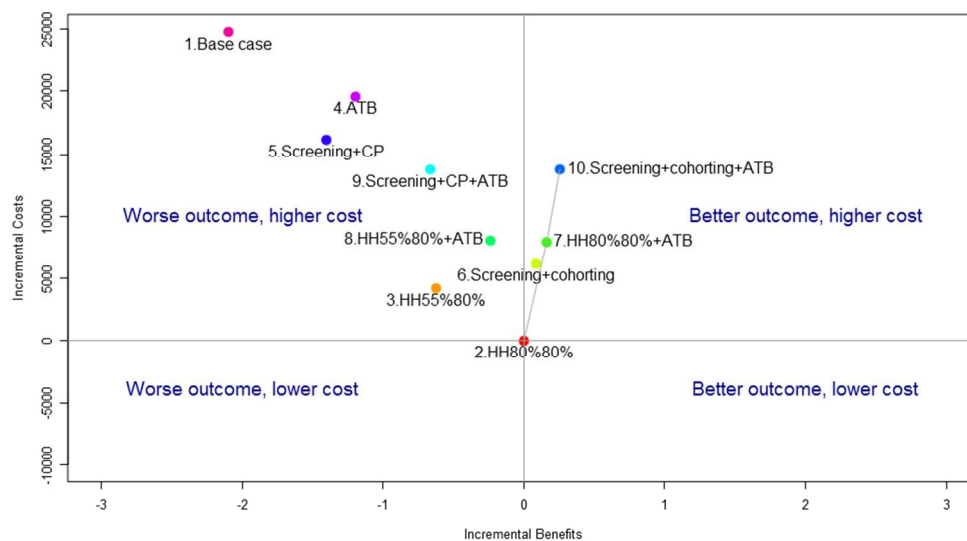


Figure 3. Cost-effectiveness plane showing the incremental health benefits (infections avoided) and costs relative to the least expensive strategy (Strategy 2). Strategies 1, 3, 4, 5, 8, 9 are dominated as they have both a worse outcome and a higher cost. The efficiency frontier (grey line), joins Strategy 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.

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 with 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.

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 HCWs⁴. 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 period⁵.

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:

$$\begin{aligned} \beta_{p,a} &= a \cdot b_{p,a} \cdot (1 - p_p) \\ \beta_{p,n} &= a \cdot b_{p,n} \cdot (1 - p_p) \end{aligned} \quad \left. \vphantom{\begin{aligned} \beta_{p,a} \\ \beta_{p,n} \end{aligned}} \right\} \text{Transmission from contaminated HCWs to uncolonized patients (receiving antibiotics or not)}$$

$$\begin{aligned} \beta_{h,a} &= a \cdot b_{h,a} \cdot (1 - p_h) \\ \beta_{h,n} &= a \cdot b_{h,n} \cdot (1 - p_h) \end{aligned} \quad \left. \vphantom{\begin{aligned} \beta_{h,a} \\ \beta_{h,n} \end{aligned}} \right\} \text{Transmission from non-identified, colonized patients (receiving antibiotics or not) to HCWs}$$

$$\begin{aligned} \beta_{h,a,I} &= a \cdot b_{h,a,I} \cdot (1 - p_{h,Is}) \\ \beta_{h,n,I} &= a \cdot b_{h,n,I} \cdot (1 - p_{h,Is}) \end{aligned} \quad \left. \vphantom{\begin{aligned} \beta_{h,a,I} \\ \beta_{h,n,I} \end{aligned}} \right\} \text{Transmission from identified, colonized patients (receiving antibiotics or not) to HCWs}$$

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

$\beta_{p,a} = a \cdot b_{p,a} \cdot (1 - p_p)$	}	Transmission from contaminated HCWs to uncolonized patients (receiving antibiotics or not)
$\beta_{p,n} = a \cdot b_{p,n} \cdot (1 - p_p)$		
$\beta_{h,a} = a \cdot b_{h,a} \cdot (1 - p_h)$	}	Transmission from non-identified, colonized patients (receiving antibiotics or not) to HCWs
$\beta_{h,n} = a \cdot b_{h,n} \cdot (1 - p_h)$		
$\beta_{h,a,l} = 0$	}	Transmission from identified, colonized patients (receiving antibiotics or not) to HCWs (other than the dedicated HCW)
$\beta_{h,n,l} = 0$		

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

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12 The model parameters and their values are presented in **Supplementary Table 1**. Parameter
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14 values were derived from multicentre studies if available, and by default based on best evidence
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16 from the literature or expert opinion.
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20 We modelled an ICU with 10 single-rooms with continuous presence of 6 HCWs⁶. We assumed
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22 100% bed occupancy. Consequently, a shorter length of stay (LOS) implies a higher turnover and
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24 possible admission of colonized patients⁷. As reported recently, the ICU LOS of ESBL-PE
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26 carriers is longer (13 days) than uncolonized patients (5 days)⁸. The extended LOS in ESBL-PE
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28 carriers increases the colonization pressure in the ICU, consequently increasing the risk of cross-
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30 transmission.
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34 When targeted control strategies were used, colonization was detected using a screening method
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36 assuming that the time between collection of specimens and reporting results to the ward was less
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38 than 1 day. We assumed that the sensitivity of the screening method was 95%⁹. Screening results
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40 had 100% specificity.
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48 **Costs of control strategies**

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50 We estimated the costs of control strategies over the one-year simulation period. See **Table 1** for
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52 details on cost parameters. The cost of the base case strategy (reference strategy) was considered
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3 to be the cost of HH at baseline level, namely cost of the alcohol-based hand rub and costs
4 associated with the time HCWs required for hand disinfection.
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10 As reported recently, the highest cost of an HH program arose from the time people spent
11 working on the program¹⁰. We therefore assumed that the cost of an HH improvement strategy
12 included the cost of HH (hand-rub and HCWs' time) and the cost of an infection control nurse
13 working on the program, i.e. HH education, observation and feedback^{10,11}. We assumed that
14 improving hand HH compliance to 55/80% and to 80/80% required respectively a quarter and a
15 half of the working time of an infection control nurse. In accordance with staffing practices
16 common in the European Union, we assumed that one staff position requires the recruitment of
17 three nurses¹².
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31 Antibiotic stewardship programs (ASPs) have proven efficient in reducing antibiotic use and
32 antibiotic duration in hospitals^{13,14}. Interventions included in ASPs require additional resources
33 associated with higher costs¹⁵. One of the resources needed and associated with the highest costs
34 is the staff time¹⁶. We calculated the cost of an action to reduce antibiotic use as the cost of a
35 half-time infectious disease physician working on the ASP. The cost of antibiotics is considered
36 to be marginal and was not considered in our study¹⁴.
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48 The cost of screening was first based on the cost of testing materials and on the cost of laboratory
49 technician time. For the strategy in which screening at admission was combined with contact
50 precautions for identified ESBL-PE carriers, we also included the cost of contact precautions
51 such as the cost of improved HH (i.e. the cost of the alcohol-based hand rub), and the costs
52 associated with the time HCWs required for hand disinfection. Here we did not consider the cost
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3 of an infection control nurse. We hypothesized that knowing that the patient is an ESBL-PE
4 carrier, HCWs would adhere more easily to HH.
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8 For the strategy in which screening on admission was combined with cohorting of identified
9 ESBL-PE patients, the cost of cohorting was the cost of contact precautions and the cost of
10 additional HCWs caring for cohorted patients. For screening interventions, the cost of HH in non-
11 carriers and unidentified carriers was considered to be identical to the costs of the baseline level.
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16 17 18 19 20 **Cost of hospital-acquired infections**

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22 The mean cost of an ICU bed-day was estimated at €1,583 (based on the average amount paid in
23 2015 for ICUs in Paris public hospitals (AP-HP). This amount is based on French Diagnosis-
24 Related Groups and complementary revenues specific to ICU units and divided by the mean
25 length of stay in ICUs in 2015¹⁷. Based on published reports, the cost per day of a patient with
26 ESBL-PE infection was 50% higher than the cost of an uninfected patient^{18,19}. The cost of an
27 ESBL-PE infection was estimated using the ESBL-PE-attributable LOS and the cost of a hospital
28 bed-day for infected patients^{20,21}.
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42 **Model simulations and outcomes**

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44 Simulations of the model were performed using Gillespie's method and programmed in C++
45 language. The outcomes were calculated after a period of 1 year and averaged over the 1,000
46 Monte Carlo simulations. Cost-effectiveness analysis and graphics were performed in R²².
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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.

Parameter	Description	Value	Source	Sensitivity analysis	
				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	$1/d_{ATB_S}$		
θ_C	Antibiotic therapy discontinuation rate for colonized patients (/day)	0.05556	$1/d_{ATB_C}$		
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_{his}	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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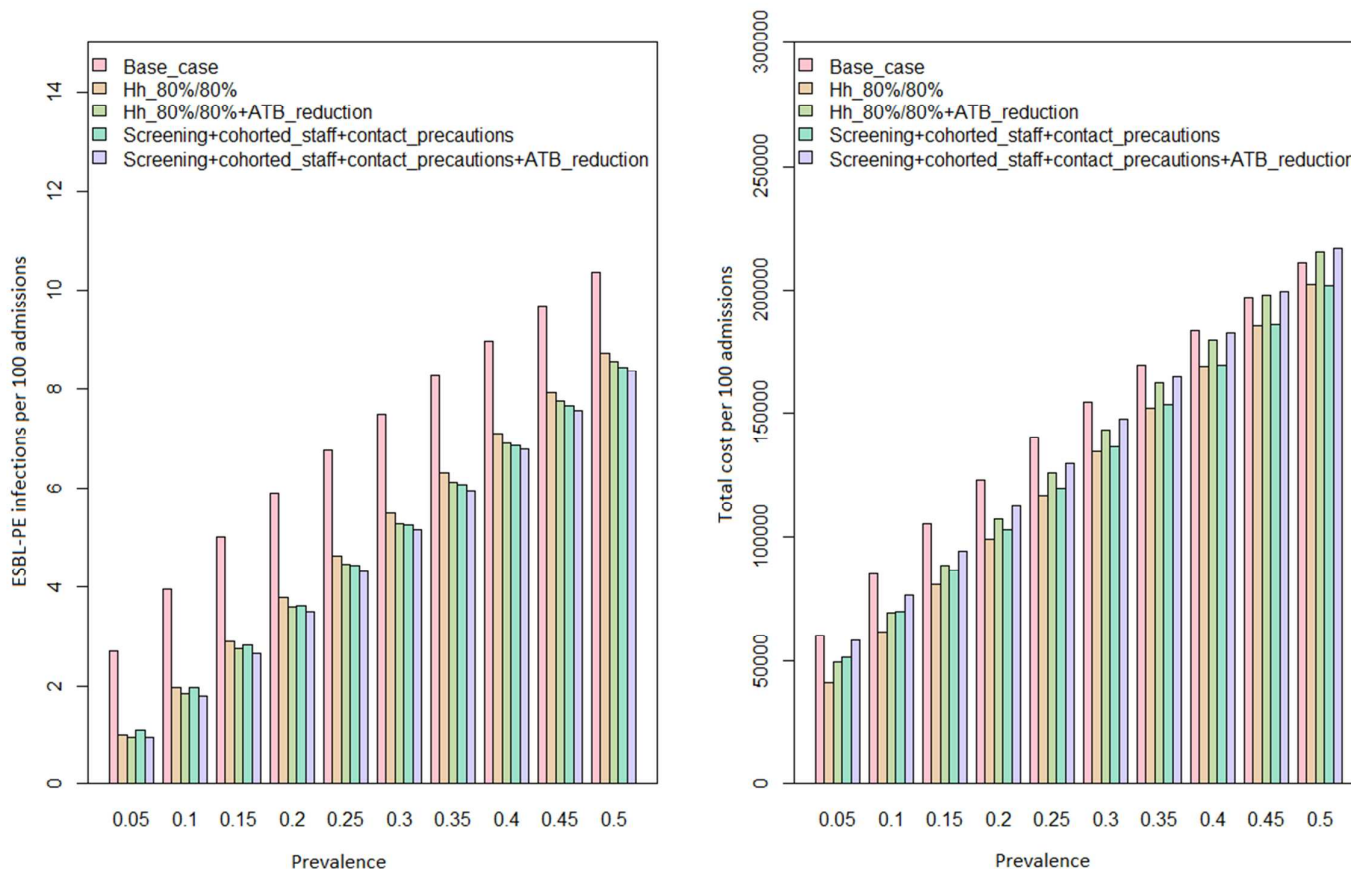
Supplementary material

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 (Strategy 6).

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 ($\Delta C/\Delta E$) (€ / 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%)**.

