Supplementary material

Model assumptions

1) 100% bed occupancy was assumed, i.e. discharge or death of a patient resulted directly in the admission of a new patient.
2) Daily time-steps were used with patient discharges from the ward occurring at the beginning of each day.
3) Patients could be admitted from the community or from a LTCF. Patients either resided in a LTCF or the community for the full simulation period (five years).
4) At time of admission, a data-informed probability (**Table 1**, **main text**) determined whether the ICU admission was directly from outside the hospital (i.e. from LTCF or community) or an internal hospital transfer. The source of the admission determined the probability of having been prescribed antimicrobials outside the ICU.
5) Transmission-events were simulated in the ICU, whereas a fixed importation rate of colonised and infected individuals from the community and LTCF was assumed. The time spent elsewhere in hospital (and thus the transmission elsewhere in hospital) prior to ICU admission is not captured in the model. However the importation rates were informed by ICU admission data (see model parameterisation), therefore implicitly incorporated acquisition during the time spent elsewhere in hospital.
6) Patients could be discharged whilst still colonised with *C. difficile.* Once discharged, colonised patients recovered from *C. difficile* colonisation at a constant rate (**Table 1, main text**) irrespective of whether they were immunised.

7) The vaccine did not protect patients from colonisation. Vaccine derived immunity was assumed to last for a period of two years (internal communication with Sanofi Pasteur).

Model parameterisation

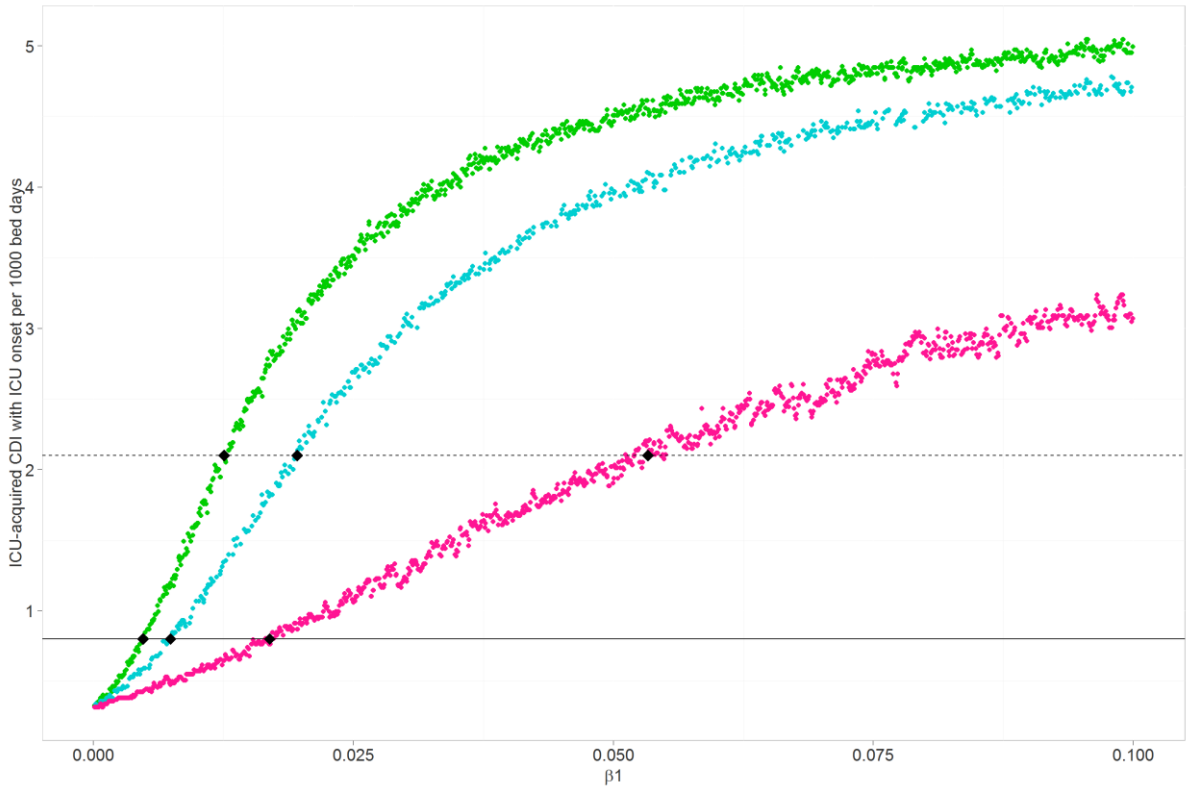
C. difficile transmission parameters (β_1 and β_2)

Little is known about the transmission potential of patients infected or colonised with *C. difficile.* Therefore, the transmission potential from symptomatic carriers (β_1) and asymptomatic carriers (β_2) was fitted to the median CDI acquisition rates in English critical care units in the financial year 2012/13 as measured in the Intensive Care National Audit & Research Centre Case Mix Programme (ICNARC) data. This data comprises 'potential performance indicators', such as unit acquired CDI, of 202 NHS adult, general critical care units, defined as ICUs, combined ICU/high dependency units (HDUs) and combined general care/coronary care units admitting mixed medical/surgical patients predominantly aged older than 16 years[1].

