Appendix A: Projections of the disease burden and effective vaccine coverage across diseases included in the current childhood vaccine programme in England

A.1 Outline

In this appendix we describe the methodology to project disease burden at different levels of effective coverage against vaccines included within the current (December 2016) childhood immunisation programme in the UK. This immunisation programme includes vaccination against twelve infectious diseases of childhood. To quantify the decline in disease burden with increased effective vaccine coverage, we aimed to use established mathematical models or build new ones. However, for some diseases no such models exist nor were feasible to be built within the timescale of this project. For these diseases, we collated and used available historic data to make our predictions. A summary of our methods (modelling or data) is given in Figure A1 and also Table S3.

A.2 Overview of mathematical models for transmission of and vaccination against infectious diseases

Transmission and spread of infectious diseases within a setting can be studied using a system of equations that tracks over time the number of individuals susceptible to infection (Susceptibles), those that are exposed to infection but are not infected (Pre-infectious/Exposed), individuals that are infected (Infected) and those that recover from the infection (Recovered). Such Susceptibles-Exposed-Infected-Recovered (SEIR) models have the following general structure

$$\frac{dS(t)}{dt} = bN(t) - \lambda S(t) - mS(t) \quad (1)$$

$$\frac{dE(t)}{dt} = \lambda S(t) - fE(t) - mE(t) \quad (2)$$

$$\frac{dI(t)}{dt} = fE(t) - rI(t) - mI(t) \quad (3)$$

$$\frac{dR(t)}{dt} = rI(t) - mR(t) \quad (4)$$

Here *S(t), E(t), I(t)* and *R(t)* represent the population that are susceptible to infection, exposed to infection but not infected, infected and recovered from infection at time t, *b* is per capita birth rate and m is per capita death rate, *N(t)* is the total population at time t so that $N(t) = S(t) + E(t) + I(t) + R(t)$, *f* is the rate at which individuals more from exposed to infected, calculated as 1/average pre-infectious (or exposed) period and *r* is the rate at which individuals recover from being infected, calculated as 1/infectious period. If the population remains unchanged over time, then the birth rate is the same as the mortality rate and calculated as 1/average life expectancy.

The force of infection $\lambda(t)$ describes the rate at which exposed individuals become infected and it depends on the number of infected individuals in the population (*I*), i.e.

$$\lambda = \beta C_E I \qquad (5)$$

where β is the probability of transmission of infection per contact between infected and susceptible individual and c_e is the number of contacts between infected and susceptible persons and, as before, I is the number of infected individuals.

When the transmission of infection among specific age or risk cohorts needs to be considered, the system of equations (1)-(5) is compartmentalised by age and risk group so that separate equations equivalent to (1)-(4) are formulated for different age and/or risk groups and transfer from one age cohort to the next is incorporated via an ageing term. The force of infection becomes age/risk specific with λ_i becoming a matrix with entries representing the infection between different age/risk groups. Social surveys may be used to describe the patterns of social contact $c_e$within and between different age/risk groups, whereas the transmission probability may be single value or have different age/risk group values, that are often fitted in the process of model calibration.

If the time of exposure to infection is short, the equation for the population of exposed individuals is omitted from the system with the SEIR model becoming an SIR model. In this case the force of infection term describes the transfer of susceptible rather than pre-exposed individuals to infected individuals.

Vaccination is accepted as one of the most effective ways of preventing transmission and spread of infectious diseases. Equations (1)-(5) can easily be adapted to include vaccination against the infectious disease considered and can be utilised to explore the impact of different vaccine strategies on transmission and spread of infectious disease. Vaccination can be incorporated in the model in two ways. Firstly, it can be incorporated by transfer at a rate *v* of susceptible individuals into immune *(R(t))* and hence the system (1)-(5) has a term $-vS(t)$ added to equation (1) and a term $v(S(t)$ to equation (4). Alternatively, vaccination can be incorporated by including a separate compartment accounting for vaccinated individuals *V(t)*:

$$\frac{dV(t)}{dt} = vS(t) - mV(t) \qquad (6)$$

Here the vaccination rate v represents the effective coverage against an infectious disease and is a product of the uptake level for the vaccine and the efficacy of the vaccine product used.

The vaccines we have considered in this work are those included in the childhood immunisation proramme in the UK as of December 2016. These vaccines, the diseases they cover against, the efficacy and references are summarised in Table S1.

Vaccine	Disease vaccinated against (efficacy used for modelling, %)	Source
Menjugate or NeisVac Primary (<1 year old)	Men C (99.4)	Electronic Medicines Compendium (EMC)
Menjugate or NeisVac Booster (>1 year old)	Men C (100)	EMC
Menitorix Primary (<1 year old)	Men C (99.3), Hib (100)	EMC
Menitorix Booster (>1 year old)	Men C (98 different primary, 100 otherwise), Hib (100)	EMC
MMR VAXPRO/Priorix after one dose (>1 year old)	Measles (90), Mumps (64),Rubella (99)	Green Book
MMR VAXPRO/Priorix after two doses (>1 year old)	Measles (99), Mumps (87),Rubella (99.9)	Green Book
Pediacel (<1 year old)	Tetanus (100), Polio (100),Diphtheria (99.2),Pertussis (98.7),Hib (91)	EMC
Pediacel (>1 year old)	Tetanus (100), Polio (100),Diphtheria (99.1),Pertussis (96.7),Hib (99.1)	EMC
Prevenar 13 (both doses)	Pneumococcal (94.8)	EMC
Repevax or Infanrix IPV (>3 years old)	Tetanus (100), Polio (100), Diphtheria (100),Pertussis (99.6)	EMC
Rotarix (<1 year old)	Rotavirus (91.8)	EMC
HBVaxPRO (both doses)	Hep B (96)	EMC
Infanrix Hexa (<1 year old)	Tetanus (100), Polio (100), Diphtheria (100),Pertussis (100), Hib (96.4), Hep B (99.5)	European Medicines Agency
Infanrix Hexa (>1 year old	Tetanus (99.9), Polio (99.9), Diphtheria (99.9),Pertussis (99.9), Hib (99.7), Hep B (98.4)	European Medicines Agency
Bexsero	Men B (83.6)	EMC

Table S1: A summary of vaccines considered in this work, the disease they vaccinate against and the efficacies used in the modelling references. This is reproduced with permission from Crowe S et al.. BMC Infect Dis. (2015) 15:585. doi: 10.1186/s12879-015-1299-8

A.2.1 Model parametrisation, calibration and projections

In order for the model describing the transmission of and vaccination against an infectious disease to be specific disease, it needs to be parametrised to available epidemiological and biological data for that disease and also within the setting considered. The parametrised model is then used to project outcomes such as the number of invasive or clinical disease cases, deaths or hospitalisations due to the disease. The model is validated/calibrated by comparing these model projected outcomes with available historic data. The calibrated model has a parameter set for which the model and the date best match, and the calibrated model is then used to explore how diseases' burden changes under different vaccination strategies (e.g. vaccinating all susceptible individuals in contrast to vaccinating a specific age or risk cohort).

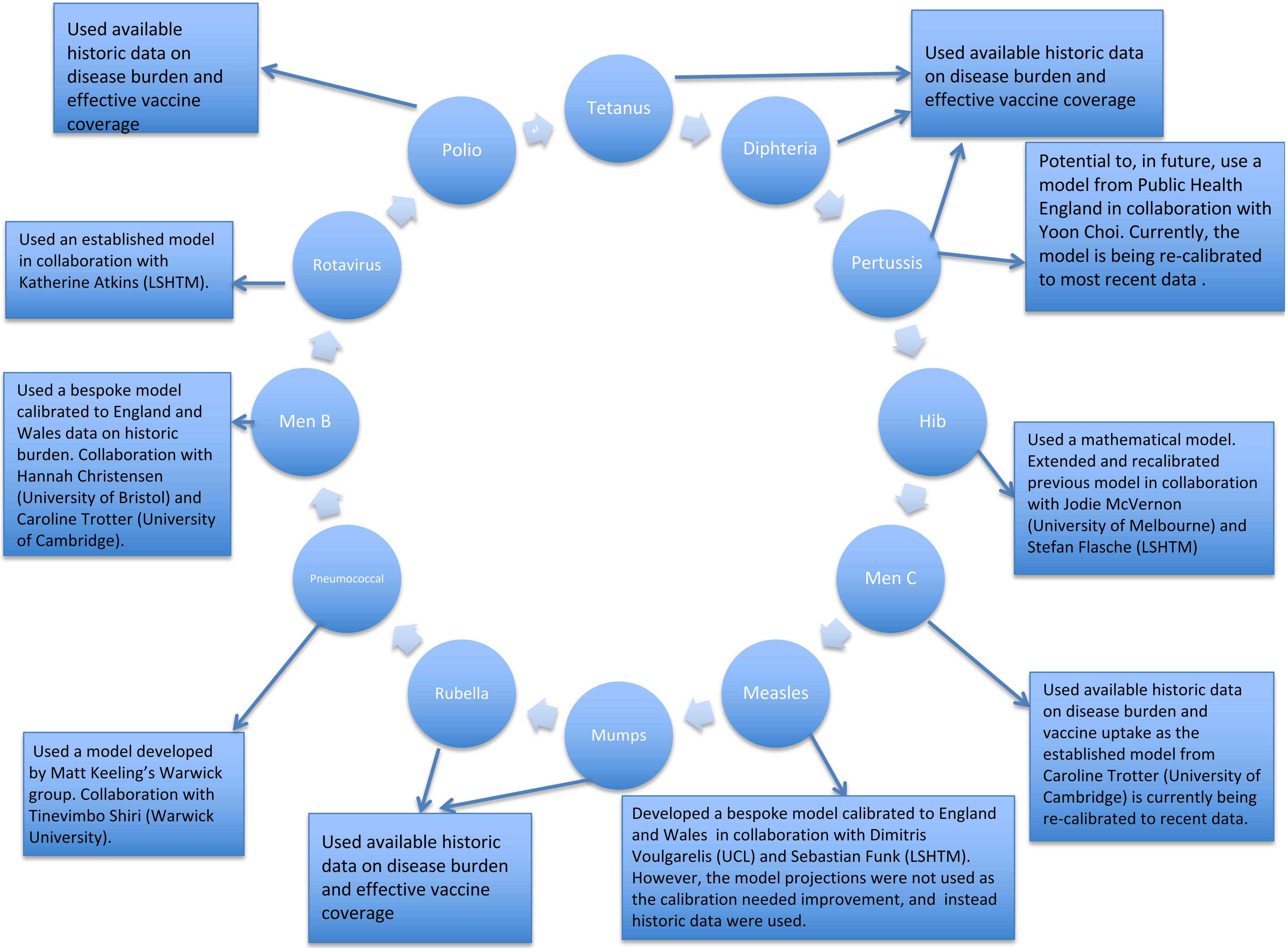
For different infectious disease, the force of infection, the period of infectiousness and the rate of disease recovery will be different. Therefore, whilst the mathematical structure of the model (1)-(6) may remain the same across different diseases considered, the model parameters that calibrate the model will be different and the projected outcomes will be disease and scenario specific.