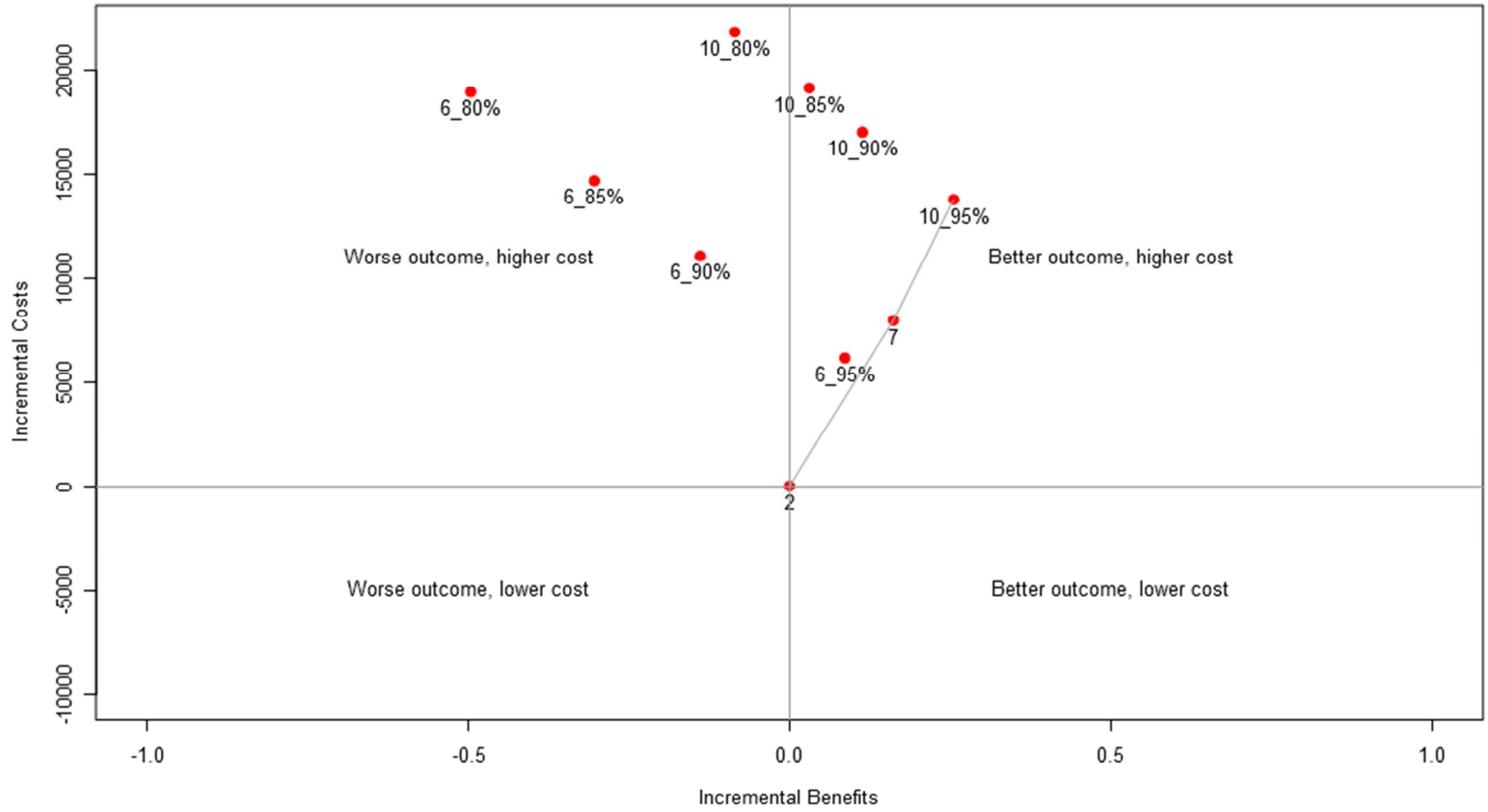
Strategy	Total cost/ 100 admissions (€)	Infections/ 100 admissions	Incremental cost/100 admissions (ΔC) (€)	Incremental effect (ΔE) (infections avoided/100 admissions)	ICER (ΔC/ΔE) (€ / infection avoided)
2: Hh 50%/60%	81 676	3.14			
6: Screening + cohorting	82 867	2.772	1 191	0.368	3 236
10: Screening + 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

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7 4. Impact of lower **sensitivity to detect ESBL-PE carriage** in screening strategies.
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10 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
11 2) and HH 80%/80% and antibiotic reduction (Strategy 7) always dominated the screening strategies (Strategy 6 and 10) (**Supplementary**
12 **Figure S2**).
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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 than 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

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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 Screening and cohorting strategy. The cost-effective ratio (CER) was calculated when the screening and cohorting strategy was more expensive but more effective than the hand hygiene.

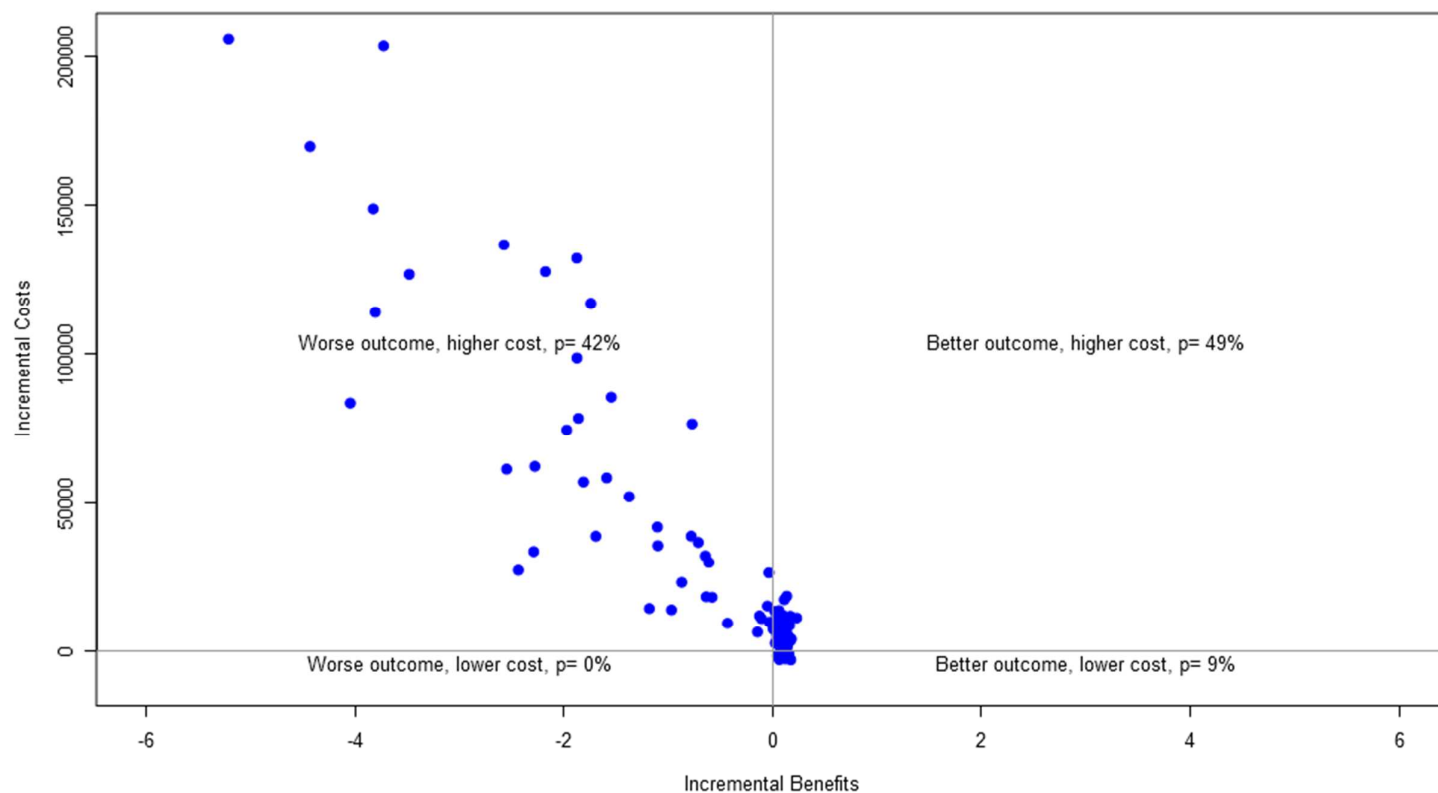
Level of hand hygiene before contact with patient (%)	Level of hand hygiene after contact with patient (%)	Mean increase in hand hygiene from baseline (%)	Number of infections/100 admissions	Total cost/100 admissions (€)	CER (vs Hand hygiene strategy)
Screening and cohorting					
55 (with non cohorted 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 €

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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

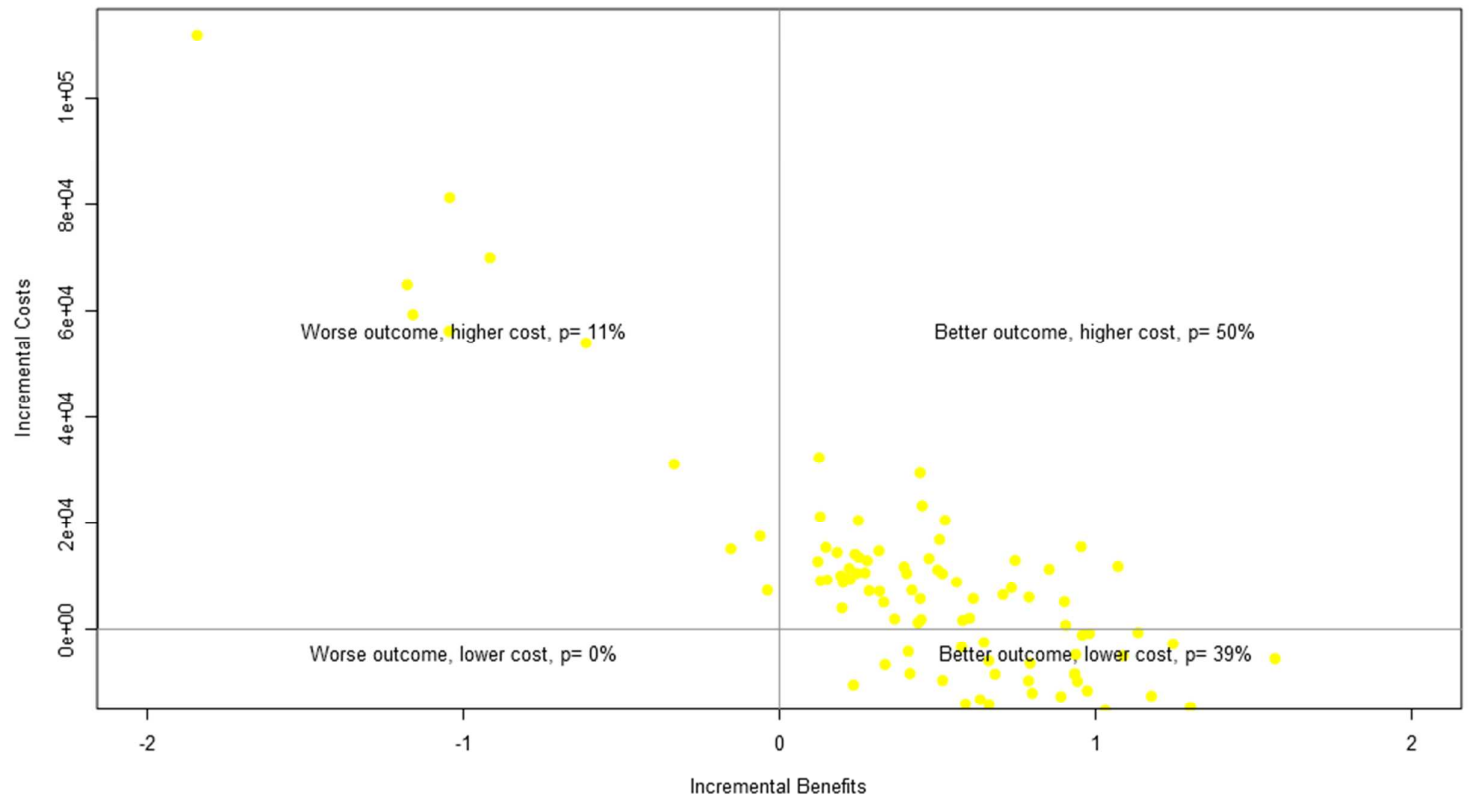
Supplementary Figure S3 Results of probabilistic sensitivity analysis. Cost-effectiveness plane shows the incremental health benefits (infections avoided) and costs for Screening and cohorting (Strategy 6), relative to horizontal strategies: A) Hand hygiene improvement to 80%/80% (Strategy 2); B) Hand 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)