The following three steps were applied. Firstly, we sampled 1000 parameter values for β_1 from a uniform distribution over range 0 to 1 (as negative values were considered biological implausible) using LHS and let β_2 depend on β_1 according to $\beta_2 = \beta_1/2$. Secondly, we ran the model for each of these 1000 values for β_1 and β_2 one hundred times (to minimise stochastic variation) whilst keeping all remaining model parameters at their base value (**Table 1, main text**) Thirdly, we compared the median ICU-onset acquisition rates resulting from each set of one hundred model simulations against the median CDI acquisition rates in the ICNARC data, i.e. 0.8 [IQR: 0 – 2.1] per 1000 bed days[2], and evaluated which values of β_1 (and thus β_2) minimised the difference between the model output, and the data (Figure S1). This process was repeated for the two alternative assumptions for the transmission

potential of asymptomatic carriers (i.e. 1:0 (β_2=0) and 1:1 (β_2=β_1) see Figure 1 and Table S1 for fitted values). Moreover, a similar step-wise process was followed for the scenario of high transmission, where β_1 and β_2 were fitted against the seventy-fifth percentile of the aforementioned CDI acquisition rates in the ICU, i.e. 2.1 cases per 1000 patient days (**Error! Reference source not found.**).

Figure S 1: Model output of 1000 values for β_1 (and $\beta_2 = \beta_1/2$; $\beta_2 = 0$ or $\beta_2 = \beta_1$)



Solid horizontal black line: median CDI acquisition rates in English ICUs (ICNARC data), representative for ICUs with average transmission. **Dashed horizontal black line:** seventy-fifth percentile of CDI-acquisition rates in English ICUs, representative for ICUs with high CDI transmission**. Blue dots:** Model output for each of the values of β_1 in the base case, where asymptomatic carriers have half the transmission potential compared to symptomatic carriers, i.e. $\beta_2 = \beta_1/2$ (scenario 2:1)**. Pink dots:** Model output for each of the values of β_1 in the scenario where asymptomatic carriers have no transmission potential, i.e. $\beta_2 = 0$ (scenario 1:0). **Green dots**: Model output for each of the values of β_1 in the scenario were asymptomatic and symptomatic carriers have equal transmission potential, i.e. $\beta_2 = \beta_1$ (scenario 1:1)**. Lower black dots:** Best fit for β_1 (and implicitly for β_2) for each of the three asymptomatic transmission scenarios when transmission levels are at national average**. Upper black dots:** Best fit for β_1 (and implicitly for β_2) for each of the three asymptomatic transmission scenarios when transmission levels are high compared to the national average.

Table S 1: Values used in scenario analysis

Scenario	β_1	β_2	α_{icu}	α_{gm}	e
Scenario 1 (AT+AA+VE=100%)	0.0074	0.0037	0.219	0.081	1
Scenario 2 (HT+AA+VE=100%)	0.0196	0.0098	0.219	0.081	1
Scenario 3 (AT+LA+VE=100%)	0.0074	0.0037	0.149	0.052	1
Scenario 4 (HT+LA+VE=100%)	0.0196	0.0098	0.149	0.052	1
Scenario 5 (AT+AA+VE=70%)	0.0074	0.0037	0.219	0.081	0.7
Scenario 6 (AT+AA+VE=50%)	0.0074	0.0037	0.219	0.081	0.5
Asymptomatic 1:0 (and AT+AA+VE=100%)	0.0169	0	0.219	0.081	1
Asymptomatic 1:1 (and AT+AA+VE=100%)	0.0047	0.0047	0.219	0.081	1

Daily discharge and death probabilities (d_n, d_i, μ_n and μ_i)

Estimates for ICU-specific daily discharge probabilities and mortality risks for CDI-negative patients and asymptomatic carriers (d_n and μ_n respectively) were derived from studies estimating these parameters for MRSA negative patients[3,4], under the assumption that these MRSA negative patients did not suffer from CDI. For daily discharge probabilities of CDI positive patients (d_i) the daily discharge probabilities of CDI-negative patients were reduced by 28%, based on the findings of the previously presented Cox proportional hazards model estimating excess LoS associated with CDI[5]. These discharge probabilities were estimated using whole hospital data. A review of the literature identified two studies on excess length of stay (LoS) and mortality associated with CDI in the ICU specifically using appropriate methods [6,7]. Using a Cox proportional hazard model, one study found reduced daily discharge probabilities for CDI patients as well (HR: 0.82 [95%CI 0.72 – 0.94]). The second study used a multistate model and found an excess ICU stay of 6 days (6.3 [2.0 – 10.6]) similar to our results. In contrast to our overall hospital estimate, both studies did not find an increased probability of death due to CDI in the ICU[6,7]. Therefore, the daily risk of death in our model for CDI negative (μ_n) and CDI positive (μ_i) were assumed identical (Table S2)

Table S 2: Daily probability of discharge and death in the ICU ward for CDI- and CDI+ patients

