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1 **Abstract**

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

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

13 *Results:* Without vaccination, 10.9 [Interquartile range: 10.0 – 11.8] patients per 1000 ward  
14 admissions developed CDI, of which 31% were ward-acquired. Immunising all three patient  
15 groups resulted in a 43% [42 – 44], reduction of ward-onset CDI on average. Among the  
16 strategies restricting vaccination to one target group, vaccinating elective surgical patients  
17 proved most effective (35% [34 – 36] reduction), but least efficient, requiring 146 [133 –  
18 162] courses to prevent one ICU-onset case. Immunising LTCF residents was most efficient,  
19 requiring just 13 [11 – 16] courses to prevent one case, but considering this only comprised a  
20 small group of our hospital population, it only reduced ICU-onset CDI by 9% [8 – 11].  
21 Vaccination proved most efficient when ward-based transmission rates and antimicrobial  
22 consumption were high.

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

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

28

## 29 **Introduction**

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

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

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

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

75

## 76 **Methods**

### 77 *Model framework*

78 A discrete-time, individual-based dynamic transmission model[41] was developed,  
79 simulating the transmission and control of CDI in a 30-bed single ICU, serving a community  
80 of 100,000 individuals, over a five-year time period. Individual patient movements between  
81 the hospital, the surrounding community and LTCF were modelled (Figure 1).  
82 Transmission-events were explicitly simulated in the ICU, whereas patients could be  
83 admitted and re-admitted from the general community or LTCFs[42], each holding patients  
84 with different characteristics (Table 1). If a patient developed symptom-onset post-ICU  
85 discharge, the model captured this, however, onward-transmission in the community and  
86 LTCFs from these cases was not considered. Likewise, the time spent elsewhere in hospital  
87 (and thus the transmission elsewhere in hospital) prior to ICU admission and post-ICU  
88 discharge is not captured in the model. However, the importation rates of colonised and  
89 infected individuals ( $a_{i\_ltof}$ ,  $a_{c\_ltof}$ ,  $a_{i\_com}$ ,  $a_{i\_com}$ ) were informed by ICU admission data (Table  
90 1, Table S5), therefore we implicitly incorporated acquisition during the time spent elsewhere  
91 in hospital, as well as readmission of still colonised individuals from outside the hospital.

### 92 *Transmission process*

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

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

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

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

### 126 *Interventions*

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

### 141 *Model parameterisation and validation*

142

143 Table 1 summarises the model parameter values. These values were derived from  
144 extensive analysis of national and regional healthcare data and peer-reviewed research  
145 articles otherwise. The transmission potential from symptomatic carriers ( $\beta_1$ ) and  
146 asymptomatic carriers ( $\beta_2$ ) in English ICUs is largely unknown. Therefore we estimated  
147 these parameters by fitting the model output to CDI acquisition rates as reported in English



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

### 152 *Scenario and sensitivity analysis*

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

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

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

### 173 *Model output*

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

## 177 **Results**

### 178 *Simulation Results: Base Case Scenario*

#### 179 No vaccination

180 In the base-case scenario, without vaccination (strategy 0), the median number of  
181 ICU-onset cases per 1000 admissions was 10.9 [IQR: 10.0 – 11.8] (Figure 2A). A majority of  
182 these cases (69%) were imported from outside the ICU. In total, 14.1 [13.2 – 15.0] ward-  
183 acquired (symptomatic and asymptomatic) cases were observed per 1000 admissions (Figure  
184 2B). Seventy-nine per cent of acquisitions resulted in symptomatic infection (Figure 2B), but  
185 over half developed symptoms post ward discharge (57%), and thus remained asymptomatic  
186 whilst in the ICU.

#### 187 Vaccine programme effectiveness & efficiency

188 Vaccinating all target populations (strategy 4) resulted in a 43% [IQR: 42 – 44]  
189 reduction in ICU-onset cases over five years, equal to 4.7 [4.3 – 5.1] CDI cases per 1000  
190 admissions (Table 3). Reviewing the strategies restricting vaccination to one target group,  
191 vaccinating all patients awaiting elective surgery (strategy 3) was the most effective. For all  
192 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

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

#### 225 Impact of vaccine efficacy

226 With vaccine efficacy reduced to 70% (scenario 7), vaccinating all target groups still  
227 averted 32% [31 – 33] of the ICU-onset CDI cases (Table S7). This was 24% [23 -25] when  
228 efficacy was as low as 50% (scenario 8). However, while the number of vaccine courses  
229 required for strategy 2 remained low even under our lowest vaccine efficacy scenario (23 [18  
230 – 32]), strategy 3 and 4 became very inefficient, with 281 [251 – 313] and 229 [206 – 255]  
231 courses required to prevent one case of CDI in the ICU (Table S7).

#### 232 **Discussion**

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

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

241 We did not conduct a formal cost-effectiveness evaluation, since costs are likely to be highly  
242 specific to a particular setting. However, we did consider efficiency – measured as the  
243 number of vaccination courses needed to prevent one case of CDI. In our study, the balance  
244 between ward-importations and ward-acquisitions of CDI drove the projected efficiency of  
245 vaccination. Previous statistical and molecular studies have questioned the importance of in-  
246 hospital transmission from symptomatic patients in the development of CDI in endemic  
247 settings[12,13,15], and hint at other acquisition sources. The fitted model suggested that the  
248 majority (~70%) of ICU-onset cases were imported from outside the ICU. These importations  
249 were primarily asymptomatic admitted patients who developed CDI following antimicrobial  
250 treatment. As a result, the identification and targeting of patients groups at heightened risk of  
251 colonisation, became increasingly important when hospital-based CDI-onset was not  
252 primarily driven by hospital-based acquisitions. Vaccinating LTCF residents would be an  
253 example of such target populations [19,20]. We found that vaccinating LTCF residents  
254 proved highly efficient in terms of courses per case prevented (13 [11 – 16]), primarily as  
255 asymptomatic colonisation is frequent among the elderly residents of LTCF[57], and the high  
256 rates of antimicrobial prescribing in this group[58,59] compared to the rest of the population  
257 [60,61]. For the least efficient strategy, i.e. vaccinating elective surgery patients, this was 146  
258 [133 – 162]. To compare, for the human papilloma virus (HPV) vaccine, it is suggested that  
259 about 129 [62] up to 324 [63] young women will need to be vaccinated to prevent one case of  
260 cervical cancer, whereas for influenza in individuals >65 years old this is estimated to be 43  
261 (95% CI: 16–192) and as high as 3,333 (1,429–12,500) respectively [64]. Importantly, the  
262 low total number of admissions from LTCF means that this strategy only resulted in a small  
263 reduction in the overall reduction of cases in the ICU. Therefore, the proportion of

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

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

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

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

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

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

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



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

340

### 341 ***Conclusions***

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

### 350 **Conflict of interest statement**

351 None.

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363

364

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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<sub>imm</sub>** = Patients colonised with *C. difficile* that are protected from disease due to natural immunity or vaccination; **C<sub>n\_imm</sub>** = 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 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