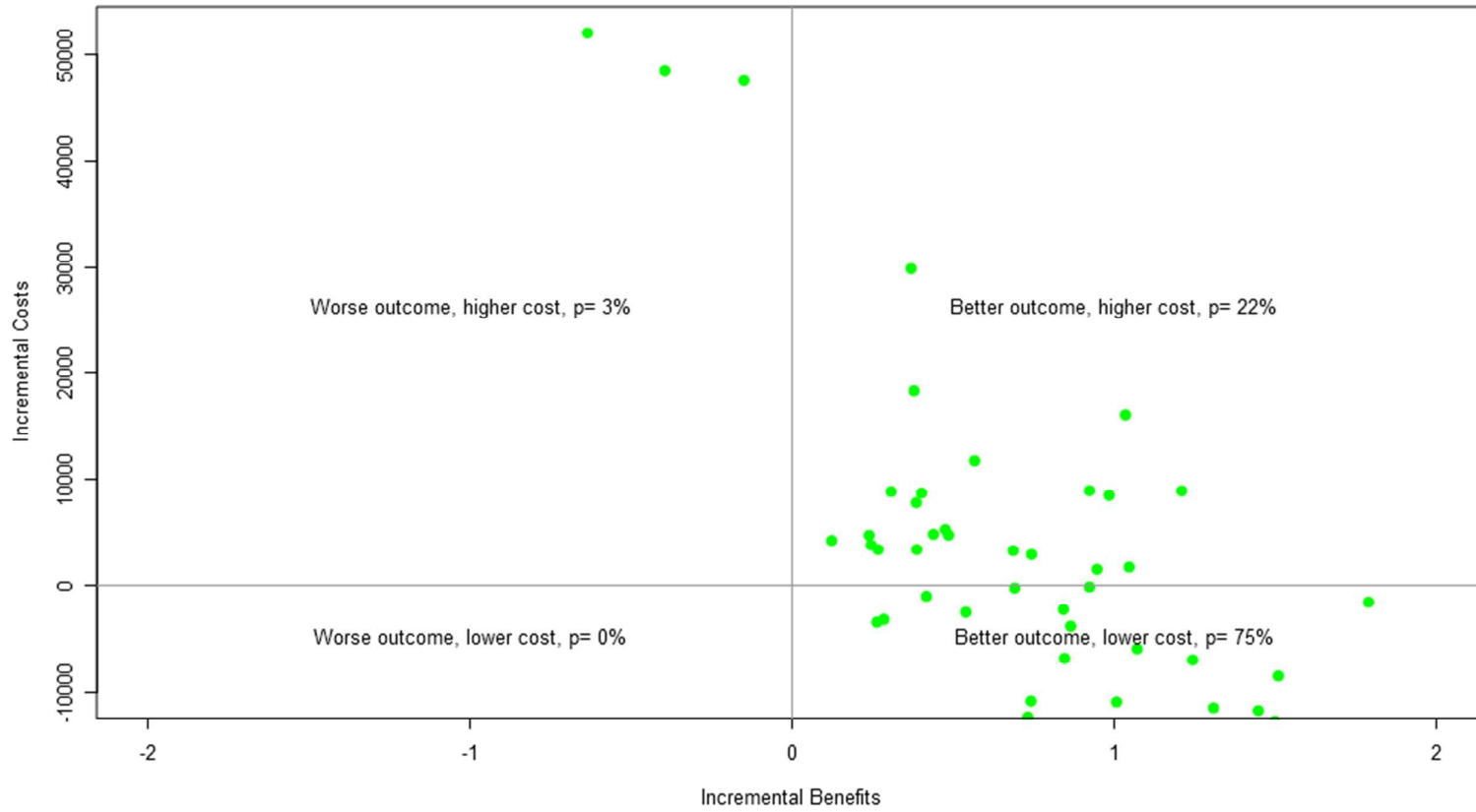


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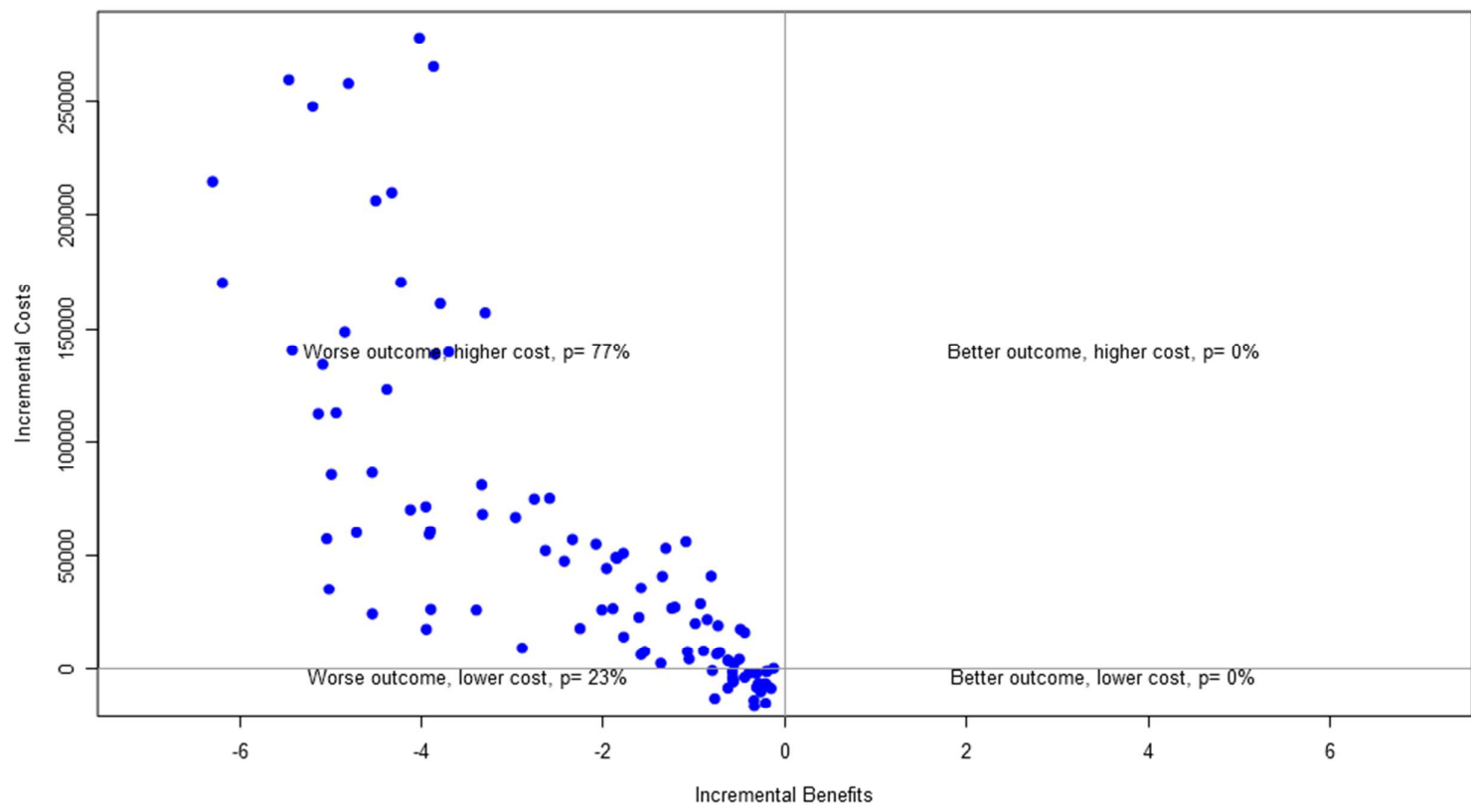
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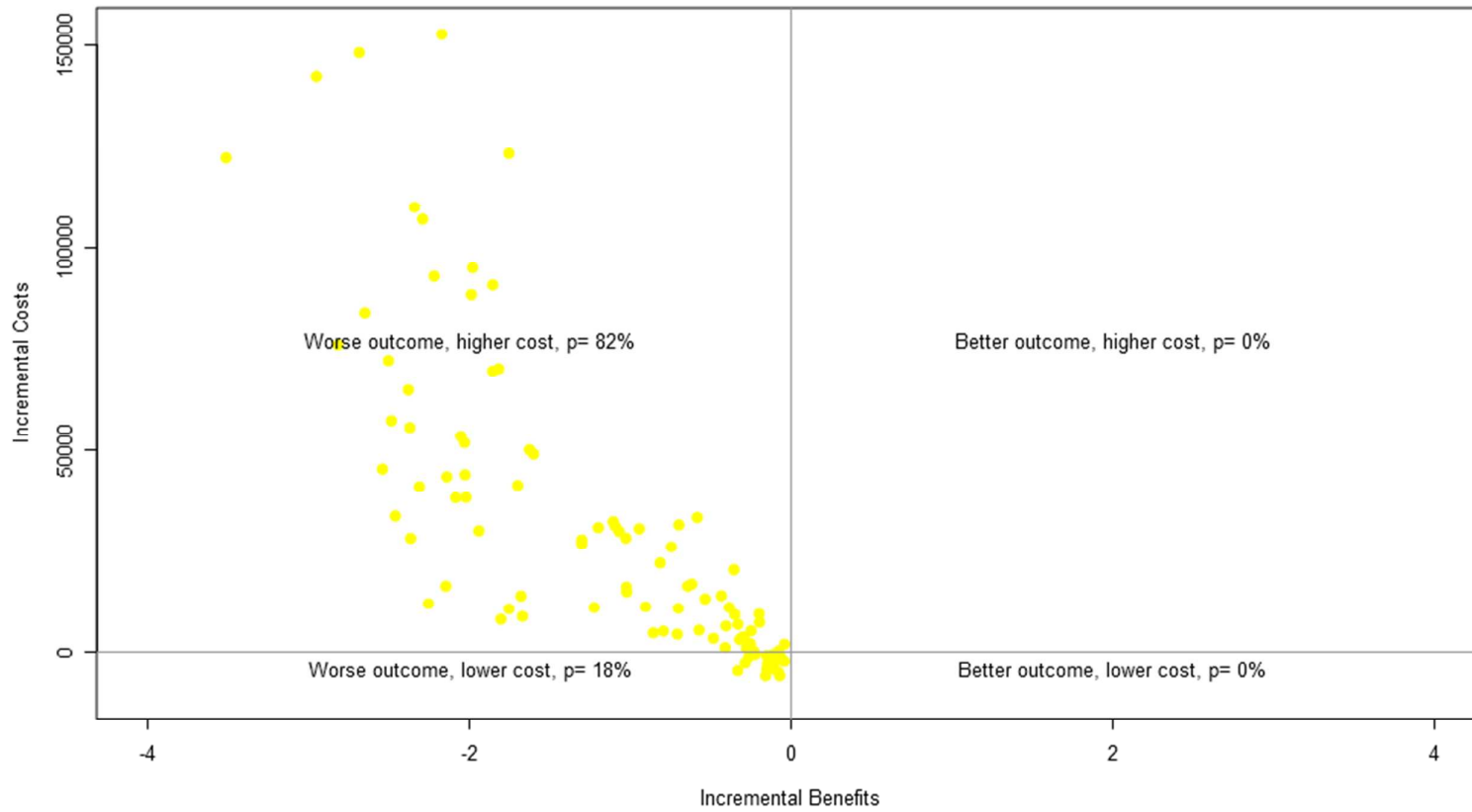
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Supplementary Figure S4 Results of probabilistic sensitivity analysis. Cost-effectiveness plane shows the incremental health benefits (infections avoided) and costs for Screening and contact precautions (Strategy 5), relative to horizontal strategies: A) Hand hygiene improvement to 80%/80% (Strategy 2); B) Hand hygiene improvement to 55%/80% (Strategy 3); C) Antibiotic reduction (Strategy 4). The frequency that the Strategy 6 was in one of four quadrant of CE plane is represented by “p”.

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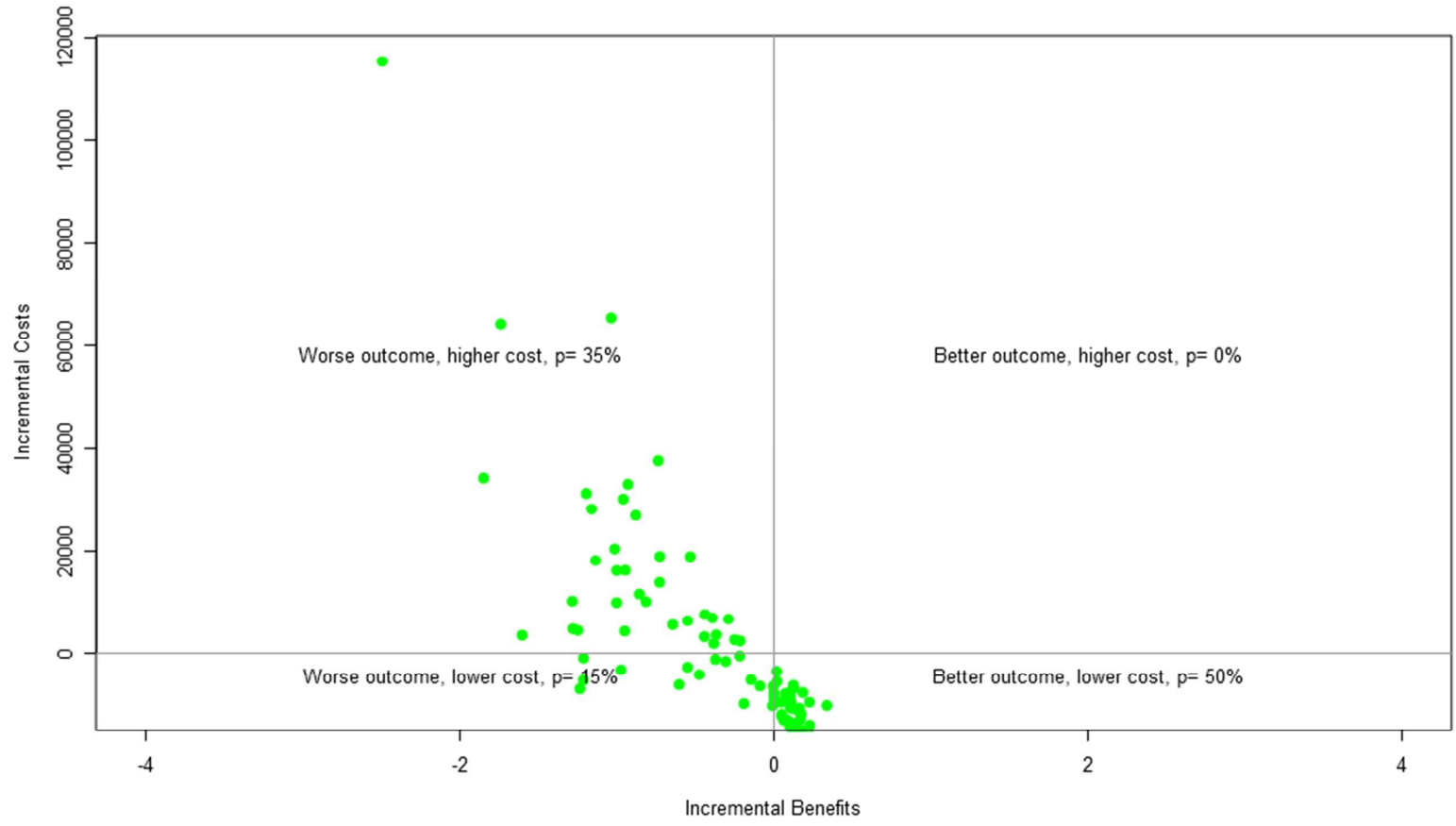


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BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017402.R1
Article Type:	Research
Date Submitted by the Author:	01-Aug-2017
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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Health economics, Public health, Intensive care, Health policy
Keywords:	Infection control < INFECTIOUS DISEASES, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Cost-effectiveness

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3 1 Intended category: Research
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6 2 **Universal or targeted approach to prevent the transmission of**
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9 3 **extended-spectrum beta-lactamase-producing *Enterobacteriaceae* in**
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11 4 **intensive care units? A cost-effectiveness analysis**
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22 ABSTRACT

23 Objective

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

29 Design

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

32 Patients and setting

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

35 Interventions

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

40 Main Outcomes and Measures:

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

43 Results

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3 44 In the base case scenario, 15 transmissions and 5 infections due to ESBL-PE occurred per 100
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5 45 ICU admissions, representing a mean cost of €94 792. All control strategies improved health
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7 46 outcomes and reduced costs associated with ESBL-PE infections. The overall costs (cost of
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9 47 intervention and infections) were the lowest for HH compliance improvement from 55%/60%
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11 48 before/after contact with a patient to 80%/80%.

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13 49 Two strategies required higher investments than the HH programme, but also improved health
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15 50 benefits; 1) HH improvement to 80%/80% combined with antibiotic stewardship and 2) screening
16
17 51 and cohorting strategy combined with antibiotic stewardship.

52 **Conclusions**

23
24 53 Improved compliance with HH was the most cost-saving strategy to prevent the transmission of
25
26 54 ESBL-PE. Antibiotic stewardship was not cost-effective. However, adding antibiotic restriction
27
28 55 strategy to HH or screening and cohorting strategies slightly improved their effectiveness and
29
30 56 may be worthy of consideration by decision-makers’.

31 32 33 34 35 36 58 **Strength and limitations of this study**

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- 39 60 ▪ We used a dynamic transmission model to take into account that the risk of colonization
 - 40 61 in the ICU depends on the number of ESBL-PE carriers and could change over time.
 - 41 62 ▪ Parameters used in the model were derived from recent multicentre studies.
 - 42 63 ▪ We undertook sensitivity analyses to show the impact of uncertainty in parameter
 - 43 64 estimation and the impact of model assumptions on the conclusions.
 - 44 65 ▪ Direct HCW-to-HCW transmissions as well as environmental contamination were not
 - 45 66 included in the model.
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67 INTRODUCTION

68 The incidence of infection and colonization with extended-spectrum beta-lactamase-producing
69 *Enterobacteriaceae* (ESBL-PE) has increased worldwide¹⁻⁴. In Europe, in 2014, the percentage
70 of *Escherichia coli* and *Klebsiella pneumoniae* resistant to 3rd generation cephalosporins in
71 invasive isolates was 12% and 23%, respectively¹. A similar trend was observed in the United
72 States, although with large variations between states².

73 In hospital settings, ESBL-PE acquisition is mainly due to indirect transmission between patients
74 with the hands of healthcare workers (HCWs) as vectors⁵. Increased prevalence of colonization
75 augments the risk of acquiring ESBL-PE infection⁶. Such infections represent a serious socio-
76 economic burden and are associated with a raised mortality, more frequent hospital admissions in
77 comparison with non-carriers, and additional costs⁷.

