Abstract

Background: Early clinical trials of a *Clostridium difficile* toxoid vaccine show efficacy in preventing *C. difficile* infection (CDI). The optimal patient group to target for vaccination programmes remains unexplored. This study performed a model-based evaluation of the effectiveness of different CDI vaccination strategies, within the context of existing infection prevention and control strategies such as antimicrobial stewardship.

Methods: An individual-based transmission model of CDI in a high-risk hospital setting was developed. The model incorporated data on patient movements between the hospital, and catchment populations from the community and long-term care facilities (LTCF), using English national and local level data for model-parameterisation. We evaluated vaccination of: 1) discharged patients who had an CDI-occurrence in the ward; 2) LTCF-residents; 3) Planned elective surgical admissions and 4) All three strategies combined.

Results: Without vaccination, 10.9 [Interquartile range: 10.0 – 11.8] patients per 1000 ward admissions developed CDI, of which 31% were ward-acquired. Immunising all three patient groups resulted in a 43% [42 – 44], reduction of ward-onset CDI on average. Among the strategies restricting vaccination to one target group, vaccinating elective surgical patients proved most effective (35% [34 – 36] reduction), but least efficient, requiring 146 [133 – 162] courses to prevent one ICU-onset case. Immunising LTCF residents was most efficient, requiring just 13 [11 – 16] courses to prevent one case, but considering this only comprised a small group of our hospital population, it only reduced ICU-onset CDI by 9% [8 – 11]. Vaccination proved most efficient when ward-based transmission rates and antimicrobial consumption were high.

Conclusions: Strategy success depends on the interaction between hospital and catchment populations, and importantly, consideration of importations of CDI from outside the hospital

which we found to substantially impact hospital dynamics. Vaccination may be most desirable in settings or patient groups where levels of broad-spectrum antimicrobial use are high and difficult to reduce.

Introduction

Clostridium difficile infection (CDI) is a source of considerable morbidity and mortality and places a substantial burden on healthcare systems[1]. Though traditionally viewed as a healthcare-associated bacteria, intensivied surveillance reveal increasing reports of CDI cases without recent hospitalisation [2]. Antimicrobial stewardship, mandatory surveillance, and enhanced infection prevention and control measures (IPC) to prevent *C. difficile* transmission have been implemented in hospitals and the community with success in some countries[3]. Nonetheless there remains the need to prevent CDI in settings and vulnerable patient groups where strict antimicrobial stewardship or IPC is not possible or desirable.

Three vaccines targeting the main virulence factors of *C. difficile* (TcdA and TcdB) are currently under development and have showed promising results in phase I and II clinical trials [4–9], with the first Phase III trials now underway[10]. These vaccines induce an IgG antibody response against TcdA and TcdB and therefore aim to prevent the development of symptomatic disease in exposed individuals[e.g. 2,6,7]. A successful vaccine that prevented primary or recurrent onset of CDI would reduce morbidity and mortality directly in the vaccinated individual. It could also have a population-level effect by reducing the spread of infectious spores from infected individuals into the environment, and thus preventing onward transmission of the bacteria. Current evidence, based on highly discriminatory genetic typing-methods[12–14] as well as statistical modelling[15], suggests patients with symptomatic CDI are not the only sources of infection and have pointed to the possible role of asymptomatic carriers. Therefore, any examination of the overall impact of vaccination needs to account for *C. difficile* transmission, including the potential role of asymptomatic carriers [14,16].

Previous studies have shown direct healthcare costs due to excess length of hospital stay to be the main driver of infection costs[17,18]. Hospital admissions from LTCF have been associated with increased risk of hospital-onset CDI[19] and residing in LTCF was identified as an independent risk-factor for developing CDI[20]. Hence, this group of individuals are a potential target population for vaccination, as are patients with planned elective surgery who share many of the underlying risk factors (frailty, hospital admission and antimicrobial usage) in common with the LTCF cohort [10]. Moreover, about 20% of CDI patients experience recurrent CDI[21], either due to re-infection or relapse[22], and primarily as a result of continued exposure to factors disturbing the gut flora post identification of CDI[23]. Therefore, patients with a history of CDI are a potential third target group for vaccination.

