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The Impact of Vaccination on Antimicrobial Resistance in Gonorrhoea

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Abstract

Antibiotic resistant gonorrhoea is a growing threat to public health. Gonorrhoea has developed resistance to all major classes of antibiotics, with some cases now resistant to the last line treatment — ceftriaxone. Vaccinations for gonorrhoea have not previously been developed due to the bacteria's antigenic diversity. However, a meningitis vaccine, MeNZB, has recently been found to offer some limited cross protection against gonorrhoea — it is presumed to protect with an efficacy of 31% over a duration of 3 years. Vaccination has the potential to limit the growth of antibiotic resistance by reducing the spread of infection and therefore reducing the number of antibiotic doses required to treat it, thus limiting the opportunity for the pathogen to develop resistance.

We present a study into the impact of implementing the MeNZB vaccine using three different strategies: vaccination before entry to the sexually active population, at sexual health screening, and when a person is diagnosed with gonorrhoea.

We use a simple equation based model to explore the impact of vaccinations with a wide variety of properties, as other vaccinations in development may prove more effective than MeNZB. We see that a vaccine with just 31% efficacy and a duration of 3 years can reduce prevalence by more than 90% if it was implemented using vaccination at screening. We see that vaccination at screening and vaccination at diagnosis are effective at much lower efficacies and durations than required by vaccination administered before entry. Our second model is a more representative individual based model, which incorporates realistic treatment and screening pathways, and uses a dynamic sexual contact network. This model is used to explore the impact of the MeNZB vaccine on prevalence and antibiotic doses, using the different vaccination strategies, in depth. We show that vaccination with MeNZB given at at screening, or at diagnosis can both lead to a significant drop in prevalence. Vaccination at screening can reduce prevalence by 70% and vaccination on diagnosis can reduce it by 50%. Vaccination before entry has limited impact in this model, reducing prevalence by just 40%.

We find that vaccination at screening is a reliable strategy for reducing prevalence of the disease, whereas vaccination at diagnosis prevents more infections per vaccine dose, as it is targeted to the most active individuals in the population.

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Chapter 1

Introduction

Gonorrhoea is a sexually transmitted infection (STI) caused by the gram-negative bacterium *Neisseria Gonorrhoeae*. Repeated or untreated infections can lead to complications, including epididymitis in men, and chronic pelvic pain and infertility in women [1].

Gonorrhoea is becoming increasingly resistant to antibiotics. In the UK the current first line treatment — ceftriaxone — is also the last line, with no drugs currently in the pipeline to replace it [2]. Internationally there have been reports of ceftriaxone-resistant gonorrhoea; without intervention this could become widespread [3].

Gonorrhoea diagnoses in England rose by 221% between 2009-2018 and diagnoses in men who have sex with men (MSM) increased by 643% between 2009-2019. MSM account for 47% of gonorrhoea diagnoses despite making up just 2.6% of the population [1].

There is no vaccine currently available for gonorrhoea but several potential candidates are in development. A meningitis B vaccine — MeNZB — has been shown to incidentally confer some protection for gonorrhoea [4]. It is currently believed to have an efficacy of 31% and offers protection for a duration of 3 years [4, 5]. While there have not been large scale tests on the ability of this vaccine to protect against gonorrhoea it does have the benefit of having already been prescribed to humans, so it is known to be safe, meaning it could be deployed faster than other possible vaccines which still require approval. The potential impact of the MeNZB at preventing gonorrhoea, and the strategy that should be used to deploy such a vaccine, are as yet unknown.

The main aim of any vaccination is to reduce the prevalence of a disease. The World Health Organisation (WHO) has the goal of reducing gonorrhoea incidence by 90% (from 2016 levels) by 2030 [6]. Vaccination is a well regarded method of preventing antibiotic resistance as it has the potential to dramatically reduce the number of infections, which in turn reduces the need for treatment with antibiotics. This means the bacterium has fewer opportunities to develop antimicrobial resistance (AMR) [7]. In this project we look at the potential for gonorrhoea vaccines to reduce prevalence and therefore to reduce the number of antibiotic doses needed to treat the infection.

Mathematical models are an essential tool for epidemiology — the study of the spread of infectious diseases. Models that represent observed data and transmission dynamics well can be used to model the impact of interventions, such as vaccination, or non-pharmaceutical interventions, including current national lockdowns, imposed to limit the spread of Covid-19. There are multiple types and features of epidemiological models, the costs and benefits of which will be discussed in due course.

Using mathematical modelling to explore the possible impact of vaccination allows us to compare the benefits of different vaccination strategies and vaccine properties. Studying the impact of vaccination on prevalence and drug dosage is helpful to public health bodies when making decisions about how to implement a vaccination programme. A study such as this, into the effects of vaccination on prevalence,

may be a helpful tool in initially deciding whether a vaccine is worth distributing and which vaccination strategy is most effective. Other information, for example about the costs of the vaccine, and its influence on behaviour of vaccinated individuals, would also be considered when making decisions surrounding vaccine implementation [8].

The aim of this project is to model the impact of vaccinating MSM against gonorrhoea, we do this using two different types of mathematical model. We focus on the effect on the endemic prevalence and the number of antibiotic doses administered to treat the infection.

We use two different classes of mathematical model: an *equation based* and an *individual based model*. The former is used to obtain results on the effect of different strategies and a wide variety of vaccine properties on the endemic prevalence. The latter model is more detailed, representative, and computationally intensive. It is used to explore, in far greater depth, the impact of a smaller number of possible vaccines using different strategies on prevalence and drug doses. Our results from the equation based model show that a wide variety of vaccinations can meet the WHO goals. We see that the MeNZB vaccine — with efficacy 31% and duration of 3 years (or 40% efficacy and a duration of 2 years, or 20% efficacy and a duration of 6 years) — can reduce prevalence by more than 90% if we offer the vaccination to MSM at screening. The same vaccines reduce prevalence by more than 80% if offered alongside treatment for the infection. We also find that a vaccination given before entry to the sexually active population would reduce prevalence by less than 10%, even if it offered complete protection and lasted 10 years.

The individual model explores fewer scenarios in greater depth, and is calibrated to current expected levels of gonorrhoea prevalence in the population. We find the MeNZB vaccine can reduce prevalence by 70% when given at screening, 50% when given with treatment and 40% when given before entry to the sexually active population. The individual based model also allows us to see the impact on the number of antibiotic doses prescribed to treat the infection, we find that all of the vaccination strategies we model MeNZB reduces the need for antibiotics by at least 15% over 10 years.

Overall we see that vaccination on diagnosis and vaccination at screening lead to a significant drop in prevalence, although this drop is not as large as predicted by the equation based model. Vaccination before entry has limited impact, as it cannot achieve the coverage of vaccination at screening, and does not target the most active individuals like vaccination at diagnosis. Vaccination at screening is the most consistently impressive method. But vaccination at diagnosis, although it leads to a smaller reduction in prevalence, averts significantly more cases per dose of the vaccination.

Chapter 2

Background: Epidemiological Modelling

There are two main types of techniques used to model the spread of infectious diseases: equation based and individual based models [9]. These epidemiological models will be explored in detail below along with a discussion of their costs and benefits.

Equation based compartmental models split the population into compartments depending, at the most basic level, on whether individuals are susceptible to a disease (S) or infected with a disease (I). People move between these compartments at rates depending on the interaction rate between the groups, the infectiousness of the disease, and the duration of the infection.

Individual based models are much more detailed, describing the infection state and contacts of every individual in the population. They provide additional information that an equation based model cannot capture, such as treatment pathways [9]. But this comes at a cost, as these models are more computationally intensive to run than equation based models, and may require a greater number of parameters to be selected or fitted.

2.1 Equation Based Models

The most basic equation based model for epidemiology is the susceptible – infected – susceptible (SIS) model [10]. Here the population is divided into compartments, people move from the susceptible compartment to the infected compartment and then back to susceptible again — the model is given by:

$$\frac{dS}{dt} = -\frac{\beta SI}{N} + \gamma I, \tag{2.1}$$

and,

$$\frac{dI}{dt} = \frac{\beta SI}{N} - \gamma I, \tag{2.2}$$

where β represents the rate of infection, and γ represents the rate of recovery. The size of the population is given by N, and S and I represent the number of people in each compartment. In this report all rates are measured per day, for example γ is the probability an infected person will recover on any given day. The value of γ is equal to $1/d$, where d is the average length of infection in days. These models can also include other compartments such as those who have recovered and derived immunity (R), those who have been vaccinated (V), and those who have maternally derived immunity (M). An SIS model is applicable to gonorrhoea resistance to subsequent infection is not observed in people who have been previously infected [10].

Hethcote and Yorke present a wide ranging study of gonorrhoea transmission using deterministic equation based SIS models [10]. One of their modelling methods splits the population into groups based on levels of sexual activity; the core — a small and highly sexually active group — are found to be involved in a disproportionate number of infections, compared to the non-core — the majority of the population with average levels of sexual activity. This is an example of how compartmental models can be made more representative through the introduction of more specific compartments. Another example of this would be if we introduced a compartment for people with asymptomatic infections. This could be a useful subsection of the infected population, as asymptomatic individuals will be unlikely to seek treatment, but will still be able to infect people. We would also expect that they will move back to the susceptible compartment at a slower rate, due to the lack of incentive to seek treatment. Increasing the number of compartments, until they represent the spectrum of behaviour and disease presentation, rapidly becomes unfeasible, not least because of the growth in the number of parameters such as transmission rates, which may be difficult to find accurate values for, due to the lack of data on untreated, asymptomatic infections. The preferred way to model this level of detail is with an individual model where behaviour is stochastic.

2.2 Individual Based Models

Individual based models (IBMs) are the natural extension of compartmental models, as they massively increase the number of compartments to the level of the individual. Every individual modelled could have different properties governing their behaviour. IBMs can represent the observed high degree of heterogeneity in number of sexual partners as well as more realistic (and complicated) diagnosis and treatment pathways.

Individual based models are the cutting edge used for public health modelling, including the current Covid-19 pandemic. The UK government has taken advice based on Ferguson et al.'s study of the impact of non-pharmaceutical interventions on controlling Covid-19 using an individual based model [11]. IBMs allow us to make more accurate predictions by modelling the world in far more detail. IBMs typically use a network to describe connections between individuals in the population through which the disease may be spread, in this case sexual connections. An IBM allows for a wider range of agent behaviour, and can represent variability in the way a disease presents; for example, some people will be less likely to seek treatment than others, and a disease may or may not present the same symptoms in all infectees. IBMs may also model age and gender of individuals to better represent the population being modelled. These models allow us to incorporate stochasticity, which is essential when human behaviour is involved as individual decisions can have a significant impact on the spread of a disease [12].

This level of detail is helpful as it more accurately reflects the state of the disease. However, modelling this level of detail and variety comes at a cost, as IBMs require considerably more computational power to run than equation based compartmental models; this explains why IBMs have only been widely used recently [9, 12]. Although there are significant costs associated with setting up and running these models, once they are built they are often easier to amend than equation based models [9].

Equation based models offer speed; this allows us to investigate vaccines with a wide variety of parameter values which is useful here, as there are currently multiple vaccines in development, meaning duration and efficacy of a potential vaccine are presently unknown. However equation based models cannot incorporate realistic treatment pathways or replicate the high level of heterogeneity in sexual behaviour seen in the population [13]. Due to their computationally intensive nature IBMs are better suited to analysing a small number of situations in detail, whereas equation based models can give us broad predictions about many situations. There are many differences between the two types of models as well as variation within them, which we now discuss in greater detail. We also discuss different ways to vaccinate — including targeted and non-targeted methods — and how we calibrate models to observed

data in order to study the impact of interventions.

2.3 Modelling the Spread of Infection

There are different ways to model the spread of an STI. Equation based models generally assume a well mixed population and homogeneous behaviour, meaning all susceptible individuals have the same chance of contracting a disease. However, in reality those with more partners are more likely to become infected as their exposure to the pathogen is greater [5, 10]. Hethcote and Yorke's model addresses this by splitting the population into the core and non-core [10]. Similarly — in their study of the impact of a vaccine on the emergence of drug resistant gonorrhoea using an equation based model — Whittles et al. split the population into different sexual activity classes [14]. However, as discussed above, increasing the number of compartments quickly becomes intractable, and cannot easily represent the true distribution of number of sexual partners.

2.3.1 Sexual Partnership Networks

Many models build sexual partnership networks using data from the population they wish to model [5, 15, 16, 17]. This allows them to model each connection through which the disease may be spread, and better represent heterogeneity in number of partners. Sexual partnership networks are well modelled by *scale-free networks*, where the degree distribution follows a power law [18]. The probability of an individual having k partners is proportional to $k^{-\gamma}$ where γ represents the rate of decay of number of the partners each individual has [18]. The data shows there is a large number of people with just one partner

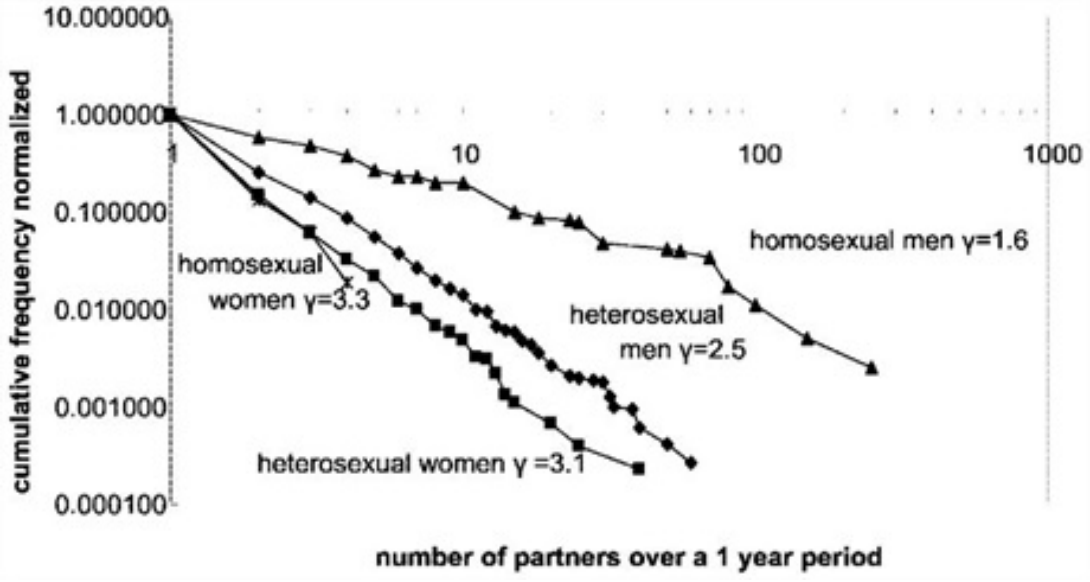


Figure 2.1: From Schneeberger: 'Cumulative degree distribution of men and women (National Survey of Sexual Attitudes and Lifestyles Natsal 2000 data, Britain) in the order: homosexual women (star), heterosexual women (filled quadrangle), heterosexual men (filled diamond), homosexual men (filled triangle). Values for γ are: 3.3, 3.1, 2.5, and 1.6, respectively.' [18]

and an exponential decay in the number of individuals who have more partners. Figure 2.1 shows this pattern on a log-log plot. Scneeberger et al. find that the value of γ varies between 1 and 3 depending on the population modelled, for MSM it is between 1.5 and 2 [18].

