Assessment of the Potential of Vaccination to Combat Antibiotic Resistance in Gonorrhea: A Modeling Analysis to Determine Preferred Product Characteristics

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Summary: A gonorrhea vaccine offering partial protection for several years, pragmatically targeted to people testing for gonorrhea due to symptoms or screening due to sexual risk behavior, could substantially reduce gonorrhea incidence, combating increases in antibiotic resistance.

ABSTRACT

Background. Gonorrhea incidence is increasing rapidly in many countries, whilst antibiotic resistance is making treatment more difficult. Combined with evidence that MeNZB and Bexsero meningococcal vaccines are likely partially-protective against gonorrhea, this has renewed interest in a gonococcal vaccine, and several candidates are in development. Key questions are how protective a vaccine needs to be, how long protection needs to last, and how should it be targeted. We assessed vaccination's potential impact, and the feasibility of achieving WHO's target 90% reduction in gonorrhea incidence 2016-2030, by comparing realistic vaccination strategies under a range of scenarios of vaccine efficacy and duration of protection, and emergence of extensively-resistant gonorrhea.

Methods. We developed a stochastic transmission-dynamic model, incorporating asymptomatic and symptomatic infection and heterogeneous sexual behavior in men-who-have-sex-with-men (MSM). We used data from England, which has a comprehensive, consistent nationwide surveillance system. Using particle Markov Chain Monte Carlo methods we fitted the model to gonorrhea incidence in 2008-17, and then used Bayesian forecasting to examine an extensive range of scenarios.

Results. Even in the worst-case scenario of untreatable infection emerging, the WHO target is achievable if all MSM attending sexual health clinics receive a vaccine offering ≥52% protection for ≥6 years. A vaccine conferring 31% protection (as estimated for MeNZB) for 2-4 years, could reduce incidence in 2030 by 45% in the worst-case scenario, and by 75% if >70% of resistant gonorrhea remains treatable.

Conclusions. Even a partially-protective vaccine, delivered through a realistic targeting strategy, could substantially reduce gonorrhea incidence, despite antibiotic resistance.

Keywords: gonorrhea, vaccination, antibiotic resistance, transmission model, treatment failure.

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INTRODUCTION

The World Health Organization (WHO) classifies *Neisseria gonorrhoeae* as a priority bacterial pathogen, due to the high global burden of infection combined with evolution and global spread of resistance to every antibiotic historically used against it[1,2]. Countries such as the USA[3], Australia[4], UK[5] and other European countries[6] have reported rapidly growing epidemics, particularly among men-who-have-sex-with-men (MSM).

Due to the threat of antibiotic resistant gonorrhea it has been suggested that that vaccination may be the only sustainable solution to gonorrhea control[7]. Vaccine development has been hampered by genetic variability in the gonococcus, and the lack of a measurable correlate of protection and a suitable animal model[8]. None of four vaccine candidates that progressed to clinical trials was effective[9]. However, indication that vaccination against gonorrhea might be feasible came from surveillance reports from Cuba and New Zealand showing a decline in gonorrhea incidence following vaccination initiatives against the closely-related *Neisseria meningitidis*[10–12]. A retrospective case-control study of 15,000 young adults in New Zealand who had received an outer-membrane vesicle meningococcal B vaccine (MeNZB) estimated 31%(95%CI:21%-39%) protection against *N. gonorrhoeae*[13], and a recent study reported that the Bexsero meningococcal B vaccine may be more protective than this[14]. There are now multiple vaccine candidates in preclinical development[11,15].

Key questions to inform development and use of vaccines to control gonorrhea are the preferred product characteristics of a gonorrhea vaccine (i.e. what efficacy and duration of protection are required)[16], and how best to deploy vaccines to decrease the overall burden of disease[17–19]. In 2016, the WHO announced a global health sector strategy on sexually transmitted infections, with

a target of 90% reduction in gonorrhea incidence by 2030[2]. We investigated how protective and long-lasting a vaccine would need to be to reduce total incidence below the WHO target using a stochastic model (accounting for variability due to random chance) of gonorrhea epidemiology in MSM in England calibrated to recent incidence data[20,21], with varying future levels of antibiotic resistance. We compared the impact and efficiency of three realistic vaccination strategies, studied the interplay between vaccination and antibiotic resistance levels, and quantified the effect of differing levels of vaccine uptake. Finally, we assessed the potential impact of vaccines with a partially protective profile similar to MeNZB.