Mathematical modelling is a well-established tool that can be used to extrapolate vaccination trial results to the population-level[24]. In the case of *C. difficile*, these methods would allow the exploration of the impact of vaccination, taking into account the different modes of acquisition[25], as well as the indirect effect of prevention of onward transmission. Therefore, a dynamic transmission model[26–37] was developed to investigate the effectiveness of four vaccination strategies, in terms of preventing CDI in a hospital-ward setting with patients at greater risk of acquiring the infection, such as the Intensive Care Unit (ICU)[38]. Although ICUs can vary markedly in their case mix, their critically ill status often causes a state of immunosuppression[39], and requires high levels of antimicrobial prescribing[40]. The model was designed to capture potential population-effects, as well as uncertainties related to the epidemiology of CDI, and is among the first to incorporate heterogeneous community populations.

Methods

Model framework

A discrete-time, individual-based dynamic transmission model[41] was developed, simulating the transmission and control of CDI in a 30-bed single ICU, serving a community of 100,000 individuals, over a five-year time period. Individual patient movements between the hospital, the surrounding community and LTCF were modelled (Figure 1). Transmission-events were explicitly simulated in the ICU, whereas patients could be admitted and re-admitted from the general community or LTCFs[42], each holding patients with different characteristics (Table 1). If a patient developed symptom-onset post-ICU discharge, the model captured this, however, onward-transmission in the community and LTCFs from these cases was not considered. Likewise, the time spent elsewhere in hospital (and thus the transmission elsewhere in hospital) prior to ICU admission and post-ICU discharge is not captured in the model. However, the importation rates of colonised and infected individuals (a_{i_ltcf}, a_{c_ltcf}, a_{i_com}, a_{i_com}) were informed by ICU admission data (Table 1, Table S5), therefore we implicitly incorporated acquisition during the time spent elsewhere in hospital, as well as readmission of still colonised individuals from outside the hospital.

Transmission process

Patients with normal gut flora were assumed to be protected against C. difficile colonisation (compartment P, Figure 1). Although colonisation in healthy individuals with a normal gut flora has been reported, this is likely to be transient, with persistent colonisation among this group found to be rare [43–45]. Moreover, such healthy individuals are at a much lower risk of progressing to symptomatic disease. Consumption of ‘high risk’ antimicrobials (defined as broad-spectrum penicillins, cephalosporins, clindamycin, and quinolones) was assumed to result in susceptibility to colonisation (compartment S) because of their deleterious effect on

the microbiota [46]. Each day, susceptible patients (S) could become colonised with C. difficile through transmission, with the daily risk of colonisation (λ_t) increasing linearly with the number of transmitting CDI patients in the ICU ward (Table 1). The per day probability of colonisation, given at least one CDI or colonised patient on the ward, described the likelihood of transmission through direct contact between susceptible and infectious patients, and indirect contact between susceptible patients, contaminated staff and the environment. As vaccination is unlikely to affect the level of *C. difficile* carriage in the gastrointestinal tract, vaccinated and non-vaccinated colonised individuals were considered to contribute equally to the bacterium's daily probability of colonisation. It was assumed that contacts (with patients, staff or the environment) occurred randomly and were homogenously distributed among patients.

A proportion of patients can mount a natural immune response against *C. difficile* toxins, and are protected from infection[47]. Therefore, a distinction was made between patients that remained asymptomatic (compartment C) and those that suffered from CDI (compartment I) following an incubation period. After successful treatment, patients lost their infection status but remained colonised with *C. difficile*. Colonisation status was lost after an average period of four weeks[48]. To simulate relapse whilst still colonised, the model allowed recovered patients to have another episode of CDI following successive antimicrobial use, but without transmission from another patient. Post-discharge, colonised patients recovered from *C. difficile* colonisation at a constant rate $1/c$, where c is the average duration of colonisation [48,49] in days (Table 1). For individuals with onset post-discharge, this was $1/(s+c)$, with s representing the duration of symptomatic disease [12,50]. Finally, post-vaccination, patients were assumed protected from CDI, but not from colonisation[47,51]. For further model assumptions on bed occupancy, admission and

discharge dynamics and transmission dynamics in the community-settings see supplementary material.