Both compartmental and individual based models can model heterogeneity in behaviour using scale-free sexual partnership networks. However, individual based models lend themselves to this more readily,

as we can explicitly model sexual connections between individuals and thus model exactly who is being infected and by whom. For equation based models we can only approximate the influence of sexual partnership networks. Ferguson et al. model individuals with one partner and those with two concurrent partners to represent heterogeneous behaviour [17]. This strategy misses the small, but important, number of individuals in the population who have more than two partners, this illustrates the difficulty in using equation based models to represent the high degree of heterogeneity observed in sexual behaviour.

Sexual partnership networks can be static or dynamic. Dynamic networks update periodically throughout the simulation. This more accurately represents the nature of sexual partnerships — forming and dissolving over time. Whittles et al. show that a dynamic network based on a power law within an individual based model provides a more realistic representation of an outbreak of gonorrhoea than a static partnership network could [5].

Using dynamic rather than static networks requires more parameters to model the rate of partnership formation and dissolution, this opens up the model to more uncertainty and could increase the time required to calibrate model parameters [5]. Dynamic networks also make a model much more computationally intensive to run, than one which uses static networks [19].

Zienkiewicz et al. use a hybrid static-dynamic sexual partnership network to model the spread of gonorrhoea [15]. They create a full network — which models a person's sexual contacts over the length of a simulation — and a daily network — which models their contacts over a shorter period, which is updated every seventh simulated day. Their model is found to reproduce expected patterns of gonorrhoea transmission observed in MSM in London. Zienkiewicz et al.'s IBM does not include gender as it models only MSM, and does not include age, as it only models the most sexually active individuals — the core. Limiting the population represented increases the speed of this model, while modelling only the most active people means we still capture the disproportionately high number of infections affecting the core.

In general equation based models for STIs use homogeneous mixing models. Although there may be different compartments based on activity levels, within these compartments behaviour will be homogeneous [10, 14, 17]. Individual models tend to use sexual partnership networks (whether static, dynamic, or hybrid) to model the spread of the infection through the population [5, 15, 16, 20]. Dynamic networks require additional parameters to model the rate of partnership formation and dissolution. This introduces new uncertainties into the model, we discuss the impact of calibrating parameters to observed data at the end of this chapter.

2.4 Deterministic and Stochastic Models

Both deterministic and stochastic models have their uses in epidemiology. Despite the clear limitations of using deterministic models they may be useful for exploring many different interventions quickly. Hethcote and Yorke exclusively used deterministic models to produce useful results on the impact of multiple different modelling strategies and the impact of interventions. Even today it would be incredibly time-consuming to perform a similar analysis with stochastic individual based models. Deterministic models do not represent the inherent stochasticity observed in human behaviour, but we can use them to see the effects we may expect from a range of possible parameter values, to see how sensitive the model is to different paramterisations. This allows us to gauge the uncertainty of a result based on the uncertainty around the parameters we are using. Despite this we still miss the effect of small random variations such as whether someone decides to attend a screening on a particular day. These small effects are very important in epidemiology particularly for disease with very low prevalence which may spontaneously eradicate in a simulation [12].

Stochastic models must be run many times to allow us to see the most likely outcomes and plot confidence intervals, giving us an expectation of possible futures.

More complex equation based models, such as that used by Whittles et al. in their vaccination study, can include stochasticity [14], but this is more commonly seen in individual based models. In an IBM we can model actions to the level of each individual, meaning we can include stochasticity in every decision made and every aspect of disease presentation in every individual. Zienkiewicz et al. model stochasticity in a number of places, for example the chance of catching a disease is proportional to the number of infected partners an individual has, but also includes an element of chance, two people with the same number of infected partners will not both be certain to become infected or not but will have the same probability of doing so.

2.5 Mitigating Antimicrobial Resistance

A number of strategies have been proposed to mitigate the increasing threat of antibiotic resistance. Some of these include new treatments, such as phages, but others do not require the development of new treatments. For example reducing disease spread (possibly by increasing public awareness) and strain testing to reduce unnecessary treatment [21, 22]. In a review on tackling antimicrobial resistant (AMR) infections O'Neil proposes nine interventions, seven of which do not rely on development of new drugs, but instead focus on *antibiotic stewardship* — using existing drugs more carefully — and reducing the need for treatment [21]. Three of these interventions can be applied specifically to STIs, these are:

- improving awareness of the disease and the threat of AMR, in order to reduce the spread;
- reducing unnecessary use of antibiotics with rapid diagnostic tests;
- vaccination, to reduce incidence and treatment required.

Mathematical modelling can be used to assess the impact of these strategies, and to see the expected impact they would have on the growth of AMR strains.

Zienkiewicz et al. use an IBM to explore the impact of tailoring treatment to the strain of gonorrhoea an individual is infected with using a hypothetical, clinic-based, diagnostic test [15]. Many gonorrhoea infections can still be treated with antibiotics other than ceftriaxone, and if we treat these infections with ciprofloxacin we reduce the risk of ceftriaxone resistance developing. An infected person is given strain test before treatment is prescribed, and if the strain is found to be resistant to the previous first line treatment, ciprofloxacin, only then would the last line treatment, ceftriaxone, be prescribed. This test was found to reduce the amount of ceftriaxone required which reduces opportunities for the pathogen to develop resistance.

Vaccination is another strategy used to combat drug resistant infections, by reducing incidence of an infection we also reduce the number of people requiring treatment, which will slow the growth of AMR strains [21]. Tagliabue & Rappuoli report that vaccination, rather than antibiotics, may offer longer lasting control for infections that are at risk of becoming untreatable [23]. They state that new technologies for vaccination appear more promising than the search for new antibiotics. Whittles et al. briefly explore different strategies to decrease the transmission of gonorrhoea in a study using an individual model with a dynamic sexual partnership network. They explore vaccination, increasing condom usage, and more frequent screening. They find that, among these strategies, vaccination leads to the most significant reduction in gonorrhoea cases [5].

2.6 Modelling Vaccination

Vaccination is a well regarded method to reduce antimicrobial resistance [7, 21, 23, 24]. We therefore explore the impact of a vaccine on preventing untreatable gonorrhoea in this report. We now explore

the ways that vaccination is modelled, and the different strategies used to administer a vaccination to a population.

Vaccines offer either *take-type* or *degree-type* protection. Take-type protection means a percentage of those vaccinated will have full immunity to a disease, and degree-type means everyone vaccinated will be partially protected from infection. For example, if a vaccine has degree-type protection with an efficacy of 90% then the probability of a vaccinated individual becoming infected is reduced by 90%. If a vaccine has take-type protection of 90% efficacy then 90% of those vaccinated will be completely protected from infection. Another common way of measuring the efficacy of a vaccine is given by the Center for Disease Prevention and Control (CDC) [2] as

$$\frac{\text{risk for unvaccinated population - risk for vaccinated population}}{\text{risk for unvaccinated population}}. \tag{2.3}$$

Craig et al. discuss the impact of a potential gonorrhoea vaccine using an individual based model [16]. They find that after 20 years a non-waning vaccine with just 50% efficacy could lead to a 90% drop in prevalence, if all children were vaccinated. They also find that a vaccine with limited duration and efficacy could reduce prevalence if it had high coverage of individuals at the time of highest sexual partner change. This finding agrees with Hethcote and Yorke's conclusion that the core group keeps the disease endemic, and therefore, if this group can be targeted for vaccination it will have a greater impact than offering the vaccination indiscriminately, for the same number of doses [10]. An effective strategy for targeting the core group is giving the vaccination when providing treatment for gonorrhoea. This works because the core has a much higher incidence of gonorrhoea, so vaccinating people who are known to have already contracted the disease leads to vaccinating more members of the core than vaccinating indiscriminately.

In their study on the effect of a gonorrhoea vaccination Whittles et al. use a stochastic equation based model to explore the outcomes of vaccinations which protect for between 1 and 20 years with an efficacy of between 1-100% using different strategies [14]. They focus on the possibility of using a vaccine to meet the WHO goal to reduce worldwide gonorrhoea prevalence by 90% between 2016-2030 [14]. They conclude that a vaccination given in childhood does not get close to achieving the WHO goal but vaccination at attendance and on diagnosis can lead to a significant reduction in cases even with a vaccine that offers limited protection. For example they report that a 53% degree-type protective vaccine lasting for at least 6 years would meet the goal if all men attending sexual health clinics were vaccinated.

To gain a broader picture we have also reviewed theoretical vaccination studies for other STIs. Because of the common transmission pathway these models are often adapted for different STIs. For example Craig et al. use a model adapted from a study of chlamydia to study gonorrhoea. However these studies may include models that would require significant work to be adapted to model gonorrhoea amongst MSM in the UK, some STIs (HIV and syphilis) are passed from mother to child in-utero so we cannot use models for such diseases without significant alterations being made.

A study on the impact of a vaccine on herpes showed that even a low efficacy vaccine that reduced viral shedding, which is closely related to the chance of transmission, can have a significant impact on prevalence [25].

Champredon et al. use an individual based model to show that a vaccination for syphilis can lead to a sharp drop in prevalence, and that vaccination has a much greater impact on prevalence than increased screening efforts. They also find that in some scenarios it is possible a vaccination for syphilis can lead to an increase in HIV, as a decrease in the number of individuals with syphilis symptoms may lead to more interactions which spread HIV [20]. This shows that it is important to consider the impact of a vaccine on wider behaviour and on the incidence of other diseases.

Vaccination studies tend to focus on strategies for vaccinating randomly or vaccinating a targeted group [10, 14, 20]. In general they conclude that targeting the most active individuals leads to a sharper drop in prevalence than random vaccination with the same number of vaccine doses.

There are three main strategies that appear in the literature for vaccination for gonorrhoea specifically, these were first presented by Hethcote and Yorke and have been used since by Whittles et al. [10, 14, 16], these are:

- vaccination in childhood,
- vaccination at sexual health screening,
- vaccination alongside treatment for gonorrhoea.

Vaccination in childhood is a mass vaccination strategy that is generally more useful for vaccines that last well into adulthood. Vaccination at screening is an example of random vaccination [10]. Vaccination on diagnosis represents a method of targeting the most active people. More sexually active people are the more likely to have gonorrhoea, so by vaccinating only those who we know have already become infected we vaccinate more of those who are high risk. We discuss these strategies in more detail below.

Strategy 1: Childhood Vaccination

In this strategy we vaccinate children for gonorrhoea before they join the sexually active population. We expect this strategy would lead to high vaccine coverage, based on figures for the HPV vaccine — a vaccine for another STI also offered to school children, with the main aim of preventing some types of cancer — which has uptake of around 85% [1].

When using this strategy, the benefits of vaccination happen with a delay. If people are vaccinated at 13 it will take a while for them to enter the core population of high risk individuals. This would also mean the vaccine would have to have a long duration to protect people well into adulthood when they are at risk. Vaccinating at 16 could alleviate this, although to what degree depends on the age distribution of the core population.

Childhood vaccination is a blanket, not targeted, form of vaccination. Even if we vaccinated only boys we would still be targeting a much larger group than only MSM. This may be prohibitive if the vaccine is expensive.

Strategy 2: Vaccination at Screening

In this strategy vaccination is offered to MSM when they attend a sexual health clinic for sexual health screening. The results of a pilot program offering the HPV vaccine to MSM attending sexual health screenings has so far led to 45% of attendees receiving the first dose [1]. We assume that a gonorrhoea vaccine would have the same level of acceptance. Both the HPV and MeNZB vaccines require three doses, meaning people have to attend a clinic for two follow-ups after the initial vaccine [26]. The HPV vaccination study has not been running long enough to categorically give figures for the proportion of men who complete the vaccination courses[1].

Vaccination at sexual health screening is an example of random vaccination method if we assume individuals attend screening at the same rate independent of their level of sexual activity, meaning we do not target more active or less active individuals. However, in reality people who are more sexually active may be more likely to attend screening as they are aware they are at higher risk of contracting an STI [1].

Strategy 3: Vaccination on Diagnosis

For this strategy people are offered the vaccine when they are treated for gonorrhoea. There is currently no vaccine for an STI offered in this way so there is no readily available data on uptake of a similar vaccine. Therefore, we use the same uptake figure as for vaccination at screening of 45% in the absence of any comparable figure in the literature. This may be an underestimate given people who have been diagnosed may be more aware of the risk. A large proportion of gonorrhoea infections are thought to be asymptomatic [1], we assume people with asymptomatic infection are unlikely to seek treatment and will only be vaccinated using this strategy when they test positive at screening or are traced through an infected contact. Therefore this strategy will lead to the vaccine being offered to everyone who is treated, not everyone who is infected.

2.7 Calibration of Epidemiological Models

Models are only useful if they represent the world well. Some model parameters cannot be found in public health data, for these we may find fitted values based on calibration of a model. It is generally faster to calibrate equation based models to observed values, such as prevalence, than it is to do the same for individual based models, because there are fewer parameters to fit. For an equation based model we may calibrate using simple maximum likelihood calculations but, for an individual based model we often need to calibrate using *simulation-based calibration*. This process entails running the simulation multiple times while varying parameter values until suitable values are found for the baseline scenario we want to replicate. This is a very computationally intensive process, the more complicated the model the more difficult it becomes [27]. For example, the parameter which represents the transmission rate, labelled β, may require calibration. While there is data available on how likely individual sexual acts are to confer gonorrhoea from an infected to a non infected partner, it is too complicated to model every individual act between all partners, so likelihood of transmission is represented by one parameter, β [28]. In an individual based model parameters such as β are fitted to real world data through simulation-based calibration. Zienckiewicz et al. use simulation-based calibration the details of which are included in their supplementary material [15]. They show the prevalence and diagnosis rates for a variety of different values of parameters they fitted to the model, in order to achieve a prevalence of 2.5% and 2-5 daily diagnoses, which represents the presumed incidence of gonorrhoea among MSM in London. However it is possible this value is inaccurate. It is very difficult to parameterise epidemiological models due to the complexity of human behaviour and the fact that people may not want to report symptoms due to stigma surrounding STIs. This can make it difficult to parameterise models and assess their accuracy. The effect of stigma is particularly acute for this project as MSM are a group that face discrimination, which is known to be a barrier to seeking healthcare [29, 30].

In this report we use two models to assess the impact of vaccination. We build our equation based model using the work of Hethcote and Yorke because these models are simple enough to be run quickly and include some (albeit limited) heterogeneity in number of sexual partners. This allows us to get a general sense of the impact of a vaccine based on its values for the properties of duration and efficacy.

Our individual based model is based on that used by Zienkiewicz et al. and is chosen because it includes built in pathways for treatment, which will be necessary to see the impact of vaccination on the number of antibiotics administered, and thus the number of chances for antibiotic resistance to evolve.

Chapter 3

Methods

We now describe the ways in which we use the two models chosen in the previous section to explore the impact of vaccination.

We use an equation based model to study vaccines with a wide variety of parameter values for efficacy and duration. Our model is based on the work of Hethcote and Yorke, is used to obtain figures for the impact of each vaccination strategy. This particular equation based model has been chosen as it allows us to split the population by sexual activity levels, this is an important feature of any model as individuals with the highest number of partners bear a disproportionate burden of gonorrhoea cases [10, 28]. We use this model to see the impact on prevalence of vaccinations with a large variety of parameter values.