METHODS

Model structure

We developed a stochastic compartmental transmission-dynamic model to project the future course of a gonorrhea epidemic under different vaccination scenarios, considering antibiotic-sensitive and antibiotic-resistant (ABR) strains. We used data from England, which has comprehensive, consistent, nationwide surveillance system[20,21]. We considered transmission within men-who-have-sex-with-men (MSM) as they have the highest per-capita rate of infection. We simulated gonorrhea transmission from 2008 to 2030, using surveillance data 2008-2017 for calibration and then projecting scenarios to 2030. We extended a previous model[22] to incorporate heterogeneity in sexual risk behavior by dividing the population into low- and high-risk groups with characteristic rates of sexual partner change, based on the Natsal-3 survey[23].

Following acquisition of gonorrhea, individuals initially pass through a short incubation period, after which they either develop symptoms or remain asymptomatically infected (Figure 1).

Surveillance data are not stratified by infection site (rectum, pharynx, urethra), hence estimated parameters can be interpreted as an average across infection sites. Infected individuals are treated after seeking care due to symptoms or after testing positive in sexual health screening. Treated individuals become uninfected, except for a proportion of those infected with the ABR strain for whom treatment fails, leading to persistent infection for which the same dynamics are assumed as for asymptomatic cases[22]. Recovery from untreated infection also occurs naturally over time. Infection does not confer natural immunity[24,25]. We consider a situation in which the ABR strain emerges globally in 2020 and is imported into the highly-sexually-active group.

Model calibration and accounting for uncertainty

We calibrated the model, in a Bayesian framework, to the annual number of gonorrhea cases in MSM in England between 2008-2017[20]. These data were considered as the observed realizations of a complex underlying unobserved Markov process (Figure 1). Prior parameter distributions were based on published evidence where available, and uninformative priors used otherwise. All unknown parameters were calibrated, with a particle filter[26] used to produce an unbiased estimate of the likelihood of the observed data given the model, in a particle Markov Chain Monte Carlo (pMCMC) process which produced a posterior sample of the model parameters given the observed data[27,28]. We accounted for uncertainty in estimated parameters by using 1,000 samples from the joint posterior distribution. Full details of the model, the parameter values, and prior distributions are in Supplementary Material. We varied the frequency of treatment failure for the ABR strain (0%-100%).

Vaccination scenarios

We considered 500 hypothetical vaccine profiles of varying protection (1%-100%) and duration

(1-20 years). Partial protection was assumed to be "leaky" (i.e. degree-type)[29], with all vaccinees being less likely, but still able, to acquire infection. Vaccine protection only affects the probability of acquisition and does not affect progression through stages of infection after acquisition.

We considered three realistic strategies for the vaccine deployment: "vaccination-before-entry" into the sexually-active population (where adolescents are vaccinated before they become sexually-active); "vaccination-on-diagnosis" with gonorrhea (a practical strategy designed to target those most at risk, as gonorrhea diagnosis is used as a proxy measure for risk of future exposure); and "vaccination-on-attendance" at a sexual health clinic for any reason, including seeking testing and treatment for symptoms or asymptomatic screening (which broadens the eligibility criteria of the "vaccination-on-diagnosis" strategy to include all clinic attendees). Vaccine uptake among eligible individuals was varied (50%-100%) for each strategy. Scenarios were compared to baseline projections without vaccination.

RESULTS

The model was successfully calibrated, with simulated epidemic curves being in close agreement with the observed data for all years (Figure 2A). For example, the model estimated 21,900(95%CI:18,900-25,200) cases in 2017, in good agreement with the data (21,300 cases)[20]. In the best-case scenario, with no worsening of resistance, the model predicted 23,500(20,000-27,600) cases in 2030. However, emergence of an antibiotic-resistant (ABR) strain causing treatment failures would increase the projected number of cases (Figure 2B): the higher the frequency of treatment failure, the greater the onward transmission of drug-resistant infections and the greater the predicted number of cases. In the worst-case scenario of 100% treatment failure for the ABR strain, the model predicted 48,500(23,600-80,100) gonorrhea cases in 2030.