78 Many interventions have been proposed to limit the transmission of multidrug-resistant
79 organisms (MDROs) in hospitals. They can be classified as either 1) a 'universal' or 'horizontal'
80 approach, applied to all patients e.g. improvement of hand hygiene (HH) among HCWs or
81 antibiotic stewardship or 2) a 'targeted' or 'vertical' approach, e.g. screening and isolation of
82 asymptomatic carriers in addition to infected patients, with the aim of identifying carriers and
83 implementing measures to prevent the transmission from carriers to other patients⁸.

84 There is general agreement that HH reduces the transmission of MDROs, especially MRSA⁶.
85 However, few studies have evaluated the impact of HH on the prevention of ESBL-PE
86 dissemination and they have provided conflicting results^{9,10}. The effectiveness of targeted
87 measures in controlling the spread of MDROs, and especially ESBL-PE, remains controversial.
88 This approach is mainly recommended in high-risk units, e.g. intensive care units (ICUs)¹¹.

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3 89 The implementation of interventions with demonstrated effectiveness in reducing ESBL-PE
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5 90 infections is associated with costs that are generally supported by hospitals. However, when
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8 91 evaluating implementation of an infection prevention programme, one should also take into
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10 92 account savings associated with these interventions, but this has been largely ignored in previous
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13 93 studies.

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15 94 In this study, we used a mathematical model to evaluate the effectiveness and cost-effectiveness
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17 95 of universal and targeted control strategies for the prevention of ESBL-PE transmission in an
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20 96 ICU in a high-income country.
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25 98 **METHODS**

28 99 The model

30 100 We extended a previously described stochastic, compartmental and dynamic model of ESBL-PE
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32 101 transmission¹² to assess the economic impact of infection control strategies implemented in a
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35 102 hypothetical, ICU setting. We run the model over a one-year to capture all costs and health
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37 103 effects relevant to implemented control strategies.

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40 104 The model simulated the spread of ESBL-PE among patients through contacts with HCWs in an
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42 105 ICU, taking into account hospital admissions and discharges of patients, antibiotic exposure, and
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44 106 control interventions (**Figure 1**).

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47 107 The **Supplementary Text S1** provides details of the model and its assumptions.

49 108 **Model simulations and outcomes**

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52 109 Simulations of the model were performed using Gillespie's method and programmed in C++
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54 110 language. The outcomes (cases of ESBL-PE transmission, infections, cost of intervention, cost of
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3 111 infections) were calculated after a period of 1 year and averaged over the 1,000 Monte Carlo
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5 112 simulations. Cost-effectiveness analysis and graphics were performed in R¹³.
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10 114 Base case scenario

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12 115 In the base case scenario, with no control intervention, we considered that compliance with hand
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14 116 hygiene before/after contact with a patient was 55%/60% respectively¹⁴ and 56% of patients
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16 117 received antibiotics at ICU admission¹⁵.
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20 118 Infection control strategies

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25 120 **Universal approaches**

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27 121 We evaluated control strategies implemented in all patients (independently of their colonization
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29 122 status), that comprised one or both of the following interventions: 1) improved compliance with
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31 123 HH, and 2) antibiotic stewardship. For HH, we considered different levels of compliance. First,
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33 124 compliance with HH before/after contact with a patient was improved from 55%/60% at baseline
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35 125 to 55%/80% or 80%/80%. Second, antibiotic stewardship resulted in halving the proportion of
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37 126 patients on antibiotics at ICU admission and in reducing by 25% the duration of antibiotic
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39 127 treatment.
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47 129 **Targeted approaches**

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49 130 We evaluated 2 strategies that combined screening of patients for ESBL-PE at ICU admission
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51 131 and one of the following interventions implemented: 1) contact precautions (improved
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53 132 compliance with HH before/after contact with carriers to 80%/80%); or 2) cohorting of ESBL-PE
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3 133 carriers with dedicated HCWs. HH compliance for other patients was maintained at baseline
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5 134 level.

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8 135 **Mixed approaches**

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10 136 We evaluated two strategies combining the targeted approaches with antibiotic stewardship.

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15 138 Model parameters

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18 139 Model parameters and their values are presented in **Supplementary Table 1**.

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20 140 Based on recent French data, we assumed that 15% of patients were colonized with ESBL-PE at
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22 141 ICU admission¹⁶.

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25 142 Infection status was not included in the model, so we estimated the number of infections by
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27 143 multiplying the cumulated number of colonized patients after one year by the probability of
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29 144 developing an infection during an ICU stay, set at 16.4%¹⁷. Even though this value came from a
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31 145 recent large multicentre study, we also considered the impact of lower (8%) and higher (30%)
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33 146 probability of infection in alternative analyses.

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39 148 Costs

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41 149 The analysis was performed from a public hospital perspective. Cost estimates are based on
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43 150 values reported in Euros from 2015 (1 € = US \$0.94). We considered the following costs in the
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45 151 model: 1) costs of intervention (material resources and personnel costs), 2) costs of ESBL-PE
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47 152 infections. The cost of an ESBL-PE infection was estimated using the ESBL-PE-attributable LOS
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49 153 and the cost of a hospital bed-day for infected patients^{16,18,19}. See **Table 1** for cost parameters and
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51 154 **Supplementary Text 1** for more details.

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3 156 Cost-effectiveness evaluation
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6 157 To conduct the cost-effectiveness²⁰, we estimated the costs associated with each intervention
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8 158 implemented, and the health benefits were related to the number of avoided cases of ESBL-PE
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10 159 infections. First, we determined whether any strategy was dominated by another in terms of costs
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12 160 and health benefits. Second, we determined whether any strategy was dominated through
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14 161 principles of extended dominance (i.e. whether the incremental cost-effectiveness ratios
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16 162 [ICERs] decrease as the strategies increases in cost^{20,21}). Finally, for the non-dominated strategies,
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18 163 we calculated the incremental cost per case of infection avoided, which is the ratio of the
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20 164 difference in costs between two strategies to the difference in health benefits. This process
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22 165 produces an “efficient frontier” indicating more costly, but more effective strategies.
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29 167 Sensitivity analysis
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32 168 We performed supplementary analyses to assess the impact of parameter uncertainty on the
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34 169 model’s predictions. We first ran a univariate sensitivity analysis to evaluate the cost-
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36 170 effectiveness of strategies in settings with either low or high prevalence of patients colonized at
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38 171 admission (from 5% to 50%). We also considered the impact of a lower (8%) and a higher (30%)
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40 172 probability of infection in colonized patients. We then investigated the model assuming 1) a
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42 173 lower baseline compliance with HH (20%/40% or 40%/50%), 2) a lower sensitivity of the
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44 174 screening method used to detect ESBL-PE carriers at ICU admission, and 3) a lower, 30%
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46 175 reduction in antibiotic prescribing.
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53 177 We also performed an analysis to explore the uncertainty in human time required in an HH
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55 178 programme and its potential effects. In this analysis, we varied the time an infection control nurse
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3 179 works on the programme (quarter-time, half-time or full-time) simultaneously with the level of
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5 180 HH compliance achieved (from 55%/60% to 80%/80% before after contact).
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10 182 Finally, we performed a probabilistic sensitivity analysis to explore the effect of joint uncertainty
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12 183 across parameters on the cost-effectiveness of universal vs targeted strategies. We varied the
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14 184 following parameters concurrently: 1) number of HCW contacts with patients, 2) transmission
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16 185 parameters, 3) length of stay of ICU patients, 4) natural decontamination rate for HCW, 5)
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18 186 antibiotic initiation rate, 6) prevalence of ESBL-PE carriage among patients admitted to the ICU,
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20 187 7) death rate of patients, 8) probability of infection in colonized patients and 9) cost parameters.
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24 188 We randomly sampled values from each of the parameter distributions and calculated the mean
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26 189 costs and mean number of infections for each strategy (averaged over 1,000 simulations).
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30 31 191 **RESULTS**

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34 192 In the absence of control interventions (base case strategy), 15 new acquisitions (i.e.
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36 193 transmissions) and 5 infections due to ESBL-PE (those from new acquisitions and in patients
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38 194 colonized at admission) occurred per 100 admissions. Compared to the base case (Strategy 1), all
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40 195 strategies reduced ESBL-PE acquisition and infections within one year (**Figure 2**).

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43 196 Among universal strategies, HH compliance improvement to 80%/80% (Strategy 2) was the most
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45 197 effective, resulting in a mean reduction to 2.9 acquired infections per 100 admissions. Among
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47 198 targeted strategies, screening of patients on admission and cohorting of carriers (Strategy 6) was
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49 199 the most effective strategy and resulted in a mean reduction to 2.8 infections per 100 admissions.
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52 200 Screening followed by contact precautions (Strategy 5) was the least effective in comparison with
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3 201 all other options. Adding antibiotic stewardship to HH or targeted strategies only slightly
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5 202 improved their effectiveness.
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10 204 **Cost-saving analysis**

12 205 In **Table 2** we present the estimated costs and outcomes over one year for all strategies. The
14 206 mean total cost associated with the base case strategy was estimated at €105 344/100 admissions,
16 207 €94 792 of which was related to infections and €10 552 to interventions. Investments in infection
18 208 prevention was always cost-saving because they avoided cases of ESBL-PE infections and thus
20 209 costs associated with these infections. For instance, when HH compliance was improved to
22 210 80%/80%, the mean cost of the strategy implementation increased to €25 639/100 admissions,
24 211 but the costs related to infections decreased to €54 916, resulting in an overall monetary benefit
26 212 of €24 788/100 admissions in comparison with the base case. This strategy was associated with
28 213 the highest savings within all evaluated strategies.
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36 215 **Cost-effectiveness analysis**

38 216 HH compliance improvement to 80%/80% was the least expensive strategy. However, two
40 217 strategies required higher investments than the HH programme, but also improved health
42 218 benefits. To help choose between strategies we calculated the incremental cost-effectiveness ratio
44 219 (**Figure 3**). The ICER of HH improvement to 80%/80% and antibiotic stewardship (Strategy 7)
46 220 vs. HH compliance improvement to 80%/80% was estimated at €49 055/avoided infection (**Table**
48 221 **2**). The ICER of screening, cohorting and antibiotic stewardship (Strategy 10) vs. HH
50 222 improvement to 80%/80% and antibiotic stewardship was estimated at €61 994/avoided infection.
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53 223 Other strategies were dominated (more expensive and less effective).
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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).

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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**).

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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%

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3 247 of simulations. Among them, in 42% of simulations, the HH strategy was less expensive but
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5 248 more effective (dominated the Strategy 6), and in 49% of runs the screening and cohorting was
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7 249 more effective and more expensive (**Supplementary Figure S3**). Screening and contact
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9 250 precautions (Strategy 5) were always less effective than improvement of HH to 80%/80%
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11 251 (Strategy 2) (**Supplementary Figure S4**).
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18 253 **DISCUSSION**

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21 254 The impact of infection control strategies for preventing ESBL-PE transmission is controversial
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23 255 because clinical studies cannot account for the multiple confounding factors, notably both
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25 256 infection control measures and antibiotic stewardship. Despite several recent high-level
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27 257 interventional studies (Climo et al.²²; Derde et al.⁹; Huang et al.²³), the most effective and cost-
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29 258 effective interventions for controlling MDROs are still debated. Since the spread of ESBL-PE
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31 259 between patients is a dynamic and complex process, modelling can help for understanding the
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33 260 transmission mechanisms and deciding which intervention are to be preferred (Doan et al.²⁴;
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35 261 Grundmann et al.²⁵).
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40 262 Our model estimated the annual burden of ESBL-PE infections in a French ICU at €94 792 per
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42 263 100 admissions in the base case strategy. Several prior studies have reported the cost of infections
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44 264 due to multidrug resistant organisms in the ICU²⁶⁻²⁹. However, even though all authors
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46 265 underlined the high costs of infections, comparison between studies remains difficult. Estimated
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48 266 costs varied according to the country, but also to the population studied, e.g. patients with site-
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50 267 specific or microorganism-specific infections. Moreover, the methods used to estimate the costs
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52 268 were not similar in all publications.
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3 270 In recent years, mathematical models have increasingly been used to study the cost-effectiveness
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5 271 of control strategies. For example, Robotham et al.³⁰ compared a wide range of strategies to
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8 272 control MRSA transmission in ICUs and found that universal decolonization was the most cost-
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10 273 effective option. In another study, Gidengil et al.³¹ compared hospital strategies to prevent MRSA
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12 274 transmission and infections in an ICU. They confirmed that universal decolonization was the
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15 275 most cost-saving.

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17 276 While decolonization regimens have been indicated as cost-effective for MRSA, only a few
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19 277 studies have examined the effect of decolonization on ESBL-PE carriage^{32,33}. These studies have
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21 278 shown that decolonization strategies might be efficacious only in the short-term. Moreover, they
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23 279 have reported the risk of emergence of resistance to antibiotics used for decolonisation, namely to
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26 280 colimycin, which is the last line effective therapy against carbapenemase-producing
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29 281 *Enterobacteriaceae*³³. Thus, decolonization was not considered in our study.
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34 283 Our study is the first to compare the effectiveness and the costs of universal and targeted control
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36 284 strategies in the context of the spread of ESBL-PE in ICUs. Our model predicted that improving
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38 285 HH to 80%/80% in contacts with all patients would prevent 83% of ESBL-PE acquisitions and
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40 286 avoid at least two out of five infections per 100 admissions. This strategy represented the most
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43 287 cost-saving, with a monetary benefit of €24 788 per 100 admissions.
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46 288 The association between HH and reduction of MDROs infections has long been known and HH
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48 289 has been accepted as a crucial component of infection prevention³⁴. HH has in addition the
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50 290 benefit of being effective for reducing transmission of many resistant or susceptible bacteria³⁴. A
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52 291 recent publication reported that a programme designed to control MRSA by implementing
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55 292 universal components in addition to screening and contact precautions for MRSA carriers also
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3 293 effectively reduced the incidence of resistant gram-negative bacteria, the most likely being
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5 294 ESBL-PE¹⁰. Thus, an HH programme designed to reduce ESBL-PE transmission may have
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8 295 positive effects on reducing the transmission of other microorganisms, and the overall economic
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10 296 benefit of an HH programme for the hospital might be greater than reported in our study.