We then use an individual based model to provide a more realistic picture of prevalence, and to see the impact of vaccination on the number of antibiotic doses administered to treat the infection. This model incorporates a dynamic sexual partnership network to model spread, and represents stochastic, heterogeneous agent behaviour.

3.1 Equation Based Model

Hethcote and Yorke split the population into core and non core groups by relative sexual activity. The core are assumed to be a highly sexually active group, who therefore have a much higher level of gonorrhoea diagnoses, and are involved in a large proportion of the transmission. Hethcote and Yorke propose that targeting the core group is an efficient way to vaccinate as it leads to the greatest reduction in prevalence for the fewest vaccine doses [10].

Based on analysis of the Gay Men's Survey 2014 in our model the core group make up 5% of the population and are ten times more sexually active than the non-core group [31]. Hethcote and Yorke give us that where the core group makes up a x% of the population and members have y times the number of sexual partners as the rest of the population, we expect that for a randomly selected person, a fraction — given by b_c — of their partners will be a member of the core. Where b_c is given by:

$$b_c = \frac{xy/100}{xy/100 + (1 - x/100)}. \tag{3.1}$$

For $x = 5$ and $y = 10$ we have that, for an individual selected at random, we would expect 34% of all sexual encounters to be with a member of the core group and 66% to be with a member of the non-core group.

The framework for our model is given in equations (3.2 – 3.4). In these equations subscript c refers to the core and subscript n to the non-core. Subscript i is used where the equation applies to both core and non-core populations.

The rate of sexual activity — k_c or k_n — is the only difference in behaviour between the groups. We expect the core to have more partners and therefore a much higher rate of infection. The equations for the compartmental model including the vaccination framework are:

$$\frac{dS_i}{dt} = \Lambda - \frac{k_i}{d}(b_c I_c + b_n I_n)S_i - \zeta\rho S_i + \theta V_i + \frac{I_i}{d} - \mu S_i, \tag{3.2}$$

$$\frac{dI_i}{dt} = \frac{k_i}{d}(b_c I_c + b_n I_n)S_i - \frac{I_i}{d} - \mu I_i, \tag{3.3}$$

and

$$\frac{dV_i}{dt} = P + \zeta\rho V_i - \mu V_i - \theta V_i. \tag{3.4}$$

The model describes transmission of the disease between susceptible (S_i) and infected individuals (I_i), as in the model from Hethcote and Yorke [10] described in equations (2.1) and (2.2). We also model recovery: movement from I_i to S_i, vaccination of susceptibles: movement form S_i to V_i, and loss of vaccine protection: movement from V_i to S_i. It also includes vital dynamics: μ is the death rate (which is the same for all compartments) and people are born (into the susceptible compartment) at rate Λ. The term

$$\frac{k_i}{d}(b_c I_c + b_n I_n) \tag{3.5}$$

represents the rate at which people become infected (and thus move between the S_i and I_i compartments) per day, β in equations (2.1) and (2.2), the chance of a person being infected with gonorrhoea on any one day. The term k_i/d represents the number of partners a person from group i is expected to have per day during an infectious period lasting d days. The term $(b_c I_c + b_n I_n)$ tells us the fraction of infected people in the population scaled by relative sexual activity. Therefore the term given in equation (3.5) gives the likelihood of a person having intercourse with an infected partner on a given day. We assume that all sexual interactions between an infected and non-infected person will lead to the non-infected person contracting the infection. This is an overestimate of the transmissability of the disease, as some of these interactions will be protected — which will greatly decrease the probability of transmission — and there is no sex act where there is 100% likelihood of gonorrhoea transmission [28].

The recovery term — represented by γ in equations 2.1 and 2.2 — is valued at $1/d$, where d is the average length of the infection in days, every day we expect there is a $1/d$ chance of recovery for each infected person. This rate encompasses both natural recovery and recovery via antibiotic treatment. This simplification means we ignore infections that are asymptomatic, and therefore are more likely to go untreated for a longer period of time.

Our equation based model describes vaccination of susceptibles, who move from state S_i to V_i at a rate ρ. Here the vaccine offers take-type protection with probability ζ. When the protection has been lost they will move back to compartment S_i, this happens at a rate θ — $1/\theta$ gives the expected duration of the vaccine's protection in days. All of the parameters used for this model are presented in appendix A.

We have modified the framework above for each of the three vaccination strategies.

Strategy 1 — Childhood Vaccination in equation based model

In this strategy people are vaccinated before they enter the sexually active population. Therefore the vaccinated population — represented in equation (3.4) — will include a birth term: $\zeta\rho\Lambda$ representing people successfully vaccinated in childhood and who therefore enter the population in the V_i compartment. We replace the birth term, Λ, in (3.2) with $(1 - \rho\zeta)\Lambda$ to represent people who are either not given the vaccine: $((1 - \rho)\Lambda)$, or who are vaccinated but for whom the vaccine fails: $\rho(1 - \zeta)$. These individuals

enter the population in a susceptible state. This model will not include the vaccination of susceptibles as people will only be vaccinated before they enter the population modelled, so there will be no movement from S_i to V_i. Therefore the terms $\zeta\rho S_i$ and $((1-\rho\zeta))S_i$ in equations (3.2) and (3.4) respectively are omitted.

Strategy 2 — Vaccination at screening in compartmental model

In this strategy we model vaccinating people when they attend a sexual health clinic for screening. Movement between the susceptible and vaccinated compartments now includes the rate of attendance at a sexual health clinic, ϵ. The term $\zeta\rho V_i$ becomes $\zeta\rho\epsilon V_i$ in equations (3.2) and (3.4). The proportion of the population who move from the susceptible to the vaccinated compartments per day is now the fraction of people screened on any one day (ϵ), and who accept the vaccine when it is offered (ρ), and for whom the vaccine is effective (ζ). We assume the rate of attendance is once per year, $\epsilon = 1/365$ based on PHE guidelines [1].

Strategy 3 — Vaccination at treatment in compartmental model

Here we model vaccinating people when they are treated for gonorrhoea, we model the protection as beginning when a person recovers and assume the time the person is both vaccinated and infected is negligible. In this scenario people will move to the vaccinated compartment from the infected compartment only. The same proportion of people will recover, at a rate of I_i/d per day, but some of they will move to different compartments after recovering. Successfully vaccinated people will move to the V compartment, this is a group of size $\zeta\rho I_i/d$ who move from equation (3.3) to (3.4). Unsuccessfully vaccinated people, a proportion of $\rho(1-\zeta)I_i$, and people who refuse the vaccine, a proportion of $(1-\rho)I_i$, will move to the susceptible compartment — from equation (3.3) to (3.2). As we do not model treatment pathways we are vaccinating everyone who recovers even though some of these people will have recovered without medical intervention and therefore could not be offered a vaccine. This means this model will overestimate the number of people vaccinated using this strategy, the size of this overestimate will be related to how many cases of gonorrhoea are asymptomatic.

3.2 Individual Based Model

We have chosen to adapt Zienkiewicz et al.'s stochastic, discrete time, individual based model to study the impact of a vaccination in greater detail. This model has been chosen from the models in the literature for a number of reasons. One significant benefit of this model is that it provides information on the number of drug doses prescribed, which is essential information to understand the impact the vaccination could have on the growth of antibiotic resistance [15]. To minimise the possibility of widespread ceftriaxone resistant gonorrhoea it is important to minimise the number of doses of ceftriaxone given, as each dose gives the pathogen a chance to evolve resistance. This model uses a sexual partnership network based on a power law which allows us to model heterogeneity in number of partners. Splitting the population into the core and non-core misses the huge range of behaviour seen within these groups, in reality there is no a clear cut distinction between them [13, 31]. The hybrid static-dynamic network structure is faster than a fully dynamic network but is more representative than a static network. Another reason this model is faster is that it models the more active individuals in the population. This means we will miss some of the transmission but we increase the speed of the model by focusing on the individuals who bear the greatest burden of infection. In Zienkiwicz et al.'s model the AMR strain is resistant to treatment with ciprofloxacin and can only be treated with ceftriaxone and the non-AMR strain can be treated with

either antibiotic. Elsewhere in this report the term AMR has been used to refer to infections which are resistant to all antibiotics.

3.2.1 Major Processes in Model

A flow chart detailing the outline of how the model used by Zienkiewicz et al. works is presented in figure 3.1.

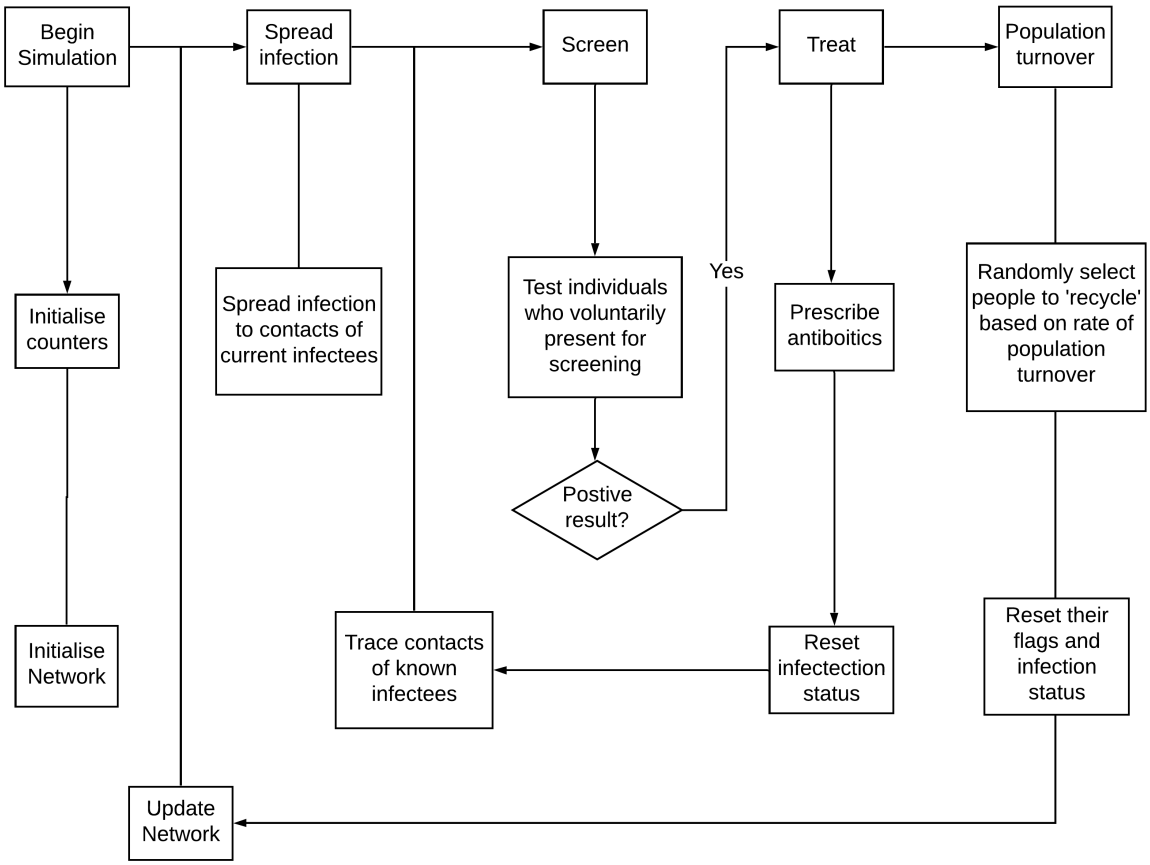


Figure 3.1: Flow chart showing major steps in Zienkiewicz et al.'s individual based model

The model uses a time step of one day to model the spread of infection between contacts as well as screening, treatment seeking behaviour, and a time dependent update of the sexual partnership network. The model keeps track of which individuals in the population are infected with both non-AMR and AMR strains of gonorrhoea using a vector representing the infection state of every individual: whether they are infected with neither, one of, or both the strains we model. As the flow chart in figure 3.1 shows, every day there are steps describing spreading the infection, screening, seeking treatment, and population recycling. Every simulated day we record the number of people infected and treated. We also set *flags* on individuals, these set the date when an individual will be treated after they have tested positive through screening or contact tracing.

The model also realistically models practical concerns around treatment and screening including delays to seeking treatment and variation in lab turnaround times. We now discuss the major processes in the model included in figure 3.1 in more detail.

Spread of Infection

Zienkiewicz et al. model sexual connections using a hybrid static-dynamic network based on a power law, calibrated to data from Scheenberger et al.'s study on fitting scale-free networks to sexual contact patterns [18]. This network is initialised at the start of a simulation and updated every seventh simulated day. The parameters used to initialise and update are described in appendix B.

On each iteration people are infected based on the infection status of their partners, the more contact a person has had with infected partners the more likely they are to become infected themselves on any simulated day. We assume half of infections are asymptomatic, meaning these people are unlikely to seek treatment but will find out they have been infected should they attend screening.

Screening

A randomly selected $1/400th$ of the population are selected for screening every simulated day. Those who are screened positive are flagged to attend treatment on a certain date. The parameter for how likely an individual is to attend screening on any day is fitted to the presumed level of prevalence and number of cases diagnosed per day. Using the same rate for everyone may not be representative. People taking the HIV preventative, pre-exposure prophylaxis (PrEP), or who have multiple partners should be screened more frequently, every 3 months [1]. In addition, data from the Gay Mens' Sex Survey [31] suggests that only around 70% of MSM had been screened in the last year.

Treatment

In this step antibiotics are administered to treat individuals who have presented for treatment, either due to symptomatic infection, a positive screen, or partner tracing. Partner tracing is the process of contacting people who may have been infected by a partner who is known to have gonorrhoea. We assume we can trace up to five contacts from each diagnosis. We also model that some people will recover without treatment, we expect untreated infections to last for an average of 5 months [15].