Focusing on the worst-case scenario where treatment of ABR gonorrhea always failed, we assessed the impact of each hypothetical vaccine profile (i.e. combination of level and duration of protection) under the three deployment strategies by calculating the expected reduction in gonorrhea cases in 2030 (Figure 3) compared with no vaccination. Achieving the WHO target corresponds to <1,800 cases in MSM in England in 2030[2]. In the vaccination-before-entry strategy, even a fully-protective vaccine lasting 20 years achieved only a 34%(17%-52%) reduction in expected cases in 2030 (Figure 3A), well below the WHO target. Under this strategy only adolescents entering the sexually-active population are vaccinated, so vaccine coverage across the entire MSM population is slow to accumulate, reducing the impact of the intervention. Vaccination-on-diagnosis with this idealized vaccine also fell short of the WHO target but achieved a much higher reduction of 92%(82%-98%) (Figure 3B). By extending vaccination to all MSM tested for gonorrhea (i.e. vaccination-on-attendance, both those seeking care for symptoms and those screened in the absence of symptoms), the WHO target could be achieved using a ≥52% effective vaccine protecting for ≥6 years, or equivalently a ≥70% effective vaccine lasting ≥3 years (Figure 3C). Under the vaccination-on-diagnosis and vaccination-on-attendance strategies, a vaccine lasting eight years had similar benefits to one offering the same protection for a longer period (Figure 3B,C).

Under the vaccination-before-entry strategy, the proportion of MSM protected in 2030 was <20% irrespective of the duration of vaccine protection (Figure 3D), because most individuals were already sexually-active, and therefore ineligible for vaccination. Under the vaccination-on-diagnosis strategy the protected proportion was generally higher (Figure 3E) because more individuals were eligible for vaccination. Interestingly, the proportion protected

decreased as vaccine efficacy increased, because a highly-protective vaccine reduced transmission, which in turn reduced the number of cases treated and hence individuals vaccinated alongside treatment. This effect also occurred under the vaccination-on-attendance strategy, but it was much less pronounced as patients attending for screening were also vaccinated. The maximum proportion protected under vaccination-on-attendance was 86%(85.8%-86.4%), if the duration of protection were 20 years (Figure 3F).

We assessed how the impact of vaccination would differ depending on the treatability of the emergent gonorrhea ABR strain and the uptake of vaccination by eligible MSM (Figure 4). The less treatable the ABR strain the more protective a vaccine would need to be to meet the WHO target. The vaccination-before-entry strategy was unable to achieve the WHO target, no matter how protective and long-lasting the vaccine, even in the best-case scenario of no treatment failure. The vaccination-on-diagnosis strategy met the WHO target for a range of vaccine profiles, in scenarios where at least 30% of ABR cases were treatable, provided almost all eligible MSM accepted the vaccine when offered and protection lasted almost 20 years (Figure 4A). With 75% vaccine uptake vaccination-on-diagnosis could not meet the target if ABR treatment failure exceeded 60% (Figure 4B). With an uptake of only 50%, the target was not met even in the best-case scenario of no treatment failure. The lower the uptake, the greater the vaccine protection level and/or duration required to achieve a given impact (Figure 4A-B). The vaccination-on-attendance strategy resulted in much higher coverage, meaning that less-protective vaccines were able to achieve the WHO target (Figure 4C). For example, in the absence of treatment failure, a 35%-protective vaccine lasting ten years could meet the WHO target, whereas, under the vaccination-on-diagnosis strategy, the vaccine would need to be 80%-protective. At the other extreme, if treatment of ABR cases always failed then the WHO target could be achieved

with the vaccination-on-attendance strategy but would require for example a protection duration of six years and efficacy of 50%-75% depending on uptake (Figure 4C-E).

Currently the only vaccine with estimated effectiveness of protection against gonorrhea is MeNZB, which offers 21%-39% protection[13]. While there are no robust estimates of the duration of protection of MeNZB, we modeled a conservative 2-4 year duration in line with initial indications [13]. We considered deployment of a similar vaccine using the three strategies, and compared the expected number of cases in 2030, the proportion of ABR, the proportion of protected MSM and the number of cases averted over ten years per person vaccinated (Figure 5). If there were no emergence of ABR gonorrhea, then a vaccine with properties like MeNZB could have a substantial impact on the projected epidemic. With uptake of 100%, vaccination-on-diagnosis would reduce the expected incidence in 2030 by 41%(18%-65%), from 23,500(20,000-27,600) to 13,900(8,200-18,700), and vaccination-on-attendance would reduce incidence by 75%(40%-98%) to 5,900(450-13,600) cases. The greater impact of vaccination-on-attendance was due to much greater coverage, with much lower efficiency: the mean cases averted per vaccination was 0.10(0.07-0.13) compared with 0.51(0.32-0.75) for vaccination-on-diagnosis. It should be noted that even vaccination-on-attendance was insufficient to meet the WHO in 85% of the simulations. The vaccination-before-entry strategy was in effective with a MeNZB-like vaccine, achieving only a 7%(0%-23%) reduction in 2030 incidence, even without emergence of ABR.