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13 297 Despite the confirmed effectiveness of HH and national and international recommendations,
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15 298 compliance with HH remains low and is often lower than values used in our base case
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18 299 analysis^{35,36}. Furthermore, improving HH compliance from 60% to 80% may be far more difficult
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20 300 and costly, challenging than improving from lower baseline level. However, we showed in a
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23 301 sensitivity analysis that improving HH remained the most cost-saving strategy even in a low
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25 302 baseline compliance scenario. Different strategies have been suggested to improve HH in
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28 303 hospitals³⁷, but the evidence-based approach is still lacking. Recently, a review³⁸ concluded that
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30 304 a multimodal strategy proposed by the WHO and consisting of five components: 1) system
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32 305 change, 2) training and education, 3) observation and feedback, 4) reminders in the hospital, and
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34 306 5) a hospital safety climate, was effective at increasing HH among HCWs. Moreover, the authors
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37 307 underlined that additional measures (e.g. reward incentives for reaching a certain level of
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39 308 compliance) could lead to further improvements. In our study, we assumed that a key component
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42 309 of an HH programme was a dedicated staff working on the programme (i.e. HH education,
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44 310 observation and feedback). We hypothesized, for example, that to improve HH compliance an
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46 311 infection control nurse working half-time would be sufficient. However, this assumption was
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49 312 based on expert opinion; we performed a sensitivity analysis to explore the uncertainty of the
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51 313 required time dedicated to the HH programme and its expected effects.

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53 314 Screening strategies have been used to prevent transmission of MDROs, however, in a sensitivity
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56 315 analysis, we showed that improvement of HH to 80%/80% was always more effective than
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3 316 screening and contact precautions and mostly less expensive than the screening and cohorting
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6 317 intervention. However, we can hypothesize that in the case of highly resistant bacteria (e.g.
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8 318 Carbapenem-resistant *Enterobacteriaceae*) where there is a highest clinical impact on the
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10 319 outcomes of infected patients, given the lack of therapeutic options, a rapid identification and
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12 320 cohorting of carriers may be more beneficial from the hospital but also societal perspective.

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15 321 Antibiotic use is the major driver for the selection of antibiotic-resistant bacteria³⁹ and many
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17 322 strategies have been proposed to reduce the use of antibiotics in hospitals⁴⁰. These strategies
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19 323 could be implemented and associated with different efficacies and costs⁴¹. Here, we considered
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21 324 that antibiotic stewardship, based on the introduction of an infectious disease specialist to the
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23 325 ward, led to a 50% reduction in antibiotic use⁴². However, despite this optimistic scenario, we
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25 326 found that antibiotic stewardship was less effective than HH or a screening and cohorting
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27 327 strategy.

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32 328 Under the hypotheses used in our model, we also demonstrated in a previous study through
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34 329 sensitivity analyses that antibiotic parameters did not significantly influence the effectiveness of
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36 330 interventions¹².

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40 331 However, adding antibiotic stewardship to an HH strategy slightly improved its effectiveness and
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42 332 may be worthy of consideration if the decision-makers are willing to pay at least €49 055 per
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44 333 infection avoided (we calculated that it would be equivalent to €5 562 per life-year gained
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46 334 (LYG)). Combining antibiotic stewardship with screening and cohorting was even more effective
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48 335 than combining HH and antibiotic stewardship, but with an additional cost of €61 994 per
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50 336 infection avoided (or €7 030/LYG).

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3 338 Our study has several strengths. Firstly, we used a dynamic model to represent interactions
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5 339 between patients and HCWs and to take into account that the risk of colonization in the ICU
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7 340 depends on the number of ESBL carriers and could change over time. Moreover, our model
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9 341 incorporated the key elements of ESBL-PE transmission, such as the impact of prevalence at
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11 342 admission or antibiotic treatment. Secondly, we used input parameters derived from recent
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13 343 multicentre studies. Thirdly, we estimated the cost of HCW according to the time they spend
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15 344 working on the programme based on the best evidence from the literature and expert opinion.
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17 345 Finally, we assessed the impact of uncertainty in parameter estimation and the impact of model
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19 346 assumptions on the model's predictions by performing multiple sensitivity analyses.
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24 347 Our study also has several limitations. ICU parameters and costs were based mostly on French
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26 348 data, and ESBL-PE infections, prevalence, compliance with control measures and costs may be
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28 349 different in other countries.
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31 350 A recent multicentre cohort study¹⁷ found no difference in LOS between infected and colonised
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33 351 patients. Thus, in order to simplify assumptions, the “infected” state was not included to the
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35 352 model. However, infected patients are potentially more contaminating HCW hands,
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37 353 disseminating the organism in the environment and increase the transmissibility⁴³. Thus,
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39 354 consequently we may have underestimated the number of acquisitions in the ICU and the impact
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41 355 of control measures.
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45 356 The epidemiologic characteristics of ESBL-PE are complex and may vary, depending on ESBL-
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47 357 PE species. For example, Thiébaud et al.⁴⁴ showed that *E.coli* ESBL was mainly imported (66%)
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49 358 and *K. Pneumoniae* ESBL was acquired (77%). Furthermore, the differential capacity of cross-
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51 359 transmission between ESBL *E. coli* and other *Enterobacteriaceae* has been clearly established⁴⁵.
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53 360 In a previous publication from our group¹², however, we showed no difference in the
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55 361 effectiveness of control measures, whatever the *Enterobacteriaceae* considered, either *E. coli* or
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3 362 another *Enterobacteriaceae*. We therefore decided to consider *Enterobacteriaceae* globally, a
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5 363 situation that can be extended to carbapenemase-producing *Enterobacteriaceae*.
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10 365 We modelled an ICU as a single-room unit where transmission among patients results via
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12 366 contacts with HCWs. In the absence of detailed information on transmission of ESBL-PE in
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14 367 hospital wards, we ignored direct HCW-to-HCW transmissions as well as environmental
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16 368 contamination or excreta management.
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22 370 ESBL-PE acquisition in the ICU can lead to transmission from an ICU-acquired case and
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24 371 infection in downstream units, thus increasing costs of hospitalization. Moreover, colonization
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26 372 with ESBL-PE may persist several months after hospital discharge⁴⁶, therefore increasing the risk
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28 373 of infection with potential subsequent treatment failure. Thus, an efficient intervention to prevent
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30 374 the inhospital cross-transmission may also have an impact on the prevention of post-discharge
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32 375 infections and the need for readmissions.
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36 376 Our cost evaluation therefore underestimated health benefits and cost savings resulting from
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38 377 inhospital interventions to control ESBL-PE, but participate to demonstrate the usefulness of
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40 378 inhospital intervention to prevent further costs.
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45 46 380 **CONCLUSION**

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49 381 Our study suggests that a universal approach with improved compliance with HH was the most
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51 382 cost-saving strategy to prevent the transmission of ESBL-PE in an ICU setting. Screening and
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53 383 cohorting of carriers had comparable effectiveness to HH improvement, but was more expensive.
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3 384 Antibiotic stewardship was not cost-effective in comparison with other options. However, adding
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5 385 antibiotic restriction to the HH or the screening and cohorting strategies slightly improved their
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8 386 effectiveness and may be worthy of consideration by decision-makers.
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11 12 13 388 **ACKNOWLEDGMENTS**

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16 389 We thank Dr. Laurence Armand for useful discussion on our study.
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20 21 391 **FOOTNOTES**

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23
24 392 **Contributors:** YY, JCL, CP and LKS designed the study. YY, JCL, PYB, AA, CP and LKS
25
26 393 contributed to the development of the model. CP, AP, GB, ER and LKS collected the data. CP
27
28 394 and LKS wrote the code. LKS conducted computer simulations and result analysis. LKS, JCL
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31 395 and YY drafted the manuscript. All authors read and critically revised the manuscript.

32
33 396 **Funding:** This work was supported by the French government (PREPS program [grant number
34
35
36 397 13-0693]) and by the National Institute for Health and Medical Research (INSERM).

37
38 398 **Competing interests:** None declared.
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41 399 **Data sharing statement:** Details of the computer code for the model are available from the
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43 400 corresponding author.
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3 539 **FIGURE LEGENDS**
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5 540 **Figure 1.** Model of transmission of ESBL-PE between patients through contacts with health-care
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8 541 workers (HCWs) and impact of infection control measures in the transmission process. Solid
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10 542 lines represent the transitions between population groups and dashed lines represent the
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12 543 transmission between patients and HCWs.

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15 544**A.** Impact of universal (horizontal) control measures: 1) hand hygiene (reduces the transmission
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17 545 among patients and HCWs); 2) antibiotic restriction (reduces the risk of transmission from
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19 546 colonized patients receiving antibiotics to HCWs or from contaminated HCWs to uncolonized
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21 547 patients receiving antibiotics).
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27 549**B.** Impact of targeted (vertical) control measures: screening of patients on ICU admission and
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29 550 identification of patients who had positive screening results (patients surrounded by a shaded
30
31 551 box). Implementation of: 1) contact precautions (hand hygiene reduces the transmission from
32
33 552 identified ESBL-PE carriers to HCWs); 2) cohorting of identified ESBL-PE carriers and
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35 553 attribution of a dedicated HCW (prevents the transmission from cohorted patients to other HCWs
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37 554 and patients). Note that we included two categories of colonized patients: 1) who had false
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39 555 negative admission screening results; 2) who had positive admission screening results (patients
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41 556 surrounded by a shaded box).
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48 558 **Figure 2.** Patient outcomes after one year under the different control strategies tested. (A) New
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50 559 acquisitions (transmissions) of ESBL-PE per 100 admissions, (B) Total number of ESBL-PE
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52 560 infections per 100 admissions in patients who: 1) acquired colonization in the ICU, and 2) those
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54 561 who were already colonized at ICU admission.
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3 562 Strategies are: (1) Base case (reference strategy with no control intervention and hand hygiene
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5 563 compliance of 55%/60% before/after patient contact); (2) Hand hygiene improvement to
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8 564 80%/80%; (3) Hand hygiene improvement to 55%/80%; (4) Antibiotic reduction; (5) Screening
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10 565 of all admissions and contact precautions for identified carriers; (6) Screening of all admissions
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12 566 and cohorting of identified carriers; (7) Hand hygiene improvement to 80%/80% and antibiotic
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14 567 reduction; (8) Hand hygiene improvement to 55%/80% and antibiotic reduction; (9) Screening of
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16 568 all admissions, contact precautions with identified carriers and antibiotic reduction; (10)
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18 569 Screening of all admissions, cohorting of identified carriers and antibiotic reduction.
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24 571 **Figure 3.** Cost-effectiveness plane showing the incremental health benefits (infections avoided)
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26 572 and costs relative to the least expensive strategy (Strategy 2). Strategies 1, 3, 4, 5, 8, 9 are
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28 573 dominated as they have both a worse outcome and a higher cost. The efficiency frontier (grey
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30 574 line), joins Strategy 2 with more expensive and more efficient strategies (7 and 10). Strategy 6 is
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32 575 extended to this frontier and excluded by the principle of extended dominance. The slope of the
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34 576 efficiency frontier represents the incremental cost-effectiveness.
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38 577 Strategies are: (1) Base case (reference strategy with no control intervention and hand hygiene
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40 578 compliance of 55%/60% before/after patient contact); (2) Hand hygiene improvement to
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44 580 of all admissions and contact precautions with identified carriers; (6) Screening of all admissions
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46 581 and cohorting of identified carriers; (7) Hand hygiene improvement to 80%/80% and antibiotic
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48 582 reduction; (8) Hand hygiene improvement to 55%/80% and antibiotic reduction; (9) Screening of
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52 584 Screening of all admissions, cohorting of identified carriers and antibiotic reduction.
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586 **TABLES**587 **Table 1.** Cost parameters, their sources and ranges for sensitivity analyses.

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

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	<u>Resource</u>	<u>Cost (€[*])</u>		<u>Source</u>	<u>Distribution</u>
		<u>mean</u>	<u>SD</u>		
	ICU bed-day	1,583	226	AP-HP ^a	Gamma
<u>Universal strategies</u>					
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
<u>Targeted strategies</u>					
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

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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

592 ^a AP-HP: The Assistance Publique – Hôpitaux de Paris

593 ^b Assumption based on expert opinion

594 ^c Cost of staff from a hospital perspective (salary + employer contributions)

595 * 1€ = US \$0.94

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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 (€)	of Infections due to ESBL-PE/100 admissions	Incremental cost/100 admissions (€)	Incremental effect (infections avoided/100 admissions)	Incremental (ΔE)	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

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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

600 ^a Relative to strategy 2

601 ^b Relative to strategy 7

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

603 ^d Dominated by extended dominance: Strategy is dominated by extended dominance if the linear combination of other strategies produces

604 greater benefit at lower cost.

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For peer review only

Figure 1A

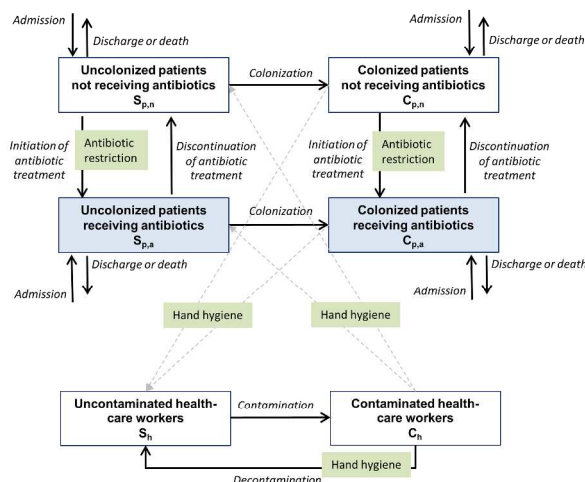


Figure 1B

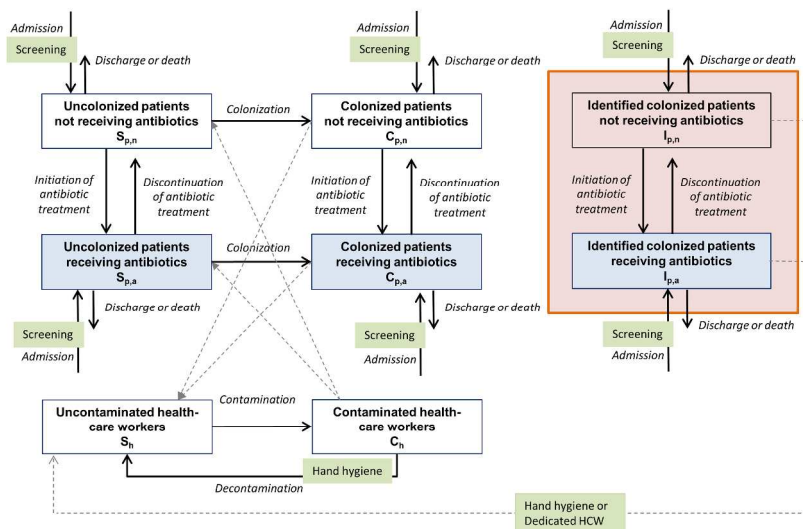


Figure 1. Model of transmission of ESBL-PE between patients through contacts with health-care workers (HCWs) and impact of infection control measures in the transmission process. Solid lines represent the transitions between population groups and dashed lines represent the transmission between patients 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 by 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 cohorting patients to other HCWs and patients). Note that we included two categories of colonized patients:

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4 (patients surrounded by a shaded box).
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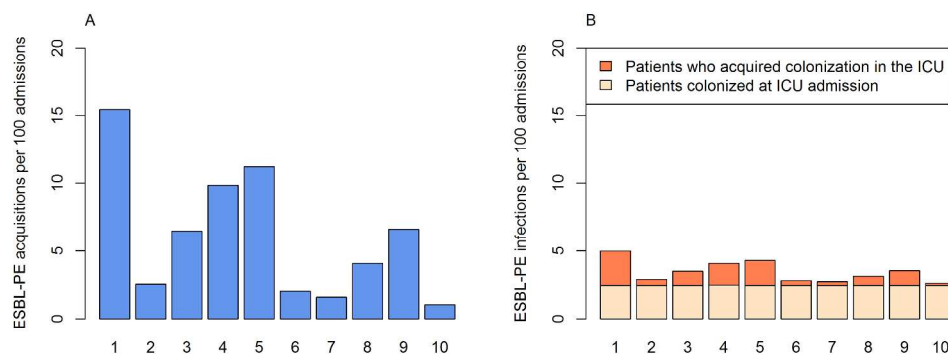


Figure 2. Patient outcomes after one year under the different control strategies tested. (A) New acquisitions (transmissions) of ESBL-PE per 100 admissions, (B) Total number of ESBL-PE infections per 100 admissions in patients who: 1) acquired colonization in the ICU, and 2) those who were already colonized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

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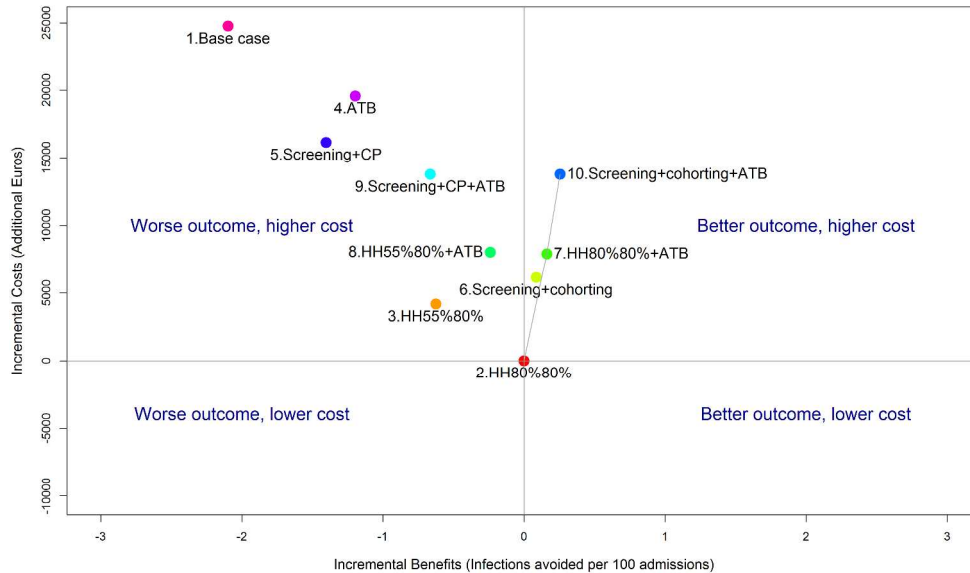


Figure 3. Cost-effectiveness plane showing the incremental health benefits (infections avoided) and costs relative to the least expensive strategy (Strategy 2). Strategies 1, 3, 4, 5, 8, 9 are dominated as they have both a worse outcome and a higher cost. The efficiency frontier (grey line), joins Strategy 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.

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 with 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.

359x229mm (300 x 300 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 $C_{p,a}$).

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 HCWs⁴⁻⁶. 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 ($b_{..}$), 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.

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3 Firstly, we modelled the implementation of contact precautions (improvement of HH) in contacts
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5 with identified ESBL-PE carriers. HH for other patients was maintained at baseline level.
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8 The transmission parameters were defined as follows:
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11 $\beta_{p,a} = a \cdot b_{p,a} \cdot (1 - p_p)$
12 } Transmission from contaminated HCWs to
13 $\beta_{p,n} = a \cdot b_{p,n} \cdot (1 - p_p)$ } uncolonized patients (receiving antibiotics or not)
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17 $\beta_{h,a} = a \cdot b_{h,a} \cdot (1 - p_h)$
18 } Transmission from non-identified, colonized
19 $\beta_{h,n} = a \cdot b_{h,n} \cdot (1 - p_h)$ } patients (receiving antibiotics or not) to HCWs
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23 $\beta_{h,a,I} = a \cdot b_{h,a,I} \cdot (1 - p_{h,Is})$
24 } Transmission from identified, colonized
25 $\beta_{h,n,I} = a \cdot b_{h,n,I} \cdot (1 - p_{h,Is})$ } patients (receiving antibiotics or not) to HCWs
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29 Secondly, we modelled the introduction of a dedicated HCW to interact only with identified,
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31 colonized patients. The transmission parameters were defined as follows:
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37 $\beta_{p,a} = a \cdot b_{p,a} \cdot (1 - p_p)$
38 } Transmission from contaminated HCWs to
39 $\beta_{p,n} = a \cdot b_{p,n} \cdot (1 - p_p)$ } uncolonized patients (receiving antibiotics or not)
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42 $\beta_{h,a} = a \cdot b_{h,a} \cdot (1 - p_h)$
43 } Transmission from non-identified, colonized
44 $\beta_{h,n} = a \cdot b_{h,n} \cdot (1 - p_h)$ } patients (receiving antibiotics or not) to HCWs
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48 $\beta_{h,a,I} = 0$
49 } Transmission from identified, colonized
50 $\beta_{h,n,I} = 0$ } patients (receiving antibiotics or not) to HCWs
51 (other than the dedicated HCW)
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3 Once colonized, patients do not clear ESBL-PE colonization before discharge. HCWs are
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5 transiently contaminated and they become decontaminated either by performing HH or after a
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7 mean waiting time of one hour.
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11 The model parameters and their values are presented in **Supplementary Table 1**. Parameter
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13 values were derived from multicentre studies if available, and by default based on best evidence
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15 from the literature or expert opinion.
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18 We modelled an ICU with 10 single-rooms with continuous presence of 6 HCWs⁸. We assumed
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20 100% bed occupancy. Consequently, a shorter length of stay (LOS) implies a higher turnover and
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22 possible admission of colonized patients⁹. As reported recently, the ICU LOS of ESBL-PE
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24 carriers is longer (13 days) than uncolonized patients (5 days)¹⁰. The extended LOS in ESBL-PE
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26 carriers increases the colonization pressure in the ICU, consequently increasing the risk of cross-
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28 transmission.
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32 When targeted control strategies were used, colonization was detected using a screening method
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34 assuming that screening results were instantaneous. We assumed that the sensitivity of the
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36 screening method was 95%¹¹. Screening results had 100% specificity.
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42 **Costs of control strategies**

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45 We estimated the costs of control strategies over the one-year simulation period. See **Table 1** for
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47 details on cost parameters.
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50 We used gamma distribution to represent uncertainty in cost parameters. Cost data are
51
52 constrained to be non-negative and gamma distribution is often used in decision modelling. To
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54 estimate the parameters of the gamma distribution to cost data, we used the method of moments.
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57 When data were available from the hospital data base, e.g. cost of ICU bed-day, we performed a
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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 program¹². 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 nurses¹⁴.

Antibiotic stewardship programs (ASPs) have proven efficient in reducing antibiotic use and antibiotic duration in hospitals¹⁵⁻¹⁷. Interventions included in ASPs require additional resources associated with higher costs¹⁸. One of the resources needed and associated with the highest costs is the staff time¹⁹. 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 study¹⁷.

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3 The cost of screening was first based on the cost of testing materials and on the cost of laboratory
4 technician time spend on a rapid screening test (e.g. PCR).
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8 For the strategy in which screening at admission was combined with contact precautions for
9 identified ESBL-PE carriers, we also included the cost of contact precautions such as the cost of
10 improved HH (i.e. the cost of the alcohol-based hand rub), and the costs associated with the time
11 HCWs required for hand disinfection. Here we did not consider the cost of an infection control
12 nurse. We hypothesized that knowing that the patient is an ESBL-PE carrier, HCWs would
13 adhere more easily to HH.
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17 For the strategy in which screening on admission was combined with cohorting of identified
18 ESBL-PE patients, the cost of cohorting was the cost of contact precautions and the cost of
19 additional HCWs caring for cohorted patients (based on expert opinion). For screening
20 interventions, the cost of HH in non-carriers and unidentified carriers was considered to be
21 identical to the costs of the baseline level.
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37 **Cost of hospital-acquired infections**

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39 The mean cost of an ICU bed-day was estimated at €1,583 (based on the average amount paid in
40 2015 for ICUs in Paris public hospitals (AP-HP). This amount is based on French Diagnosis-
41 Related Groups and complementary revenues specific to ICU units and divided by the mean
42 length of stay in ICUs in 2015²⁰. Based on published reports, the cost per day of a patient with
43 ESBL-PE infection was 50% higher than the cost of an uninfected patient^{21,22}. The cost of an
44 ESBL-PE infection was estimated using the ESBL-PE-attributable LOS and the cost of a hospital
45 bed-day for infected patients^{23,24}.
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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 period⁷.

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 R²⁵.

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.

Parameter	Description	Value	Source	Sensitivity analysis	
				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_{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	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

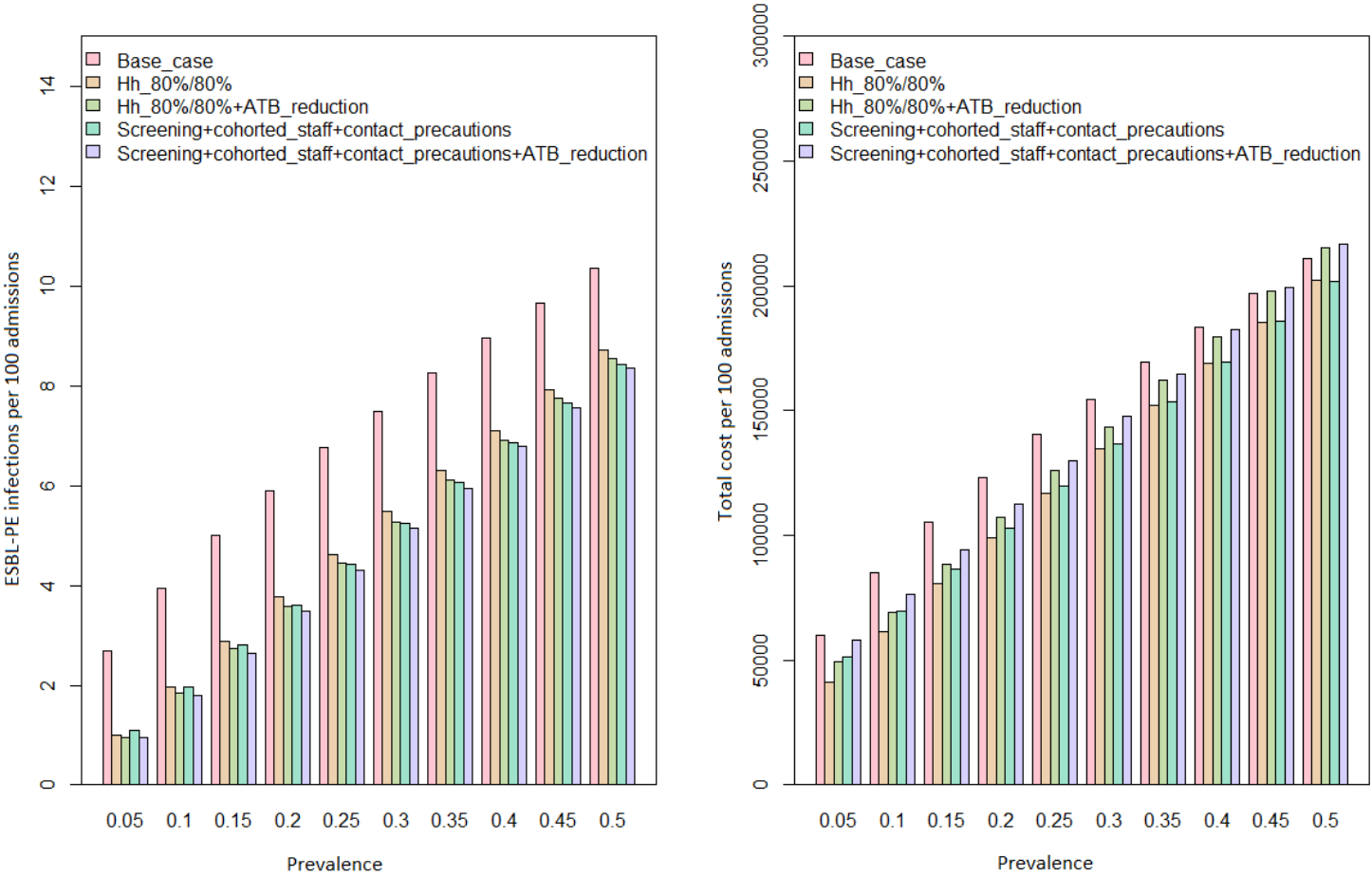
Supplementary Text S2- Sensitivity analyses

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).

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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

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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%)**.