A.2.2 Outcomes across different diseases

Our initial aim in undertaking this work was to develop relevant transmission model for each infectious disease included in the current routine childhood vaccine schedule in the UK: Polio, Diphtheria, Tetanus, Pertussis, Haemophilus influenzae B (Hib), Rotavirus, Measles, Mumps, Rubella, Pneumococcal disease (Pneumococcal), Neisseria Meningitides Group C (Men C) and Meningitides Group B (Men B).

For some of these diseases, modelling groups within Public Health England (PHE) and across different university in the UK already undertake extensive modelling analysis for individual diseases (as outlined in Figure S1). These models (for pertussis, Hib, rotavirus, measles, pneumococcal, Men C and Men B) have SEIR/SIR structure and stratified into different age and/or risk groups, are parametrised for England or England and Wales and calibrated against available historic data for each disease. The calibrated models are then used to evaluate different vaccination strategies. For the purpose of this work, and in collaboration with the relevant experts who develop and use these models, where possible we applied the available validated models to England to project the relevant burden for that diseases as the annual number of disease cases across all age groups at different levels of effective coverage against the relevant disease over the first 5 years of life. For some of the diseases (Men C and pertussis) the available models are currently reassessed and re-calibrated against the more recent data and as such these models were not available for us to use within the timescale of this project. In this case, in agreement with the experts, we used the available historic data, and regression models, to make our disease burden and effective vaccine coverage projections. For some diseases, we needed to extend existing models to account for recent vaccine changes that have not been incorporated in the previous models (e.g. Hib) or develop a new model (e.g. measles). For some of the diseases for which vaccine uptake in England is high and the diseases are currently near elimination (polio, diphtheria, tetanus, rubella) the burden is already very low. As a consequence, no modelling work is currently ongoing nor is necessary to explore different optimal strategies to reduce burden. For the purpose of this work, for these diseases we used publicly available data, and regression models, to quantify disease burden at different levels of effective vaccine coverage.

In Figure A1 we highlight the key modelling experts for each of the 12 diseases included in the current routine childhood vaccination programme in the UK and we indicate the approach (model or data synthesis) that we utilised to quantify disease burden. In the sections A.4-A.14, we then give more details on specific methodology we used and the projections we obtained.



Used available historic data on disease burden and effective vaccine coverage

Potential to, in future, use a model from Public Health England in collaboration with Yoon Choi. Currently, the model is being re-calibrated to most recent data .

Used a mathematical model. Extended and recalibrated previous model in collaboration with Jodie McVernon (University of Melbourne) and Stefan Flasche (LSHTM)

Used available historic data on disease burden and vaccine uptake as the established model from Caroline Trotter (University of Cambridge) is currently being re-calibrated to recent data.

Developed a bespoke model calibrated to England and Wales in collaboration with Dimitris Voulgarelis (UCL) and Sebastian Funk (LSHTM). However, the model projections were not used as the calibration needed improvement, and instead historic data were used.

Used available historic data on disease burden and effective vaccine coverage

Used a model developed by Matt Keeling's Warwick group. Collaboration with Tinevimbo Shiri (Warwick University).

Used a bespoke model calibrated to England and Wales data on historic burden. Collaboration with Hannah Christensen (University of Bristol) and Caroline Trotter (University of Cambridge).

Used an established model in collaboration with Katherine Atkins (LSHTM).

Used available historic data on disease burden and effective vaccine coverage

Figure A1: Schematic of the methodology (model or historic data) used to quantify disease burden at different levels of effective coverage over the first 5 years of life against the twelve diseases included in the current immunisation programme in the UK. For each disease we list the collaborating groups we have worked with and the lead modellers within each group and we highlight whether we used model or data synthesis for our projections.

A.3 Calculating the time-averaged effective vaccine coverage

A.3.1 Effective vaccine coverage

With the current immunisation programme in the UK, protection is given against twelve infectious diseases, with associated vaccines administered at different times over the first 5 years of life (see Table 1 in the main text). Data from the Cover of vaccination evaluated rapidly (COVER) programme (https://www.gov.uk/government/statistics/cover-of-vaccination-evaluated-rapidly-cover-programme-2015-to-2016-quarterly-data) reports the uptake levels for different vaccines at 12, 24 and/or 60 months and the Electronic Medicines Compendium (EMC) (https://www.medicines.org.uk/emc/) reports the efficacy of the vaccine product against associated diseases in different age cohorts (as per Table S1). Combining these we can calculate, at a time point, the effective vaccine coverage against each disease as a product of vaccine uptake level and efficacy of the vaccine product used. This effective vaccine coverage varies over the first 5 years of life depending on when the vaccine is administered and what its' efficacy is in that age cohort.

Mathematical models, including the SEIR/SIR models described in section A.2, tend to apply a single level of effective coverage to the 0-5 years old.

A.3.2 Disease burden

The burden of infectious diseases for England and Wales is reported either annually or per quarter of the year as the number of disease cases (either notifications or laboratory confirmed) as collected by Public Health England (https://www.gov.uk/government/collections/notifications-of-infectious-diseases-noids).

As mentioned in section A.2, models for transmission of infectious disease are calibrated against such historic data and can then be used to quantify the impact of immunisation by, for example, projecting future disease burden for different levels of effective vaccine coverage.

A.3.3 Relating effective vaccine coverage against a disease with disease burden

In this work, we want to understand the relationship between disease burden and effective vaccine coverage over the first 5 years of life across all 12 disease included in the current immunisation programme in the UK. To do this, as per Figure A1, we use either validated mathematical model projections or synthesised historic data to determine a relationship between effective vaccine coverage (EC) against the infectious disease over the first 5 years of life and the associated disease burden in all ages.

If we use a mathematical model, we calculate the annual number of disease cases in all ages for different levels of effective coverage to the 0-5 years old and determine an average over 10 years post vaccination start.

If we use historic data, then for each reported year we need to choose an appropriate time point at which to link the product of reported vaccine uptake and efficacy with disease notifications for the disease in question. This can be the time point when primary (e.g. 12 or 24 months) or booster (e.g. 40 months) vaccine doses are completed, but these can differ across different vaccines. To keep consistency and uniformity across the twelve diseases in the current UK childhood immunisation programme, instead of calculated the effective vaccine coverage at one time point in a year, we calculated the time-averaged effective vaccine coverage against each disease over the first 5 years of life for that year (see section A.3.4). We then linked this to the associated disease burden value quantified by the annual number of disease cases across all ages for that year.

A.3.4 Calculating time-averaged effective vaccine coverage against a disease

To illustrate how we calculate this, let’s consider a disease A that has a primary vaccine administered at time T_1(<12 months) and a booster vaccine given at T_2 (>12 months). Let’s assume the uptake level for this vaccine is reported at the completion of the primary dose (>T_1months) to be $c_1$and the uptake at completion of booster dose (>T_2 months) is reported to be c_2. This means that the uptake of the vaccine against disease A is $c_1$for the time period (T_1, T_2) months and it is c_2 for the time period $(T_2, 60)$ months.

The efficacy of different vaccine products is related to the strength of the immune response and it is often reported for two age cohorts (e.g. up to 1 year old and over 1 year old). For the purpose of this work we will assume that the efficacy of the vaccine product used against disease A is e_1 for the time from primary to booster vaccination i.e. (T_1, T_2) and it is e_2 after administration of the booster vaccine i.e. for $(T_2, 60)$.

Then the effective coverage (EC) against disease A is $e_1 * c_1$for the time period (T_1, T_2) months and it is $e_2 * c_2$ for the time period $(T_2, 60)$ months. Then the time-averaged effective coverage against disease A over the first 5 years of life is then calculated as:

$$TA_{EC_A} = \frac{T_1}{60} \times 0 \times e_1 + \frac{T_2 - T_1}{60} \times c_1 \times e_1 + \frac{60 - T_2}{60} \times c_2 \times e_2 \qquad (7)$$

Using this formula we calculated the annual time-averaged effective vaccine coverage (henceforth effective vaccine coverage) for different years and across different infectious diseases using the reported uptake values for England (https://www.gov.uk/government/collections/vaccine-uptake). This allowed us to derive a single value for the effective vaccine coverage per year per disease across the twelve infectious diseases we considered.

A.4 Projection for Poliomyelitis

Poliomyelitis (polio) is an acute illness that follows invasion through the gastrointestinal tract by one of the three (1,2 and 3) serotypes of polio virus [1]. The virus then replicates in the gut and spreads via the bloodstream to susceptible tissues or to the central nervous system. Since infection is clinically not apparent and symptoms are very variable (ranging from fever or paralysis), polio is often difficult to diagnose [1]. Prior to routine vaccination against polio, in the 1950s there was a polio epidemic with as many as 8,000 annual polio infections reported in England and Wales [1,2].

Routine vaccination with inactivated polio vaccine (IPV-Salk) [1] started in the UK in 1956. In 1962 this vaccine was replaced with a live attenuated oral polio vaccine (OPV-Sabin) [1], and in 2004, this was replaced with a combined 5-in-1vaccine which in addition to containing inactive polio product also has vaccine products against tetanus, diphtheria, pertussis (whooping cough) and Hib. As part of the primary childhood immunisation schedule in the UK, this 5-in-1 vaccine is given at 2,3 and 4 months as two alternative products: Pediacel or Infanrix. In addition, a preschool booster vaccine against polio is also given as a combined 4-in-1 product protecting in addition against diphtheria, tetanus and pertussis and given at 40 months as two alternative products: Infranrix or Repevax.