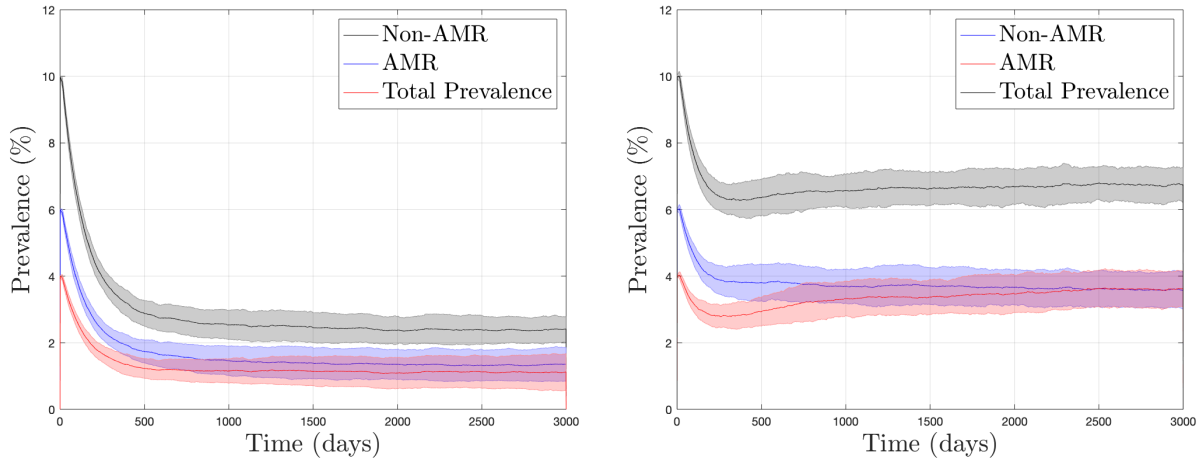
Modelling treatment pathways allows us to keep track of the number of antibiotic doses used to treat the infection. Zienkiewicz et al.'s model shows the impact of different prescription strategies. They model two strains — a non-AMR strain which can treated with ciprofloxacin or ceftriaxone, and an AMR strain which can only be treated with ceftriaxone. The default treatment is ceftriaxone — which will successfully treat both strains. Current PHE treatment guidelines state that all gonorrhoea infections should be treated with ceftriaxone. However Zienkiewicz et al. find that there is only 86% adherence to this guideline, hence they also model this 86-14 treatment scenario as well as a 50-50 split between the two antibiotics for comparative purposes [15]. In this report we only consider the 100% ceftriaxone treatment strategy for simplicity. If some infections were treated with ciprofloxacin we would expect to see some treatment failures as a proportion of infections are resistant to this antibiotic, this would mean the number of ciprofloxacin resistant infections would increase as they are less likely to be successfully treated. Considering the impact of different treatment strategies would be a useful extension as under-treatment (using ciprofloxacin to treat an infection that is resistant to it, thus prolonging the infection) has an impact on prevalence, and of the ratio of infections involving each strain, if ciprofloxacin resistant strains are being under treated the prevalence of this strain will increase [15]. Current practises leading to treating individuals reached through contact tracing before a positive screen. This leads to some antibiotic doses being wasted, as they are used to treat uninfected people. This unnecessary use of antibiotics reiterates the need for rapid diagnostics [15, 21].

Population Turnover

As discussed previously we model only the most active individuals in the population to speed up the process while still capturing the majority of the transmission of gonorrhoea. The population turnover function represents the movement of the population to and from the core group we are modelling. This is to reflect the fact that there is significant movement between the core and non-core groups, the rate of partner change is not consistent over a lifetime [13]. We model the length of time an individual is in this core group as having an average duration of 8 years. Every day, each individual has a 1/2200 chance of being *recycled*. When this recycling occurs, the individual is replaced by one with infection status reset for both strains, and all flags relating to treatment and screening cleared, if applicable. A more realistic way to represent population turnover would be to remove a node in the sexual partnership network, along with its associated edges, and then add a new node and edges to maintain the power law distribution. This would be significantly more computationally intensive [15]. The value we use for rate of population turnover is very different to the birth and death rate used in the equation based model. This has an impact on the implementation of childhood vaccination in this model. We will discuss the impact of this parameter on the results in due course.

3.2.2 Calibration of Model

Our model uses parameters, such as β, that have been fitted to the data on prevalence and number of diagnoses per day to the observed values amongst MSM in London. The other fitted parameters are detailed in the appendix B. More detailed information can be found in the supplementary material of the paper by Zienkiewicz et al. [15]. Prevalence of gonorrhoea is increasing [32]. Zienkiwiecz et al.'s model is



(a) (b)

Figure 3.2: Prevalence of both strains of gonorrhoea with one standard deviation over a 3000 day burn in period using two different values of the transmission parameter, β. Subfig. (a) has $\beta = 2.2^{-3}$ and represents the current presumed prevalence of gonorrhoea in MSM in London, (b) has $\beta = 2.9^{-3}$ and represents a possible much higher future prevalence level

calibrated to a stable level of gonorrhoea but by the time a vaccine is ready to be dispensed the prevalence could have risen [15]. To address this issue we will model the vaccination with prevalence levels as they are now, around 2.5% and at a higher level of 6.5%. This higher level is achieved by increasing β by 30%. The second, higher prevalence level is more than double the current expected level and is used to show the different impact Due to the length of time required to run this individual based model for a population of 10,000 individuals we use it only to explore the impact of a vaccine with properties similar

to that of MenZB, a vaccination for meningitis which was shown to offer cross protection for gonorrhoea with an efficacy of 31% and a duration of 3 years [4, 14].

In producing our results we run each simulation 100 times with a population size of 10,000. To find stable prevalence levels for every simulation we first allow the prevalence to settle during a burn-in period of 3000 days before we include vaccination. We use initial values of 10% prevalence (4% AMR and 6% non-AMR) to avoid spontaneous eradication which may occur if the prevalence is low. Because prevalence of gonorrhoea is rising we model the impact of a vaccine on both current expected levels of prevalence and a theoretical higher level of prevalence, which represents a possible future [32]. The results showing average prevalence and one standard deviation over 100 burn-in periods for two simulations with different β parameter values are shown in figure 3.2. These values are around 2.4% prevalence (standard deviation: 0.5%) for the value of prevalence based on current data and 6.7% (standard deviation: 0.5%) for the theoretical higher initial prevalence scenario. For both values of β we see that by the end of the 3000 day burn in period that ratio of the prevalence of both strains (AMR and Non-AMR) has settled and that they are approximately equal. For the low prevalence scenario we have around 1.1% (standard deviation: 0.5%) AMR and 1.3% (0.5%) non-AMR. For the high prevalence it is 3.6% (0.5%) for both. These prevalence values may sum to greater than the total prevalence values as we allow co-infection, people can be infected with both strains at once.

The MeNZB vaccination has not yet been studied in detail so there is not yet any observed data we want to replicate. This makes is all the more important that the baseline model is well calibrated, to show the impact of the vaccination, we model introducing it at different prevalence levels, and using different strategies to study the different impacts we can expect.

3.2.3 Addition of Vaccine to Individual Based Model

We have expanded model used by Zienkiewicz et al. to include vaccination using three different strategies in a manner that will be explained below. Our newly developed code is available at `github.com/rm15186/GonoVac`.

The vaccine we model here gives degree type protection, if a person has been vaccinated and the protection has not yet worn off they will be less likely to be infected, depending on the preset level of protection provided by the vaccine. We model vaccine protection by scaling down the *infect force* for vaccinated people according to the vaccine's efficacy. This is inline with the CDC's definition of efficacy, previously described in equation (2.3). The infect force gives the probability of an individual becoming infected, its value depends on the amount of contact they have had with infected partners. The new infect force for vaccinated individuals is given by

$$\text{New Infect Force} = \text{Old Infect Force} \times (1 - \text{Efficacy}). \tag{3.6}$$

If the vaccine is 90% effective then a vaccinated person should be ten times less likely to be infected than a non infected person in otherwise identical circumstances.

The MeNZB vaccine requires three doses [26]. However, in our model, for simplicity, we model protection beginning after one dose. This may mean we have overestimated the number of people vaccinated as not everyone who receives a first dose will complete the course. The HPV vaccination study — on which we have based our parameter of 45% of men accepting a vaccination when offered — states that it is too early to know how many people will complete the course, as it could take up to two years for each individual [1]. We do not model any partial protection given by an unfinished course of treatment. Modelling protection as beginning after one dose rather than three means our results may show the impact of the vaccine faster than would be seen in reality as a full vaccination course could take up to two years.

The flow chart in figure 3.3 shows the points at which the vaccine is offered, where vaccination

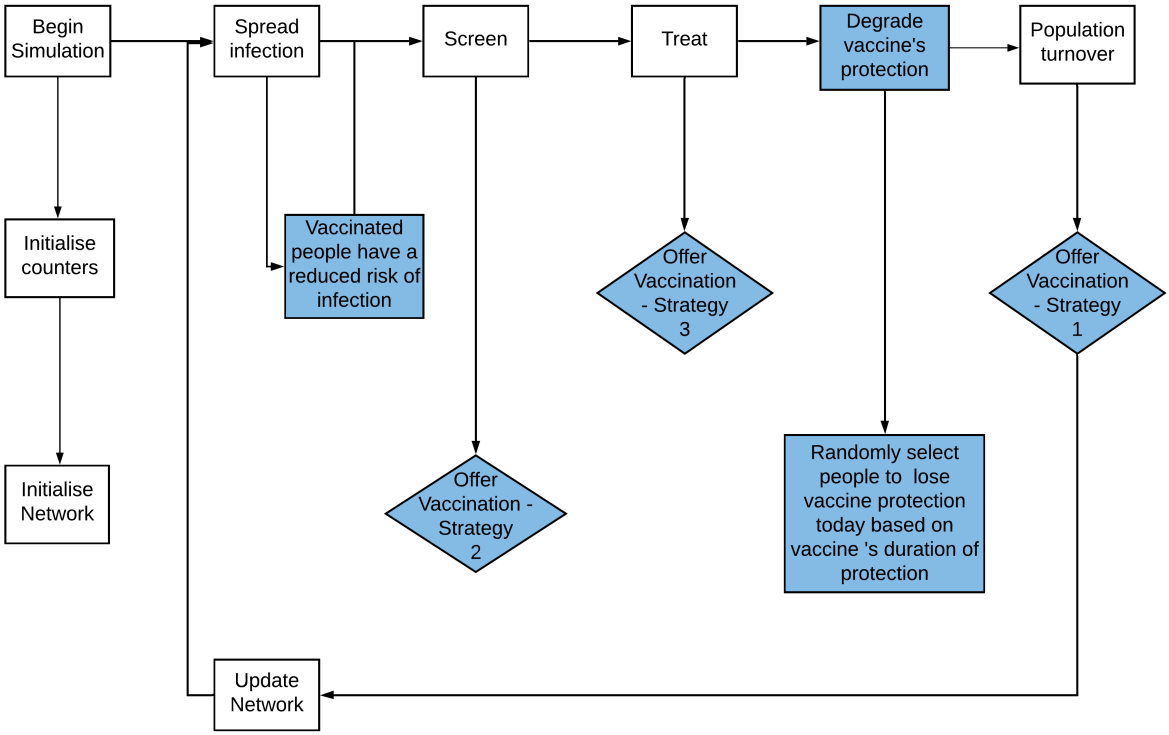


Figure 3.3: Flow chart showing major processes in model including vaccination, the model's existing processes are shown in white, and the new steps relating to the vaccine are shown in blue

status affects the original model's processes, and where it runs out in blue, while the processes that are unchanged by vaccination are in white. We record which individuals are vaccinated using the *vaccination state* vector, which is of length N, where N is the number of individuals in the population being modelled. The value at each position represents the efficacy of the vaccine, between 0 and 1. The duration and efficacy of the vaccine can be changed before each simulation. We assume that the vaccine offers the same efficacy to everyone in the population and that this value does not change during the simulation. As seen in figure 3.3 the vaccine's protection is currently either *on* or *off*, however, it may be more accurate to model the protection as fading over time. The vaccination we model has an expected lifetime of three years but this will vary between people, every simulated day there is a chance of the protection disappearing. A subsequent model could include having the protection falling by a certain amount each day, leading to it fading over time instead of being either on or off.

We assume there is no behavioural change in vaccinated individuals, for example, they are not more likely to have a greater number of partners. We also assume that there is no change to how the disease presents itself in vaccinated individuals who become infected — they are not more or less likely to experience asymptomatic infections, nor do they recover at a different rate to their non-vaccinated counterparts.

Later we discuss the impact of these assumptions and the possibility of making the way the vaccine is modelled more adaptable to different vaccination properties, not just efficacy and duration. For example the fact that MeNZB requires multiple doses or the possibility that the protection may take a while to reach its full efficacy. We may also want to model variation in protection, the efficacy of the vaccine for each individual could be taken from a random distribution. We now discuss how each strategy is implemented in our individual based model.

Strategy 1 — Childhood Vaccination in IBM

As seen in figure 3.3, vaccination in childhood is included in the population turnover function. Every simulated day a random $1/2200th$ of the population is replaced in our model, their infection status and all flags are removed. When vaccination is included we also remove any vaccination status. We then randomly select a percentage of these people to be vaccinated. This percentage is set to 85% — the same as the percentage of children who are receive the HPV vaccine [1] — but it can easily be preset to another value should new data become available.

We assume people are vaccinated as soon as they join the core group, this is not a practical vaccination method, as the age at which sexual partner change occurs varies between individuals [13, 31]. This assumption has less of an impact on the results the longer the duration of the vaccine modelled, for a vaccination that lasts a lifetime it doesn't matter how long ago an individual is vaccinated. As the replacement rate in this model is not a birth/death rate — as it is in the equation based model — the effect on prevalence of vaccination using this strategy will be seen much faster than in our equation based results. We are modelling the case in which people are protected for, approximately, the first 3 years of the time they are in the core group. We assume vaccination occurs at 16 and the core population are aged between 16-24, we discuss the impact and accuracy of this assumption and how we could model this strategy more accurately later. This approximation gives us some insight into how a vaccine that is given before entry into the sexually active population could work.

Strategy 2 — Vaccination at Screening in IBM

In this strategy a proportion of people being screened every day are vaccinated. This process is attached to the screening function in our model, this can be seen in figure 3.3. Every simulated day a random $1/400th$ of the population are selected for screening, from this we select those who have either never been vaccinated before or for whom we would expect the protection to have expired — for a vaccine that lasts three years we offer it no less than three years after a previous dose — even though some people may still be protected at this point, and some may have had the protection run out long before. We randomly select 45% of these presumably not protected people attending screening to vaccinate. As discussed previously the figure of 45% comes from data from a pilot study vaccinating MSM against HPV [1].

Strategy 3 — Vaccination on Diagnosis in IBM

A proportion of people who attend a clinic for treatment on any simulated day — either from a positive screen, voluntarily seeking treatment due to symptoms, or being traced via an infected partner — will be offered the vaccination. As there is no data available for a similar scenario we will use the same rate as men accepting the HPV vaccine at attendance at a sexual health clinic — 45% [1]. This strategy may also lead to vaccinating some people who were not infected; we model PHE treatment guidelines which stipulate that someone who has been traced from contact with a known infectee may be treated without a test being performed [15], meaning we could treat individuals who are not infected.

We now move on to the results we find using these models.

Chapter 4

Results

In this section we present simulation results for both the equation based and individual based models, for all three vaccination strategies, as described in chapter 3 above. For both models we have found the results over a period of 4000 days — just over 10 years. This is to ascertain the ability of each vaccine to meet the WHO's goal of reducing gonorrhoea incidence by 90% by 2030 [33]. We focus on studying the impact of the MeNZB vaccine as there is preliminary data on its efficacy and duration of protection, and because it may be the fastest way to vaccinate people as it is already approved for use in humans.

4.1 Results of Equation Based Model

We have used our equation based model to study how vaccinations with a wide variety of parameter values can impact prevalence.

The results are obtained by numerical integration — using a six stage, fifth order Runge-Kutta method with tolerance 10^{-3} — of the equations 3.2 to 3.4, which model the system for each vaccination strategy. Solving the model without vaccination gives us initial values for prevalence, which we use as control values. The period of equilibration where we see these prevalence levels emerge is seen in figure 4.1a. It gives a core prevalence of 32.5% and a non core prevalence of 4.6%. This gives a total prevalence of 6.3%. We use these values as the initial values for the models which include vaccination to see how the prevalence reacts. A prevalence of 6.3% is considerably higher than the presumed incidence of gonorrhoea amongst MSM which is around 2.5% [15]. This discrepancy highlights the issues with parameterising models without any calibration, although the values we have chosen to model the interaction and transmission of the disease are justifiable in isolation they miss out on important steps, for example we do not model any use of prophylactics but instead assume every sexual interaction has the same chance of spreading the infection. Calibrating the transmission parameter, β, to account for the use of condoms and different sexual acts could make this model more representative of the true prevalence and thus make this model more useful to see the impact of different interventions.