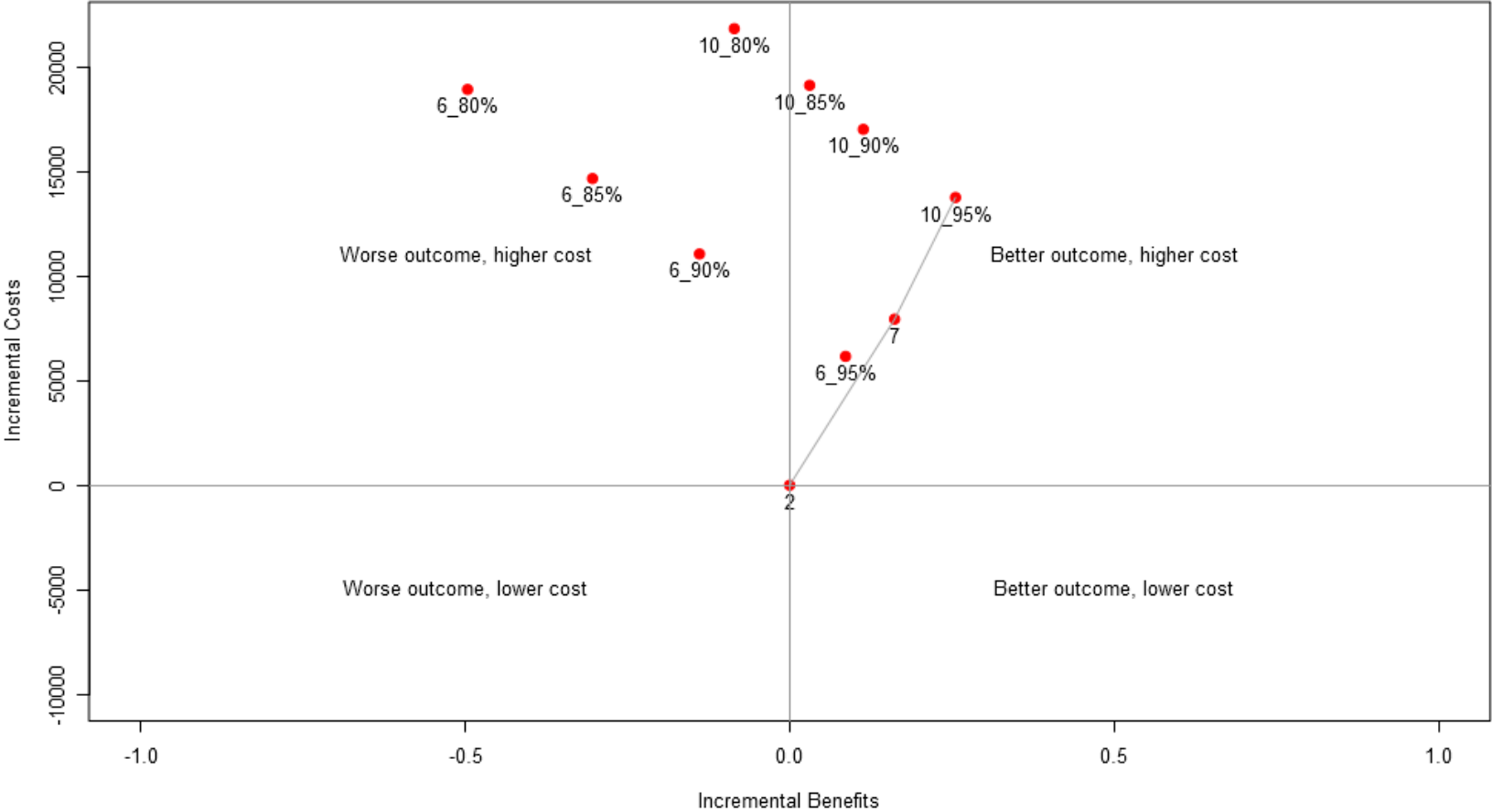
Strategy	Total cost/ 100 admissions (€)	Infections/ 100 admissions	Incremental cost/100 admissions (ΔC) (€)	Incremental effect (ΔE) (infections avoided/100 admissions)	ICER (ΔC/ΔE) (€ / infection avoided)
2: Hh 60%/70%	84 331	3.191			
6: Screening + cohorted staff + contact precautions	84 561	2.77	230	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

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3 4. Impact of lower **sensitivity to detect ESBL-PE carriage** in screening strategies.
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6 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
7 2) and HH 80%/80% and antibiotic reduction (Strategy 7) always dominated the screening strategies (Strategy 6 and 10) (**Supplementary Figure**
8 **S2**).
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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 than 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

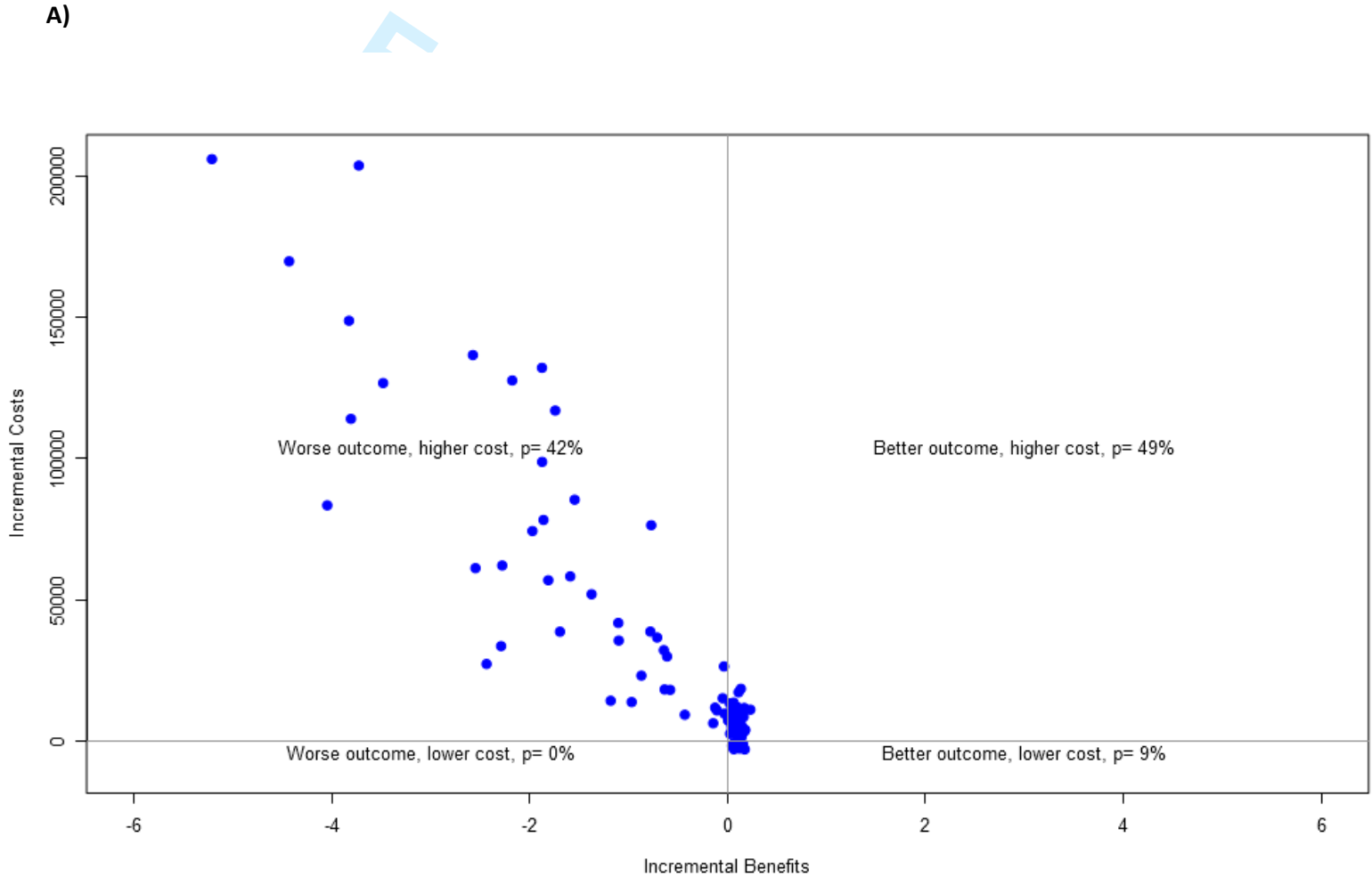
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Supplementary Table S5B Impact of infection control nurse’s time working on the hand hygiene strategy and the level of hand hygiene achieved on model predictions compared to the Screening and cohorting strategy. The cost-effective ratio (CER) was calculated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

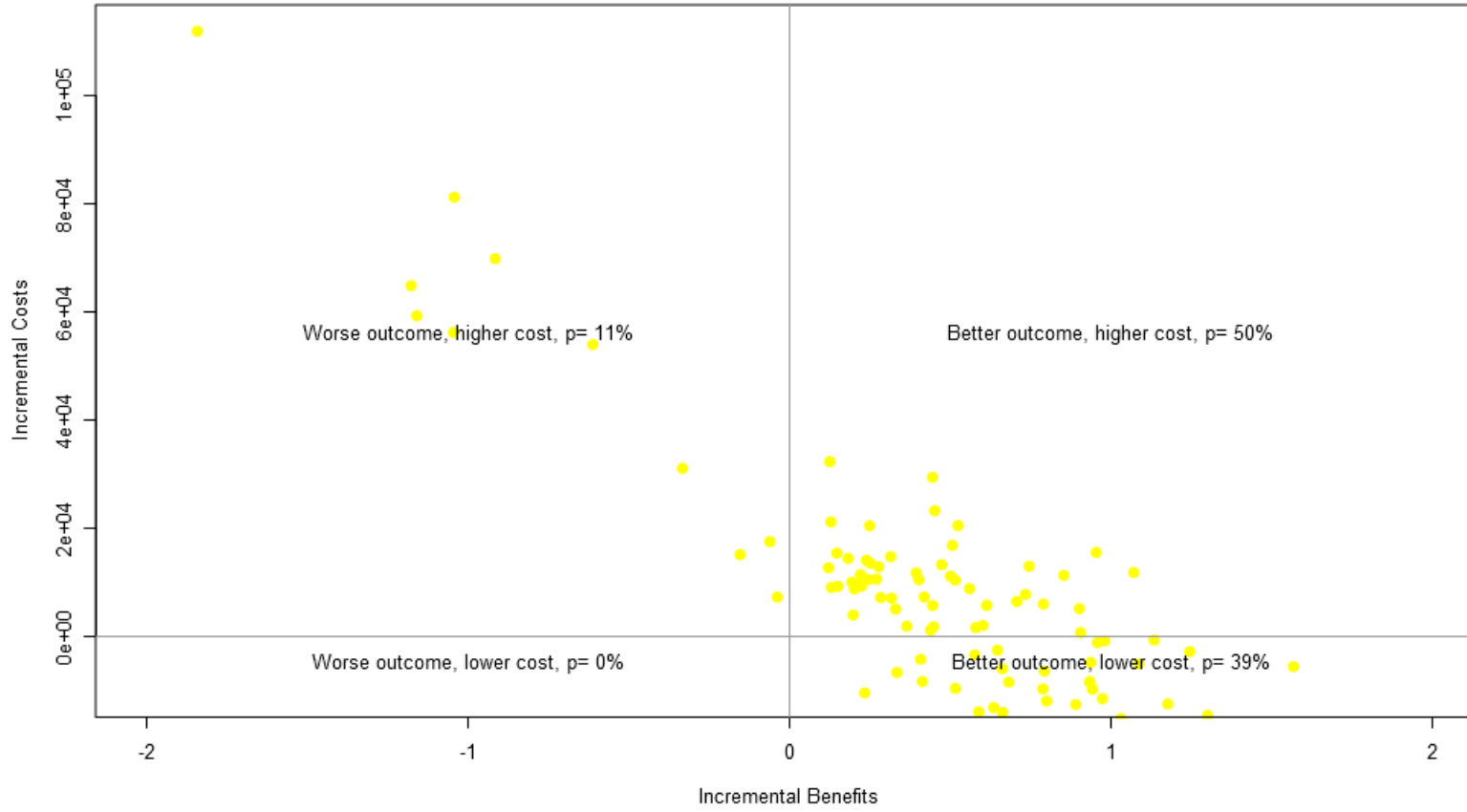
Level of hand hygiene before contact with patient (%)	Level of hand hygiene after contact with patient (%)	Mean increase in hand hygiene from baseline (%)	Number of infections/100 admissions	Total cost/100 admissions (€)	CER (vs Hand hygiene strategy)
Screening and cohorting					
55 (with non cohorted 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”.