The greater the frequency of treatment failure for ABR infections, the greater the predicted incidence in 2030 and the less likely the epidemic could be controlled by a MeNZB-like vaccine (Figure 5A). Vaccination-on-attendance was always the most effective strategy, regardless of the treatability of the resistant strain. In the extreme case where ABR treatment always failed,

vaccination-on-attendance with a MeNZB-like vaccine with 100% uptake reduced the expected number of cases by 45%(18%-77%). This equated to the prevention of around 20,900 cases in 2030, reducing the expected diagnoses from 48,500(23,600-80,100) to 27,600(8,000-55,800). The proportion of cases expected to be ABR in 2030 was unaffected by vaccination, regardless of the vaccination strategy: vaccination reduced the expected diagnoses of both the resistant and susceptible strains proportionately (Figure 5B). The proportion of individuals protected by the vaccine, and the corresponding number of vaccine doses dispensed, depended more on the vaccination strategy than on the treatability of the ABR strain (Figure 5C), with vaccination-on-attendance resulting in a much higher proportion of protected individuals. Vaccination-on-diagnosis proved to be the most efficient strategy overall, with on average about one averted case for every two vaccine doses administered, which remained constant for almost all resistant strains (Figure 5D).

DISCUSSION

We developed a stochastic transmission-dynamic model of gonorrhea that incorporates heterogeneity in sexual behavior and considers use of health services for care-seeking and screening. The model was calibrated using 10 years' data using Bayesian inference methods to estimate model parameters, and then used to examine the population-level impact of potential vaccines, administered via three realistic strategies. Our results show that even a partially-protective vaccine could be valuable in controlling the gonorrhea epidemic and combating the spread of antibiotic resistance. Provided infections remain ultimately treatable, vaccinating all MSM attending sexual health clinics from 2020 onwards with a 45%-protective vaccine lasting at least four years, or a 60%-protective vaccine lasting at least two years, would be sufficient to meet the WHO target of a 90% reduction in annual incidence between 2016 and

2030[2]. Whilst this requires greater protection than the 31%(95%CI:21%-39%) that MeNZB appears to offer[13], Bexsero is expected to be more protective due to its Neisserial heparin binding antigen component[14]. In addition to protecting against infection with gonorrhea, vaccination with MeNZB might also be protective against severe disease if infection is nevertheless acquired[30].

We investigated the interplay between antibiotic resistance and vaccination, making the conservative (and likely pessimistic) assumption that antibiotic resistance did not incur a fitness cost. In the extreme case where treatment for the ABR strain always fails, a 52%-protective vaccine lasting six years, administered to all MSM attending sexual health clinics would be necessary to achieve the WHO target.

Imperfect vaccines are usually modeled as providing either take-type protection (where a proportion of vaccinees are fully protected and the remainder not at all), or degree-type protection (where all vaccinees have a partial reduction in the probability of infection upon exposure)[29]. Here we used the latter, even though it is unknown what type of protection a future gonorrhea vaccine might provide, or indeed if it would conform to one type or another or a mixture of both. For vaccines with degree-type protection, greater coverage is necessary to reduce the prevalence of infection than with take-type protection[31], so that our choice is conservative. Furthermore, a take-type protection vaccine is similar in result to the effect of partial uptake for a highly protective degree-type vaccine, which we considered separately (Figure 4). Degree-type protection could conceivably manifest as a reduction in infectiousness[32], rather than the reduction in susceptibility we model here; previous modeling has found the impact to be similar[17].

Uptake of vaccination is clearly a critical determinant for the success of any vaccination program, and societal concerns about vaccines are a potential barrier to achieving high coverage[12]. However, a recent pilot program for human papillomavirus (HPV) vaccine in UK MSM recorded uptake of 45%, which is likely to be an underestimate due to incomplete recording[33]. Therefore, the 50% uptake scenario we modeled could be considered a realistic lower bound, especially for the vaccination-on-diagnosis and vaccination-on-attendance strategies, in which the vaccine would be offered to individuals likely to be concerned about gonorrhea infection.