An illustrative example of the results over time for strategy 3 — vaccination on diagnosis — is shown in figure 4.1b. We see that for this strategy the percentage of people in each compartments oscillates before settling down. This is expected, if we vaccinate people who are infected we expect the prevalence to drop initially as these people are protected from becoming infected for the duration of the vaccines protection, in this case three years. As the vaccine from the first wave wears off, the number of people newly vaccinated will be lower than at the start of the simulation. Because fewer have been infected due to the initial wave of vaccination. This will lead to the prevalence increasing slightly. This negative feedback loop will mean the prevalence will oscillate before settling.

From table 4.1 we see the effects of a vaccine with 31% efficacy and a duration of 3 years (equivalent to

the MenZB vaccine based on current understanding [4, 14]) using the three different vaccination strategies we have previously explored.

Strategy	Control	1	2	3
Core prevalence	32.5%	31.3%	1.4%	4.7%
Non-core prevalence	4.6%	4.4%	0%	0.7%
Total prevalence	6.3%	5.7%	0.1%	0.9%
Core vaccinated	0%	0.8%	28.4%	27.6%
Non-core vaccinated	0%	0.8%	28.4%	3.9%
Total vaccinated	0%	0.8%	28.4%	5.1%

Table 4.1: Percentage infected and vaccinated after 4000 days using the MeNZB vaccine with three different strategies: strategy 1 — vaccination in childhood, strategy 2 — vaccination at screening, strategy 3 — vaccination on diagnosis

From these results it is clear that childhood vaccination has very limited impact, total prevalence is reduced by just 10%. The other two strategies show greater success at reducing prevalence. Vaccination at screening (strategy 2) eradicates the infection amongst the non-core and reduces total prevalence by 99%. In contract strategy 3 — vaccination on diagnosis achieves an 85% reduction in cases by targeting the core group, and that we vaccinated 27.6% of core members compared to 3.9% of non-core members. This represents just 5.1% of the total population being vaccinated at the end of the simulation, compared to 28.4% for vaccination at screening.

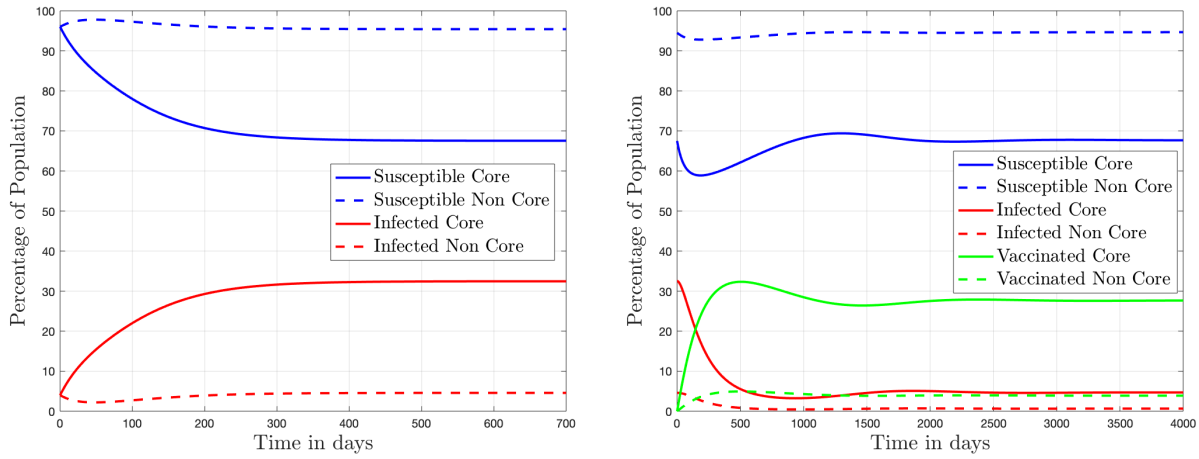
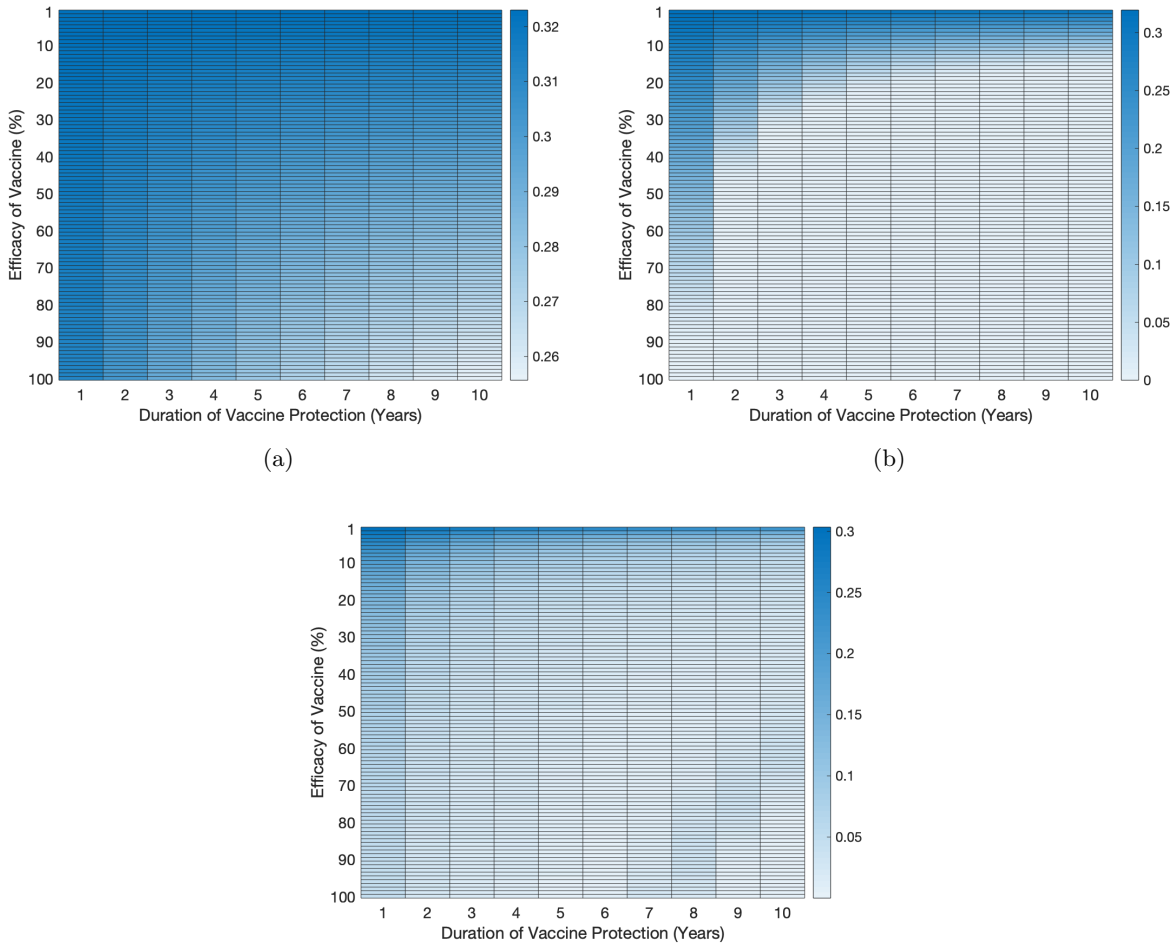


Figure 4.1: Results of equation based model based on the work of Hethcote and Yorke. Figure (a) shows the result of an SIS model which is used to give baseline figures for the percentage of people in each compartment. Figure (b) shows the results of introducing vaccinating at diagnosis using the MeNZB vaccine

As the equation based model is simple it can be run very quickly, this allows us to explore, not just the impact of the MeNZB vaccine, but the impact of a vaccine with any parameter values. We solved the equations as above, but with varying parameter values for efficacy (between 1-100%) and duration (between 1-10 years) to give us the prevalence of the infection in the core at the end of each 4000 day simulation. The results are presented as heatmaps in figure 4.2.

From the heatmaps we also see that, as expected, for all strategies the higher the efficacy and duration the better the outcome. The heatmaps also show the difference between the three strategies very clearly. Both vaccination at screening and vaccination on diagnosis can reduce prevalence by more than 99% with a vaccine similar to MeNZB (with an efficacy of 31% and a duration of 3 years), whereas vaccination in



(a)

(b)

(c)

Figure 4.2: Heatmaps showing gonorrhoea prevalence in the core after 4000 days of vaccination in our equation based model. Subfigure (a) shows the results of Strategy 1 — Vaccination in childhood, (b) shows the results for strategy 2 — vaccination at screening, and (c) shows the results for strategy 3 — vaccination alongside treatment

childhood does not lead to a significant fall in prevalence for any vaccine. Even using the best vaccine modelled, which protects for 10 years and offers complete protection, childhood vaccination reduces the core prevalence by less than 8%. Vaccination in childhood is the least effective strategy in this model because the birth rate parameter is very small which limits the growth of the vaccinated population. If we were to model the prevalence over a much longer period we may notice a much more significant drop as at this point we would expect a significant proportion of the population to be vaccinated. The number of people vaccinated is likely to be representative, but we have not accounted for the fact that we have to consider the age distribution of those vaccinated to understand the impact of vaccination against gonorrhoea. Protecting children or the elderly with a vaccine will not have a significant impact on the prevalence of gonorrhoea, but vaccinating people around the age of expected peak sexual partner change will [10, 16]. The impact of a vaccine given in childhood is highly dependent on the age at which it is given, especially if it is presumed to protect for a very short amount of time. Vaccinating people at 16 rather than 13 would lead to protecting more people who are sexually active, although it would still wear off at an age where sexual partner change is likely to be high [13].

This equation based model has allowed us to see how well a variety of vaccines will work to reduce prevalence. However, this model cannot give us detailed information on the number of vaccine doses

prescribed and, more importantly, the number of antibiotic doses administered.

We now discuss the results of the individual based model, which give us a deeper insight into the impact of vaccinating using the MeNZB vaccine.

4.2 Results of Individual Based Model

We have used the individual based model to explore the impact of vaccination on prevalence and number of antibiotic doses prescribed to treat gonorrhoea. We have modelled the impact of vaccinations with three different levels of efficacy to see the impact of different theoretical vaccinations. The first is the MeNZB vaccine which we have previously described, with an efficacy of 31% and duration of 3 years. We then increase the value for efficacy. The second vaccine we explore has an efficacy of 62% and the third offers complete protection, 100% efficacy; both vaccines protect for a duration of three years. We also briefly explored the impact of increasing the duration but found it made a less significant difference on the vaccine's impact than changing efficacy.

As there is currently no vaccine, we cannot reproduce existing data on the impact of a particular vaccination. Therefore, to increase confidence in our results, we have modelled the impact against backgrounds of varying levels of initial prevalence. In addition, we know that gonorrhoea prevalence is rising globally, therefore, it is important to measure the impact of a potential vaccine for higher initial prevalence values which may represent possible futures [32]. The first initial endemic prevalence level is around 2.4% which is obtained using the parameters Zienkiewicz et al. use. These parameters have been calibrated to the expected current prevalence of gonorrhoea in MSM in London [15]. The second initial prevalence of around 6.5% is achieved by increasing the value of β, the parameter that rules how infectious the disease is. The new β value was chosen using Zienkiewicz et al.'s supplementary material for values of β that give stable prevalence levels. Increasing the transmission parameter β represents the disease becoming more infectious, possibly due to changes in behaviour, for example individuals having more partners or being less likely to use protection. There are other ways to alter the prevalence in the model. For instance we could increase the length of infection or increase the average number of partners people have.

Our results were obtained by running each vaccination simulation 100 times with a population of 10,000 individuals using the university's high performance computing facility. We present the average values over time for each scenario. For the prevalence figures we show the results for overall prevalence and do not show the impact on the two individual strains as both are affected equally by the vaccine and there is no competition between them as we assume treatment is all ceftriaxone so there is no treatment failure.

We henceforth refer to the vaccines according to their efficacy, the vaccine with efficacy and duration expected of the MeNZB vaccine will be MeNZB31, the vaccine with 62% efficacy will be MeNZB62, and the completely protective vaccine will be MeNZB100. All three vaccines will have an expected duration of protection of 3 years. We ran brief simulations for a vaccine with an improved duration (6 years rather than 3) and standard efficacy (31%) and found it made a less significant difference to our results than improving the efficacy.

Prevalence

From figures 4.3 to 4.5 we see that in general vaccination at screening, and vaccination on diagnosis, (strategies 2 and 3) reduce prevalence more effectively than vaccination in childhood (strategy 1). This is true for every scenario we have modelled with the exception of the completely protective vaccine where prevalence is low, seen in figure 4.5a. Where vaccination in childhood overtakes vaccination at diagnosis

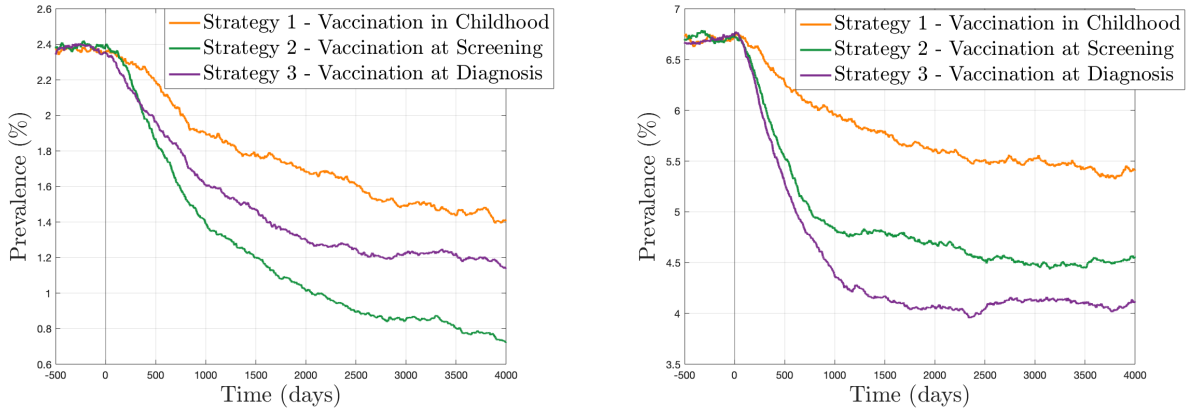


Figure 4.3: Impact of MeNZB31 vaccine (with efficacy of 31% lasting for 3 years) on prevalence of gonorrhoea using different strategies. Vaccine introduced on day 0. (a) shows the impact of the results on current expected prevalence — 2.4% — and (b) shows the results on a theoretical higher initial prevalence — 6.7%

