PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Universal or targeted approach to prevent the transmission of extended-spectrum beta-lactamase–producing Enterobacteriaceae in intensive care units? A cost-effectiveness analysis
AUTHORS	Sloma, Lidia; Lucet, Jean-Christophe; Perozziello, Anne; Pelat, Camille; Birgand, Gabriel; Ruppé, Etienne; Boelle, Pierre-Yves; Andremont, Antoine; Yazdanpanah, Yazdan

VERSION 1 - REVIEW

REVIEWER	David RM Smith Modelling and Economics Unit, National Infection Service, Public Health England; United Kingdom
REVIEW RETURNED	16-May-2017

GENERAL COMMENTS	This mathematical modelling study estimates the cost-effectiveness of interventions to reduce the transmission of ESBL-PE in a high-income ICU setting. This is a timely study and it has several strengths, such as its use of parameters from recent multicentre studies, its thorough probabilistic sensitivity analysis and its clear results and figures. However, there are also important problems with the work, such as poorly justified model assumptions, unclear methods, and a lack of discussion about important aspects of the model and ESBL-PE interventions and transmission. Other more more minor problems, such as a lack of references to the literature and unclear writing style, also need attention. If these issues are addressed, and in particular if authors are more clear and open about the uncertainties, assumptions and limitations that underlie their model, then this study could be a meaningful contribution to the field and could be of use to decision-makers. Major comments: 1. A fundamental model assumption is that exposure to antibiotics increases the rate of transmission from colonised patients to HCWs, but the only reference provided is to a modelling study that also made this assumption (D'Agata et al. 2005 J Infect Dis). This assumption needs to be properly defended with citations or rationale/arguments. 2. Calculated ICER values in Table 2 do not correspond with incremental costs and effects, even if rounding error is accounted for (e.g., 7 941/0.1618 = 49 079, but the reported ICER = 49 025). Have all calculations been double-checked? 3. The authors report that two recent high-profile modelling studies

	(Robotham et al. 2016 Lancet Infect Dis; Gidengil et al. 2015 Infect Control Hosp Epidemiol) found decolonisation to be the most cost-effective intervention for MDROs. So then why was this intervention not included in this study? 4. Expert opinion is cited as a source of parameter estimates, but no information is provided on how expert opinions were quantified, neither in the methods nor the supplement. Was formal expert elicitation methodology followed? Which parameters were obtained through experts -- the ones with no source in Table 1? 5. I'm not convinced the antibiotic stewardship intervention (halving prescribing) is realistic. We recently conducted a review of antibiotic prescribing in English primary care and found room for up to a 30% reduction in prescribing when the most extreme assumptions were made – is there any reason to believe a 50% reduction in the (French) ICU is achievable? Furthermore, although admittedly difficult to quantify, there are likely costs to dramatically reducing antibiotic use (i.e., complications) that are worth discussing. It also seems surprising that reducing the use of antibiotics by 50% is really a “negligible” cost savings, especially when other minor costs such as hand rub are included. 6. The “Screening test + laboratory costs” (Table 1) intervention is unclear. The supplement states that the time between collection of specimens and reporting results was <1 day, but the rest of the paper (in Fig 2 and main text) seems to indicate that screening results are instantaneous – no mention is made of colonised patients spending <1 day in the ICU before being “isolated”. The way that this was modelled and costed needs to be made more clear, and the legitimacy of the assumptions made will depend on the intervention used. For example, past studies (e.g., Robotham et al. 2016 Lancet Infect Dis) have carefully differentiated between options such as PCR (faster, more expensive) and chromogenic agar (slower, cheaper). 7. Known and unknown ecological differences between ESBL-PE species are completely ignored. It is not uncommon for studies to group ESBL-PE/HRE together, particularly when AMR is the primary focus, but it is not clear that these differences can be ignored in a dynamic transmission model, especially given that there is likely to be substantial heterogeneity in colonisation and transmission (e.g., hospital-associated E. coli infections seem to occur mostly in patients colonised on admission, whereas in K. pneumoniae within-hospital transmission plays a larger role). Furthermore, the structure of the transmission model is predicated on HCWs acting as vectors. Although this has been shown in organisms such as MRSA, no source for this in ESBL-PE is provided (line 70), and indeed transmission routes and rates may vary substantially between ESBL-PE species. Although the authors acknowledge that environmental and HCW-to-HCW transmission are omitted, and it may be true that such simplifying assumptions are necessary at this time due to lack of data (and there is no doubt that the role of HCW as vectors is important), the above points merit substantial discussion as they are great sources of uncertainty not just in the model's parameterisation but in its structure. 8. Inclusion of other hospital settings, let alone the community, was beyond the scope of this study. Nevertheless, the community is likely to play an important role (e.g., to my knowledge a substantial