Vaccination against polio is reported to be highly effective with results from several randomised controlled trials showing that 96-100% of infants given the polio vaccine at two, three and four months of age develop protective levels of antibodies against polio [1]. Furthermore, the Electronic Medicines Compendium (EMC) reports a value of 100% efficacy for all polio vaccine products in all age cohorts ([7] and as per Table S1).

The uptake level of polio vaccination in England and Wales (1966-1977) and England (1978-2012) at completion of the primary course (at 24 months) is reported in [4] whereas the levels of polio vaccine coverage at 12, 24 and 60 months for the years 2004/05-2015/16 are reported in [5,6]. Combining these uptake levels with the efficacy levels of vaccination against polio, we used the method in section A.3.4 to calculate the time-averaged effective coverage over the first 5 years for each year 1966-2015.We plot this in Figure A2(a) (dashed line)

As a result of the routine vaccination against polio, the number of polio infections in England fell rapidly (from 7,054 in 1950 to 4 in 1973 [2]-rescaled to England only). In the UK, the last polio outbreak occurred in late 1970s, whereas the last case of a natural polio infection acquired in the UK was in 1984 [1]. The annual polio notifications for England and Wales across all age groups are available separately for the period 1912-1981 and 1982-2014 [2]. Using the most recent population sizes for England and Wales versus England only from the Office of National Statistics (https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates) we rescale these notifications for England only and plot over the period 1966-2014 line in Figure A2(a) (full line).

Since routine vaccination against polio has been very effective in dramatically reducing and almost eliminating the burden of polio, there has been no need for mathematical modelling of different vaccination strategies. Therefore, to determine a relationship between polio burden and effective vaccine coverage against polio we link the data from Figure A2(a), together with a constraint that pre-vaccination levels of polio are 4,427 for England (calculated as a 10-year pre-vaccination average number from [2] and rescaled to England only) and assuming that at 100% effective coverage polio will be eliminated. We use the Curve Fitting Toolbox in MATLAB to determine the best-fit ($R^2 = 1$) curve as an exponential function $y = 4025e^{-0.08594x}$ and project the polio burden at different levels of EC in Figure A2(b) as the black, solid curve. We understand that due to lack of effective coverage values below the 70% value, there are uncertainties around fitting the correct decreasing function in this region [0%,70%] effective coverage in Figure A2(b) and various different curves might equally well fit the historic data points. However, these curves would all fit the dataset in the range [70%,100%] effective coverage almost identically as the exponential function we have used, and we arbitrarily chose to use this exponential fit.

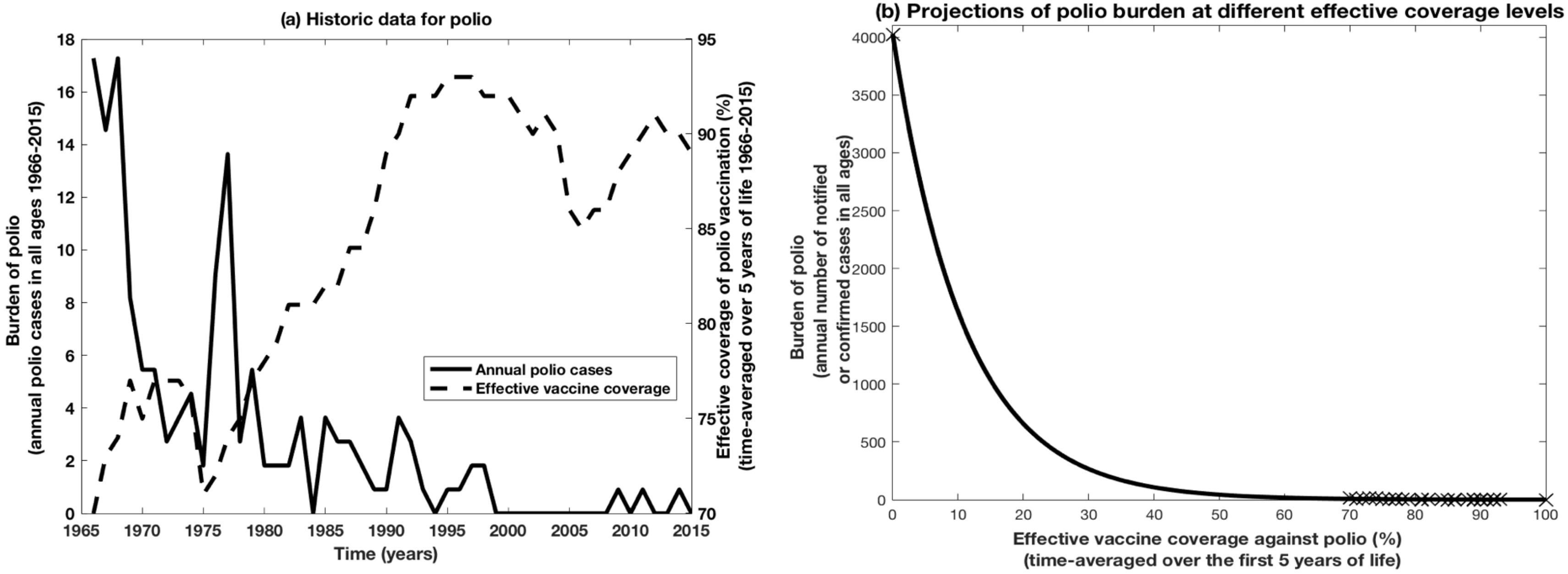


Figure A2(a)-(b). (a) Projections of polio burden (full line) and calculated time-averaged over first 5 years of life polio effective vaccine coverage (dashed line) for the period 1966-2015 for England using publicly available data. (b) Relationship between historic polio burden and effective vaccine coverage. The historic data (‘x’) from (a) are fitted to an exponential function ($f(x) = 4025 * e^{-0.08594*x}$with $R^2 = 1$ using the Curve Fitting Toolbox in MATLAB.

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A.5 Diphtheria

Diphtheria is an acute infectious disease caused by infection with toxigenic bacterium Corynebacterium diphtheriae or Corynebacterium ulcerans and often spread by coughing of an infected person [1]. Prior to vaccination against diphtheria, in the 1940s, diphtheria was a common disease: in 1940 there were more than 61,000 notified diphtheria cases and 3,283 notified deaths in England and Wales [1,2].

Vaccination against diphtheria in the UK started in 1948 with a combined 3-in-1 vaccine protecting against diphtheria, tetanus and pertussis [1]. In 1996 this was extended to a 4-in-1 vaccine by including protection against Hib [1,2]. Since 2004 this vaccine also includes immunisation against polio, with the combined 5-in-1 vaccine available as two alternative products: Pediacel or Infanrix. The primary immunisation course is administered at 2,3 and 4 months of age. In addition, a pre-school booster is also given at 40 months old as a 4-in-1 (diphtheria, tetanus, pertussis and Hib) vaccine and as an alternative product: Infranrix or Repevax. The efficacy of the historic 3-in-1 and 4-in-1 vaccine against diphtheria has been shown to be similar, with studies suggesting that both vaccines had 100% of infants develop protective bodies against diphtheria [3]. The efficacy of the 5-in-1 vaccine products against diphtheria are age dependent and available from the Electronic Medicines Compendium (EMC) [4] and summarized in Table S1.

The historic level of diphtheria vaccination uptake is reported at completion of primary course (24 months) for period 1966-2012 in [5], with more recent (since 2004) uptake levels at 24 months and 60 months, reported in [6,7]. Combining these uptake levels with the efficacy of the vaccines used, and using the method from section A.3.4 we calculate the annual time-averaged effective coverage against diphtheria for children under 5 years old in the period 1966-2015 and plot it as a dashed line in Figure A3(a).

Implementing a routine national immunisation against diphtheria dramatically reduced the number of toxigenic cases and deaths from the disease: in 1940, more than 61,000 cases with 3,283 deaths were notified in England and Wales, compared with 38 cases and six deaths in 1957, and only 4 deaths over the last twenty years with all occurring in unvaccinated individuals [2,8]. Nowadays the burden of diphtheria is low: in the period 1986-2014 there were only 200 cases of toxigenic diphtheria and two deaths in England and Wales [1,8]. As a consequence, there isn't an ongoing modelling work on diphtheria vaccination. Following discussion with diphtheria experts, we have decided to refer to historic data to relate effective vaccine coverage with diphtheria burden. However, we note that although the current burden of diphtheria is negligible, continual vaccination as part of the childhood vaccination schedule is necessary since in the last two years two unvaccinated children have died of diphtheria in Europe (one in Spain in 2015 [9], and one in Belgium in March 2016 [10]).

The historic burden of diphtheria in England and Wales is reported as annual notifications until 1985 and as laboratory confirmed cases since 1986 across all age cohorts [8]. Using the most recent population sizes for England and Wales versus England only from the Office of National Statistics (https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates) we rescale the historic number of diphtheria cases for England only and plot these for the period 1966-2015 line in Figure A3(a) (solid line). In Figure A3(b) ('x') we combine the data from Figure A3(a) to plot the historic diphtheria burden in all ages against different levels of time-averaged effective coverage against diphtheria in children under 5 years old. To quantify the pre-vaccination burden of diphtheria we calculated the number of diphtheria notifications in the 10 year-period before vaccination started from [8], scaled to England only (36,839 notifications). Using this as a constraint at 0% effective coverage and assuming that at 100% effective coverage diphtheria it will be eliminated, we use the Curve Fitting Toolbox in MATLAB to determine the best-fit ($R^2 = 1$) curve as the exponential function $y = 3.986e^{-1.482x}$ (solid curve in Figure A3(b)). We understand that due to lack of effective coverage values below the 70% value, there are uncertainties around fitting the correct decreasing function in this region [0%,70%] effective coverage in Figure A2(b) and various different curves might equally well fit the historic data points. However, these curves would all fit the dataset in the range [70%,100%] effective coverage almost identically as the exponential function we have used, and we arbitrarily chose to use the exponential fit.