Time (days)	Daily ICU discharge probability CDI^-	Daily ICU discharge probability CDI^+ (↓28%)	Daily ICU death probability CDI^-/CDI^+
0	0.00000	0.00000	0.00000
1	0.08547	0.06154	0.02610
2	0.16822	0.12112	0.04064
3	0.23596	0.16989	0.02714
4	0.17647	0.12706	0.02583
5	0.16071	0.11571	0.02491
6	0.12766	0.09191	0.02668
7	0.07317	0.05268	0.01765
8	0.07895	0.05684	0.01885
9	0.14286	0.10286	0.01893
10	0.20000	0.14400	0.02631
11	0.04167	0.03000	0.01367
12	0.04348	0.03130	0.01637
13	0.18182	0.13091	0.02334
14	0.05556	0.04000	0.02143
15	-	-	0.02229
16	-	-	0.01598
17	-	-	0.01847
18	-	-	0.01474
19	-	-	0.01289
20	-	-	0.01387
21	-	-	0.02734
22	-	-	0.01204

Antimicrobial prescribing in the hospital setting (α_{icu}, α_{gm} and p_{icu})

In the model, patients could be either admitted directly to the ICU from a community-setting (i.e. LTCF or community), or as a result of an internal-hospital transfer, from a GM ward. Therefore, the prescribing prevalence for GM (α_{gm}) needed to be obtained, in addition to the daily risk of being prescribed antimicrobials in the ICU (p_{icu}). To obtain the national prevalence of ward-prescribing in England, a mixed-effects logistic regression model, with a

normally distributed random-intercept (to account for clustering on a Trust level) and ward specialty included as an explanatory variable, was fitted to individual patient-level antimicrobial consumption data from a nation-wide point prevalence survey on health-care associated infections and antimicrobial use[8]. For this survey, data was collected from 99 NHS acute Trusts in England on the number of patients on antimicrobials on the one single day the survey was conducted[8].

For the analysis, antimicrobial usage data was restricted to CDI-associated antimicrobial classes only, i.e. broad-spectrum penicillins, third-generation cephalosporins, clindamycin, and quinolones. The mean probability of being on CDI-associated (or 'high-risk') antimicrobials for each ward specialty on a random single day (α_w) was calculated using the logistic function, given by the inverse-logit:

$$\alpha_w = 1/(1 + exp(-x_w)),\ w = GM, ICU \quad \text{(Equation 1)}$$

where x_w corresponds to the estimated regression coefficients for each ward specialty (Table S3). The within-hospital variance (σ_w^2) of these estimates was used as a proxy for the second-order uncertainty around α_w.

Table S 3: Model estimates of the mixed-effect logistic regression model

Ward specialty	$\mathbf{x_w}$	$\sqrt{\boldsymbol{\sigma}^2}$	$\sqrt{\boldsymbol{\sigma}^2_{\mathbf{trust}}}$	$\alpha_w = 1/(1 + exp(-x_w))$	**25th percentile (incorporating $\sqrt{\boldsymbol{\sigma}^2_{\mathbf{trust}}}$)**
ICU	-1.274	0.08	0.401	0.219	0.149
General medicine	-2.431	0.06	0.403	0.081	0.052

In the earlier mentioned probabilistic sensitivity analysis (main text), 1000 samples were randomly drawn from a normal distribution with mean = x_w and standard deviation = $\sqrt{\sigma_w^2}$ using LHS. As these estimates were fitted with a log-link, these 1000 randomly drawn samples were then transformed to the identity scale using equation 1. Considering x_w was fitted to hospital antimicrobial consumption data of one single day, α_w represents overall ward prescribing prevalence. This estimated prevalence for the GM ward was used to represent the risk of being on CDI-associated antimicrobials when admitted from a GM ward (α_{gm}) to the ICU in our model. However, as our model explicitly simulated CDI-transmission dynamics in the ICU, and in daily time steps, α_{icu} needed to be converted to a daily risk of being prescribed CDI-associated antimicrobials. Assuming each patient in the point prevalence data was receiving one CDI-associated antimicrobial only, and the average length of ICU stay (L_{icu}) was six days[5], we used the following:

$$\alpha_{icu} = 1 - (1 - p_{icu})^{L_{icu}} \qquad \text{(Equation 2)}$$

Where 1 - p_w is the risk of avoiding a CDI-associated antimicrobial prescription in the ICU per day. Equation 2 can be rearranged to calculate daily risks of starting on CDI-associated antimicrobials for each patient:

$$p_{icu} = 1 - (1 - \alpha_{icu})^{1/L_{icu}} \qquad \text{(Equation 3)}$$

Finally, for the scenario analysis, an alternative scenario of low hospital prescribing of CDI-associated antimicrobials was represented by the twenty-fifth percentile of these estimates' confidence intervals, calculated when including both the within ($\sqrt{\sigma_w^2}$) and between-Trust variation ($\sqrt{\sigma^2_{trust,}}$ Table S2).

Antimicrobial prescribing in the community and LTCF (α_{ltcf} and α_{com})

The fraction of LTCF residents and patients admitted from the community that received CDI-associated antimicrobials prior to ICU admission (α_{ltcf} and α_{com}) were parameterised by European Centre of Disease Control (ECDC) point prevalence antimicrobial consumption data from the United Kingdom (UK), collected through the European Surveillance of Antimicrobial Consumption Network in 2010 and 2011[9,10] and the Healthcare Associated infections in LTCF (HALT) point prevalence studies of 2010 and 2013[11,12]. These data report the Defined Daily Doses (DDD) of antimicrobials per 1000 individuals (Table S4) using the Anatomical Therapeutic Chemical (ATC) Classification System (http://www.whocc.no).