Interventions

Compared to no vaccination, we simulated four strategies: 1) patients who have experienced an episode of CDI in the ward, at the time of discharge from the hospital, as they are at risk of experiencing recurrent infection; 2) LTCF residents in the catchment area of the hospital irrespective of whether they are to have planned elective surgery; 3) patients with planned elective surgery in the hospital catchment area and 4) all the above listed patient groups. The strategies involving LTCF residents and elective patients both concerned community-based strategies. All LTCF residents were assumed vaccinated and protected at the start of the simulation and for a period of two years after which a booster vaccine course was provided. Elective patients were vaccinated and protected pre-admission, assuming the time of their appointment being made allowed for enough time to receive vaccination and mount a successful immune response before hospital admission. Finally, ICU-patients that experienced CDI that hospital episode, were vaccinated at the time of hospital discharge, and assumed to be protected from that time onwards for a period of two years to represent waning immunity.

Model parameterisation and validation

Table 1 summarises the model parameter values. These values were derived from extensive analysis of national and regional healthcare data and peer-reviewed research articles otherwise. The transmission potential from symptomatic carriers (β_1) and asymptomatic carriers (β_2) in English ICUs is largely unknown. Therefore we estimated these parameters by fitting the model output to CDI acquisition rates as reported in English

national ICU audit data [52]. Furthermore, we populated the model with national Hospital Episode statistics data on patient movements[53,54]. Model parameterisation is discussed in further detail in the supplementary material. We validated the model by comparing our model outputs to a list of targets based on external data sources, depicted in supplementary table S7.

Scenario and sensitivity analysis

Due to a lack of knowledge regarding vaccine efficacy and the role of asymptomatic carriers in the transmission of *C.difficile* [14,16], scenario analysis was performed. This incorporated three levels of vaccine efficacy (1, 0.7 and 0.5) and three assumptions for asymptomatic transmission (where asymptomatic carriers transmitted at half the rate of symptomatic carriers (2:1), i.e. the "base case"; no asymptomatic transmission (1:0); and asymptomatic carriers transmitted as efficiently as symptomatic carriers (1:1), Table 2). Analysis of national data (described in more detail in previous publications [52,55]), showed that CDI acquisition rates and ward-based antimicrobial use varied nationally (Table S3). Therefore, two different levels of transmission (baseline and high) and three levels of antimicrobial use (baseline, low and high) were assumed. Here, the baseline scenarios represented the average acquisition and antimicrobial use rates in English hospitals as estimated from national data (Table S2)[40]. Combinations of the above listed possibilities were simulated as listed in Table 2.

To account for parameter uncertainty (Table 1), probabilistic sensitivity analysis was performed using Latin hypercube sampling [56] as follows. One thousand random samples were drawn covering the whole range of possible values for each parameter equally and combined at random to create 1000 different parameter sets. As the model was stochastic, a different result could be expected for a given parameter set. Hence the medians of 100

simulation runs per parameter set were combined to obtain the overall median and interquartile range (IQR) of the model output encompassing parameter uncertainty.

Model output

The absolute reduction in number of cases per 1000 admissions for each strategy compared to a strategy without vaccination (strategy effectiveness) was evaluated, as well as the number of courses required to avert one case in the ICU (strategy efficiency).

Results

Simulation Results: Base Case Scenario

No vaccination

In the base-case scenario, without vaccination (strategy 0), the median number of ICU-onset cases per 1000 admissions was 10.9 [IQR: 10.0 – 11.8] (Figure 2A). A majority of these cases (69%) were imported from outside the ICU. In total, 14.1 [13.2 – 15.0] ward-acquired (symptomatic and asymptomatic) cases were observed per 1000 admissions (Figure 2B). Seventy-nine per cent of acquisitions resulted in symptomatic infection (Figure 2B), but over half developed symptoms post ward discharge (57%), and thus remained asymptomatic whilst in the ICU.

Vaccine programme effectiveness & efficiency

Vaccinating all target populations (strategy 4) resulted in a 43% [IQR: 42 – 44] reduction in ICU-onset cases over five years, equal to 4.7 [4.3 – 5.1] CDI cases per 1000 admissions (Table 3). Reviewing the strategies restricting vaccination to one target group, vaccinating all patients awaiting elective surgery (strategy 3) was the most effective. For all four strategies, vaccination prevented more imported cases than cases acquiring CDI within

193 the ICU (Table 3). This was particularly true for strategy 1 (vaccinating patients with a
194 history of CDI) and 2 (LTCF residents). Strategy 2 proved the most efficient, i.e. required the
195 lowest number of courses to avert one case of ICU-onset CDI in the base case scenario (13
196 [11 – 16]), despite the low effectiveness of this strategy. In contrast, strategy 3 proved highly
197 inefficient, requiring 146 [133 – 162] to prevent on case in the ICU (Table 3).