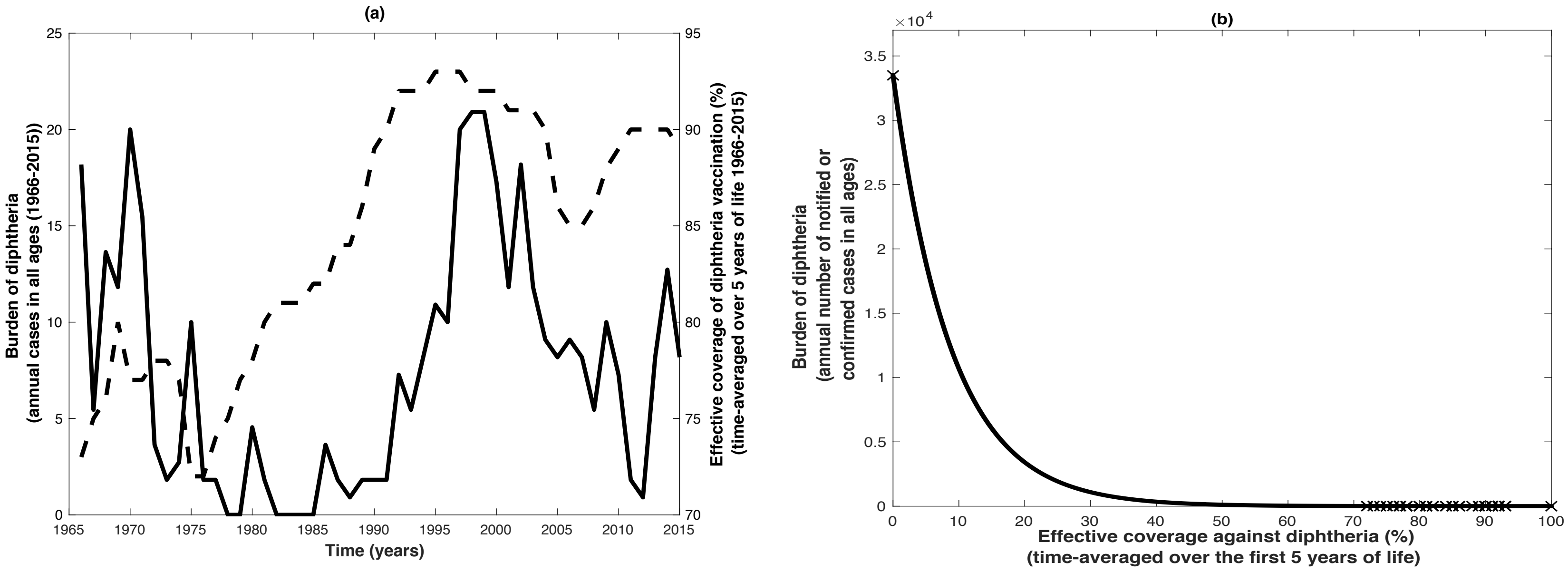

Figure A3(a)-(b). (a) Projections of the historic burden of diphtheria (solid line) and the time-averaged effective vaccine coverage against diphtheria in 0-5 years old (dashed line) over the period 1966-2015 using historic data [6]-[8]. (b) Projection of the relationship between diphtheria burden and effective vaccine coverage in children under 5 years old for England using the data from (a) (‘x’). The data is fitted to an exponential function as the best-fit curve (with $R^2 = 1$) sing the Curve Fitting Toolbox in MATLAB.

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   http://ecdc.europa.eu/en/publications/Publications/diphtheria-spain-rapid-risk-assessment-june-2015.pdf

10. Report on diphtheria case in Belgium March 2016 http://ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?List=4f55ad51-4aed-4d32-b960-af70113dbb90&ID=1458

A.6 Tetanus

Tetanus is an acute disease caused by the action of tetanus toxin, released following infection by the bacterium Clostridium tetani [1]. Tetanus spores are present in soil or manure and may be introduced into the body through a puncture wound, burn or scratch and this often may go unnoticed for a long time. The tetanus bacteria grow anaerobically at the site of the injury and have an incubation period of between four and 21 days [1].

Prior to introduction of a routine vaccination against tetanus, the burden of this disease was large with reported around 200 annual deaths due to tetanus in England and Wales. The number of notified cases in England are only available since 1969, but the USA Centre for Disease Control (CDC) reports that the death-to-case ratio is 10% [2] suggesting that pre-vaccination level was about 1800 annual tetanus cases in England and Wales.

Routine vaccination against tetanus was introduced in 1961 as a combined 3-in-1 vaccine against diphtheria, tetanus and pertussis [1,3]. In 1996, this was extended to a 4-in-1vaccine to also include protection against Hib, and since 2004 tetanus vaccination is part of the combined 5-in-1 vaccine protecting against diphtheria, pertussis, polio and Hib and administered at 2,3 and 4 months of age. In addition, since 2004, a pre-school 4-in-1 booster-vaccine protecting against diphtheria, tetanus, pertussis and polio is also given at 40 months. The efficacy of the vaccination against tetanus is reportedly very high ([4] and as per Table S1).

The historic level of tetanus vaccination uptake is reported at completion of primary course (24 months) for period 1966-2012 in [5], with more recent (since 2004) uptake levels reported at 24 months and 60 months [6,7]. Combining these uptake levels with assumed 100% efficacy of the vaccines used [4], we use the method from section A.3.4 to calculate the annual time-averaged effective coverage against tetanus in children under 5 years old in the period 1966-2015. We plot this as a dashed line in Figure A4(a).

The implementation of routine vaccination against tetanus has almost diminished tetanus in the UK and hence there has not been a need to employ mathematical modelling work for tetanus vaccination. Following discussion with experts, we decided to use the historic projections and collated the number of notified tetanus cases across all ages available annually for the period 1969-2015 [8,9] and plot this data in Figure A4(a) (solid curve).

In Figure A4(b) ('x') we combined the data from Figure A4(a) to plot the historic tetanus burden in all ages at different levels of time-averaged effective coverage against tetanus in children under 5 years old. The burden of tetanus in the pre-vaccination era was estimated assuming 10% death-to-case ratio from [3] and using the estimation of around 1800 annual cases of tetanus in England and Wales (or 1655 when rescaled to England only) from [2]. We used this as a constraint at 0% effective coverage and assumed that at 100% effective coverage tetanus will be eliminated. Using the Curve Fitting Toolbox in MATLAB we determined the best-fit curve to this data (with $R^2 = 0.998$) to be the exponential function $y = 1655e^{-0.06146x}$ (solid curve in Figure A4(b)). We note that due to lack of effective coverage values below the 70% value, there are uncertainties around fitting the correct decreasing function in this region [0%,70%] effective coverage in Figure A2(b) and various different curves might equally well fit the historic data points. However, these curves would all fit the dataset in the range [70%,100%] effective coverage almost identically as the exponential function we have used, and we arbitrarily chose to use the exponential fit.

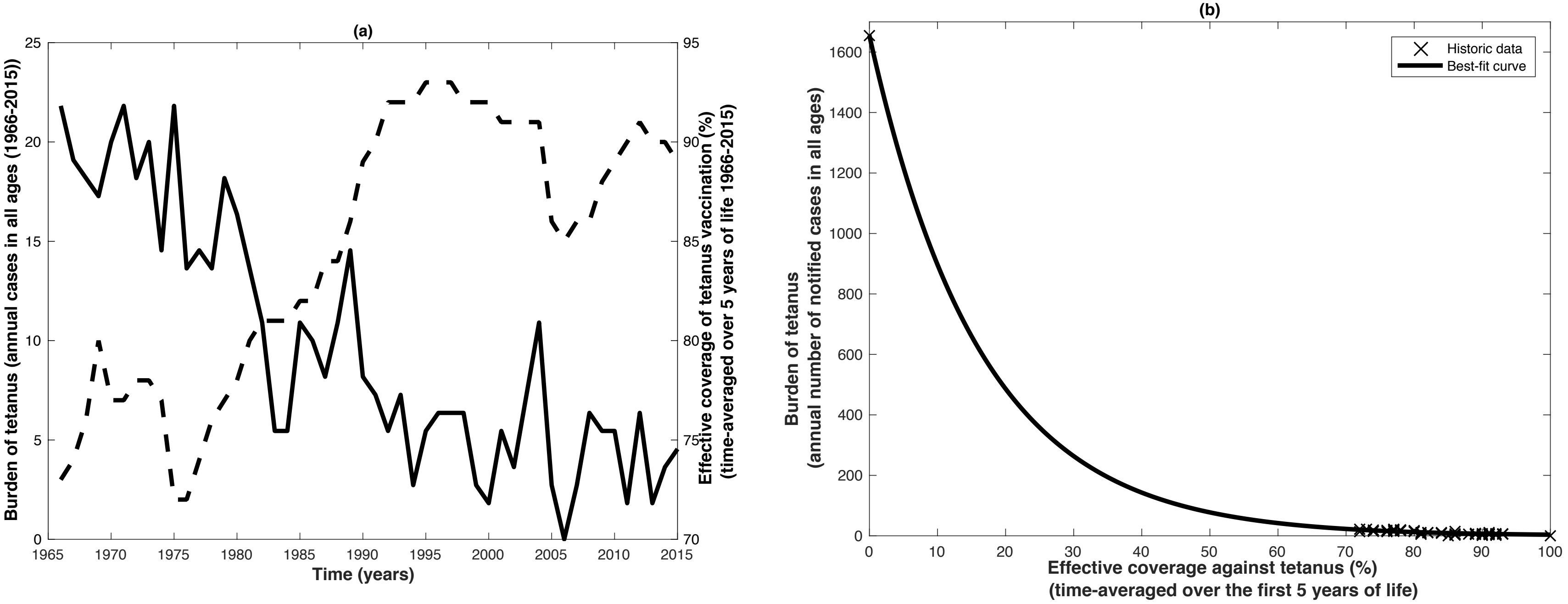

Figure A4(a)-(b). (a) Projections of the historic (1965-2015) burden of tetanus (solid line) and historic level of effective vaccine coverage against tetanus (1966-2015) (dashed line) using the publicly available data [5]-[9]. (b) Combining the historic data from (a) and subject to constraints at 0% (1655 tetanus cases) and 100% (0 tetanus cases) effective coverage levels, we fit the data from (a) (as 'x') to an exponential function as the best fit curve (with $R^2 = 0.998$) using the Curve fitting toolbox in MATLAB.