	proportion of healthcare-associated Enterobacteriaceae infections are in patients who are colonised when in hospital, are then discharged, and are later readmitted with infection). Authors should discuss the potential impacts that knock-on effects of interventions may have in a real-world setting and on cost-effectiveness. 9. The exclusion of an “infected” state was not justified anywhere in the paper (although I gather that this decision was implicitly justified because a recent multicentre cohort study by Barbier et al. 2016 (J Antimicrob Chemother) found no difference in LoS between infected and colonised patients). However, from my point of view it seems very possible that infected hosts differ from colonised hosts in epidemiologically relevant ways, both in terms of parameters within the confines of this model (e.g., transmissibility, likelihood of being on antibiotics), and parameters with knock-on effects beyond the scope of this model (e.g., if infected and colonised patients have different rates of readmission with infection, different rates of transmission in the community setting, etc.), which are nevertheless important and merit discussion. Minor comments: line 33: Should emphasise high-income setting 45: “HH compliance improvement to 80%/80%” – 80%/80% is not defined 51: Conclusions are unclear with respect to ATB. Why is this not phrased in terms of cost-effectiveness, and why does it not acknowledge that the added benefits of ATB and cohorting to HH come at a great cost? 64: “The incidence of infection and colonization...” Citation needed. 72: Authors imply that ESBL-PE infection is tied to longer hospitalisation, but later state that infected patients do not stay longer than colonised patients 82: Authors make a statement about “most studies” yet only cite one (albeit a very good one) 187: If a colonised patient has a 16.4% chance of developing infection while in the ICU, should 15 new acquisitions/100 admissions not result in ~2.5 new infections/100 admissions? It seems from Fig 2 that this is the case, since only half of the 5 infections are “new” due to within-ICU transmission 263-5: This transition is unnecessary and tautological 277-9: Citations needed for both sentences. 282-4: Make more clear that ESBL-PE interventions may have positive effects on reducing the transmission of other microorganisms 291: Review, not revue 298: Why not refer to the results of your sensitivity analysis here instead of a hypothesis? 310: The major driver? Citation needed. Figure 3: Axes need units Table 1: Why were gamma distributions chosen? CHEERS: there is no justification given for the one-year time horizon CHEERS 11: in this study are there not efficacy estimates derived from the literature? Supplement: Why can't patients clear colonisation before discharge? Supplement: The layout is confusing and jumps back and forth between discussing parameters and model layout.

REVIEWER	Jeroen Schouten Radboud University Medical Centre, IQ Healthcare department Nijmegen CWZ Hospital, ICU department, Nijmegen
REVIEW RETURNED	20-May-2017

GENERAL COMMENTS	This is a very nice simulation study on a relevant subject. Although the link with real clinical care is obviously not completely predictable, this study can help decision makers and guide future reseachers in application of a simulation model in real life models. I have some remarks though: 1. There are some preassumptions made that may need some reconsideration: line 111-113 while HH compliance in some ICUs may be 60% as referenced in French hospitals, this is definitely not the case in many different other countries. Also it has been repeatedly shown that improving HH compliance from 60 to 80% is far more difficult challenging than improving from 40 to 60%. Very little ICUs manage to consistently improve HH compliance to > 60%, so costs on improving 40->60 described in referenced studies, may underestimate the effort that is required for 60-80%, inducing extra cost 2. On this same vein, the authors suggest that with antibiotic stewardship measures % of patients on antibiotics in ICU can be reduced from 56% to 28% (halved!) and a 25% reduction in duration of therapy can be achieved using stewardship interventions. One has to question if both for HH as for ABS such goals are AT ALL realistically achievable. 3. as the only stewardship intervention a 0.5 FTE ID physcian per month is taken into account. There is no supporting literature that the presences of an ID physicain at a word garantuees reduction of AB use either by reduced prescribing or shorter AB use. Also employing a 0.5 FTE ID physician on an ICU ward is expensive, ABS in ICU e.g. by reducing DOT by the use of procalcitonin (ref de Jong E, Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. Lancet Infect Dis. 2016 Jul;16(7):819-27)) reduces DOT by appr. 25% In other words, have the authors thought about other potential ABS interventions? and their costs? Have they considered that costs of an ABS could be far LESS costly than they assume 4. In ICUs where chloorhexidine decontamination policies OR SDD/SOD are used the assumptions that authors make re: the relationship between restrictive antibiotic policies and colonization probabiltiy. I would like the authors to comment on that.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:

David RM Smith
Modelling and Economics Unit, National Infection Service, Public Health England; United Kingdom

This mathematical modelling study estimates the cost-effectiveness of interventions to reduce the

transmission of ESBL-PE in a high-income ICU setting. This is a timely study and it has several strengths, such as its use of parameters from recent multicentre studies, its thorough probabilistic sensitivity analysis and its clear results and figures. However, there are also important problems with the work, such as poorly justified model assumptions, unclear methods, and a lack of discussion about important aspects of the model and ESBL-PE interventions and transmission. Other more minor problems, such as a lack of references to the literature and unclear writing style, also need attention. If these issues are addressed, and in particular if authors are more clear and open about the uncertainties, assumptions and limitations that underlie their model, then this study could be a meaningful contribution to the field and could be of use to decision-makers.

Major comments:

1. A fundamental model assumption is that exposure to antibiotics increases the rate of transmission from colonised patients to HCWs, but the only reference provided is to a modelling study that also made this assumption (D'Agata et al. 2005 J Infect Dis). This assumption needs to be properly defended with citations or rationale/arguments.

We thank the Reviewer for this remark. We have replaced the reference (D'Agata et al. 2005 J Infect Dis) in Supplementary Text S1 by three more appropriate references: Ruppé and Andremont, Front Microbiol, 2013; Lerner et al. Clin Microbiol Infect, 2015; Pultz and Donskey, Antimicrob Agents Chemother, 2007.

2. Calculated ICER values in Table 2 do not correspond with incremental costs and effects, even if rounding error is accounted for (e.g., 7 941/0.1618 = 49 079, but the reported ICER = 49 025). Have all calculations been double-checked?

We thank the Reviewer for the detailed review of the data presented. The error was due to rounding error in incremental costs and effects. We have corrected the ICER values and corresponding incremental costs and effects in the Table 2.

3. The authors report that two recent high-profile modelling studies (Robotham et al. 2016 Lancet Infect Dis; Gidengil et al. 2015 Infect Control Hosp Epidemiol) found decolonisation to be the most cost-effective intervention for MDROs. So then why was this intervention not included in this study?

We strongly believe that in the case of ESBL-PE, decolonisation is a very short-term solution with long-term adverse effects. Huttner and colleagues in J Antimicrobial Chem 2013 reported that selective digestive decontamination (SDD) leads to a reduction of the ESBL faecal concentration the days following the SDD but with a raise at day 7. Moreover, Halaby et al. 2013 Antimicrob Agents Chemother showed that using an antibiotic regimen (colistin-tobramycin) participated to the emergence of resistance to colimycin, the last line of antibiotics effective against Multidrug-resistant Gram negative bacilli (MDR GNB). Regarding the cutaneous decolonization, we are facing an increasing concern about chlorhexidine gluconate (CHG) resistance, with few European ICUs performing decolonisation with daily CHG body washing.

We have included in the Discussion section an explanation on why a decolonization strategy is not included in our study (line 277):

"While decolonization regimens have been indicated as cost-effective for MRSA, only a few studies have examined the effect of decolonization on ESBL-PE carriage32,33. These studies have shown that decolonization strategies might be efficacious only in the short-term. Moreover, they have reported the risk of emergence of resistance to antibiotics used for decolonisation, namely to colimycin, which is the last line effective therapy against carbapenemase-producing

Enterobacteriacae 33. Thus, decolonization was not considered in our study."