198 Population-effect of the vaccine

199 We assumed that vaccination did not provide direct protection against *C. difficile*
200 colonisation. Therefore, vaccination is likely to result in an increase in asymptomatic cases.
201 Indeed, the number of asymptomatic acquisitions did increase post-vaccination for strategy 2,
202 3 and 4 (Figure 2B). However, as the drop in symptomatic infections was higher, the total
203 number of acquisitions for these three strategies decreased, indicating a population-effect was
204 present (Figure 2B). Of note, in the ICU alone, this meant that, post-vaccination, a reduction
205 was observed in both symptomatic and asymptomatic acquisitions (Figure 2A) as without
206 vaccination, a large fraction of patients would have developed symptoms post-discharge.

207 *Simulation Results: Scenario analysis*

208 Cross transmission and antimicrobial use

209 The ordering of the most effective and efficient strategies remained unchanged under
210 all the simulated scenarios of transmission and antimicrobial use (Figure 3). All strategies
211 proved most effective and efficient under scenarios of high transmission and high
212 antimicrobial usage (scenario 6, Table S7). In particular, vaccination of elective patients
213 (strategy 3) and therefore vaccination of all target groups (strategy 4) became more efficient,
214 as they were most successful in preventing onward transmission (Figure 3).

215 Impact of asymptomatic carriers

The comparative effectiveness and efficiency of each strategy also remained unchanged under different asymptomatic transmission assumptions. Post-vaccination, reduction in ward-based acquisition was greatest when asymptomatic carriers were not transmitting, and marginal when equal transmission between symptomatic and asymptomatic carriers was assumed (Figure S2). As a result, in the scenario without asymptomatic transmission, the marked decrease in ICU-acquisitions resulted in a reduction in asymptomatic carriers in- and also outside the ICU. Under the equal asymptomatic transmission assumption, vaccination resulted in a slight increase of asymptomatic carriers both in- as well as outside the ICU for the most effective strategies 3 and 4 (Figure S3).

Impact of vaccine efficacy

With vaccine efficacy reduced to 70% (scenario 7), vaccinating all target groups still averted 32% [31 – 33] of the ICU-onset CDI cases (Table S7). This was 24% [23 -25] when efficacy was as low as 50% (scenario 8). However, while the number of vaccine courses required for strategy 2 remained low even under our lowest vaccine efficacy scenario (23 [18 – 32]), strategy 3 and 4 became very inefficient, with 281 [251 – 313] and 229 [206 – 255] courses required to prevent one case of CDI in the ICU (Table S7).

Discussion

This study is the first dynamic-transmission model of different vaccination strategies against CDI in a high-risk hospital setting. We observed that immunising all three patient groups (LTCF residents, elective patients and patients with a history of ICU-onset CDI) could prevent up to 43% of CDI-onset cases in our simulated 30-bed ward. With ~17 CDI cases observed annually, representing current average incidence rates in English ICUs[52], this represented the prevention of ~7 ICU-onset cases per year. Of the three individual target

groups, vaccinating all patients awaiting elective surgery yielded the largest net reduction in ICU-onset cases.

We did not conduct a formal cost-effectiveness evaluation, since costs are likely to be highly specific to a particular setting. However, we did consider efficiency – measured as the number of vaccination courses needed to prevent one case of CDI. In our study, the balance between ward-importations and ward-acquisitions of CDI drove the projected efficiency of vaccination. Previous statistical and molecular studies have questioned the importance of in-hospital transmission from symptomatic patients in the development of CDI in endemic settings[12,13,15], and hint at other acquisition sources. The fitted model suggested that the majority (~70%) of ICU-onset cases were imported from outside the ICU. These importations were primarily asymptomatic admitted patients who developed CDI following antimicrobial treatment. As a result, the identification and targeting of patients groups at heightened risk of colonisation, became increasingly important when hospital-based CDI-onset was not primarily driven by hospital-based acquisitions. Vaccinating LTCF residents would be an example of such target populations [19,20]. We found that vaccinating LTCF residents proved highly efficient in terms of courses per case prevented (13 [11 – 16]), primarily as asymptomatic colonisation is frequent among the elderly residents of LTCF[57], and the high rates of antimicrobial prescribing in this group[58,59] compared to the rest of the population [60,61]. For the least efficient strategy, i.e. vaccinating elective surgery patients, this was 146 [133 – 162]. To compare, for the human papilloma virus (HPV) vaccine, it is suggested that about 129 [62] up to 324 [63] young women will need to be vaccinated to prevent one case of cervical cancer, whereas for influenza in individuals >65 years old this is estimated to be 43 (95% CI: 16–192) and as high as 3,333 (1,429–12,500) respectively [64]. Importantly, the low total number of admissions from LTCF means that this strategy only resulted in a small reduction in the overall reduction of cases in the ICU. Therefore, the proportion of

admissions from the LTCF is an important consideration in the generalisability of our findings.