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A.7 Pertussis

Whooping cough (pertussis) is a highly infectious disease that is usually caused by Bordetella pertussis bacteria [1]. Although England and Wales have experienced an extended period of high vaccine coverage and as a consequence disease incidence has fallen dramatically, pertussis remains the most common vaccine-preventable cause of hospitalisation and death in infants [2]. Prior to introduction of immunisation against pertussis there were around 100,000 annual pertussis cases in England and Wales [1,3].

Routine vaccination against pertussis started in 1957 with a whole-cell pertussis (wP) vaccine from 3 months of age. This dramatically reduced the annual pertussis cases with reported 2,069 notifications in 1972, when vaccine coverage was around 80% [3]. Public anxiety about the safety and efficacy of the wP vaccine reduced the level of this vaccine uptake in the 1970s and 1980s with reported vaccine uptake falling to around 30%

by 1978. As a consequence, pertussis resurged and there were two major pertussis epidemics the UK in 1977–79 and 1981–83 characterised with around 65,000 pertussis notifications and 12 deaths [3]. To deal with the anxiety surrounding the wP vaccine and an increasing pertussis burden, but also to accommodate the change of oral to inactivated polio vaccine that could only be combined with acellular pertussis component, in 2004 an acellular pertussis (aP) vaccine was introduced made from highly purified selected components of the Bordetella pertussis organism. The reported incidence of local and systemic reactions is lower with aP vaccines than with the wP vaccine [4-6].

Currently the aP vaccine in the UK is part of the combined 5-in-1 primary vaccine administered at 2,3 and 4 months of age and the pre-school 4-in-1 booster vaccine given at 40 months. Historical levels of uptake of the vaccine against pertussis at 2 years old (i.e. at completion of the primary course) are reported annually for the period 1966-2015 in [7]. In [8] the uptake levels for both the primary wP (1957-2003) and aP (2004-2015) vaccines as well as the aP booster vaccine are also reported. The efficacy of protection against pertussis is different for the wP and the aP vaccines. For the wP vaccine 87% efficacy against pertussis infections was reported in [9] over the epidemic periods (1977-79, 1981-83) and 93% efficacy in non-epidemic periods (1968-2004 apart from the 1977-79, 1981-83). Within the mathematical model in [8], this protection against pertussis was varied in the fitting process. To be within the 5% of the best-fit model projection, protection of 80% for the wP vaccine was suggested, whereas the protection for the aP vaccine varied between 50-90% (Figure 4 in [8]). In other studies, the efficacy of the aP vaccine was suggested to be higher and between 92-95% across different settings: Sweden [10,11], Denmark [12,13] or USA [14]. Finally, the efficacy reported by Electronic Medicines Compendium (EMC) in [15] and previously used in our work (Table 4 in [16]) was 96.7% for the aP vaccine (using Pediacel product which has been solely used from 2004 until June 2014 in England and Wales). Taking in account all of these pertussis vaccine efficacy values we have decided to use the 87% efficacy from [8] for the wP vaccine and the 96.7% efficacy from [15,16] for the aP vaccine. Combining these efficacy values with the reported annual values of vaccine uptake, we use the method from section A3.4 to calculate the time-averaged effective coverage of vaccination against pertussis in children under 5 years old for the period 1966-2015. We plot these in Figure A5(a) – dashed curve.

Yearly notified number of pertussis cases in all ages for the period 1954-2015 are available in the Appendix of [8] and can be used as a proxy for pertussis burden. We plot these for the period 1966-2015 in Figure A5(a)- solid curve.

To correlate the burden of pertussis with the effective coverage against pertussis, we can combine these historic data or implement a mathematical model for pertussis transmission and vaccination such as the model in [8]. At the time of undertaking this work, the lead modeler Yoon Choi was still developing the model and calibrating it to the latest available data for England and Wales (Y.Choi, personal communication). Therefore, the model was not in a state to be readily used within the timeline of our study. There is a potential that this model may be used in future, but for the purposes of this paper, and on advise of Y.Choi, we decided to use historic data on pertussis burden in all ages and the time-averaged effective coverage against pertussis in the first 5 years of life. We plot the pertussis burden against the effective coverage against pertussis in Figure A4(b)(as 'x'). Using constraints for the pre-vaccination level: as an average of the yearly notifications over the three years before the vaccination started (92,467 cases and as per [8] and rescalled to England population – 81,430 cases) and assuming that at 100% effective coverage pertussis will be eliminated, we used the Curve Fitting Toolbox in MATLAB to fit a Gaussian function $f(x) = 22250e^{\left(-\left(\frac{x+6.901}{3.552}\right)^2\right)}$ to this data (Figure A5(b)) ($R^2 = 0.9433$), giving us a relationship between pertussis burden and effective coverage against pertussis.

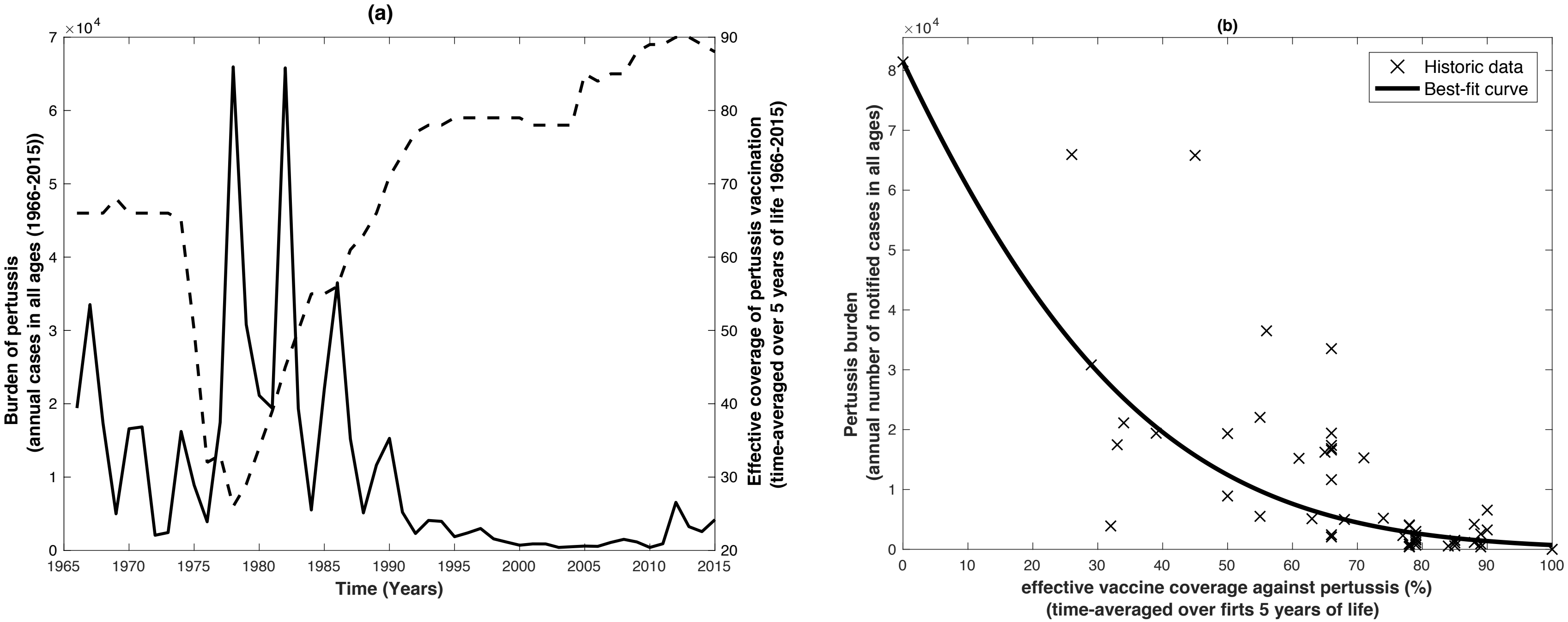

Figure A5(a)-(b). (a) Historic projections for the annual pertussis notifications in all ages (solid black line) and effective vaccine coverage levels of the vaccine against pertussis (including both wP and aP vaccine- dashed line) over the period 1965-2015 using publicly available data from [7]-[9] . (b) Projections of pertussis burden at different levels of effective vaccine coverage using the data from (a) (plotted as ‘x’) are fitted to a Gaussian function (solid black line) with $R^2 = 0.9433$ using the Curve Fitting Toolbox in MATLAB.

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A.8 Haemophilus influenzae Type B (Hib)

Haemophilus influenza type B is a bacterial invasive illness that affects the brain and may lead to meningitis, bloodstream infections, pneumonia and other serious diseases [1]. Hib is spread through coughing, sneezing or close contact with an infected person. In England and Wales Hib cases are identified by Public Health England through laboratory reports of confirmed disease infections. Before the introduction of routine immunisation against Hib in England and Wales, the estimated annual incidence of invasive Hib disease was 34 per 100,000 children under five years of age, about four in every 100 pre-school children carried the Hib organism and one in every 600 children developed some form of invasive Hib disease before their fifth birthday [2,3]. Vaccines against Hib were first produced in the early 1970s containing purified capsular polysaccharide. These vaccines were effective in children over 18 months of age, but failed to protect younger children, in whom the risk of disease was highest [4]. Introduction and usage of conjugate Hib vaccines overcame this problem and in 1992, Hib conjugate vaccine was introduced into the routine UK immunisation schedule [4]. In 1996, the single Hib vaccine was incorporated in a combined 4-in-1 vaccine also protecting against diphtheria, tetanus and pertussis and since 2004, this was extended to a combined 5-in-1 vaccine which additionally protects against polio and is part of the routine childhood immunisation programme given at 2,3 and 4 months of age [1]. An additional booster vaccine with combined protections against Hib and Men C was introduced into the routine childhood immunisation programme in 2006 and is given at 12 months of age.

The routine use of vaccines to protect against Hib since 1992 has dramatically reduced the incidence of Hib, with disease incidence falling almost four-folds [1-3]: in 2014 there were only 12 reported cases of invasive Hib across all ages in England and Wales compared with respective 849 cases in 1992 [8]. The historic number of laboratory confirmed cases of invasive Hib infections across all ages are publicly available in [8] for the period 1990-2014 and we plot these in Figure A6(a) (solid line).