4. Expert opinion is cited as a source of parameter estimates, but no information is provided on how expert opinions were quantified, neither in the methods nor the supplement. Was formal expert elicitation methodology followed? Which parameters were obtained through experts -- the ones with no source in Table 1?

An expert group of microbiologists (Prof Antoine Andremont, Dr Etienne Ruppé and Dr Laurence Armand), infection control (Prof Jean-Christophe Lucet, Dr Gabriel Birgand) and infectious diseases specialists (Prof Yazdan Yazdanpanah) met four times to estimate parameters' values not found in the medical literature especially the time spent by health care workers on infection control programs. This was mainly based on the practices at the Bichat-Claude Bernard hospital.
Estimates regarding these parameters are reported in Table 1.

5. I'm not convinced the antibiotic stewardship intervention (halving prescribing) is realistic. We recently conducted a review of antibiotic prescribing in English primary care and found room for up to a 30% reduction in prescribing when the most extreme assumptions were made – is there any reason to believe a 50% reduction in the (French) ICU is achievable?

We thank the Reviewer for this comment. We assumed a 50% reduction in antibiotic prescriptions that was the most favourable result following the introduction of antibiotic stewardship in a French ICU. Despite this 50% reduction, we illustrated that the antibiotic stewardship strategy was less effective than hand hygiene improvement or a screening and cohorting strategy. In other words, even with a very optimistic antibiotic stewardship effectiveness, this strategy was less effective than other startegies. However, in this version of the manuscript, we performed an additional sensitivity analysis with 30% reduction in antibiotic prescription and this was added to the Supplementary Text S2). Moreover, we modified the discussion section (line 325):

"Antibiotic use is the major driver for the selection of antibiotic-resistant bacteria39 and many strategies have been proposed to reduce the use of antibiotics in hospitals40. These strategies could be implemented and associated with different efficacies and costs 41. Here, we considered that antibiotic stewardship, based on the introduction of an infectious disease specialist to the ward, led to a 50% reduction in antibiotic use 42. However, despite this optimistic scenario, we found that antibiotic stewardship was less effective than HH or a screening and cohorting strategy. "

Furthermore, although admittedly difficult to quantify, there are likely costs to dramatically reducing antibiotic use (i.e., complications) that are worth discussing.

In a recent study, Gulliford MC et al. BMJ 2016 have shown that reducing antibiotic use for respiratory tract infections in primary care doesn't lead to an increase in serious complications. However, they found that reduction of antibiotics slightly increased the incidence of pneumonia and peritonsillar abscess in patients with respiratory tract infections.

It also seems surprising that reducing the use of antibiotics by 50% is really a "negligible" cost savings, especially when other minor costs such as hand rub are included.

We estimated the cost of hand hygiene program based on guidelines of WHO (WHO Guidelines on Hand Hygiene in Health Care, 2009). The cost of antibiotic use was considered negligible in our study, as many antibiotics used in French ICUs are mostly generic, including 3rd generation cephalosporins, fluoroquinolones, aminoglycosides, and several carbapenems (imipenem and meropenem). Only rarely used antibiotics, such as linezolid or daptomycin of new combinations of Bl

BLI are not generic.

6. The “Screening test + laboratory costs” (Table 1) intervention is unclear. The supplement states that the time between collection of specimens and reporting results was <1 day, but the rest of the paper (in Fig 2 and main text) seems to indicate that screening results are instantaneous – no mention is made of colonised patients spending <1 day in the ICU before being “isolated”. The way that this was modelled and costed needs to be made more clear, and the legitimacy of the assumptions made will depend on the intervention used. For example, past studies (e.g., Robotham et al. 2016 Lancet Infect Dis) have carefully differentiated between options such as PCR (faster, more expensive) and chromogenic agar (slower, cheaper).

We agree and thanks to the Reviewer for pointing this out. Indeed, using PCR for diagnosing ESBL is not currently available commercially. We also agree that pre-emptive isolation pending results of surveillance cultures may be an important parameter to include in a modelling study. Furthermore, the results of PCR is rarely available within the hours after entering the ICU. However, we wanted to test three different major strategies for controlling MDR GNB, keeping in mind that additional parameters could be included, at the price of more complicated analysis and interpretation.