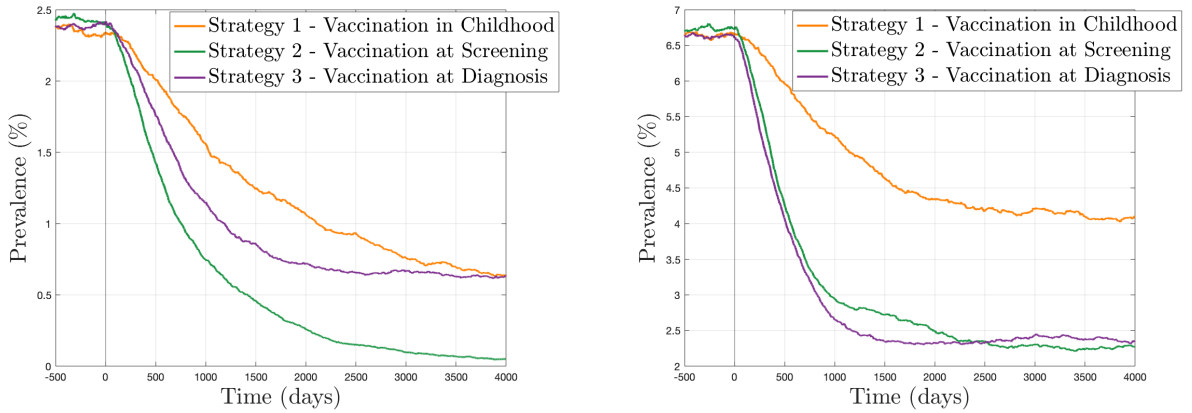
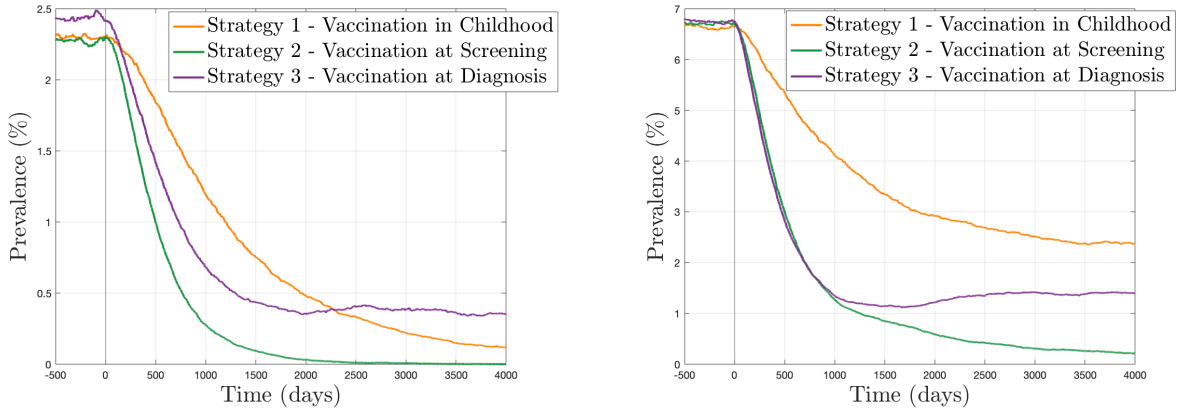


Figure 4.4: Impact of MeNZB62 vaccine (with efficacy of 62% lasting for 3 years) on prevalence of gonorrhoea using different strategies. Vaccine introduced on day 0. (a) shows the impact of the results on current expected prevalence — 2.4% — and (b) shows the results on a theoretical higher initial prevalence — 6.7%

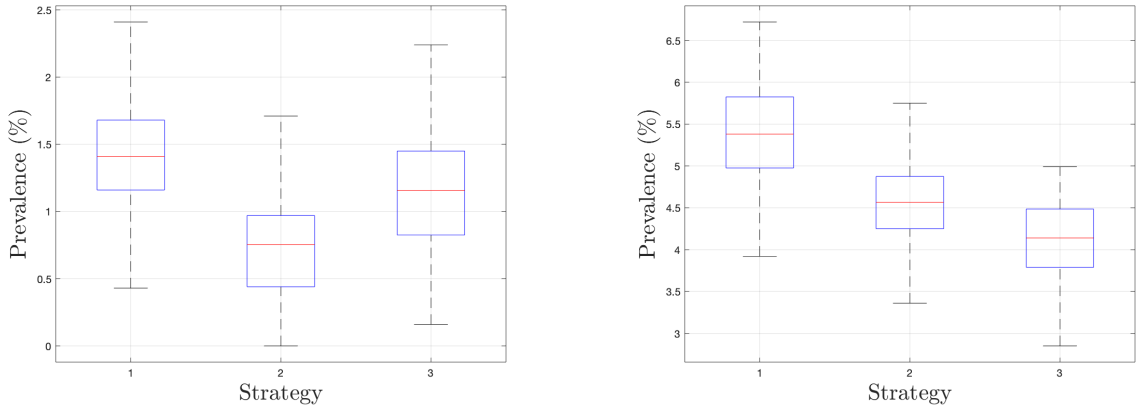
but not vaccination at screening.

For MeNZB31 and MeNZB62 which strategy is most effective depends on the initial prevalence of the infection; for low prevalence — figures 4.3a and 4.4a — we see that for both vaccines delivering the vaccination at screening is the more effective strategy. For MeNZB31 this strategy leads to a 70% (95% for MeNZB62) drop compared to 50% (75% for MeNZB62) drop for strategy 3 — vaccination at diagnosis. For the higher initial prevalence seen in figures 4.3b and 4.4b there is less difference between the two strategies. For MeNZB31 vaccination at diagnosis is the more effective strategy, reducing prevalence by 38% — compared to 32% for vaccination at screening. Using MeNZB62 leads to there being almost no difference between the outcome of two strategies, both reduce the prevalence by 65%. The results in figures 4.3a to 4.4b suggest that vaccination at screening is the better strategy for low prevalence and vaccination on diagnosis is the better strategy for high prevalence. However, our results for a vaccine that is 100% protective against gonorrhoea, seen in figure 4.5 show a different pattern. We see that vaccination at screening is the better method for reducing prevalence for both levels of initial prevalence. We also



(a) (b)

Figure 4.5: Impact of MeNZB100 vaccine (with efficacy of 100% lasting for 3 years) on prevalence of gonorrhoea using different strategies. Vaccine introduced on day 0. (a) shows the impact of the results on current expected prevalence — 2.4% — and (b) shows the results on a theoretical higher initial prevalence — 6.7%

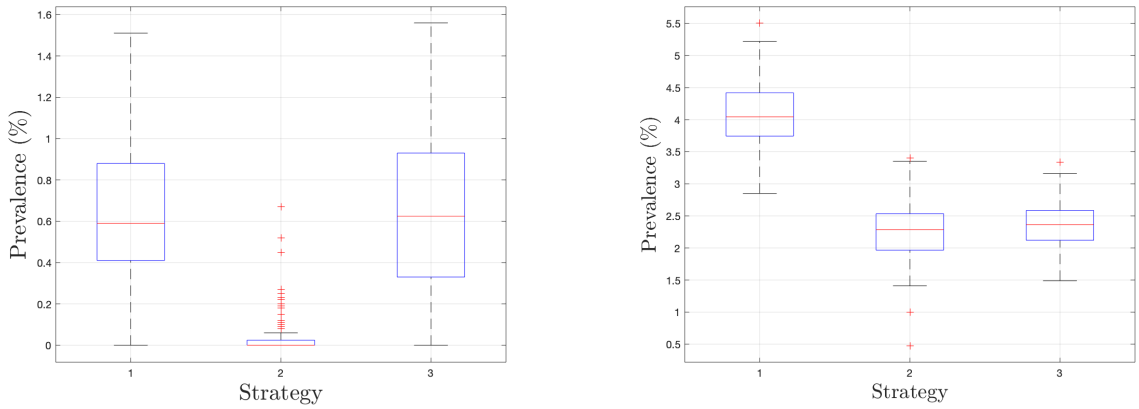


(a) (b)

Figure 4.6: Boxplots for prevalence at the end of a 4000 day simulation with differing levels of initial prevalence using vaccination lasting 3 years, efficacy 31%. We use three different strategies: 1 — vaccination in childhood, 2 — vaccination at screening, 3 — vaccination at diagnosis. (a) is for current expected initial prevalence — 2.4% — and (b) is for theoretical higher initial prevalence — 6.7%.

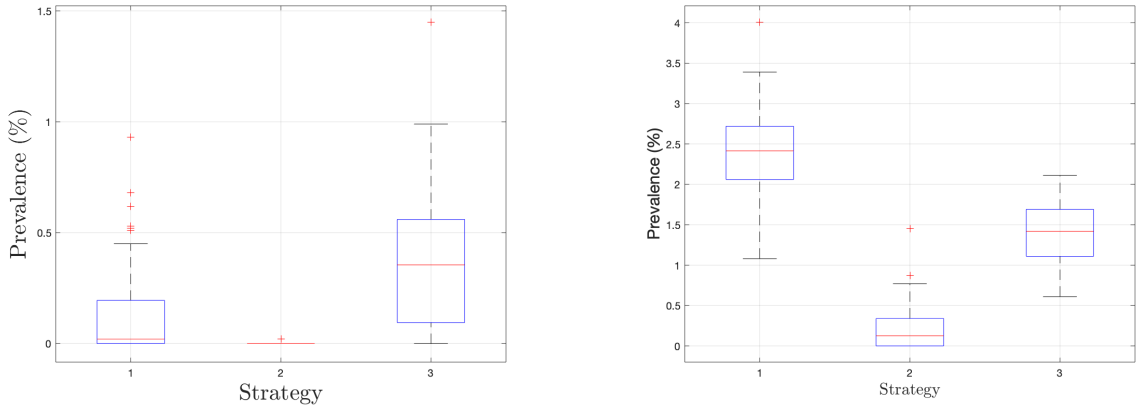
have that childhood vaccination, which is a distant third in our previous results, is now a better method of vaccination than vaccination at screening when prevalence is low — figure 4.5a. For low prevalence vaccination in childhood reduces prevalence by 95% compared to 85% for vaccination at diagnosis and more than 99% for vaccination at screening. When prevalence is higher we would expect childhood vaccination to once again be relegated to third place reducing prevalence by just 65% while vaccination at screening leads to a 97% drop and vaccination at diagnosis, an 80% drop. These results suggest that for a highly effective vaccine the initial prevalence has a less significant impact on how well the vaccine reduces incidence of gonorrhoea if it is given at screening or at diagnosis (strategies 2 and 3). This set of results also highlights the limitations of vaccination on diagnosis. As the number of people vaccinated depends on the number of people infected it will be difficult to dramatically reduce the incidence of gonorrhoea and perhaps impossible to eradicate it although more simulations with differing parameters for duration of the vaccine and initial prevalence would be needed to confirm this.

For some of our strategies it appears that prevalence has settled to a new stable level — for example



(a) (b)

Figure 4.7: Boxplots for prevalence at the end of a 4000 day simulation with differing levels of initial prevalence using vaccination lasting 3 years, efficacy 62%. We use three different strategies: 1 — vaccination in childhood, 2 — vaccination at screening, 3 — vaccination at diagnosis. (a) is for current expected initial prevalence — 2.4% — and (b) is for theoretical higher initial prevalence — 6.7%.



(a) (b)

Figure 4.8: Boxplots for prevalence at the end of a 4000 day simulation with differing levels of initial prevalence using vaccination lasting 3 years, efficacy 100%. We use three different strategies: 1 — vaccination in childhood, 2 — vaccination at screening, 3 — vaccination at diagnosis. (a) is for current expected initial prevalence — 2.4% — and (b) is for theoretical higher initial prevalence — 6.7%.

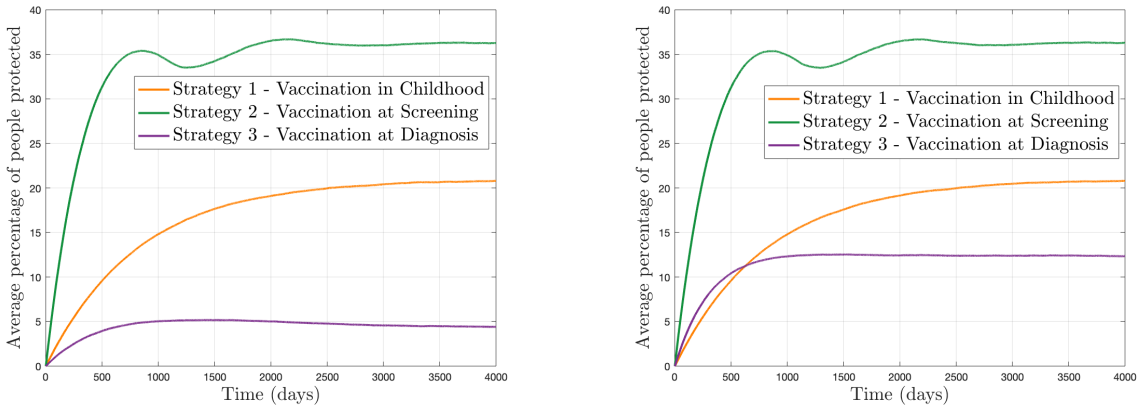
figure 4.4b. However, in others it appears prevalence is still decreasing, for example 4.4a, here vaccination at diagnosis seems to have settled to a stable prevalence level at 0.6% by the end of the simulation; vaccination in childhood has also reached this value for prevalence by the end of the simulation but it appears to still be decreasing. This suggests that for some possible scenarios a vaccination may take longer than 10 years to reach its full potential in reducing prevalence.

In figures 4.4a and 4.5a we see that vaccination at screening gets close to eradicating the infection, reducing prevalence by more than 95%. For infections with low prevalence we may see spontaneous eradication which is why it is essential to run multiple simulations to find averages and measure the spread of results [12]. We record interquartile range and standard deviation for all results presented in this report. For prevalence of gonorrhoea in a scenario where it could fall to zero, standard deviation is not an adequate measure of spread, as the results on the lower side will be truncated by zero because we cannot have negative prevalence. Therefore, to see the spread of results for prevalence we produce boxplots seen in figures 4.6 and 4.7, and 4.8; these show the distribution of results from each of the 100

simulated runs for each vaccination strategy and initial prevalence level at the end of the simulation. From figure 4.7a we see that more than half of our simulations culminated in eradication, but also that there are considerably more outliers than we see in other simulations, though the overall spread of the results is more narrow than other results with the same efficacy and/or initial prevalence. For MeNZB100 with low prevalence we see from figure 4.8 that all but one of our simulations ended with eradication of the disease, this increases confidence in this vaccination and strategy. From these boxplots we also see that there is considerable overlap between the outcomes of many different pairs of strategies that appear distinct from the prevalence plots, which show only the mean prevalence across the simulations. This suggests that there may be less to gain than expected from, for example, switching between vaccination at screening and childhood vaccination for a MeNZB31 vaccine with low initial prevalence. However, it is likely that the benefit of childhood vaccination is overestimated here as the core population will not include only 16-24 year-olds [13].