Our study is the first to consider vaccination against gonorrhea in the context of antibiotic resistance, and to assess the potential real-world impact that could be achieved using a vaccine with protection profile similar to MeNZB as well as potentially superior gonorrhea vaccines, which is expected to include Bexsero[14]. Previous modeling studies have focused on assessing the potential impact of hypothetical vaccines in small populations of either heterosexual individuals[17] or MSM[34]. In accordance with our findings, they concluded that a vaccine of moderate level and duration of protection (60% for 10 years) could substantially reduce prevalence of infection by >30%[17]. Our analysis is novel in considering the effect of vaccination on the scale of all MSM within a country, by comparing alternative realistic deployment strategies, and by incorporating the possible global emergence of a new extensively resistant strain, as well as incorporating a statistically rigorous fit to incidence data.

We considered scenarios in which sexual health services are able to meet the additional demand caused by increasing levels of gonorrhea incidence and antibiotic resistance. However, in recent years, access to UK sexual health services has worsened for individuals with symptoms of an acute sexually transmitted infection[35]. This insufficient capacity in sexual health clinics could create a

vicious circle, where treatment delays cause onward transmission, increased incidence, and further unmet treatment need, a situation that would be exacerbated by antibiotic resistance[36,37]. A gonococcal vaccine would offer important benefits of easing this pressure by averting infections, thereby reducing demand on clinics and avoiding the vicious circle.

There are two important areas for attention by public health researchers and policy-makers: firstly, the criteria on which treatment guidelines are formulated, and secondly, the need for well-designed vaccine trials which incorporate the aim of improving our understanding of the natural history of *N. gonorrhoeae*. Treatment guidelines are currently based on the proportion of diagnosed cases that are drug-resistant, with exceedance of a 5% threshold prompting changes to recommendations. However, it is important for policymakers also to consider the total number of resistant cases - especially in scenarios where resistant gonorrhea becomes more difficult and costlier to treat, as exemplified by a recent case of multi-drug resistant gonorrhea that required three days of inpatient treatment with intravenous ertapenem[38].

Trials of vaccine candidates need to be designed to address important gaps in knowledge, including the possibility of perverse outcomes. For example, if vaccination reduces the bacterial load then this might reduce transmission by reducing infectivity. Alternatively, it might promote transmission if it reduces the probability or severity of symptoms and thereby increases the proportion of infections that are left untreated and hence persistent[32]. Not only could persistent infections lead to increased transmission, but they may increase the probability of drug resistance evolving within asymptomatic hosts[39]. Conversely, the resistance selection pressures could be reduced if fewer infections are being treated with antibiotics[18]. The relationship between determinants of drug-resistance and antigenicity is not known and trials should monitor the

diversity of lineages of *N. gonorrhoeae*. If a determinant of drug resistance is immunogenic and included in the vaccine, then this would enhance the beneficial impact of vaccination, whilst a vaccine that is more effective against drug-sensitive strains could increase the relative prevalence of resistance. Notwithstanding these interrogations and need for further research, a gonococcal vaccine could offer the hope of bringing the current epidemic of gonorrhea under control.

NOTES

Disclaimer. The study sponsors had no role in study design, data collection, data analysis, data interpretation, report writing, or decision to submit for publication. The views expressed are those of the authors and not necessarily those of the UK Department of Health and Social Care, Department for International Development (DFID), European Union (EU), UK Medical Research Council (MRC), National Health Service, National Institute for Health Research (NIHR), or Public Health England (PHE). The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

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Potential conflicts of interest. .

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FIGURE LEGENDS

Figure 1. Model structure flow diagram. The population is divided into compartments representing different states, with changes of state occurring due to various processes. Individuals enter the sexually-active population (arrow 1) at age 15 years. They are initially uninfected (*U*), and belong to a sexual activity group *g* (low or high). Individuals become infected with either the antibiotic-sensitive (ABS) strain (2) or antibiotic-resistant (ABR) strain (3). Infected individuals pass through an incubating state (*I)*, before either developing symptoms (4) and entering the symptomatic infection state (*S*), or remaining asymptomatic (5) and entering the asymptomatic infection state (*A*). Symptomatic individuals seek treatment (6) and enter the treatment state (*T*). Asymptomatic infections can be identified through screening and treatment (7), with individuals entering the treatment state (*T*), or there can be natural recovery (8), returning individuals to the uninfected state (*U*). All treated infections are cured (9), with the exception of a proportion of ABR infections for which treatment fails, resulting in persistent infection (10). Depending on the vaccination strategy, individuals are vaccinated before entry into the sexually-active population (VbE, in which case all vaccinees are uninfected), on gonorrhea diagnosis (VoD, with vaccination given to those who are treated), or on clinic attendance for gonorrhea screening (VoA, with individuals in all states being eligible). Upon vaccination individuals enter corresponding compartments indicated with a circumflex (^). Vaccine protection eventually wanes (11), with individuals moving into the corresponding compartments without circumflex. Individuals leave the sexually-active population at age 65 years, regardless of infection or vaccination status (12).