In the model, we assumed that screening results were instantaneous and the cost of screening was based on the cost of testing materials and on the cost of laboratory technician time spend on a rapid screening test (e.g. PCR). We now specified this issue in the Supplementary Text S1, in Model parameters and Costs of control strategies section:

“When targeted control strategies were used, colonization was detected using a screening method assuming that screening results were instantaneous.”

“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). “

7. Known and unknown ecological differences between ESBL-PE species are completely ignored. It is not uncommon for studies to group ESBL-PE/HRE together, particularly when AMR is the primary focus, but it is not clear that these differences can be ignored in a dynamic transmission model, especially given that there is likely to be substantial heterogeneity in colonisation and transmission (e.g., hospital-associated E. coli infections seem to occur mostly in patients colonised on admission, whereas in K. pneumoniae within-hospital transmission plays a larger role). Furthermore, the structure of the transmission model is predicated on HCWs acting as vectors. Although this has been shown in organisms such as MRSA, no source for this in ESBL-PE is provided (line 70), and indeed transmission routes and rates may vary substantially between ESBL-PE species. Although the authors acknowledge that environmental and HCW-to-HCW transmission are omitted, and it may be true that such simplifying assumptions are necessary at this time due to lack of data (and there is no doubt that the role of HCW as vectors is important), the above points merit substantial discussion as they are great sources of uncertainty not just in the model's parameterisation but in its structure.

We agree with the Reviewer. The differential capacity of cross-transmission between ESBL E coli and other Enterobacteriaceae is clearly established, see our recent review (Tschudin–Sutter S, Lucet JC et al, Clin Infect Dis 2017). In a previous publication from our group (Pelat C, Kardas L et al, ICHE 2016), we showed no difference in the effectiveness of control measures, whatever the Enterobacteriaceae considered, either E. coli or another Enterobacteriaceae. We therefore decided to consider enterobacteriacae globally, a situation that can be extended to carbapenemase-producing Enterobacteriacae
We modified the limitation section in the Discussion (line 360):

“The epidemiologic characteristics of ESBL-PE are complex and may vary, depending on ESBL-PE species. For example, Thiébaut et al. 44 showed that E.coli ESBL was mainly imported (66%) and K. Pneumoniae ESBL was acquired (77%). Furthermore, the differential capacity of cross-transmission between ESBL E. coli and other Enterobacteriaceae has been clearly established45. In a previous publication from our group12, however, we showed no difference in the effectiveness of control measures, whatever the Enterobacteriaceae considered, either E. coli or another Enterobacteriaceae. We therefore decided to consider Enterobacteriacae globally, a situation that can be extended to carbapenemase-producing Enterobacteriacae.

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

Furthermore, we added a source (Peterson and Bonomo, CMR, 2005; line 74) to justify that HCWs may act as vectors for transmission of ESBL-PE.

8. Inclusion of other hospital settings, let alone the community, was beyond the scope of this study. Nevertheless, the community is likely to play an important role (e.g., to my knowledge a substantial proportion of healthcare-associated Enterobacteriaceae infections are in patients who are colonised when in hospital, are then discharged, and are later readmitted with infection). Authors should discuss the potential impacts that knock-on effects of interventions may have in a real-world setting and on cost-effectiveness.

We agree, that placing our viewpoint in a longer time frame would even increase the impact of interventions in terms of effectiveness and health benefits and expenses avoided. We modified the section “limitations” in the Discussion, line 375:

“ESBL-PE acquisition in the ICU can lead to transmission from an ICU-acquired case and infection in downstream units, thus increasing costs of hospitalization. Moreover, colonization with ESBL-PE may persist several months after hospital discharge46, therefore increasing the risk of infection with potential subsequent treatment failure. Thus, an efficient intervention to prevent the inhospital cross-transmission may also have an impact on the prevention of post-discharge infections and the need for readmissions.
Our cost evaluation therefore underestimated health benefits and cost savings resulting from inhospital interventions to control ESBL-PE, but participate to demonstrate the usefulness of inhospital intervention to prevent further costs. “

9. The exclusion of an “infected” state was not justified anywhere in the paper (although I gather that this decision was implicitly justified because a recent multicentre cohort study by Barbier et al. 2016 (J Antimicrob Chemother) found no difference in LoS between infected and colonised patients).