Table S 4: Antimicrobial use in the community and LTCF

	Community		**LTCF**	
	DDD/100		**N (per 100 residents)**	
	2010	**2011**	**2010**	**2013**
Number of eligible individuals included in sample	59,255,000	63,232,700	7,498	3,954
J01C BETA-LACTAM ANTIBACTERIALS,	0.856	0.872	166 (2.21)	109 (2.76)
J01D OTHER BETA-LACTAM ANTIBACTERIALS	0.055	0.042	62 (0.83)	29 (0.73)
J01F MACROLIDES, LINCOSAMIDES AND	0.273	0.281	29 (0.39)	27 (0.68)
J01M QUINOLONE ANTIBACTERIALS	0.046	0.043	24 (0.32)	9 (0. 23)
Total	**1.230**	**1.238**	**281 (3.75)**	**174 (4.40)**

DDD represent the assumed average maintenance dose per day for a drug used, for its main indication in adults. The ACT classification system is developed by the World Health Organisation and divides drugs according to their therapeutic, pharmacological and chemical properties using five different levels, where level 1 corresponds to the main group and level 5 to the chemical substance. The ECDC point prevalence survey results are reported at ATC

level 4. The DDD per 100 population of the ATC level 4 groups J01D (other beta-lactam antibacterials); J01C (Beta-lactam antibacterials, penicillins); J01F (Macrolides, lincosamides and streptogramins); and J01M (Quinolone antibacterials) were combined to obtain an estimate of the proportion of patients receiving CDI-associated antimicrobials in the community and LTCF.

Importation rates of colonised and infected patients (a_{i_ltcf}, a_{c_ltcf}, a_{s_ltcf}, a_{i_com}, a_{c_com}, a_{s_com})

The fraction of individuals admitted from the community/LTCF that were infected (a_{i_com}/a_{i_ltcf}), colonised (a_{c_com}/a_{c_ltcf}) or susceptible (a_{s_com}/a_{s_ltcf}) on admission were parameterised using ICU-screening data collected over 18 months from a 30-bed ICU ward in a large London teaching hospital[13]. The particular provenance status (i.e. community home or LTCF) of the patients was not collected as part of this study. As an alternative, it was assumed that 4% of the total admissions to the ICU were LTCF residents, as was shown by sentinel data collected from seven acute Trusts through The National One Week Prevalence Audit of MRSA[14]. For the patients that screened positive for colonisation and/or had symptomatic infection, provenance status was obtained by retrieval of the patients' postcodes of residence, which were subsequently matched with LTCF postcodes (using Care Quality Commission data further explained later)[15].

Using this procedure, 53 of the admissions originated from LTCFs, and 30 of these were screened for *C. difficile*. On admission, infection prevalence among patients admitted from their own home (a_{i_com}) was 0.3% (95%CI: 0.1 – 0.8) and colonisation prevalence (a_{c_com}) 2.8% (1.8 – 4.3), whereas this was 0% (0 – 11.4) and 0% (0 – 11.4) respectively for patients from LTCFs (Table S5). A recent systematic review of the literature showed a significantly higher weighted mean prevalence of asymptomatic carriage in LTCFs of 14.8%

(95% CI 7.6 – 24.0), though did find high levels of heterogeneity among individual care homes.

For this reason, we constructed prior distributions for asymptomatic and symptomatic *C. difficile* importation rates from the LTCF, and updated them using the screening data (Table S5).

Table S 5: Importation rates of infected and colonised individuals

Status	Cases	Total screened	Total admissions	Proportion	Lower#	Upper#
Carrier ICU	20	744	1332	0.027	0.017	0.041
Infected ICU	4	744	1332	0.003	0.001	0.008
Carrier ICU AND LTCF	0	30	53	0	0	0.114
Infected ICU AND LTCF	0	30	53	0	0	0.114
Carrier ICU and Community	20	714*	1279*	0.028	0.018	0.043
Infected ICU and community	4	714*	1279*	0.003	0.001	0.008

* Under the assumption that four per cent of the total admissions are patients from LTCFs; # 95% confidence intervals calculated using the Wilson score method[16]

As a conservative estimate, it was assumed that importation rates of colonised (a_{c_ltcf}) and infected (a_{i_ltcf}) individuals from the LTCF could be 0-3 times higher than importations from the general community. Two beta distributions with shape parameters informed by the above screening data (Table S6) were used to represent community importation rates of infected and colonised cases respectively, whereas a triangular distribution (mode 1.5, min=0,

max=3) represented the differences in importation rates between community and LTCF settings.