The historic levels of uptake of the Hib vaccine at 2 years old (i.e. at completion of the primary course) are also publically available [9] and suggest that after the initial year low (75%) vaccine uptake, since 1991 the uptake level of Hib vaccination has been high and at least 91%. The efficacy and safety of the conjugate Hib vaccines have been demonstrated in large field trials in Finland, the United States and England and Wales, where efficacy ranged from 83 to 100% [5,10-12]. In addition, studies comparing different vaccines, used in the current UK primary schedule, have shown that 90 to 99% of children developed protective levels of antibodies following three doses of vaccine [5]. In our previous study, we used the efficacy values of 99.1% (Pediacel) or 99.7% (Infranrix Hexa) as per Table S1. Taking an average of these two values, we assume the efficacy levels against Hib infection to be 99.5%, and use the reported uptake levels at 2 years and at 60 months to calculate the time-averaged effective coverage against Hib for the period 1993-2014 using the method from section A3.4. This is plotted it in Figure A6(a) (dashed line).

Combining the data from Figure A6(a), and using two constraints: at 0% effective coverage 849 reported Hib cases across all ages pre-vaccination (in 1991) [8] and at 100% effective coverage we assume Hib will be eliminated. Using the Curve Fitting Toolbox in MATLAB we determine a best-fit decreasing curve to the data ‘x’ to be the exponential function $y = 101.5e^{-0.4764x}$ with $R^2 = 0.8461$ (Figure A6(b) solid line).

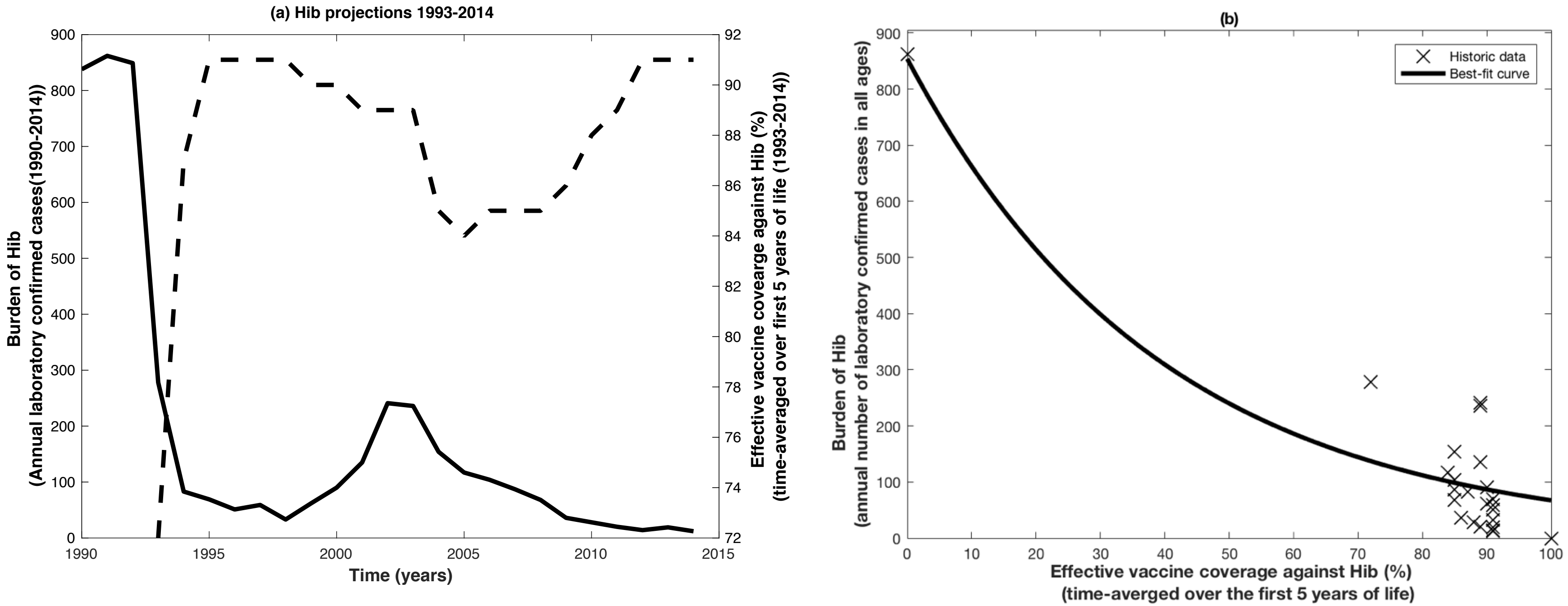


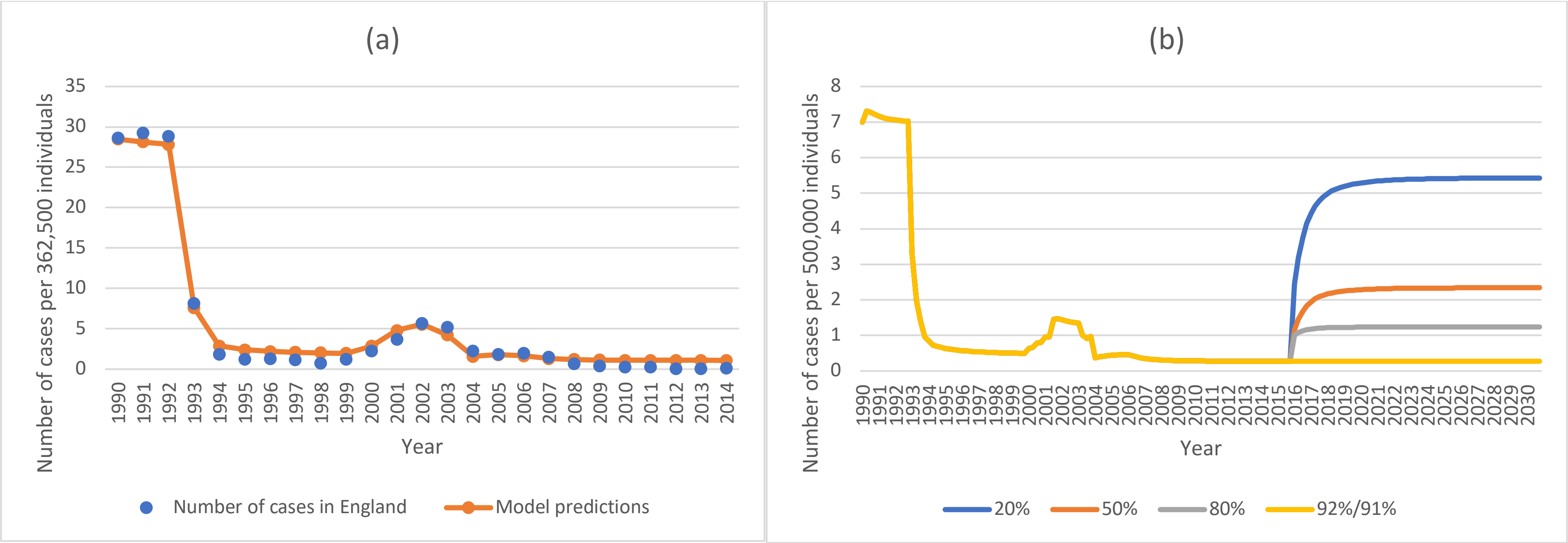
Figure A6(a)-(b). (a) Projections of the historic (1993-2014) burden of Hib disease in all ages (solid line) and the effective vaccine coverage (as time-averaged over the first 5 years of life) against Hib (dashed line) using publicly available data. (b) Combining the data from (a), we correlate the burden of Hib and the effective vaccine coverage against Hib. Historic data (x) are fitted to a decreasing best-fit curve ($R^2 = 0.8461$) using the Curve Fitting Toolbox in MATLAB.

Mathematical model for Hib transmission

SEIR/SIR models for Hib transmission provide a useful framework for exploration of the impact of Hib vaccination [13-15]. In this section, we illustrate how we adapt and use a previously published model for Hib transmission and vaccination in England and Wales [13] to project the burden of Hib disease at different levels of effective coverage against Hib. The model is an age-structured deterministic SIR model with initial conditions and model parameters chosen to reflect the England and Wales setting (details in Appendix 1 from [13]). All infections in the model were episodes of oropharyngeal carriage. Invasive disease cases, which are rarer in comparison, were not explicitly described but were calculated as a proportion of colonization events. In [13] the model was calibrated against Hib carriage prevalence in US by age for 1976 and Hib antibodies in English children for 1990-1991 (Figure 2 in [13]). To calculate the number of Hib cases quasi-steady state approximations were used (Appendix 4 of [13] and the method of characteristics was used to find a solution to the PDE system in Model Maker Version 4 (Cherwell Scientific, UK).

The model [13] only included the primary vaccination and not the additional vaccine boosters that were introduced in in England and Wales in 2003 (to everyone <4 years old) and in 2006 (as additional booster within the routine childhood vaccination programme administered at 12 months old) in response to the resurgence in Hib invasive cases between 1999-2003. To account for these changes, we extended the model from [13] to include these boosters and explored their impact on Hib incidence. The model equations were re-coded in MATLAB and recalibrated to available Hib incidence data from Public Health England until 2014 [8]. The model was calibrated against yearly reported Hib incidence per 500,000 people for England and Wales over the period 1990-2014 (Figure A7(a)). Further details of the calibration and re-evaluation of the Hib vaccination for England and Wales will be published elsewhere (Sillifant L, McVernon J, Flasche S, Panovska-Griffiths J. The impact of booster vaccination on the burden of Haemophilius influenza type B in England and Wales, in preparation) and including the equations and the parametrisation of the calibrated model here will deduct from the novelty of that work.

For the purpose of this work, we used the calibrated model (as per Figure A7(a)) to project Hib burden at different levels of effective coverage against Hib (Figure A7(b)). To achieve this, we simulated a change in the vaccine uptake in 2016 and projected the Hib incidence over the period 2016-2013. We then scaled this incidence to the 2016 midpoint population for England and Wales to calculate the number of invasive Hib cases per year. We then calculated an average yearly number of invasive Hib cases over the period 2016-2030 for each effective coverage value (Figure (A7(c)). Vaccine efficacy was taken to be 99.5% as before, and we used the constraints that pre-vaccination there were 849 invasive Hib cases in all ages and that at 100% effective coverage Hib will be eliminated. Using the Curve Fitting Toolbox in MATLAB we determined that the exponential function $y = 72.05e^{-1.636x}$ is the best-fit to the data ($R^2 = 0.962$).


