Age-targeted vaccination for reducing *Clostridioides difficile* infection in England: a coupled mathematical-economic modelling analysis

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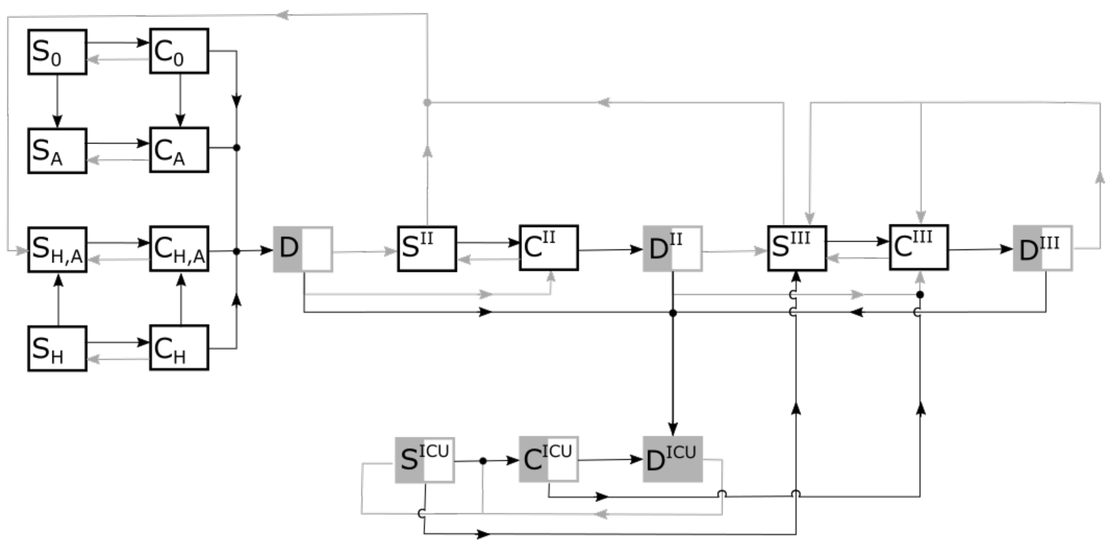
Background

> *Clostridioides difficile* remains the leading cause of healthcare-associated infectious diarrhea and is also increasingly associated with community-associated disease.[1] Symptoms of *C. difficile* infection (CDI) range from mild diarrhea to severe illness which may lead to complications such as pseudomembranous colitis, toxic megacolon, sepsis and death. Treatment failure is common, leading to the reemergence of symptoms, necessitating complex treatment plans and worsened prognosis.[2] Results from an international, phase 3, placebo-controlled and randomized study to evaluate the efficacy, safety, and tolerability of the leading *C. difficile* vaccine candidate, PF-06425090 demonstrated 100% reduction in medically attended CDI.[3]