Table S 6: Values used in probabilistic sensitivity analysis

Parameter	Description	Distribution LHS
α_{icu}	Fraction of patients on antimicrobials in the ICU on a given day	Logitnormal(-1.274; SD 0.08)
α_{gm}	Fraction of patients admitted from GM on antimicrobials on admission to the ICU	Logitnormal(-2.431; SD 0.06)
α_{ltcf}	Fraction of patients directly admitted from LTCF on antimicrobials on admission	Beta(0.040; SD 0.006)
α_{com}	Fraction of patients directly admitted from the community on antimicrobials on admission	Beta(0.012; SD 0.004)
$f_{ltcf} = f_{com}$	Fraction of patients admitted to ICU from the LTCF/ community that develop a natural immune response against disease	Beta(0.240; SD 0.077)
a_{i_ltcf}	Fraction of patients from LTCF that were infected on admission to ICU	Posterior distribution (see methods)
a_{c_ltcf}	Fraction of patients from LTCF that were colonised on admission to ICU	Posterior distribution (see methods)

Using LHS, 10,000 samples were randomly drawn from the beta and triangular distributions, and multiplied to obtain a prior distribution for a_{c_ltcf} and a_{i_ltcf}. The probability distributions of these priors were updated using the probability distribution of the data (i.e. LTCF importation rates according to the above screening data), represented by a binomial distribution (k=0 and n=30), in order to obtain posterior distributions for the desired importation rates.

Patient movement parameters (a_{direct_icu}, $a_{elect\_icu\_ltcf}$, $a_{elect\_icu\_com}$, r_{ltcf}, r_{com} and τ)

Hospital Episode Statistics (HES) contains individual patient-level data for all admissions (i.e. spells) to NHS acute Trusts in England. A fraction of this data is publicly available through (http://www.hscic.gov.uk/). However, to inform parameters describing: the fraction of individuals that was admitted directly into the ICU (a_{direct_icu}); the fraction of ICU

admissions that concerned LTCF/community patients that were originally admitted electively to the hospital ($a_{elect\_icu\_ltcf,}/a_{elect\_icu\_com}$); the readmission rates of LTCF residents and patients admitted from their own home ($r_{ltcf,}/r_{com}$) and mean time elapsed between ICU readmissions (τ), more detailed data was required. For this reason, a HES extract involving all admissions with at least one episode in the ICU (i.e. treatment specialty defined as 'critical care') from the financial year April 2012/13 to April 2013/14 was requested.

In HES, a hospital spell (i.e. hospital stay) contains multiple episodes, where a patient starts a new episode when treated by a consultant from a different treatment specialty. The proportion of patients that had their first episode defined as a critical care treatment specialty, informed the fraction of direct admissions into the ICU (a_{direct_icu}), which was used to calculate the risk of antimicrobial exposure outside the ICU as explained earlier.

The HES 'admission method' and 'admission source' data fields informed the fraction of ICU admissions that concerned LTCF/community patients that were originally admitted electively to the hospital. That is, $a_{elect\_icu\_ltcf}$ was the proportion of spells with an *'Elective'* admissions method and the admission source coded as one of the following:

- 54) NHS run nursing home, residential care home or group home**;**
- 65) Local authority Part 3 residential accommodation: where care is provided (from 1996-97);
- 85) Non-NHS (other than Local Authority) run residential care home (from 1996-97);
- 86) Non-NHS (other than Local Authority) run nursing home (from 1996-97)
- 88) non-NHS (other than Local Authority) run hospice.

$a_{elect\_icu\_com}$ concerned all elective spells with admission source coded as*:*

- 19) The usual place of residence, including no fixed abode.

Readmission rates ($r_{ltcf,}/r_{com}$) and readmission time (τ) were defined by the fraction of patients that had a readmission to the ICU within three months (considering the colonisation time of *C. difficile* is rarely found longer than three months[17,18]), and the mean number of days between these readmissions.

Number of vaccines required for strategy 1 (Patients with a history of CDI in the ICU)

The number of vaccine doses required for strategy 1 (vaccinating patients that experienced an episode of CDI in the ICU, v_{CDI_Trust}), was calculated through a counting process incorporated in the model. Over the five year simulation time, for each patient, at the time of ICU-discharge, the model checked whether the patient had experienced an episode of CDI (which could have concerned either an importation or an ICU-acquired infection) and if so, and the patient had not been vaccinated within the previous two years, added an additional vaccine dose to the cumulative total.

Number of vaccines required for strategy 2 (Patients admitted from a LTCF)

To calculate the number of vaccine doses required for strategy 2 (vaccinating residents of LTCFs), two publicly available data sources were used, held by the Care Quality Commission (CQC) and Health & Social Care Information Centre (HSCIC) respectively. The former comprises logistical data on English care homes, such as care home type, postcode and bed numbers[15]. HSCIC is the provider of England's Hospital Episode Statistics (HES). Adult Critical Care data forms part of HES and provides details on the number of NHS acute Trusts with reported ICU records[19]. Hence, these datasets provided insight into 1) the total number of LTCFs in England, using the care home criteria for elderly residents as defined by the CQC (N_{ltcf}); 2) the total number of acute Trusts with reported ICU admissions (N_{Trust}); and 3) the mean LTCF bed size ($B_{ltcf,}$ Table 1 main text).