However, from my point of view it seems very possible that infected hosts differ from colonised hosts in epidemiologically relevant ways, both in terms of parameters within the confines of this model (e.g., transmissibility, likelihood of being on antibiotics), and parameters with knock-on effects beyond the scope of this model (e.g., if infected and colonised patients have different rates of readmission with infection, different rates of transmission in the community setting, etc.), which are nevertheless important and merit discussion.

We agree with this comment. Infected patients have a high relative abundance of ESBL in the gut flora (Ruppé AAC). Moreover, infected patients treated with antibiotics get a disrupted flora by the

increase concentration of ESBL. In consequence, they are potentially more frequently contaminating HCW hands, disseminating the organism in the environment, and increase transmissibility. It means that probably we underestimated the number of acquisitions in the ICU and the impact of control measures. A paragraph was added in the limitations section, line 354:

“A recent multicentre cohort study17 found no difference in LOS between infected and colonised patients. Thus, in order to simplify assumptions, the “infected” state was not included to the model. However, infected patients are potentially more contaminating HCW hands, disseminating the organism in the environment and increase the transmissibility43. Thus, consequently we may have underestimated the number of acquisitions in the ICU and the impact of control measures. “

Minor comments:

line 33: Should emphasise high-income setting
We modified the line 33:
“Patients hospitalized in a hypothetical 10- bed intensive care unit (ICU) in a high-income country”

45: “HH compliance improvement to 80%/80%” – 80%/80% is not defined
In line 46, we defined the HH improvement.
“The overall costs (cost of intervention and infections) were the lowest for HH compliance improvement from 55%/60% before/after contact with a patient to 80%/80%. “

51: Conclusions are unclear with respect to ATB. Why is this not phrased in terms of cost-effectiveness, and why does it not acknowledge that the added benefits of ATB and cohorting to HH come at a great cost?

We modified the Conclusions and acknowledged that antibiotic restriction was not cost-effective. However, added to HH or cohorting strategies improved their effectiveness (line 53).

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

64: “The incidence of infection and colonization...” Citation needed.
We added the following citations (line 69): ECDC data 2015; CDC data 2011-2014; Sidjabat HE et al., Expert Rev Anti Infect Ther, 2015; Tansarli GS et al, J Antimicrob Chemother, 2014.

72: Authors imply that ESBL-PE infection is tied to longer hospitalisation, but later state that infected patients do not stay longer than colonised patients.
We meant that ESBL-PE infections increased hospitalization frequency in comparison with non-carriers but not the length of hospitalization; this was reworded in line 75:

“Such infections represent a serious socio-economic burden and are associated with a raised mortality, more frequent hospital admissions in comparison with non-carriers, and additional costs.”

82: Authors make a statement about “most studies” yet only cite one (albeit a very good one)

We reformulated this sentence (line 85):

“However, few studies have evaluated the impact of HH on the prevention of ESBL-PE dissemination and they have provided conflicting results9,10.”

187: If a colonised patient has a 16.4% chance of developing infection while in the ICU, should 15 new acquisitions/100 admissions not result in ~2.5 new infections/100 admissions? It seems from Fig 2 that this is the case, since only half of the 5 infections are “new” due to within-ICU transmission.

The Reviewer is correct, 15 new acquisitions/100 admissions result in ~2.5 new infections/100 admissions. However, beside new acquisitions occurring in the ICU, a proportion of patients are already ESBL-PE carriers at ICU admission. In order to estimate the total cost of infections for the ICU, we considered infections acquired and infections in patients colonized at admission.
In line 194 we clarified that 5 infections resulted from acquired and admitted ESBL-PE carriers:

“In the absence of control interventions (base case strategy), 15 new acquisitions (i.e. transmissions) and 5 infections due to ESBL-PE (those from new acquisitions and in patients colonized at admission) occurred per 100 admissions.”

263-5: This transition is unnecessary and tautological
We removed this part of discussion.