Our scenario analysis revealed that with lower levels of CDI-associated antimicrobial prescribing (e.g. clindamycin and cephalosporins), the efficiency of vaccination was greatly reduced, even under scenarios of high transmission rates, and the converse for high antimicrobial use was also true. Therefore, vaccination may be most efficient (and perhaps cost-effective) in settings where levels of broad-spectrum antimicrobial use are high and difficult to reduce.

Another important finding we observed however is that, when asymptomatic carriers contributed to transmission, the number of colonisations outside the ICU increased following vaccination. These asymptomatic cases are more likely to remain undetected than symptomatic cases. When transmission from such individuals is present, this may lead to unintended consequences for the transmission of *C. difficile* and CDI incidence outside the ICU. When asymptomatic carriers were non-transmissible, this increase in colonisations was not present. Recently, a study by Durham and colleagues (2016) estimated that asymptomatic carriers transmitted at a 15 times reduced rate compared to CDI cases in a hospital-wide setting, as well as in the community[37]. Following our scenario analysis, this would suggest that the indirect effects of the vaccine might actually be higher than identified in our study under baseline assumptions of half the rate. Until we are more certain about the role of asymptomatic patients in the transmission of CDI in different settings, it is difficult to define the true effectiveness of vaccination, as well as any infection prevention control strategy.

Only one previous modelling study by Lee *et al*, has quantified the impact of CDI vaccination in a comparative manner. They found that a CDI vaccine will most likely be cost-effective in the United States when aimed at preventing recurrent CDI[65]. In our study,

vaccinating patients with a history of CDI (in the ICU) had close to no effect on CDI incidence in the ICU, and required ~80 courses to prevent one case. Lee and colleagues assumed that recurrent CDI would always occur in hospital or result in hospitalisation. In our model, active admission of recurrent cases was not incorporated; primarily because such patients are unlikely to be admitted to the ICU. We did incorporate readmission for other reasons however, and in the absence of vaccination, less than one case per 1000 admissions of the patients with a recurrent ICU-onset CDI was seen, either in the same episode or after re-admissions. This was for two reasons: firstly we observed a low number of relapses during the same hospital stay, secondly, the risk of ICU readmission when colonised was low, as the mean colonisation time, as observed by others (e.g. [34]) was approximately similar to the average number of days between ICU-admissions in England. Admittedly, our single-ward model framework did not include re-admission elsewhere in hospital, nor discharge to other hospital wards. Hence these constraints did not allow for a full investigation of this strategy.

This study had several other limitations. The calculated number of vaccine courses for strategy 2, 3 and 4 are approximations, and in particularly for strategy 2, was likely to be an underestimate, as we did not account for the high mortality rates among LTCF residents and frequent new admissions to the cohort [66]. Secondly, due to the single-ward framework of our model, it is likely that we have underestimated the impact of vaccination: although we considered importations from and infection-onset post ICU discharge, our model only evaluated CDI-dynamics in the ICU. About 57% of the acquired C. difficile in the ICU developed onset after ICU-discharge. This is similar to estimates from active population-based surveillance data from the United States revealing that ~63% of the healthcare-associated CDI cases in 2011 developed symptoms in the community [67]. Onward transmission prevented from these cases with symptom-onset or recurrence outside the ICU was not captured, resulting in a potential underestimation of vaccine effectiveness in terms of