Assuming all LTCFs and acute Trusts are homogenously scattered across the country, the number of residents requiring vaccination per acute Trust (R_{Trust}) was then defined by:

$$R_{Trust} = \frac{N_{ltcf}}{N_{Trust}} B_{ltcf} \qquad \text{(Equation 4)}$$

Our simulation period (t) comprised five years, and it was assumed a booster vaccine course was needed every two years (ε). Provided that none of the LTCF was admitting new residents, the number of residents multiplied by the simulation period divided by the timing a booster vaccine course was required gave the average number of vaccines required per acute Trust over the full simulation period.

$$v_{ltcf\_Trust} = R_{trust} \frac{t}{\varepsilon} \qquad \text{(Equation 5)}$$

The model captured the transmission dynamics in the ICU, not elsewhere in hospital. As a result, using v_{ltcf_Trust} as a measure for calculating the number vaccines required to prevent one healthcare-onset CDI case would underestimate the vaccine efficiency of this strategy. For this reason, we decided to adjust v_{ltcf_Trust} for the proportion of admissions that included an ICU stay (a_{icu}). The total number of ICU admissions per Trust in the financial year 2013/14[19] were divided and weighted by the total number of HES admissions[20] to obtain the weighted mean proportion of yearly admissions that comprised an ICU admission (a_{icu}). The average number of vaccines required per ICU over the full simulation period was then given by:

$$v_{ltcf\_ICU} = a_{icu} v_{ltcf\_Trust} \qquad \text{(Equation 6)}$$

<u>Number of vaccines required for strategy 3 (Patients admitted for elective surgery)</u>

For strategy 3 (vaccinating elective patients), only a small fraction of ICU admissions is planned[19]. However, elective hospital patients could experience an ICU episode during

their hospital stay. Therefore, regardless of whether a vaccine would target ICU or high-risk hospital ward populations; this strategy will involve vaccination of all elective hospital patients.

To calculate the number of vaccine doses required for this strategy (v_{elect_Trust}), publicly available HES data was used. HES Admitted Patient Care data from 2013/14[20] provided detail on the total number of yearly admissions, and the yearly number of elective admissions per acute Trust. The mean of the latter multiplied by the simulation period represented the per acute Trust vaccine doses required for this strategy. For similar reasons as explained in the previous section, this number was scaled to the ICU setting using $a_{icu.}$

$$v_{elect\_ICU} = a_{icu} v_{elect\_Trust} \qquad \text{(Equation 7)}$$

Number of vaccines required for strategy 4 (all combined)

For strategy 4, as the three target groups were not mutual exclusive, v_{ltcf_ICU}, v_{ltcf_Trust} and v_{elect_ICU} were combined and deducted by the fraction of admissions that concerned LTCF patients (a_{ltcf}). Here, v_{CDI_Trust} was calculated as before, but with the model run under the assumption that all LTCF and elective patients were vaccinated, thus protected from developing CDI in the ICU.

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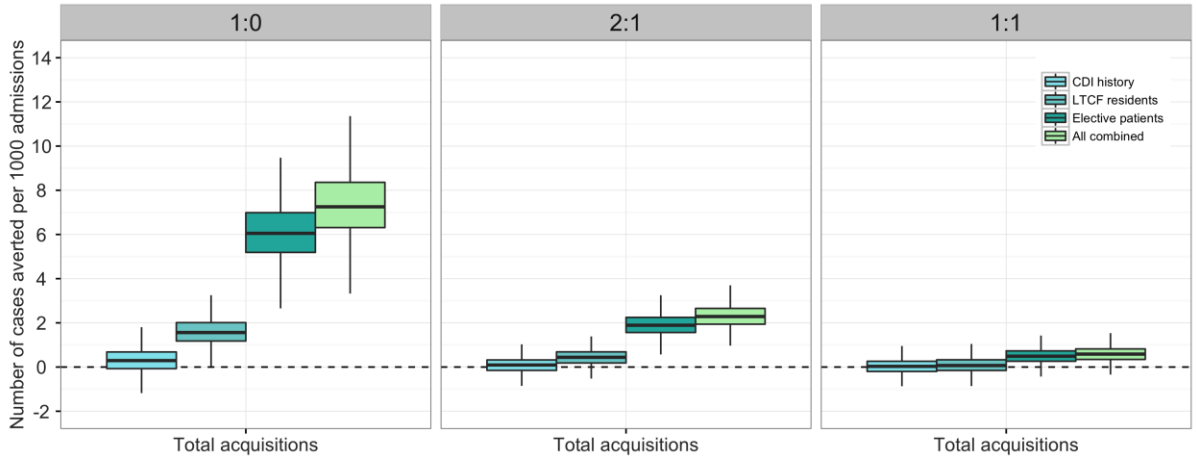
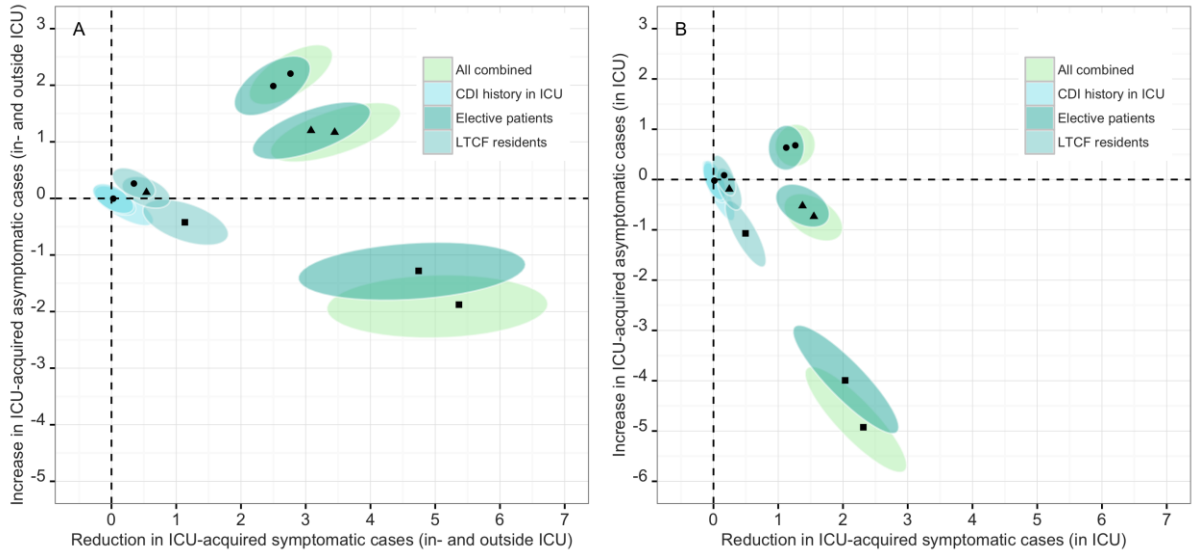
Figure S 2: Change in ICU-acquired cases (symptomatic and asymptomatic) per 1000 admissions shown for all four vaccination strategies, and all three assumptions for asymptomatic transmission