Number of people protected by the vaccine

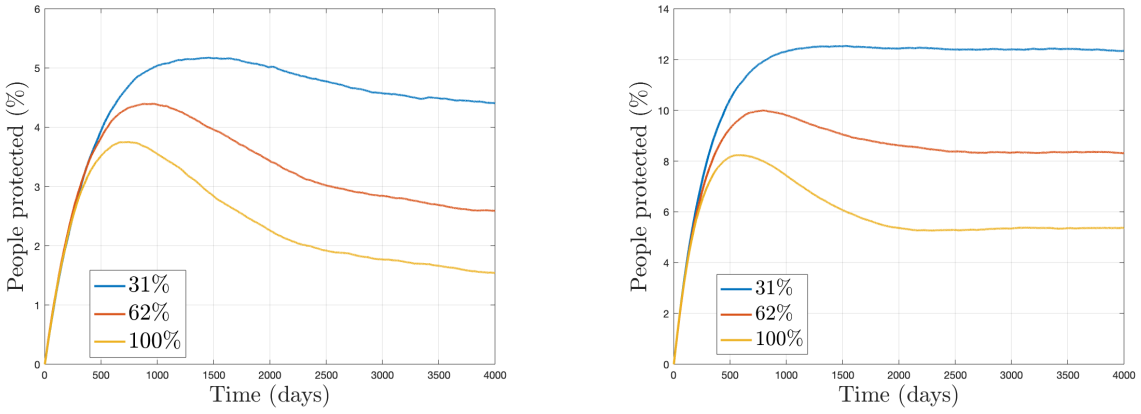
Figure 4.9 gives the average number of people vaccinated over time for each strategy for low initial prevalence using MeNZB31. We record the number of people protected by the vaccine over time to see how this relates to the prevalence, we measure how efficient each strategy is by looking at the reduction in prevalence in the context of the proportion of the population protected by a vaccine. For strategies 1 and 2 (vaccination at screening and in childhood) the number of people vaccinated is not dependent on either of our independent variables (efficacy and initial prevalence) so these values do not change noticeably between simulations. For strategy 3 — vaccination at diagnosis — the number of people vaccinated is directly related to prevalence, as we only vaccinate people who are believed to be infected. It is also dependent on the efficacy of the vaccine as this affects the prevalence of the disease throughout the simulation. The number of people vaccinated over time using vaccination at diagnosis is presented in figure 4.10. We see that the more effective the vaccine the fewer people are vaccinated.



(a) (b)

Figure 4.9: Percentage of population protected from gonorrhoea infection by different vaccines over time for different prevalence values using different vaccination strategies, for strategies 1 and 2 the number of people vaccinated over time does not change between simulations as the number of people vaccinated does not depend on our independent variables: initial percentage infected and efficacy of vaccine. (a) represents the number of people vaccinated when initial prevalence is at current presumed levels — 2.4%. (b) represents when prevalence is higher —- 6.7%

We see from figure 4.10 that for the 100% effective vaccine we find the peak is just 3.7%, the more effective vaccines reduce prevalence faster thus reducing the number of people who require treatment and reducing the number who are offered the vaccine.



(a) (b)

Figure 4.10: Average percentage of people vaccinated using strategy 3 –vaccination at diagnosis — over time for different vaccines and different levels of prevalence, figure (a) gives the results for the low initial prevalence — 2.4% — and figure (b) for the high initial prevalence — 6.7%. The legend shows the efficacy of the vaccine

For strategy 3 — vaccination at diagnosis — the number of people vaccinated per day is directly related to the prevalence of the disease. We expect the number of people vaccinated per day to be 1.5 (standard deviation: 0.4) for low prevalence and 3.8 (0.6) for high prevalence at the start of the simulation.

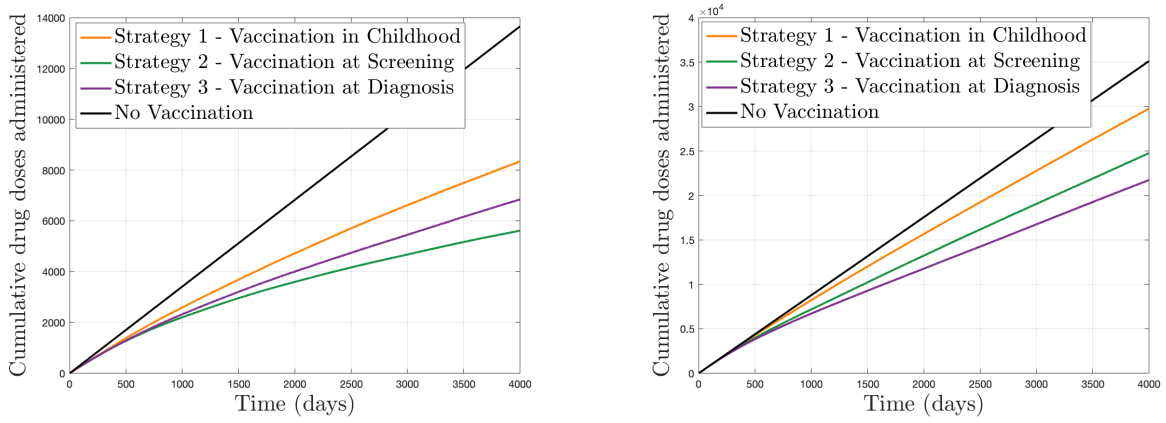
For vaccination at screening the peak is 36% and for vaccination in childhood it is 21% regardless of initial prevalence and the efficacy of the vaccine. When the vaccination is given in childhood 2.5 (standard deviation: 0.2) people are vaccinated per day, throughout the simulation. When vaccination occurs at screening we have waves of vaccination seen in figure 4.9, the initial wave lasts approximately 500 days when almost everyone attending screening has not yet been vaccinated. After this many people attending screening will have been vaccinated previously so the number of people protected by the vaccination over time plateaus. In the first wave we vaccinate 8.6 (1.5) people per day and in the second 5.0 (0.6) people per day.

Strategy 3 appears to be the most efficient vaccination strategy. Despite the fact that far fewer people are protected by the vaccine at any one time this strategy has the potential to outperform both of our other strategies when we use MeNZB62 and initial prevalence is high. This illustrates the benefit of targeted vaccination. By vaccinating only people who are known to have received treatment for gonorrhoea we target those who are most likely to catch it again as they have the most partners and are therefore at most risk of becoming infected. However, figure 4.5 shows the limitations of this method. When the vaccine is highly effective, by targeting just a small proportion of the population, we lose out on the chance to eradicate the disease should we choose vaccination at diagnosis over vaccination at screening. Vaccination at diagnosis does not lead to high enough coverage to eradicate gonorrhoea.

For strategy 2 — vaccination at screening — the number of people vaccinated over time oscillates slightly. This is due to the fact that we only offer people the vaccine if they last had it three or more years ago, this means that for around half of vaccinated people the vaccine's protection will have worn off before they are offered it again.

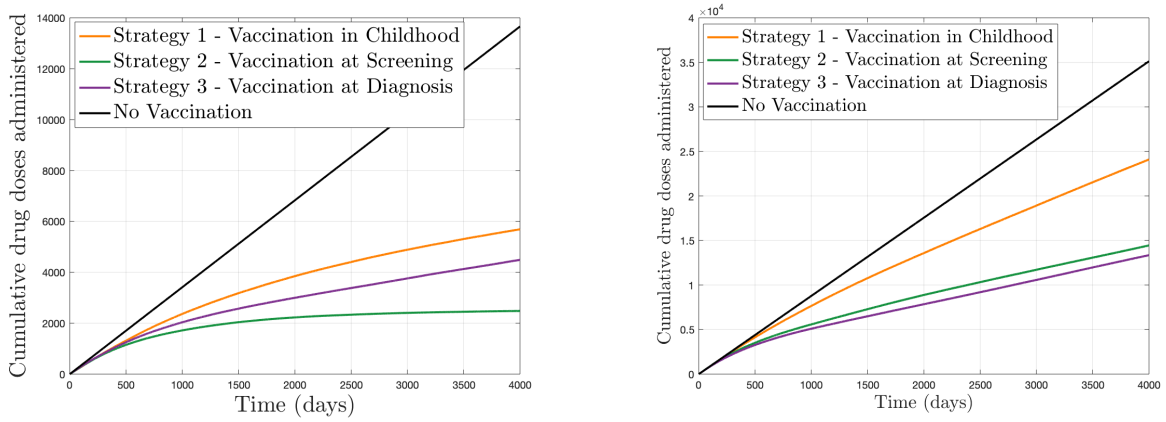
Antibiotic doses

Figures 4.11, 4.12, and 4.13 show the cumulative number of drug doses administered to treat the infection over the length of the simulation. In these figures we also plot the number of antibiotic doses we would expect to see without any vaccination for comparison. We see that in general, vaccination in childhood



(a) (b)

Figure 4.11: Cumulative number of antibiotic doses administered to treat gonorrhoea infection over time while vaccinating with MeNZB31. (a) shows the impact when initial prevalence is at current expected levels — 2.4% — and (b) shows the impact when initial prevalence is considerably higher – 6.7%



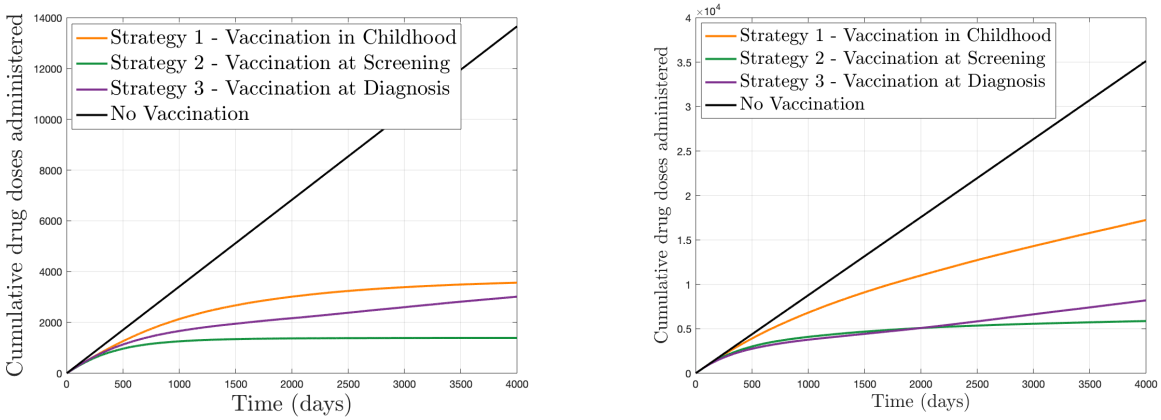
(a) (b)

Figure 4.12: Cumulative number of antibiotic doses administered to treat gonorrhoea infection over time while vaccinating with MeNZB62. (a) shows the impact when initial prevalence is at current expected levels — 2.4% — and (b) shows the impact when initial prevalence is considerably higher – 6.7%

leads to a less significant reduction in antibiotic doses than vaccination on diagnosis and at screening.

However, the impact on the number of drug doses is not dependent only on the new prevalence we achieve through vaccination, but also on the speed at which prevalence is reduced. In figure 4.4a we see that strategies 1 and 3 (vaccination in childhood and at diagnosis, respectively) reduce prevalence to the same level by the end of the simulation but figure 4.11b shows that fewer drug doses are prescribed when we use strategy 3 because the drop in prevalence is achieved more quickly.

The MeNZB31 vaccine can prevent 60% of drug doses when prevalence is at current presumed levels — 2.4% — if the most effective strategy was chosen, but just 38% if the initial prevalence is higher — 6.7%. This shows that the impact of the vaccine is not robust to prevalence, there is no predictable drop in the number of drug doses nor in the prevalence of disease due to either vaccine. For MeNZB62 when prevalence is low and we vaccinate at screening the number of antibiotic treatments required falls by 83%. If the prevalence is higher we can reduce it by 63% by vaccinating with MeNZB62 at diagnosis. For MeNZB100 we can reduce the number of drug doses by 90% for low prevalence or 83% for high prevalence by using vaccination at screening. These results show the impact on the number of drug doses



(a) (b)

Figure 4.13: Cumulative number of antibiotic doses administered to treat gonorrhoea infection over time while vaccinating with MeNZB31. (a) shows the impact when initial prevalence is at current expected levels — 2.4% — and (b) shows the impact when initial prevalence is considerably higher – 6.7%

Strategy	Control	1	2	3
Low prevalence	3.4 (1.7)			
31%		1.6 (1.3)	0.9 (1.0)	1.3 (1.4)
62%		0.8 (1.0)	0.0 (0.2)	0.7 (0.9)
100%		0.1 (0.4)	0.0 (0.0)	0.3 (0.6)
High prevalence	8.8 (3.1)			
31%		7.0 (2.9)	5.8 (2.9)	5.0 (2.4)
62%		5.2 (2.5)	2.7 (1.7)	2.6 (1.7)
100%		2.8 (1.7)	0.2 (0.6)	1.5 (1.3)

Table 4.2: Average number (and standard deviation) of ceftriaxone doses administered per day, per 10,000 people at the end of the simulation

over the length of the simulation. For most of our results we have seen prevalence settle at a new level, meaning we can use the predicted new number of antibiotic doses per day to see the ongoing risk of drug resistant gonorrhoea developing, after the initial vaccination programme. The average number of doses of ceftriaxone prescribed to treat gonorrhoea per day, per 10,000 people at the end of each simulation is shown in table 4.2.

Summary

We have seen that the vaccination strategy chosen has a significant impact on the prevalence of gonorrhoea and the number of drug doses required to treat it. We find that the best strategy varies according to the the initial prevalence of the infection when vaccination is introduced and the efficacy of the vaccine. There is not a clear best strategy.

We have shown that protecting a greater proportion of the population does not necessarily translate to preventing the greatest number of infections as long as we target those who are most at risk. However, for highly efficacious vaccines higher vaccine coverage may lead to eradication whereas using targeted vaccines may not be able to achieve as impressive results. For the more efficacious vaccines, with high coverage there is the chance to eradicate gonorrhoea.

Chapter 5

Discussion

5.1 Impact of Vaccination

Our individual based model shows that, for current presumed prevalence, vaccination at screening is the most effective method to reduce both gonorrhoea prevalence, and the number of drug doses required to treat infection, for all vaccines modelled. However, we see that when prevalence is significantly higher than currently predicted, vaccination at diagnosis is a slightly more effective method, unless the vaccine is completely protective against infection — if this is the case vaccination at screening is once again the more effective method. The fact that the relative impact of each strategy is dependent on initial prevalence highlights the importance of having up to date, and accurate data on the current incidence of gonorrhoea. However, recording exactly how many people in a population are infected with gonorrhoea at anyone time is difficult, as many infections are asymptomatic and may therefore go unreported, and due to stigma which may discourage people from accessing healthcare when needed [1, 30].

Our results show that vaccination in childhood is, in general, a less effective strategy than either of the two methods of vaccinating adults — vaccination at screening and at diagnosis. However, when we have low prevalence and use MeNZB100, vaccination in childhood is a more effective method than vaccination at diagnosis. The fact that we do not have a clear hierarchy of strategies shows that the efficacy of a vaccine and the initial prevalence of the infection are very important to a vaccine's impact.

By tracking the percentage of people protected over time we find vaccination at screening offers the highest coverage, with 37% of the population being vaccinated at the end of the simulation and vaccination at diagnosis offers the lowest — between 4-12% depending on the initial prevalence, and the efficacy of the vaccine. However, as we do not model the full population the true number of people protected, and therefore the number of vaccine doses given, will be higher. How much higher depends on the strategy used. Strategy 1 — vaccination in childhood — cannot be targeted to MSM, this strategy would more likely involve vaccinating all boys which would mean using at least 50 times more doses than the figures currently suggest (as we only model the most active MSM, who themselves make up around 2.6% of the male population). This is most significant for vaccination in childhood but, in fact, for all of the simulations presented here more people will be receiving the vaccine than is modelled as we model only the most active MSM.