Figure 2. Simulated annual gonorrhea cases between 2008 and 2030 in the absence of vaccination. The model is fitted to data in the period 2008-2017 and then projected beyond that period. **(A)** Number of cases if a novel resistant strain does not emerge. The red line depicts

surveillance data; the horizontal line shows WHO target of 90% reduction in incidence relative to 2016. Shaded areas show 99% posterior predictive intervals, based on 1,000 simulations. **(B)** Expected number of cases in 2030 depending on the frequency of treatment failure for a novel antibiotic-resistant strain emerging in 2020.

Figure 3. Impact of different vaccination strategies against gonorrhea, given the emergence of a resistant strain in 2020 for which antibiotic treatment always fails. Vaccination was implemented from 2020 and administered to individuals entering the sexually-active population **(A,D)**, or to patients diagnosed with gonorrhea **(B,E)**, or to patients on clinic attendance **(C,F)**. Level (horizontal axes) and duration of protection (vertical axes) were varied. **(A,B,C)** show the mean reduction in the expected number of cases in 2030, whereas **(D,E,F)** show the proportion of MSM protected by the vaccine in 2030. Vaccine profiles (i.e. combinations of level and duration of protection) for which the WHO incidence target was achieved by 2030 are highlighted with a dotted line (this is only achieved in part of **C**).

Figure 4. Protection level and duration of vaccine needed to reduce incidence below the WHO target by 2030 for gonorrhea strains with varying degrees of resistance. Results are shown for vaccination on diagnosis **(A,B)** or on clinic attendance **(C,D,E)**, under varying levels of vaccine uptake: 100% **(A,C)**, 75% **(B,D)** and 50% **(E)**. The vaccination-before-entry strategy is not shown as it did not achieve the WHO target for any scenario considered, and likewise for the vaccination-on-diagnosis strategy with an uptake of 50%.

Figure 5. Potential impact and efficiency of a MeNZB-like vaccine. Vaccination was implemented before entry into the sexually-active population, on diagnosis, or on clinic

attendance. Shaded bars depict 95% predictive interval; diamonds indicate the mean. **(A)** Expected gonorrhea cases in 2030, with the dashed line depicting the WHO target. **(B)** Proportion of gonorrhea cases expected to be resistant in 2030. **(C)** Proportion of MSM protected by the vaccine in 2030. **(D)** Mean cases averted per course of vaccination.