preventing hospital- as well as community-onset CDI. Incorporation of discharge and (re)admission dynamics elsewhere in the hospital may have improved the effectiveness of some strategies (notably vaccinating CDI cases) in preventing healthcare-onset CDI. However, data to more realistically inform such a holistic model would have required surveillance data on CDI occurrence in community-settings including the LTCF, which are currently lacking for most countries, including England, as is national-level data on ward movements and ward-specific CDI incidence rates. Therefore, any such model would have been highly theoretical and its results uncertain. Thirdly, our transmission parameters were estimated with all parameters at their baseline value, including antimicrobial use (i.e. the prevalence of usage of traditionally defined high-risk classes [46]). Other classes (e.g. macrolides) have been associated with CDI as well, albeit with much lower risks[46,68]. Inclusion of these classes, as well as their heterogeneity in associated CDI-risk, could potentially have resulted in a larger net-number of susceptible individuals at each ICU-day, resulting in lower fitted transmission rates, and subconsequently lower population-effects of the vaccine. As this would have affected the strategies involving elective patients and all patient groups in particular, we do not expect this would change our conclusions on the comparative performance of the strategies. Finally, our model did not explicitly consider the time required for seroconversion post-vaccination. All three vaccines under development are considering a 3-dose schedule covering a time period of ~30 days. The latest Phase II clinical trial data found seroconversion rates to peak at 60 days. With average waiting times for elective patients in England of ~70 days, this would support our assumption that elective patients were protected on admission. However, our mean time of ICU readmission was 30 days, suggesting that our strategy involving patients with a history of CDI would have been even less effective when accounting for this preliminary findings on the timing of seroconversion. Once more data is available on the optimal dose regimen for the respective

vaccines, future modelling research should take both the seroconversion rate and dosing strategies in consideration.

Conclusions

Through careful modelling of the admission and discharge dynamics between healthcare and community settings, this study has provided useful insights as to how and where respective vaccination strategies involving different target groups are most likely to have an impact on CDI incidence rates. Vaccinating LTCF residents and elective patients may aid in preventing CDI in high-risk hospital settings such as the ICU. However, in settings with comparable ICU-acquisition and antimicrobial usage rates to England, this would require a high number of vaccine courses. Therefore, vaccination may be most useful in settings where IPC or reaching low levels of antimicrobial usage proves challenging.

Conflict of interest statement

None.

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Figure legends

Figure 1: Model framework

P = Patients protected from colonisation, hence infection**; S =** Patients susceptible to colonisation, hence infection; **C_{imm} =** Patients colonised with *C. difficile* that are protected from disease due to natural immunity or vaccination**; C_{n_imm}=** Patients colonised with *C. difficile* not protected from disease whilst failing to mount natural immunity or immunity following vaccination**; I =** Patients with CDI**; LTCF =** Long-term care facility

Figure 2: Absolute number of cases averted per 1000 admissions shown for all four vaccination strategies; A) ICU-acquisitions and importations with onset in the ICU only; B) ICU-acquisitions with onset in- & outside the ICU.

Model outcomes at baseline for **strategy 0** (no vaccination); and number of cases averted under **strategy 1** (CDI history); **strategy 2** (LTCF residents); **strategy 3** (elective patients) and **strategy 4** (all combined). The middle line in the box represents the median difference of 1000 model parameter sets between strategy 0 and each vaccination strategy, and upper and lower areas of the box indicate the seventy-fifth and twenty-fifth percentiles.

Figure 3: Absolute number of imported and acquired cases averted per 1000 admissions in the ICU for the vaccination strategies under scenarios 1 to 6.

Left panels: baseline transmission scenarios with A) Baseline; C) Low; E) High antimicrobial use. Right panels: high transmission transmission scenarios with B) Baseline; D) Low; F) High antimicrobial use. Black points: median absolute number ICU-acquired cases averted (x-axis) and imported cases averted (y-axis) of the 1000 parameter sets under the different vaccination strategies.Transparent ellipses plot the 95% coverage intervals.

Table legends

Table 1: Model parameters and assumptions

* Included in probabilistic sensitivity analysis; # Included in scenario analysis. PPS = Point prevalence survey data (reference provided refers to which point prevalence data); H= Individual hospital data; HES = Hospital Episode Statistics; A = Assumption, CQC = Care Quality Commission data

Table 2: Simulated scenarios

2:1 = asymptomatic carriers transmitted at half the rate of symptomatic carriers, the "base case"; 1:0 = asymptomatic carriers did not spread *C. difficile*; 1:1 = asymptomatic carriers transmitted as efficiently as symptomatic carriers.

Table 3: Number of ICU-onset cases averted per 1000 admissions and courses required to avert 1 case of ICU-onset CDI for strategies in the base case scenario

Note NA: under some of the LHS parameter values, the CDI history strategy had no impact