We see that all of the strategies modelled reduce the number of drug doses, and that the most effective vaccines can reduce the number of drug doses prescribed at the end of the simulation, per day, per 10,000 people to 0. Even the less effective strategies reduce the number of daily prescriptions by at least 50% when prevalence is at current expected levels. The impact on drug doses is less impressive when prevalence is higher, the MeNZB reduced daily doses by just 20% when given in childhood, 35% if given at screening and 45% if given at diagnosis. We have discussed in detail the benefits of using an individual based model

over an equation based model however here we will discuss additional work to the individual based model we used that we believe could make it more representative. We also suggest other scenarios that could be explored using the vaccination capability we have added to the model. We will discuss the ways in which the properties of the individual model impact the results we have drawn from it.

5.2 Proposed Adjustments to Model

As previously mentioned the individual based model is more representative of the world than the equation based model. However, it is always difficult to model human behaviour due to its highly variable nature. We now discuss the impact of some of out assumptions on our results.

5.2.1 Modelling Age

We have not included the age of the individuals we model because people may join the core group at any point in their life [13, 31]. However this does lead to some difficulties with the implementation of childhood vaccination. Because the individual model only represents a small subsection of the population and the equation based model represents a whole population there is a significant difference between the population turnover rate in the two models. In the equation based model population turnover is based on the birth rate and in the individual model it is based on the presumed rate at which people join and leave the highly sexually active population. This explains the variation between the two models in terms of the number of people protected by childhood vaccination. In the equation based model we have a very small number of vaccinated individuals, only around 0.8% after 10 years. Whereas in the individual based model it is 21% for both high and low initial values for prevalence. The results we have found can be thought of as occurring on a delay, when we expect a large proportion of the population to have been vaccinated, the length of the delay depends on the age at which people are vaccinated and the age distribution of the core population. Our current model has no delay, we assume people are vaccinated at 16 and the core population are mostly aged between 16-24. However, the age distribution of the core group is wider than this [13], so it is likely that even fewer members of the core population will be vaccinated than is seen in our models. If we assume people are vaccinated at 13 or the core population is modelled has a wider age distribution then modelling age is more important. Another way to approximate childhood vaccination, without delays or modelling age, would be to increase the proportion of vaccinated new members of the population over time according to the age distribution of the core to simulate the fact that as the vaccinated population grows up, a greater proportion of the individuals joining the core would be be vaccinated.

The impact of childhood vaccination may also be affected by the number of people born abroad. If not every country makes a gonorrhoea vaccine freely available the model will not accurately reflect the number of adults who have been vaccinated. In 2017 36% of Londoners were born abroad, and therefore may not have had a theoretical vaccine in childhood, depending on their age when they moved to the UK [34]. Sex tourism could also have a significant impact on the emergence of drug-resistant gonorrhoea, the first case of ceftriaxone-resistant gonorrhoea diagnosed in the UK was contracted in Thailand [2]. Imported, resistant infections may lead to AMR infections becoming widespread in the UK.

5.2.2 Networks

The network we used uses a power law for distribution of number of sexual partners, because data from multiple sex surveys shows this is a representative assumption [13, 18, 31]. An extension to this project could be to look at the choice of network parameters on transmission. It would be useful to model how

well the network in this model represents observed properties, such as relationship length and degree of partnership concurrency. The current parameters used are presented in appendix B.

5.2.3 Risk Perception and Behaviour

The individual based model assumes people attend screening approximately once per year, however, the Gay Men's Sex Survey reports only 70% of MSM attended such a screening in the last year [31]. In addition PHE guidance states people should attend screening once per year or on change of partner, and that people who are more sexually active should be screened more frequently. Another way to do this would be to make the rate at which people attend screening stochastic. One way to bring the model more into line with the data could be to split individuals into those more and less likely to attend screening. For example a proportion of the population would attend screenings regularly — once per year — some would attend frequently — every 3 months — and some would only attend when they have symptoms of an infection. This might change how duration for adult vaccination strategies impacts results, currently the fact that the vaccine can be renewed frequently means the duration doesn't make a significant difference, but if there were people who attended infrequently who could now be protected for a greater period this could change.

This model also doesn't take into account any other disease. A study into the impact of a vaccine for syphilis suggested that a vaccine could in some scenarios lead to an increase in HIV transmission due to reduced levels of symptomatic syphilis infection and reduced risk perception [20]. A vaccination for gonorrhoea could also lead to an increase in other STIs for these reasons. Studying the impact of a vaccine for gonorrhoea on other STIs would be an important part of understanding its wider impact. As it stands in our model an individual's behaviour does not change when they are symptomatic, this would need to change to bring the model into line with Champredon's model in which symptomatic individuals are less likely to be involved in transmission because they are aware they are infected [20]. We currently do not include any reduced perceptions of risk associated with vaccination; vaccinated individuals are not any more likely to form new partnerships or have more interactions with their existing partners than non-vaccinated individuals. We could change this to incorporate lesser perception of risk but this may not be accurate for this population. This could be explored using data from the pilot study vaccinating MSM against HPV, or from data on risk perception in people using PReP to prevent HIV infection.

Vaccine acceptance may increase over time, currently the rate is steady because acceptance for HPV has been around 85% for vaccination in childhood since its introduction [1]. However the main reason for vaccinating against HPV infection is to prevent some types of cancer, that HPV causes. It is possible that there would be less acceptance for a gonorrhoea vaccine than is seen for the HPV vaccine, as it does not prevent cancer.

5.2.4 Susceptibility of strains to vaccination

Our current model has two strains, one that is resistant to ciprofloxacin (AMR) and one that is not (non-AMR). In this report we have assumed both strains are equally effected by the vaccine. Other situations to explore include the possibility of a strain emerging that is resistant to the vaccine or that one of the existing strains is less affected by the vaccine than the other.

5.3 Further Work with Vaccine Capability

From our results we have seen that vacciantion at diagnosis is an effective method of bringing prevalence down while vaccinating fewer people, and that vaccination at screening is a reliable method for providing high levels of protection to the population. Therefore, we believe that a combination of vaccination

on screening and at diagnosis could have a significant impact on prevalence for many possible vaccines. Vaccinating using both of these methods would mean we benefit from high coverage and vaccination of the most active people. A similar strategy would be to vaccinate on diagnosis for a period and then switch to vaccinating at screening. This could limit the number of doses required, which may be important if the cost of the vaccine is high. This strategy may be beneficial as we see that vaccination at diagnosis can successfully bring prevalence down by vaccinating a small percentage of the population. But that it cannot reduce prevalence to levels where eradication is a possibility, whereas vaccination at screening can, as it is able to achieve high coverage independent of the current prevalence of the infection.

We can currently only model one strategy in each simulation, but the existing model could easily be adapted to use two at once, or to switch strategies at a point in time. This point could be preset or dictated by prevalence.

Vaccination at diagnosis appears to be a very efficient strategy as we see a very large drop in prevalence for the number of people vaccinated. However, Garnett et al. report that targeting vaccination may reduce acceptability and that, in general, the low cost of vaccination comes from mass production. Therefore vaccinating more people may be more cost effective than targeting a vaccination to a small proportion of the population [35]. This is an important factor to consider for our third strategy (vaccination at diagnosis) which targets a small number of people. It may be unfeasible to vaccinate only these people if we can benefit from a reduced cost per dose when purchasing greater quantities of a vaccine.

Representing a wider range of vaccination properties

There are many assumptions made about the properties of the vaccine, and people's reaction to it that could be further explored in the model to see if they make a significant difference to the results produced. These include:

- introducing a delay between receiving the vaccine and being protected from infection,
- representing the fact that the vaccine requires thee doses more explicitly, including people who do not complete a course,
- reducing the vaccine protection over time rather than have it switched either on or off,
- changing the acceptance rate of the vaccine over time.

These are practical concerns about possible factors which affect other vaccines which cannot currently be represented in our framework. The biological effects of a gonorrhoea vaccination are unknown because research is in early stages. However a vaccine could affect transmission. A vaccine that did not offer full protection could lead to infections if vaccinated people being more likely to be asymptomatic or to have shorter infections. Shorter infections could lead to individuals having less time to transmit the infection to partners, but asymptomatic infections could lead to more transmission, because infected people would not seek treatment so could be infecting partners for a longer period. This, added to the possible perceived immunity, could lead to more transmission of the disease from those individuals who are both vaccinated and infected.

The case of a vaccine which does not prevent infection but does reduce transmission is seen in a study on the effect of a partially effective herpes vaccine, which showed that even a vaccine that did not reduce the chance of becoming infected but did reduce likelihood of transmission can lead to a drop in prevalence [25].

We hope our model will provide a useful tool to study the impact of a vaccination for gonorrhoea. Here we have focused on the impact of a vaccine with MeNZB like properties. More work is needed on the impact of vaccines with different properties, on different baseline prevalence levels, and on different vaccination strategies, such as vaccinating both at screening and at diagnosis.

Chapter 6

Conclusions

In this report we investigate the impact of possible vaccinations for gonorrhoea using three different strategies for administering the vaccine. We use an equation based model with two different sexual activity classes to see the impact of vaccines with a wide variety of properties. To gain a deeper understanding of the impact of the MeNZB vaccine we use an individual based model. The individual based model allows us to see how many antibiotic doses we can avoid by through vaccination.

The equation based model shows that a vaccine with an efficacy higher than 20% that lasts at least 5 years, or an efficacy higher than 30% that lasts at least 3 years can eradicate gonorrhoea infection after 10 years if it is given at screening or at diagnosis. Eradicating a disease is a process that is difficult to represent in a deterministic equation based model, because stochastic effects are essential to understanding prevalence, especially when there is a very low level of infection [12]. The equation based model suggests that childhood vaccination will have a limited impact on prevalence. We record a drop in prevalence of less than 10% for a MeNZB vaccine given in childhood, due to the fact that after 10 years only a small proportion of the population will be protected, as there is only one opportunity for each individual to be vaccinated and the vaccine does not offer long-lasting protection. The equation based model does not have the required level of detail to accurately represent the world, so we do not expect to see truly representative results. However, this model does allow us to see a general picture of the impact of vaccination with a wide variety of parameter values.

Our individual model incorporates realistic treatment and screening pathways, as well as probable vaccination pathways. It provides a useful tool for studying the possible impact of vaccination on gonorrhoea. We us our individual model to explore a small number of different vaccinations with varying levels of efficacy in greater depth. We model the impact of vaccination with the parameters expected of the MeNZB vaccine, and then vary the efficacy of this vaccine to see how this parameter effects our results. We model vaccines with a duration of 3 years and efficacies of 31% (akin to the MeNZB vaccination), 62%, and 100%. We introduce these vaccines to two different scenarios, with different levels of prevalence: the first is the current expected prevalence — 2.4% — and the second is a much higher possible future prevalence — 6.7%.

Our most representative scenario, using current expected prevalence and a vaccination with the presumed efficacy and duration of the MeNZB vaccine, shows that we can reduce prevalence by 70% if we vaccinate at screening, 50% if vaccination occurs at diagnosis, and 40% if vaccination is offered in childhood. Vaccination at screening would lead to a 60% drop in the number of drug doses required to treat the infection over 10 years, reducing the risk of AMR strains developing over this period. This set of results is particularly important as it offers a realistic hope of significantly reducing the number of gonorrhoea infections in the near future, with a vaccine that is known to be safe.

Our subsequent results for theoretical vaccines and possible future levels of prevalence give us insight

into the results we may expect should more efficacious vaccines be developed, and/or prevalence was to significantly increase. From varying the efficacy of the vaccine and the initial prevalence when the vaccine is introduced we find that the impact of each strategy varies considerably. Modelling the impact of vaccination when prevalence is significantly higher than is currently predicted shows that vaccination at diagnosis can be a slightly more effective strategy than vaccination at screening. Vaccination at diagnosis can reduce prevalence by 38% compared to 32% for vaccination at screening when we use MeNZB. This shows us that for high initial prevalence vaccination at screening can be the most effective vaccine for bringing down prevalence. But we also see that it is not capable of reducing prevalence to zero, as the number of people protected is lower than when other strategies are used. We see that, for a vaccine that is completely protective against gonorrhoea, vaccination at diagnosis does not eradicate the infection, even though vaccination at screening is able to, because it does not lead to a sufficiently high proportion of the population being protected.

Vaccination at screening leads to a drop in endemic prevalence levels possibly leading to eradication, while vaccination on diagnosis precipitates a greater drop in cases per vaccine dose but, as its rate of vaccination is directly related to the rate of diagnosis we may not be able to eradicate the disease through this method. Vaccination in childhood also reduces prevalence but it is difficult to measure the exact impact without understanding the age distribution of the core group, and using a model where the age of individuals is considered.

Our key recommendations for future study are: that it is essential to collect figures for gonorrhoea incidence as accurately as possible, and that, to understand the broader implication of a gonorrhoea vaccine, we must investigate the impact such a vaccine could have on the incidence of other STIs, including HIV.

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Appendix A

Parameters for Equation Based Model

Param.	Meaning	Constant or initial value	Justification
I_i	Infected proportion of group i i.e. core (c) or non-core (n)	0.04	Selected, prevalence is robust to this value
S_i	Susceptible proportion of group i	0.96	As above
d	Number of days an infected person can transmit, same for both groups	25 days	[10]
b_i	Measures relative sexual activity in group i [10]	0.34 — core and 0.66 — non core	Based on k_i and population sizes.
k_i	The number of people a member of group i is expected to have a sexual encounter with during an infectious period	3.42 — core, 0.342 — non core	Based on figures from the Gay Men's Sex Survey 2014 [31]
λ	Birth rate	3×10^{-5}	[36]
μ	Death rate	3×10^{-5}	[36]
θ	Rate at which vaccine's protection is lost	1/1095	[14]
ρ	Proportion of adults who will accept a vaccine	0.45	MSM uptake of HPV vaccine [1]
P	Proportion of children vaccinated	0.85	Childrens' HPV vaccine uptake [1]
ζ	Take-type efficacy of vaccine	0.31	[4]
ϵ	Rate of attendance at sexual health clinics	1/365	PHE recommendation [1]

Table A.1: Parameters used in compartmental model and their values

Appendix B

Parameters for Individual Based Model

Param.	Meaning	Constant or initial value	Justification
β	Transmissability of infection	2.2×10^{-3}	Fitted [15]
μ	Population turnover	3×10^{-4}	[15]
R	Rate of recovery without treatment	6.8×10^{-3}	Fitted [15]
θ	Rate at which vaccine's protection is lost	1/1095	[14]
ρ	Proportion of adults who will accept a vaccine when it is offered	0.45	MSM uptake of HPV vaccine [1]
P	Proportion of children vaccinated	0.85	Children's HPV vaccine uptake [1]
ζ	Degree type efficacy of vaccine	0.31	[4]
γ	Rate of attendance at sexual health clinics clinics	1/400	Fitted [15]
k_{max}	Maximum number of partners	120	[18]
k_r	Maximum degree in each update	10	[15]
α	Power law slope	1.6	[18]

Table B.1: Essential parameters used in individual model and their values