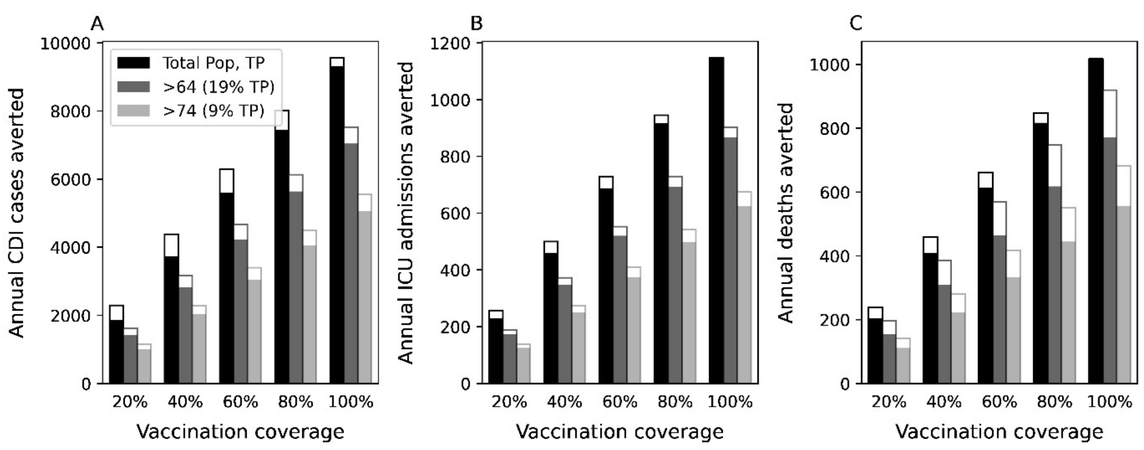
Methods

> A novel mathematical model of *C. difficile* transmission was developed to simulate the transition between epidemiological states of a population of hospital inpatients and used to evaluate the projected benefit of deploying a safe and efficacious *C. difficile* vaccine in England (Figure 1). Hospital costs and costs of years of life lost due to premature mortality averted per vaccine course were computed along with quality-adjusted life years (QALYs) associated with each health state. Alternative scenarios were simulated to compare health and economic benefits of targeting older age groups.



> Figure 1. The epidemiological states of the *C. difficile* model. Susceptible individuals (S) become colonized (C) and then diseased (D). Superscripts II and III depict those who have recently recovered from primary and recurrent CDI respectively. 'ICU' superscripts are used for those who are receiving intensive care. Patients among half-shaded compartments are not discharged and the shaded compartment denotes patients not discharged from ICU. Subscripts denote those who are taking, or have taken within the past 3 months, antibiotics (A); those who were discharged from hospital less than 1 month prior (H); and, those who have both recently taken antibiotics and been recently discharged (H,A). Individuals who have neither received antibiotics nor been discharged recently make up the remainder (0).

Results



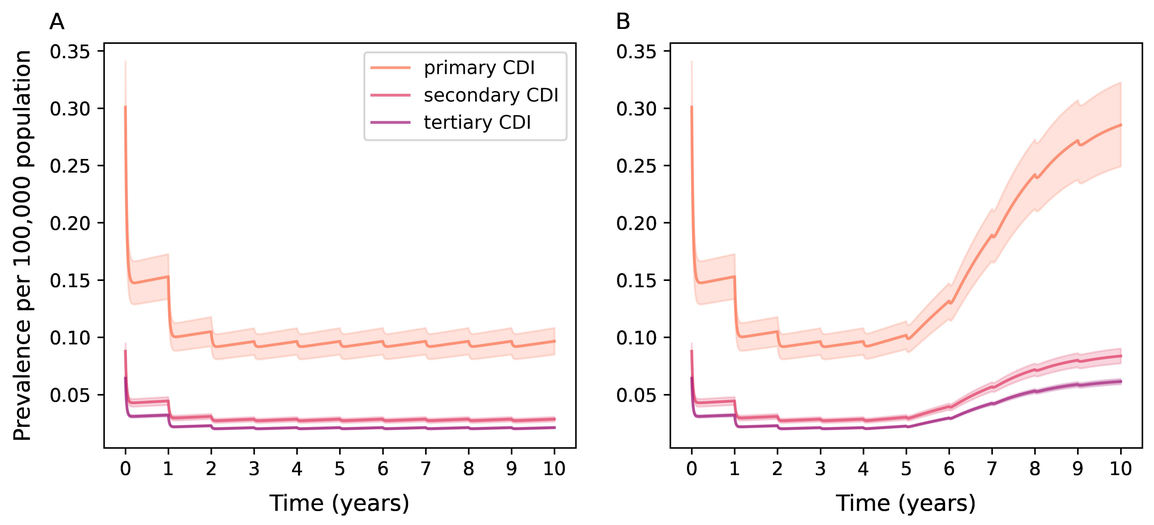
> Figure 2. Simulated impacts of different vaccine coverage levels on annual A) CDI cases, B) ICU admissions and C) deaths in England. Results are presented following 1-year simulations during which immunity was assumed not to wane. Colors correspond with different targeting strategies, including all age groups ('total population', black), just those who were older than 64 years (dark grey) and just those who were older than 74 years old (light grey).

