Supplementary material

Supplementary Text S1

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

Transmission model

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

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

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

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

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

Mathematical model under targeted infection control measures

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

Model parameters

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

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

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

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

The transmission parameters were defined as follows:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Costs of control strategies

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

We used gamma distribution to represent uncertainty in cost parameters. Cost data are constrained to be non-negative and gamma distribution is often used in decision modelling. To estimate the parameters of the gamma distribution to cost data, we used the method of moments. When data were available from the hospital data base, e.g. cost of ICU bed-day, we performed a goodness of fit test (Kolmogorov-Smirnov) to assure that a random sample comes from a gamma distribution. The test was performed using **R** software.

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

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

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

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

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

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

Cost of hospital-acquired infections

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

Model calibration

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

Model simulations and outcomes

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

TABLES

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

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

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

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

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

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

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

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