The middle line in the box represents the median of 1000 model parameter sets, and upper and lower areas of the box indicate the seventy-fifth and twenty-fifth percentiles. **1:0:** no asymptomatic transmission; **2:1:** asymptomatic carriers are half as transmissible compared to symptomatic carriers; **1:1:** asymptomatic and symptomatic carriers are equally transmissible.

Figure S 3: Change in symptomatic and asymptomatic ICU-acquired *C. difficile* per 1000 admissions shown for all four vaccination strategies, and all three assumptions for asymptomatic transmission; A) In the ICU; B) In- and outside the ICU



Black points: median absolute reduction in symptomatic cases (x-axis) and increase in symptomatic cases (y-axis) of the 1000 parameter sets. **Squared dot:** no asymptomatic transmission; **round dot:** asymptomatic carriers are half as transmissible compared to symptomatic carriers; **triangular dot:** asymptomatic carriers are equally transmissible. Transparent ellipses plot the 95% coverage intervals.

Table S 7: Scenario effectiveness and efficiency

	Transmission Symptomatic: Asymptomatic (2:1)		
Scenario	**ICU-onset CDI cases prevented/1000 admissions (Effectiveness)**	**Proportion of the ICU-onset cases prevented that were ICU-acquired**	**Doses required to avert one ICU-onset CDI case (scaled to ICU) (Efficiency)**
Scenario 1 (2:1 + AT + AA + VE = 100%)			
1) History of CDI in ICU	0.1 [0 – 0.3]	0.20	81 [38 – NA]
2) LTCF residents	1.0 [0.8 – 1.2]	0.24	13 [11 – 16]
3) Elective patients	3.8 [3.5 – 4.2]	0.36	146 [133 – 162]
4) All combined	4.7 [4.3 – 5.1]	0.34	124 [114 – 136]
Scenario 2 (2:1 + HT + AA + VE = 100%)			
1) History of CDI in ICU	0.5 [0.2 – 0.7]	0.34	44 [29 – 87]
2) LTCF residents	1.6 [1.3 – 1.9]	0.50	8 [7 – 10]
3) Elective patients	7.9 [7.1 – 8.8]	0.64	72 [65 – 80]
4) All combined	9.3 [8.4 – 10.4]	0.61	63 [57 – 70]
Scenario 3 (2:1 + AT + LA + VE = 100%)			
1) History of CDI in ICU	-	-	-
2) LTCF residents	0.8 [0.6 – 0.9]	0.19	17 [14 – 22]
3) Elective patients	2.8 [2.6 – 3.1]	0.29	199 [184 – 217]
4) All combined	3.5 [3.2 – 3.8]	0.26	166 [155 – 180]
Scenario 4 (2:1 + HT + LA + VE = 100%)			
1) History of CDI in ICU	-	-	-
2) LTCF residents	1.1 [0.9 – 1.3]	0.40	12 [10 – 15]
3) Elective patients	5.0 [4.6 – 5.5]	0.56	113 [104 – 124]
4) All combined	5.9 [5.4 – 6.5]	0.54	99 [90 – 108]
Scenario 5 (2:1 + AT + HA + VE = 100%)			
1) History of CDI in ICU	-	-	-
2) LTCF residents	1.3 [1.0 – 1.6]	0.30	10 [8 – 13]
3) Elective patients	5.3 [4.8 – 5.8]	0.42	107 [96 – 117]
4) All combined	6.4 [5.8 – 7.0]	0.39	91 [83 – 100]
Scenario 6 (2:1 + HT + HA + VE = 100%)			
1) History of CDI in ICU	-	-	-
2) LTCF residents	2.3 [1.9 – 2.7]	0.55	6 [5 – 7]
3) Elective patients	11.8 [10.9 – 13.2]	0.68	48 [44 – 53]
4) All combined	14.2 [12.8 – 15.5]	0.65	43 [39 – 47]
Scenario 7 (2:1 + AT + AA + VE = 70%)			
1) History of CDI in ICU	-	-	-
2) LTCF residents	0.8 [0.6 – 0.9]	0.24	17 [14 – 22]
3) Elective patients	2.8 [2.5 – 3.0]	0.37	205 [186 – 226]
4) All combined	3.5 [3.1 – 3.8]	0.34	168 [154 – 187]