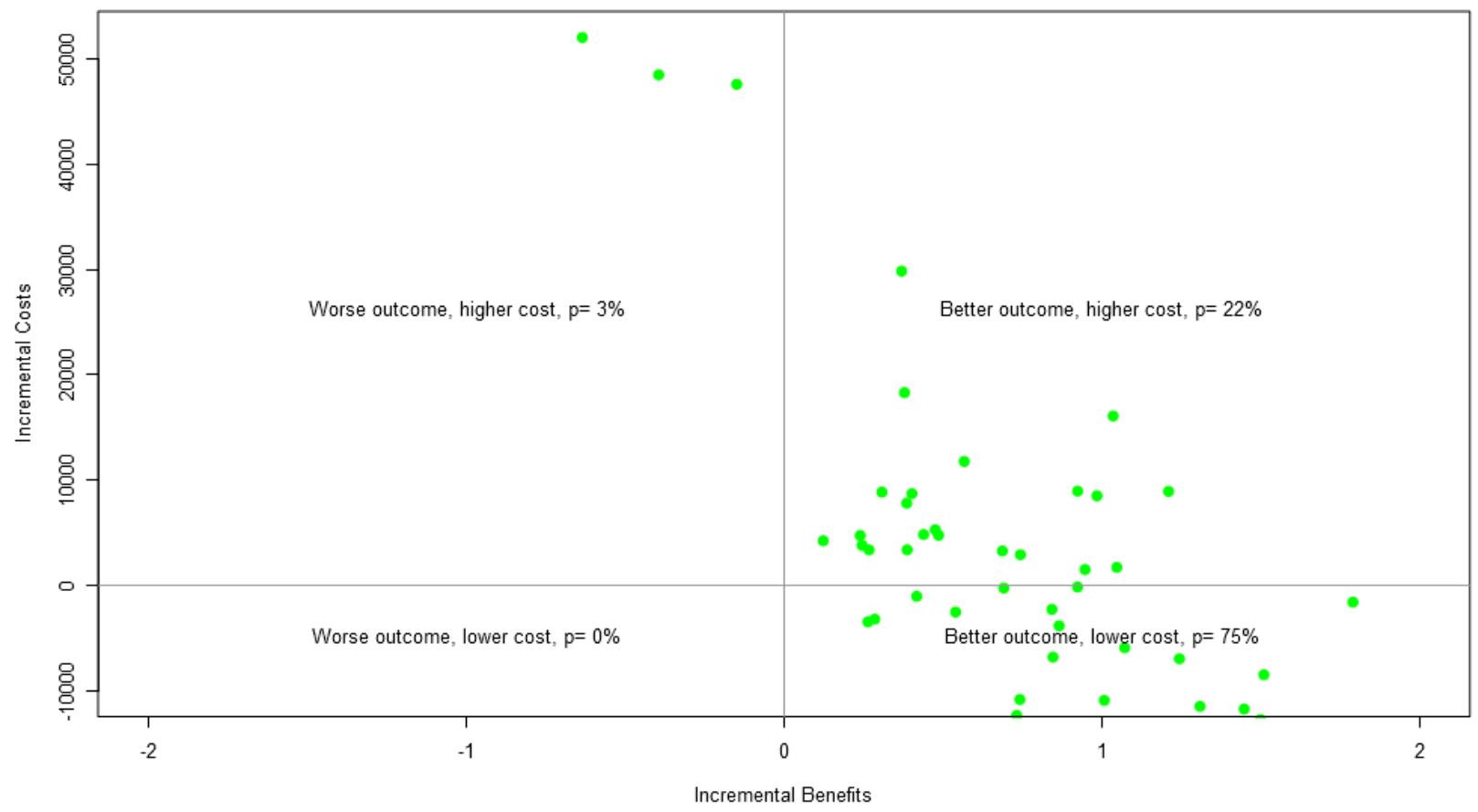


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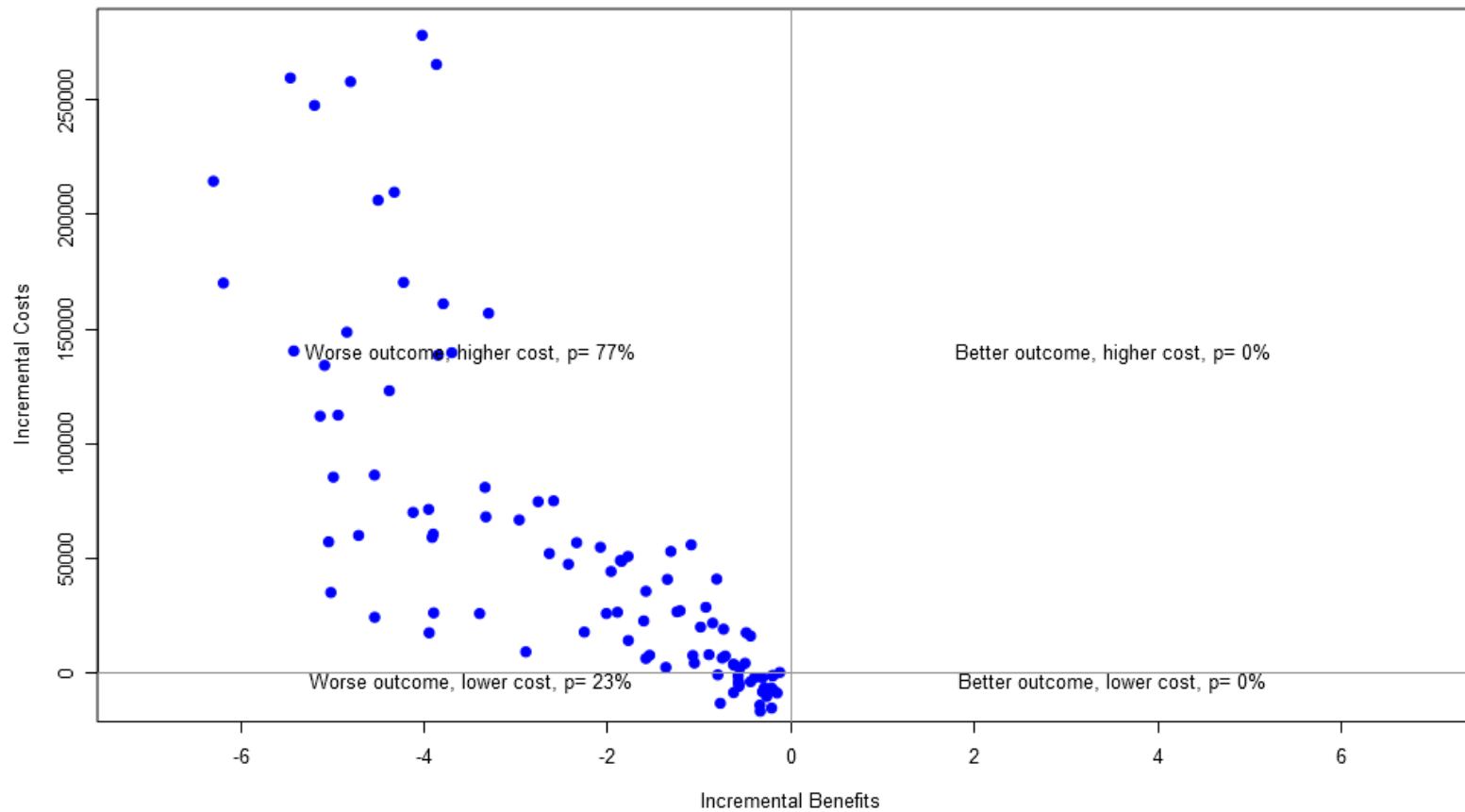
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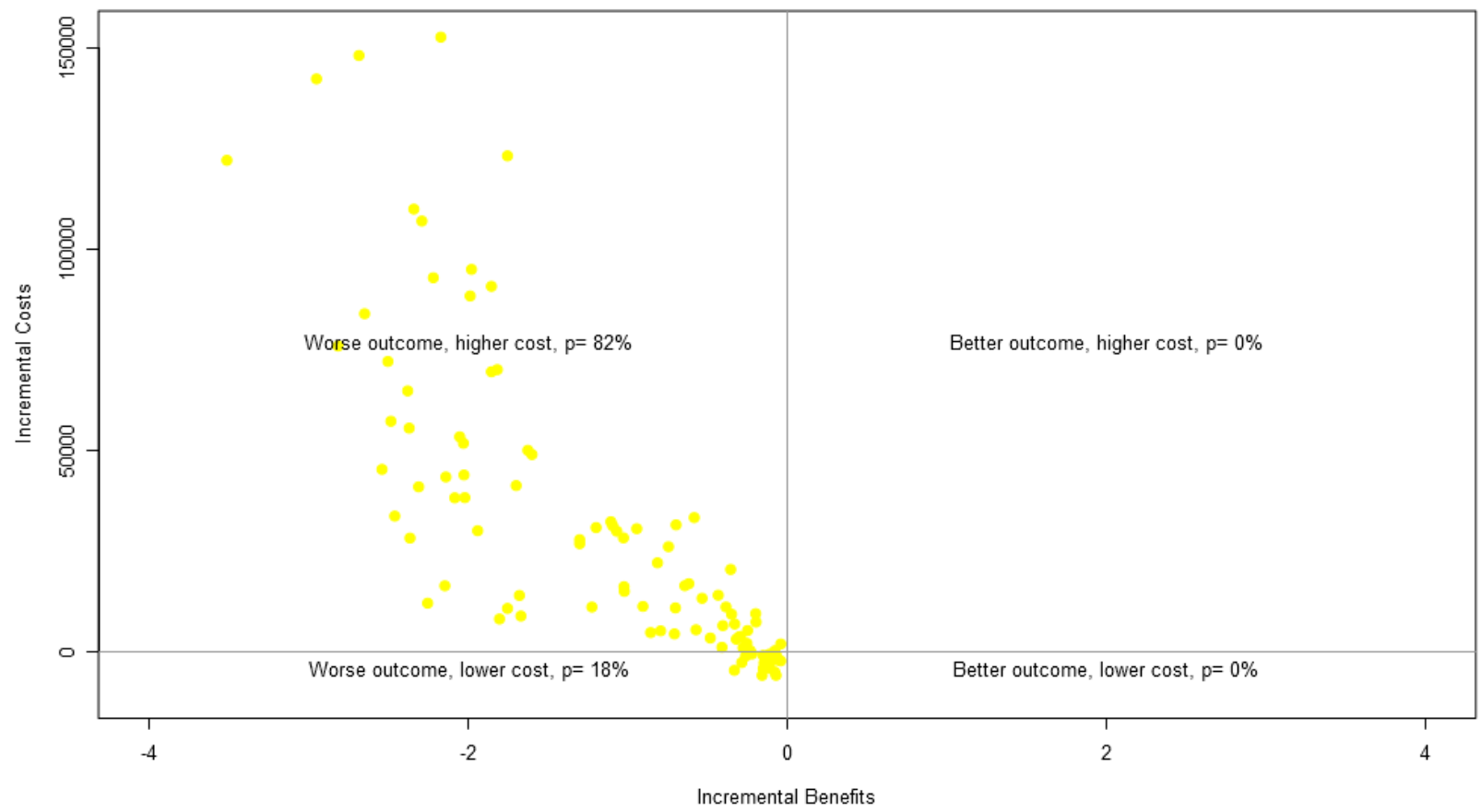
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3 **Supplementary Figure S4** Results of probabilistic sensitivity analysis. Cost-effectiveness plane shows the incremental health benefits (infections avoided)
4 and costs for Screening and contact precautions (Strategy 5). relative to horizontal strategies: A) Hand hygiene improvement to 80%/80% (Strategy 2); B)
5 Hand hygiene improvement to 55%/80% (Strategy 3); C) Antibiotic reduction (Strategy 4). The frequency that the Strategy 6 was in one of four quadrant of
6 CE plane is represented by “p”.

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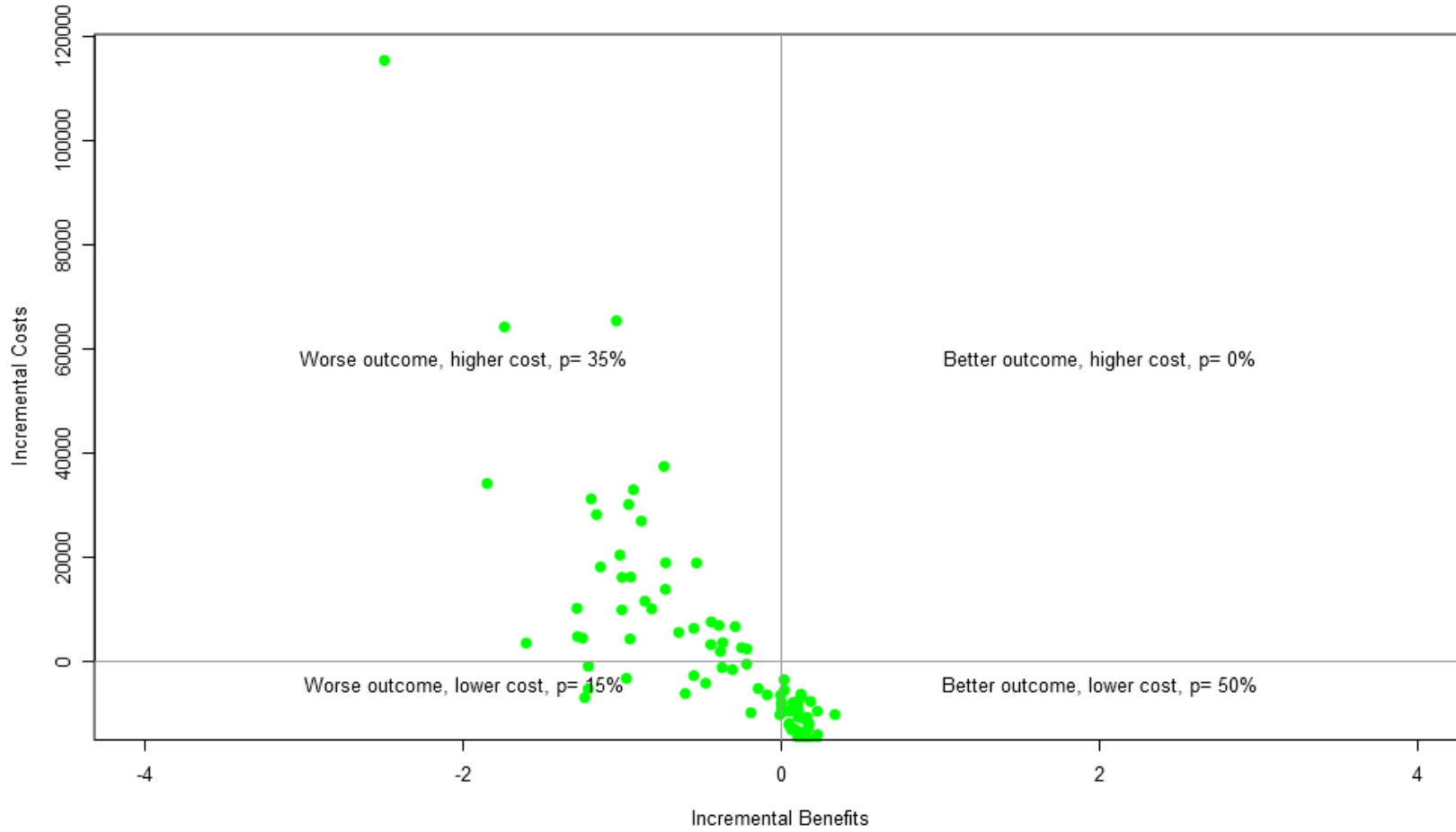


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CHEERS Checklist

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 applicable- 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	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	---



1		11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Supp.Text S1
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5	Measurement and	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	---
6	valuation of preference			
7	based outcomes			
8				
9	Estimating resources	13a	<i>Single study-based economic evaluation:</i> 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.	---
10	and costs			
11				
12		13b	<i>Model-based economic evaluation:</i> 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
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23	Currency, price date,	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
24	and conversion			
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29	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
30				
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33	Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Suppl.Text S1
34				
35	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
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43	Results			
44	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
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50	Incremental costs and	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
51	outcomes			
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55	Characterising	20a	<i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	---
56	uncertainty			
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1		of methodological assumptions (such as discount rate, study	_____
2		perspective).	_____
3			
4	20b	<i>Model-based economic evaluation</i> : Describe the effects on the	Page 11 and
5		results of uncertainty for all input parameters, and uncertainty	Suppl. Text S2
6		related to the structure of the model and assumptions.	_____
7	Characterising	21	
8	heterogeneity		
9		If applicable, report differences in costs, outcomes, or cost-	---
10		effectiveness that can be explained by variations between	
11		subgroups of patients with different baseline characteristics or	
12		other observed variability in effects that are not reducible by	
13		more information.	_____
14	Discussion		
15	Study findings,	22	
16	limitations,		Pages 12–17
17	generalisability, and	Summarise key study findings and describe how they support	
18	current knowledge	the conclusions reached. Discuss limitations and the	
19		generalisability of the findings and how the findings fit with	
20		current knowledge.	_____
21	Other		
22	Source of funding	23	
23			Page 18
24		Describe how the study was funded and the role of the funder	
25	Conflicts of interest	24	
26			Page 18
27		Describe any potential for conflict of interest of study	
28		contributors in accordance with journal policy. In the absence	
29		of a journal policy, we recommend authors comply with	
30		International Committee of Medical Journal Editors	
31		recommendations.	_____

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

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: <http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp>

The citation for the CHEERS Task Force Report is:

Husereau D, Drummond M, Petrou S, et al. 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. *Value Health* 2013;16:231-50.