277-9: Citations needed for both sentences.
We added the missing citation (WHO Guidelines on Hand Hygiene in Health Care, WHO, 2009).

282-4: Make more clear that ESBL-PE interventions may have positive effects on reducing the transmission of other microorganisms
We modified this sentence, line 296:
“Thus, an HH programme designed to reduce ESBL-PE transmission may have positive effects on reducing the transmission of other microorganisms, and the overall economic benefit of an HH programme for the hospital might be greater than reported in our study.”

291: Review, not revue
Corrected.

298: Why not refer to the results of your sensitivity analysis here instead of a hypothesis?
We modified the discussion, line 317:
“Screening strategies have been used to prevent transmission of MDROs, however, in a sensitivity analysis, we showed that improvement of HH to 80%/80% was always more effective than screening and contact precautions and mostly less expensive than the screening and cohorting intervention. However, we can hypothesize that in the case of highly resistant bacteria (e.g. Carbapenem-resistant Enterobacteriaceae) where there is a highest clinical impact on the outcomes of infected patients, given the lack of therapeutic options, a rapid identification and cohorting of carriers may be more beneficial from the hospital but also societal perspective.”

310: The major driver? Citation needed.
We added a relevant reference (Holmes et al., The Lancet, 2016), line 325.

Figure 3: Axes need units
We added units.

Table 1: Why were gamma distributions chosen?
Cost data are constrained to be non-negative and gamma distribution is often used in decision modelling to represent uncertainty in cost parameters.

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.

We added this explanation to the section “Costs of control strategies” in the Supplementary Text S1:

“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.”

CHEERS 8: there is no justification given for the one-year time horizon
We choose the one-year time horizon for the model because we judged that this period would be sufficiently large to capture all costs and health effects relevant to implemented control strategies.

We added the justification in the Method section, line 102:

“We run the model over a one-year to capture all costs and health effects relevant to implemented control strategies”

CHEERS 11: in this study are there not efficacy estimates derived from the literature?
We specified in the Cheers 11 that the measurement of effectiveness was based on synthesis-based estimates and described in the Supplemntary Text S1.

Supplement: Why can't patients clear colonisation before discharge?

It is usually considered that patients carrying MDR bacteria in the gut remain carrier during his/her stay in acute care. Several publications suggest that the median half time for clearance of carriage of MRSA or ESBL-PE in patients is about 6 months. This persistence is likely longer in ICU patients, because they are frequently exposed to antibiotic pressure.

Supplement: The layout is confusing and jumps back and forth between discussing parameters and model layout.

We changed the structure of the Supplementary Text S1.

Reviewer #2:
Jeroen Schouten
Radboud University Medical Centre, IQ Healthcare department Nijmegen
CWZ Hospital, ICU department, Nijmegen

This is a very nice simulation study on a relevant subject. Although the link with real clinical care is obviously not completely predictable, this study can help decision makers and guide future reseachers in application of a simulation model in real life models.
I have some remarks though:

1. There are some preassumptions made that may need some reconsideration: line 111-113 while HH compliance in some ICUs may be 60% as referenced in French hospitals, this is definitely not the case in many different other countries. Also it has been repeatedly shown that improving HH compliance from 60 to 80% is far more difficult challenging than improving from 40 to 60%. Very little ICUs manage to consistently improve HH compliance to > 60%, so costs on improving 40->60 described in referenced studies, may underestimate the effort that is required for 60-80%, inducing extra cost

We fully agree with this comment. We ran a sensitivity analysis in which the baseline HH compliance was lower than in our core analysis. e.g. 40% before and 50% after patient contact, to take into account that compliance in other countries may be lower than 55%/60% observed in French hospitals. We agree that we should consider that efforts to increase compliance with HH from 40% to 60% may be different that to improve compliance form 60% to 80%. However, in our sensitivity analysis with lower baseline compliance with HH, the same component of the program was considered (it means an infection control nurse at half-time/month) as in core analysis. We showed that improving HH remained the most cost-saving strategy even in a low baseline compliance scenario and with a high cost of the HH program.
We modified the discussion, line 300 and discussed this point:
“Despite the confirmed effectiveness of HH and national and international recommendations, compliance with HH remains low and is often lower than values used in our base case analysis34,35. Furthermore, improving HH compliance from 60% to 80% may be far more difficult and costly challenging than improving from lower baseline level. However, we showed in a sensitivity analysis that improving HH remained the most cost-saving strategy even in a low baseline compliance scenario.”