Figure 1

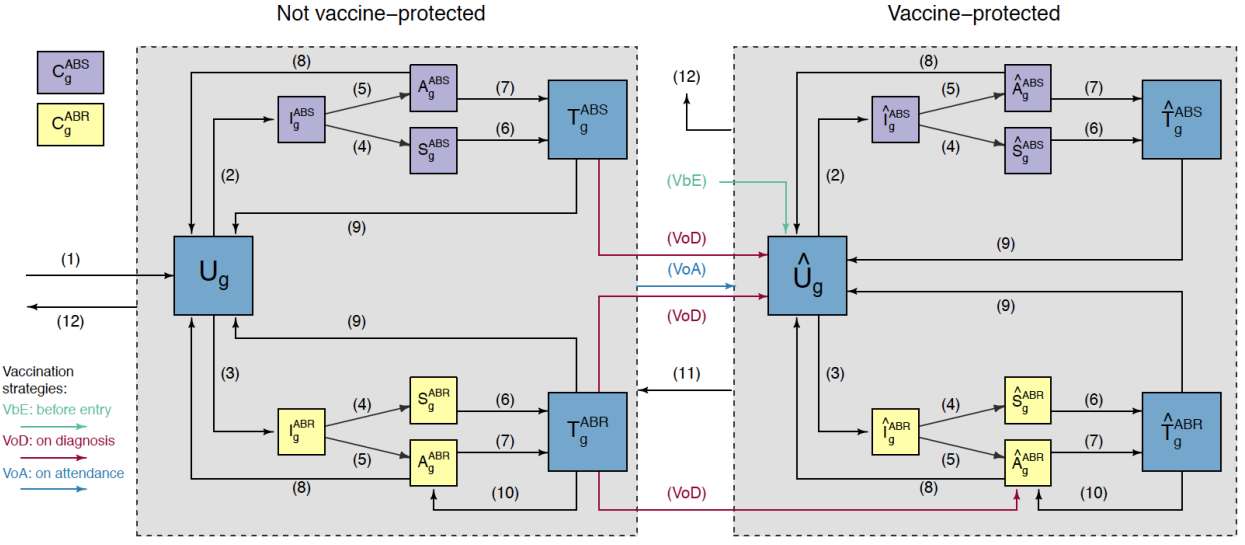

Figure 2

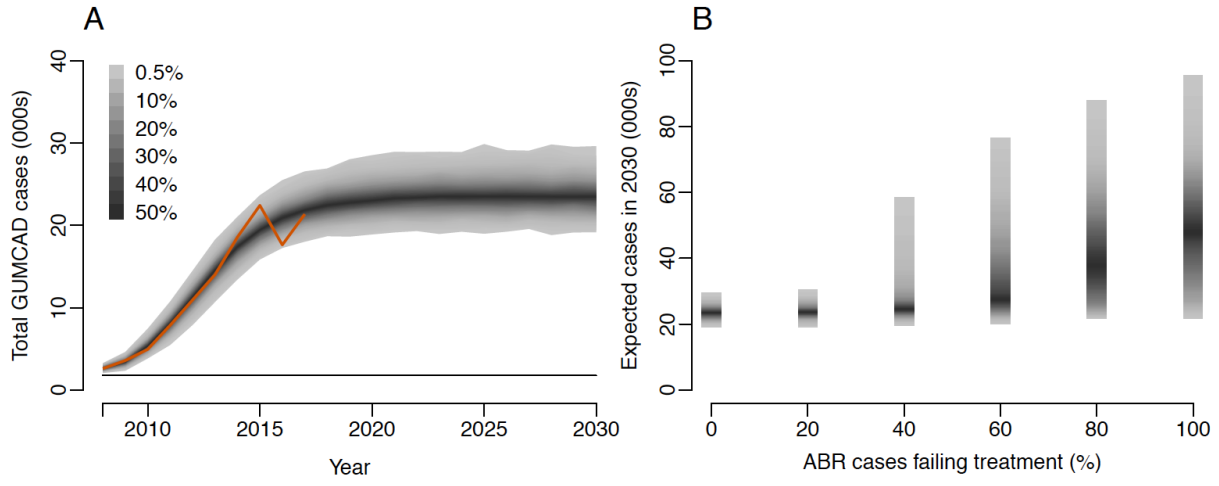