Scenario 8 (2:1 + AT + AA + VE = 50%)			
1) History of CDI in ICU	-	-	-
2) LTCF residents	0.6 [0.4 – 0.7]	0.23	23 [18 – 32]
3) Elective patients	2.0 [1.8 – 2.3]	0.36	281 [251 – 313]
4) All combined	2.6 [2.3 – 2.8]	0.33	229 [206 – 255]
Scenario 9 (*1:0 + AT + AA + VE = 100%)*			
1) History of CDI in ICU	0.2 [0 – 0.4]	0.37	55 [29 – 406]
2) LTCF residents	1.2 [1.0 – 1.5]	0.38	11 [9 – 13]
3) Elective patients	4.5 [4.0 – 5.2]	0.45	124 [109 – 140]
4) All combined	5.5 [4.8 – 6.2]	0.42	105 [94 – 120]
Scenario 10 (*1:1 + AT + AA + VE*			
1) History of CDI in ICU	0.1 [0 – 0.3]	0.04	86 [41 – NA]
2) LTCF residents	0.9 [0.7 – 1.0]	0.18	15 [12 – 18]
3) Elective patients	3.6 [3.3 – 3.9]	0.31	157 [146 – 171]
4) All combined	4.4 [4.0 – 4.8]	0.28	131 [122 – 144]
Scenario 11 (*1:0 + HT + AA + VE*			
1) History of CDI in ICU	-	-	-
2) LTCF residents	2.5 [2.0 – 3.0]	0.64	5 [4 – 6]
3) Elective patients	10.8 [9.1 – 12.5]	0.72	53 [45 – 62]
4) All combined	12.6 [10.6 - 14.5]	0.70	47 [41 – 55]
Scenario 12 (*1:1 + HT + AA + VE*			
1) History of CDI in ICU	-	-	-
2) LTCF residents	1.4 [1.2 – 1.7]	0.45	9 [8 – 11]
3) Elective patients	7.1 [6.4 – 7.7]	0.61	80 [74 – 88]
4) All combined	8.5 [7.7 – 9.2]	0.58	70 [65 – 77]

Table S 8: Calibration and model validation

Variable name	Observed value (Interquartile range)	Calibration value	Validation value	Source	Notes
Incidence rate of CDI with onset >48h after ICU-admission* per 1000 patient days	0.8 [0.7-0.9]	0.8		ICNARC [2]	
Incidence rate of CDI with onset >48h after ICU-admission* per 1000 admissions	5.6 [5.0-6.1]	-	5.8	ICNARC [2]; English Hospital Episode statistics data [20]	The mean length of ICU stay in England is 7.2 days [20]. As a result, 0.8 CDI per 1000 patient days would approximate 0.8*7.2 = 5.8 CDI per 1000 admissions
Incidence rate of CA- and HA-CDI with ICU-onset per 1000 admissions	10.9 [10.0-11.8]	-	10.0 [10 – 20]	Karinka (2015) [21]	A meta-analysis on CDI in the ICU found that 1% (95%CI 1-2%) of European ICU patients was found positive for CDI (i.e. the number of patients diagnosed with CDI while in the ICU divided among the total ICU patients was 1% on average)
Ratio of colonised vs infected acquisitions in the ICU	4.3 [4.1-4.5]:1	-	4:1	MacFarland (1989)[22]; Johnson (1990)[23]	
Fraction of HA-CDI with onset post-discharge	0.57	-	0.63	Lessa (2015)[24]	Based on population-level surveillance, Lessa (2015) found that 65.8% of CDI was healthcare-associated. Of these, 24.2% had onset during their hospital stay. Therefore 41.6%/65.8% = 63% had onset in the community.
Mean ICU LOS for all patients	7.0	-	7.2	English Hospital Episode statistics data [20]	

Mean number of symptomatic days per HA-CDI patient	4.0	-	4.0	Walker (2012)[25]; Teasley (1983)[26]; Sethi (2010)[27]	

*** ICNARC defines all CDI cases with onset >48h into ICU admission as ICU-acquired CDI. **CA-CDI = patients that were infected on admission, or patients colonised on admission that developed symptoms during their ICU-stay. HA-CDI = CDI cases that were acquired during the patient's ICU stay.**