(a)
Number of cases per 362,500 individuals
35
30
25
20
15
10
5
0
1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014
Year
Number of cases in England
Model predictions
(b)
Number of cases per 500,000 individuals
8
7
6
5
4
3
2
1
0
1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023 2024 2025 2026 2027 2028 2029 2030
Year
20%
50%
80%
92%/91%

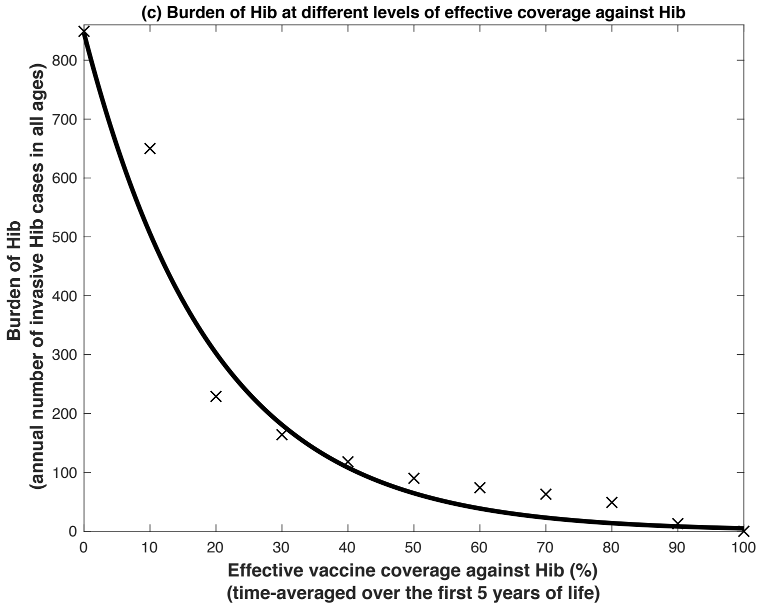


Figure A7(a)-(c): (a) Calibration of the extended model from [13] showing the fit of the model projections (orange) to historical data (blue) on annual Hib incidence for England and Wales over the period 1990-2014. R^2 =0.99 for the fit. (b) Projections using an extended version of the model from [13] of the number of Hib invasive cases over time (1990-2030) when vaccine uptake levels change in 2016. (c) Using the Hib burden projections from (b) at different levels of average uptake of the Hib over the first 5 years of life, and assuming 99.5% efficacy of the vaccine product, we calculate and plot burden of Hib against the effective coverage against Hib ('x'). We then use Curve Fitting Toolbox in MATLAB to fit an exponential function (solid line) to these values ('x').

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A.9 Rotavirus

Rotavirus infection is the primary cause of gastroenteritis (RVGE) in children [1]. Worldwide there are annually 138.5 million reported RVGE cases, more than 2 million hospitalizations and 453,000 deaths in children under 5 years [2]. In England and Wales, rotavirus infection is seasonal occurring mostly in winter and early spring, with most infections in children between one month and four years old (see Figure 2 in [1]). Approximately 130,000 children visit their GP with RVGE symptoms and approximately 12,700 children with RVGE are hospitalised every year in England and Wales [3]. Although, deaths from rotavirus infection in England and Wales are rare, these numbers are difficult to quantify accurately with reports suggesting 3-4 rotavirus associated deaths a year [4,5].

Rotavirus infection is highly contagious with most transmission occurring via the faecal-oral route [1], although respiratory transmission may also occur [3]. It usually lasts 3-8 days and is characterised by mild fever with severe diarrhoea, vomiting and/or stomach cramps. Since these symptoms are similar to those of a number of other viruses, rotavirus infection is difficult to diagnose. In addition, many people with RVGE don’t present themselves to the health services and hence laboratory checks cannot always be done. This makes it difficult to estimate the exact burden of rotavirus infection. Recent studies have shown that the burden of rotavirus measured as an incidence rate is comparable in developed and developing countries [6]. For England and Wales, Public Health England quantifies the burden of rotavirus by the number of laboratory confirmed RVGE cases. These are publicly available for the period 2000-2016 in [7] and are plotted in Figure A8(a).

Vaccination is considered the most promising public health measure for reducing the burden of rotavirus disease. There are currently two licenced vaccines Rotarix® (manufactured by GSK Biologicals) and RotaTeq® (manufactured by Sanofi Pasteur MSD) [8]. Rotarix is the vaccine offered as part of the UK national childhood vaccination programme since July 2013 and is administered orally as two doses at 2 and 3 months old. The level of rotavirus vaccine uptake in England and Wales since the start of the immunisation programme to July 2016 are publicly reported in [9] and summerised in Table S2. In clinical trials Rotarix® has been shown to be 100% effective against severe rotavirus cases and 74% effective against mild rotavirus – this on average 87% effective against any rotavirus infections as per [10] and Table S1. In England and Wales, the vaccination against rotavirus started in July 2013 and to date uptake levels of this vaccine are available for the period October 2013-July 2016. These are summarised in Table S2. These historic data (2013-2016) are not sufficient to determine a correlation between the rotavirus burden and the effective vaccine coverage against rotavirus, and therefore we will utilise a mathematical model to make these projections.

Mathematical model for evaluation of rotavirus vaccination

Dynamical modelling has previously been used to inform policy decisions on the use and implementation of rotavirus vaccination in England and Wales [4,5,11]. Since there is an ongoing research on this, for the purpose of our projections, we collaborated with Katherine Atkins at London School of Hygiene and Tropical Medicine (LSHTM) and utilised the model developed in [11] to quantify the rotavirus burden at different levels of effective coverage against rotavirus. Rotavirus burden in the model is proxied by the number of annually reported RVGE cases across all ages. The model comprises differential equations to track the epidemiological status of the total population over time, stratified by age, and mass vaccination was assumed to be given to vaccine-eligible infants from October 2011 (week 40 within the model). The seasonality and other parameters within the model were estimated by fitting to weekly age-stratified rotavirus incidence data on laboratory-confirmed RVGE infections between 1999-2009 from [7] and Figure A8(a) (see appendix of [11] for details of the calibration and the best-fit scenario).

For the purposes of our analysis, we used the calibrated model from [11] and only changed vaccine coverage (0-100%), vaccine efficacy (two values: 87% overall efficacy (100% against severe RVGE and 74% against mild RVGE) or 100% overall efficacy (100% efficacy against both mild and severe RVGE)) and waning of vaccine immunity (three values: 1 year as in [11], 1.5 years and 2 years). For each parameter scenario, we projected the number of RVGE cases over time in all ages and we illustrate these profiles for three different scenarios in Figures A9(a)-(c). We used the results as per Figure A9(a)-(c) to calculate an annual number of reported severe RVGE cases in all ages at different levels of effective coverage against rotavirus, by calculating an average number of cases over 10 years since the start of the vaccination (Oct 2011- Oct 2021 within the model). The results for different efficacy and waning scenarios are shown in Figure A8(b) and suggest that the relationship between effective vaccine coverage against rotavirus and rotavirus burden is linear when the vaccine immunity wanes after 1 year regardless of vaccine efficacy (solid and dashed lines in Figure A8(b)). The relationship becomes non-linear with burden of rotavirus diminishing at a threshold effective vaccine coverage only if the vaccine immunity wanes over longer time (see Figure A8(b)). Further discussion of these results will be published elsewhere (Panovska-Griffiths J, Atkins KE, How can burden of rotavirus infections in England and Wales be reduced with further vaccination? in preparation). But for the purposes of our study, and to project rotavirus burden at all ages for different levels of effective vaccine coverage, we will use the solid line on Figure A8(b) assuming that immunity from the rotavirus vaccination wanes after a year and the efficacy is 100% against severe and 74% against mild cases.

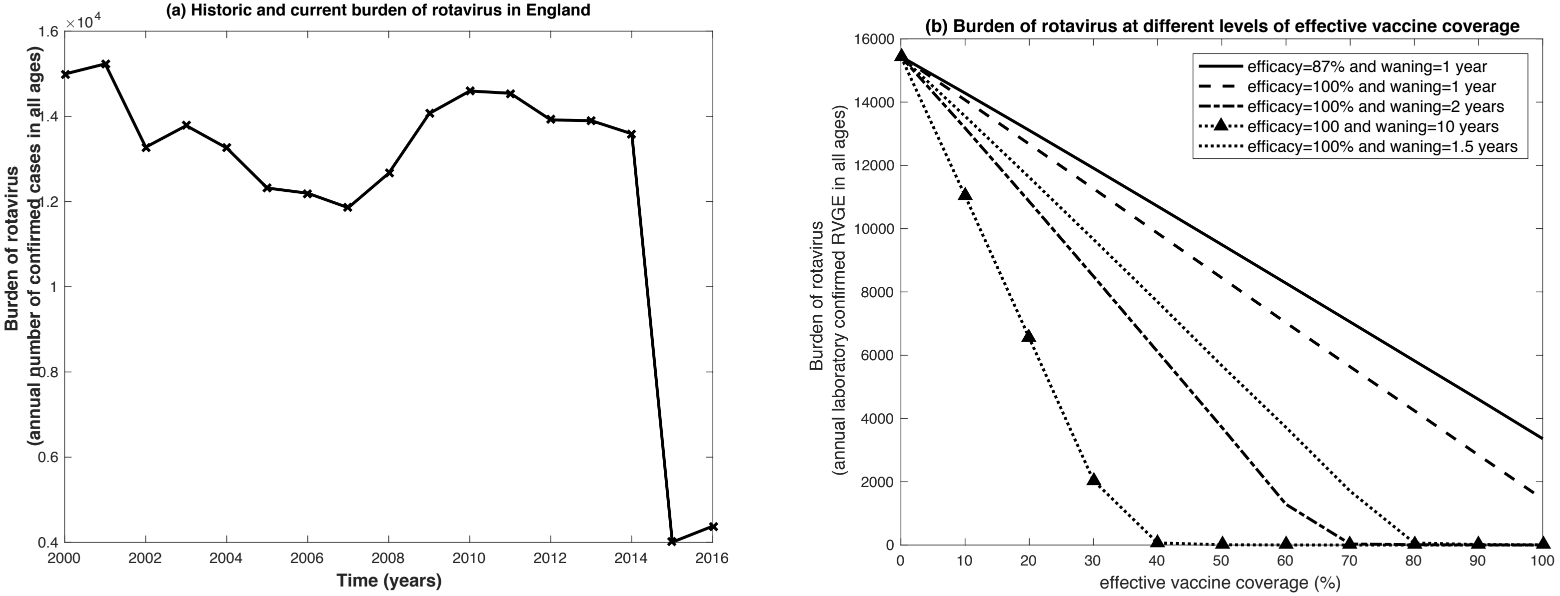
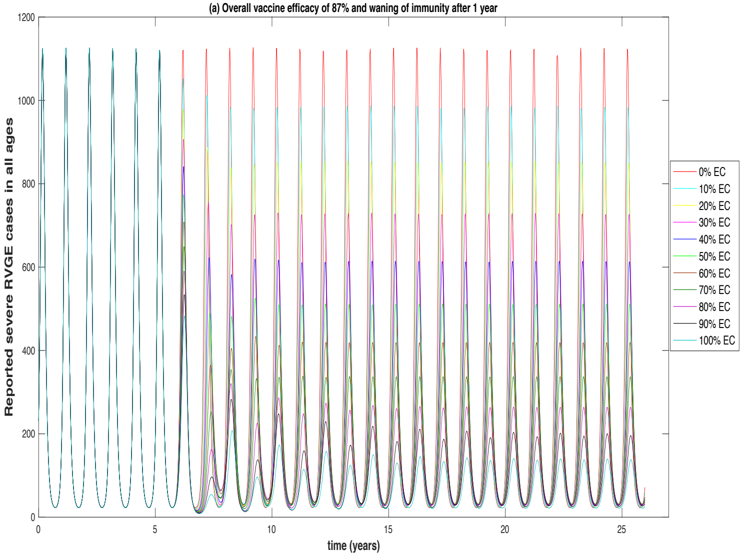