Figure 3

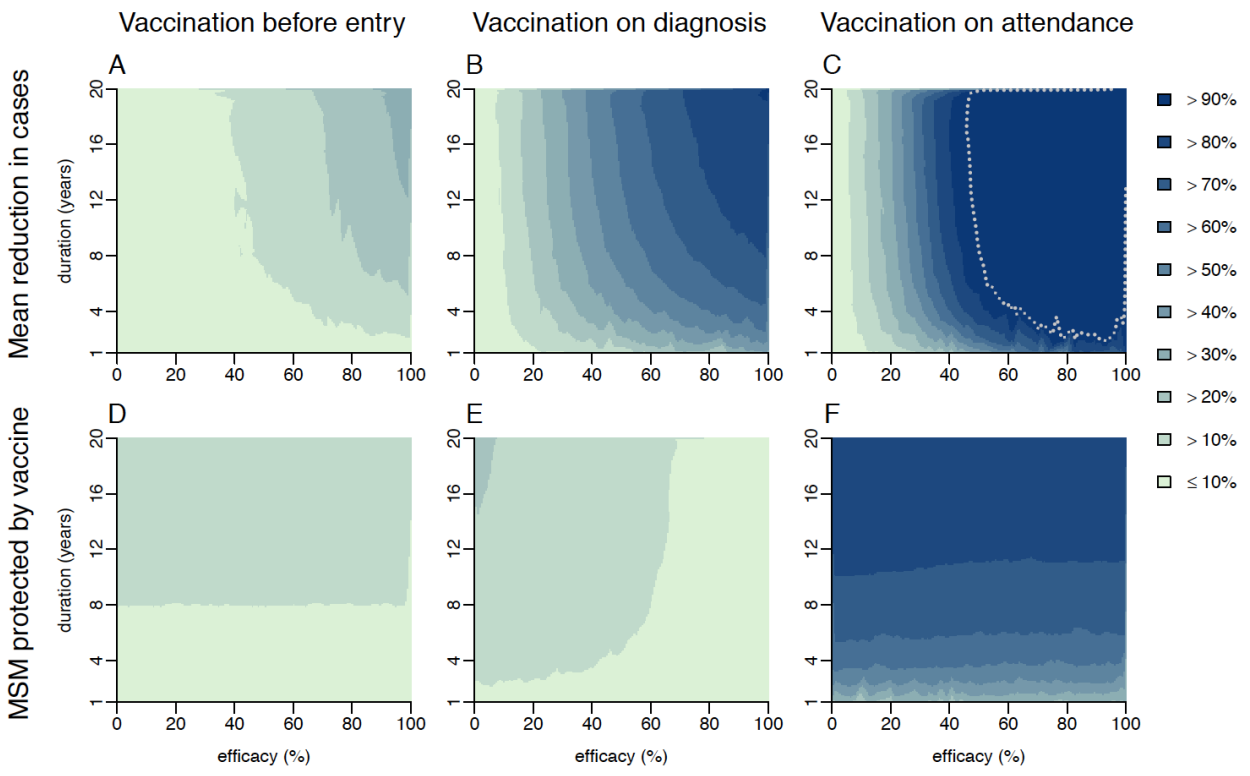

Figure 4

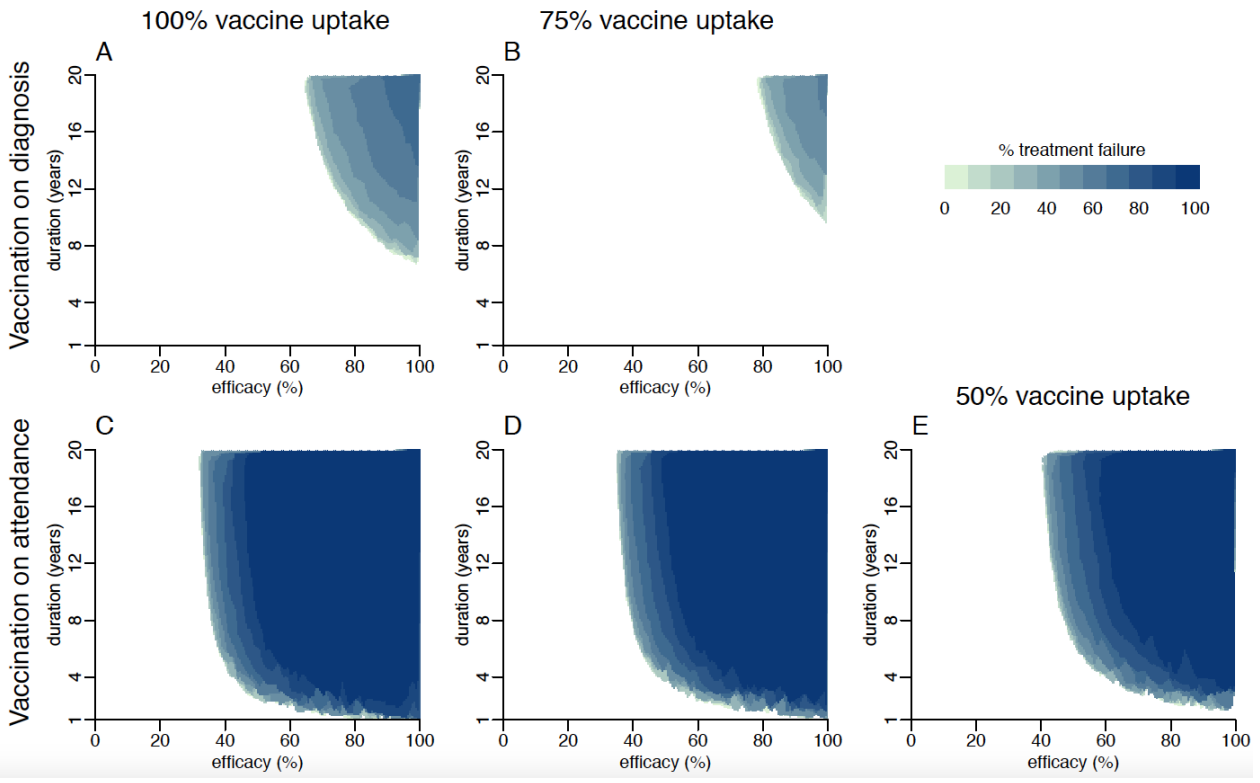

Figure 5