Results (continued)

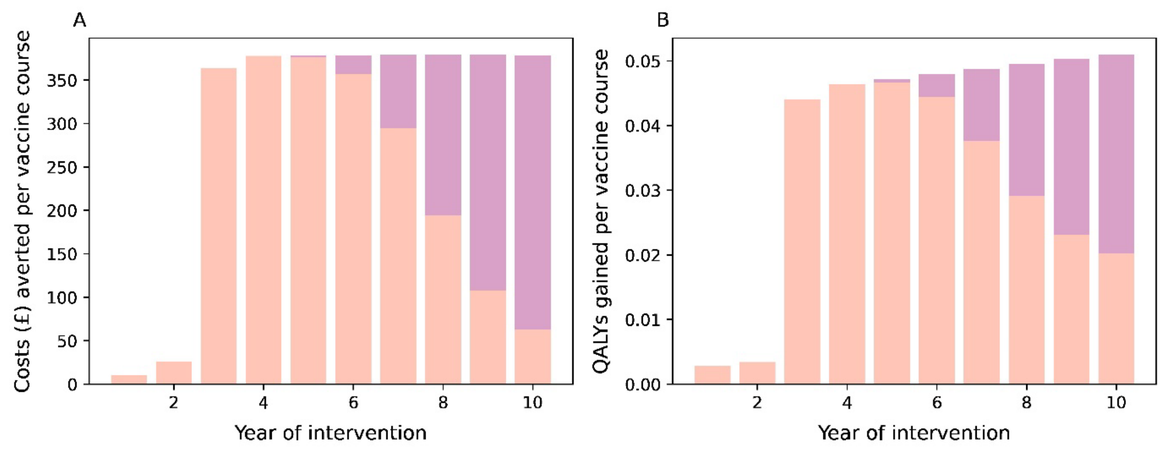
> Simulations showed that targeting over 64 year olds achieved around four-fifths the impact of targeting the total population despite requiring one-fifth the vaccine doses; and, targeting over 74 year olds achieved over half the impact despite requiring one-tenth the vaccine doses (Figure 2).

> The white spaces within the bars (Figure 2) denote the additional outcomes (CDI cases, ICU admissions, deaths) averted among unvaccinated individuals i.e., through indirect effects of the vaccine.

> No immunological waning has been found up to 4 years post-vaccination with the currently leading vaccine candidate[4]. To look at longer time horizons, two alternative waning scenarios were explored: no waning over 10 years, and, a steady decline after year 4 to 50% maximum efficacy by year 6 and 0% efficacy by year 8. Vaccine was simulated to roll-out initially to those over 74 years old, then onto over 64 with an annual top-up to capture those newly becoming 65, with resultant epidemiological and health-economic impact shown in Figure 3 and 4, respectively.



> Figure 3. The simulated impact on CDI prevalence per 100,000 population from a 10-year top-up vaccination strategy for A) a vaccine that remains efficacious throughout, and B) a vaccine that wanes from the fourth year. The darker lines represent simulations of the average CDI rates reported among hospitals in England, and the boundaries are from simulations of the 95% confidence intervals for reported CDI rates.



> Figure 4. The simulated impact on A) costs averted, and B) QALYs gained, per vaccine course for both a no-wane (purple) and waning (orange) efficacy scenario over the 10-year vaccination horizon.

Conclusions

> Achieving effective coverage of all those over 64 years old can be expected to avert 80% of medically attended CDI and 90% of CDI related deaths. This equates to £378 averted annually in hospital costs combined with years of life lost due to premature mortality costs per vaccine course. This is an extremely encouraging result for the economic viability of a safe, efficacious *C. difficile* vaccine.

Funding

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References

1. Viprey et al. (2022) *Eurosurveillance* 27(26):2100704.; **2.** Kyne et al (2001) *Gut* 49(1):152.; **3.** Phase 3 CLOVER Trial for Pfizer's Investigational *Clostridioides Difficile* Vaccine Indicates Strong Potential Effect in Reducing Duration and Severity of Disease Based on Secondary Endpoints [press release]. 2022; **4.** Remich et al (2024) *J Infect Dis* 229(2):367-75