2. On this same vein, the authors suggest that with antibiotic stewardship measures % of patients on antibiotics in ICU can be reduced from 56% to 28% (halved!) and a 25% reduction in duration of therapy can be achieved using stewardship interventions. One has to question if both for HH as for ABS such goals are AT ALL realistically achievable.

We thank the reviewer for this comment. We assumed a 50% reduction in antibiotic prescriptions that was the most favourable result following the introduction of antibiotic stewardship in a French ICU. Despite this 50% reduction, we illustrated that the antibiotic stewardship strategy was less effective than hand hygiene improvement or a screening and cohorting strategy. In other words even with a very optimistic antibiotic stewardship effectiveness this strategy was less effective than other startegies. However, in this version of the manuscript, we performed an additional sensitivity analysis with 30% reduction in antibiotic prescription and this was added to the Supplementary Text S2.

3. As the only stewardship intervention a 0.5 FTE ID physcian per month is taken into account. There is no supporting literature that the presences of an ID physicain at a word guarantees reduction of AB use either by reduced prescribing or shorter AB use. Also employing a 0.5 FTE ID physician on an ICU ward is expensive, ABS in ICU e.g. by reducing DOT by the use of procalcitonin (ref de Jong E, Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. Lancet Infect Dis. 2016 Jul;16(7):819-27)) reduces DOT by appr. 25% In other words, have the authors thought about other potential ABS interventions? and their costs? Have they considered that costs of an ABS could be far LESS costly than they assume.

In our study, we assumed that the presence of an ID physician at a ward led to the high reduction in antibiotic use. We agree with the reviewer that adding 0.5 FTE of an ID physicians may not be effective, especially in the ICU setting, in which antibiotic counselling may be difficult, because ICU physicians frequently feel they are knowledgeable about antibiotic treatment. However even under this optimistic scenario as discussed above antibiotic stewardship strategy was less effective than hand hygiene improvement or a screening and cohorting strategy. We also agree with the reviewer, that other measures (less costly) can be effective to reduce antibiotic use. The reviewer give the PCT example as such interventions; we considered that PCT was currently in use in the ICU (this is actually true in our medical ICU, with one major ICU study conducted by an ICU physician from this unit, L Bouadma, Lancet 2010) . This was added in the Discussion section, line 325:

“Antibiotic use is the major driver for the selection of antibiotic-resistant bacteria39 and many strategies have been proposed to reduce the use of antibiotics in hospitals40. These strategies could be implemented and associated with different efficacies and costs 41. Here, we considered that antibiotic stewardship, based on the introduction of an infectious disease specialist to the ward, led to a 50% reduction in antibiotic use 42. However, despite this optimistic scenario, we found that antibiotic stewardship was less effective than HH or a screening and cohorting strategy. “

4. In ICUs where chlorhexidine decontamination policies OR SDD/SOD are used the assumptions that authors make re: the relationship between restrictive antibiotic policies and colonization probability. I would like the authors to comment on that.

If we understand the point correctly, the reviewer suggests that using decolonisation can modify the relationship between ASP and the risk of ESBL acquisition. For CHG skin decolonisation, there is no reason for an effect against Enterobacteriaceae. Regarding SDD/SOD, the R GNOSIS study is underway, and will provide data about the impact of digestive decontamination on ESBL acquisition. To our knowledge, preliminary results have been presented, but without available publication.

VERSION 2 – REVIEW

REVIEWER	David RM Smith Modelling and Economics Unit, National Infection Service, Public Health England; United Kingdom
REVIEW RETURNED	07-Aug-2017

GENERAL COMMENTS	I commend the authors for their thorough revisions and for the overall quality of this study. The model assumptions are now better justified, and the study's strengths and weaknesses are more transparent. I wholeheartedly recommend this paper to be accepted, although I would advise a quick revision of the written English prior to publication (several very minor errors, particularly in some of the revisions).