Figure A8 (a)-(b): (a) Historic (2000-2016) burden of rotavirus in England as laboratory confirmed number of annual cases of RVGE across all ages using data from [7]. (b) Projections of the burden of rotavirus infections at different levels of effective coverage of the rotavirus vaccine using a dynamic model from [11]. Results are extracted from plots equivalent to Figure A9(a)-(c) for the different vaccine scenarios i.e. assuming different vaccine uptake and/or efficacy of the vaccine product used. The level of vaccine uptake was simulated as an average over the first five years of life and we calculated the burden as an average of the reported severe RVGE cases over 10 years since the start of vaccination (Oct 2011-Oct 2021).


(a) Overall vaccine efficacy of 87% and waning of immunity after 1 year
Reported severe RVGE cases in all ages
1200
1000
800
600
400
200
0
0
5
10
15
20
25
time (years)
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10% EC
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30% EC
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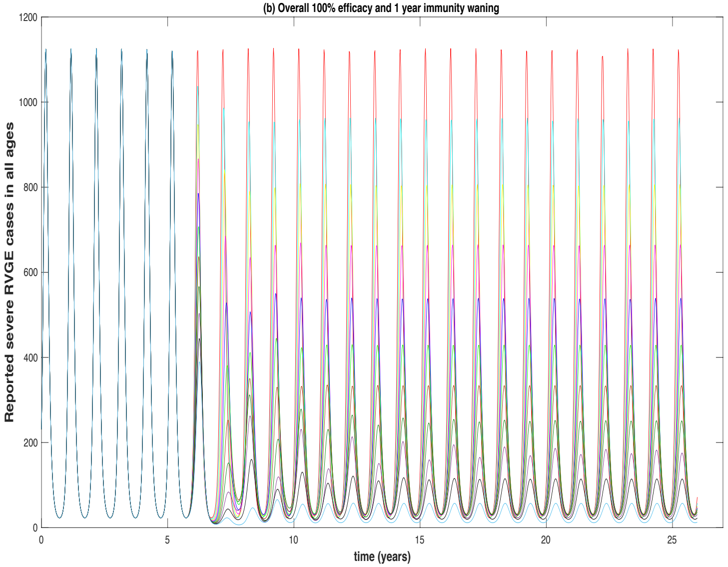
60% EC
70% EC
80% EC
90% EC
100% EC


(b) Overall 100% efficacy and 1 year immunity waning
Reported severe RVGE cases in all ages
1200
1000
800
600
400
200
0
0
5
10
15
20
25
time (years)

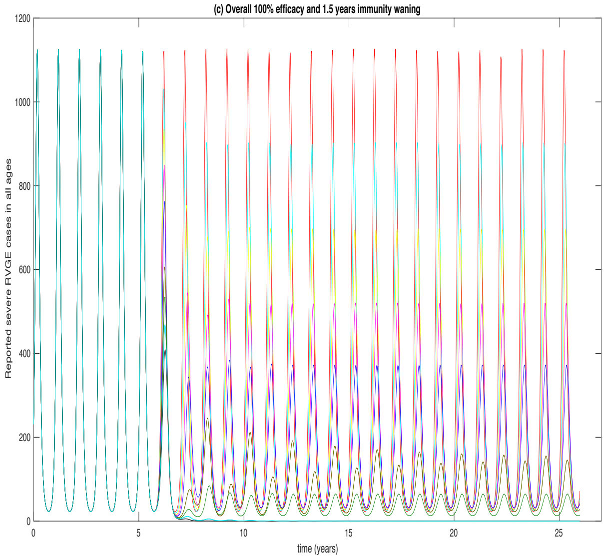


Figure A9(a)-(c): Projections using the mathematical model in [11] of the number of RVGE cases in all ages for different levels of rotavirus vaccine coverage, efficacy and immunity of the vaccine waning. The rest of the model parameter are as per the calibrated model in [11].

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A.10 Measles

Measles is an acute viral illness caused by a morbillivirus of the paramyxovirus family and is spread by airborne or droplet transmission [1]. Measles is a serious disease with complications of the infections including otitis media, pneumonia, diarrhoea, convulsions or encephalitis. The case-fatality ratio of measles is especially high in children under one year old. Measles cases have been notifiable in England and Wales since 1940 and are reported annually and available in [2]. More recently, the annual number of laboratory confirmed measles cases in England and Wales became available for the period 1996-2016 [3-5]. We plot this historical burden for measles as a combination of the number of notifiable measles cases in all ages for the period 1960-1995 and the number of laboratory confirmed measles cases in all ages for the period 1996-2015 (solid line in Figure A10(b)).

Vaccination is the most efficient way to prevent measles infections [1]. In England and Wales, vaccination against measles was introduced as a single vaccine against measles in 1968. This was replaced by the combined measles-mumps-rubella (MMR) vaccine in 1988 as a single dose given around 12 months of age. In 1994, following a measles outbreak the previous year, and to prevent a potential delayed measles epidemic, a vaccination campaign was implemented with over 8 million children aged between 5 and 16 years immunised with measles-rubella (MR) vaccine. To maintain the control of measles established after the MR campaign, a second dose of the MMR vaccine was included in the routine childhood programme from October 1996 and is given around 40 months of age.

EMC reported the efficacy of the vaccine products for measles vaccination to be 90% effective against measles after one dose, whereas the two-dose vaccine offers 99% immunity protection (Table S1). The historic levels of uptake for the measles vaccine (single measles vaccine in the period 1970-1988 and combined MMR vaccine in the period 1989-2016) at 12, 24 and 40 months are reported in [6,7]. Using these uptake and efficacy values, we utilise the method from A3.4 to calculate the time-average effective vaccine coverage against measles over the first 5 years of life and plot this in Figure A10 (a) (dashed line).

Using the data from Figure A10(a), in Figure A10(b)) we project the burden of measles at different levels of effective coverage. We used two constraints: prior to measles vaccination (i.e. equivalent to 0% EC) we use reports of about 309,090 annual measles cases in all ages in England (calculated as an average notifications number between 1960-1968 from [2] and rescalled for England) and we assume that at 100% effective coverage measles will be eliminated. The best-fit curve to the historic data is determined using the Curve Fitting Toolbox in MATLAB to be the exponential function $y = 27080e^{-0.6876x}$ with $R^2 = 0.9765$ and is plotted in Figure A10(b) (solid line).

Mathematical model for evaluation of the measles vaccine

Mathematical models have previously been used to model measles transmission and understand the impact of vaccination against measles (e.g. [8] and Chapter 4 in [9]. Based on [8] and using the parametrisation from model 4.7 in [9], we developed a bespoke SIR model to capture measles transmission and vaccination under the current vaccine strategy in England and Wales. The model was a dynamic SEIR model stratified into 5 ages cohorts (0-12 months old, 12-40 months old, 40-60 months old, 5-15 years and 15 years plus). We parametrised the model with epidemiological data for measles as per the model 4.7 in [9], and used the POLYMOD contact survey data [10] to describe the contacts pattern between different age cohorts. The calibration of the model was performed by comparing the yearly number of measles infections across all cohorts from the model to the historic number of laboratory confirmed number of measles infections 1996-2014. We mainly changed the transmission probability within the model, and achieved close agreement between the data and model. Further details of this work can be found in [11]. The paper based on this work is currently under preparation (D.Voulgarelis, S.Funk and J.Panovska-Griffiths, Re-evaluation of measles vaccination in England and Wales: insights from a modelling study, Bull.Math.Biol, in preparation) and including the equations and parameters of the calibrated model here will deduct from the novelty of that work.

For the purpose of the analysis here, we simulated the calibrated model at different levels of vaccine uptake at 2 years (i.e. at primary MMR vaccine course completion) and then calculated a time-averaged effective vaccine coverage using the method in section A 3.4. The efficacy of the MMR vaccine against measles was taken to be 90% after one does and 99% after both doses (as per Table S1), and we used a constraint that there were around 309,090 measles cases in the pre-vaccination era in England. The model projected the annual number of measles cases in all ages. Measles epidemic has an oscillatory behavior, with increased burden every couple of years and to overcome this we calculated an average number of model-projected measles cases over 10 years after vaccination. The model projected relationship between measles burden and effective coverage against measles was determined to be linear with burden diminishing at EC around 95% (Figure A11(a)). This is different to the data-projected such relationship and further calibration of the model is required for more accurate projections. This requires further work outside of the timescale of this project. Therefore, on advice of experts, we have decided to use the relationship from the historic data (solid line in Figure A10(b)).

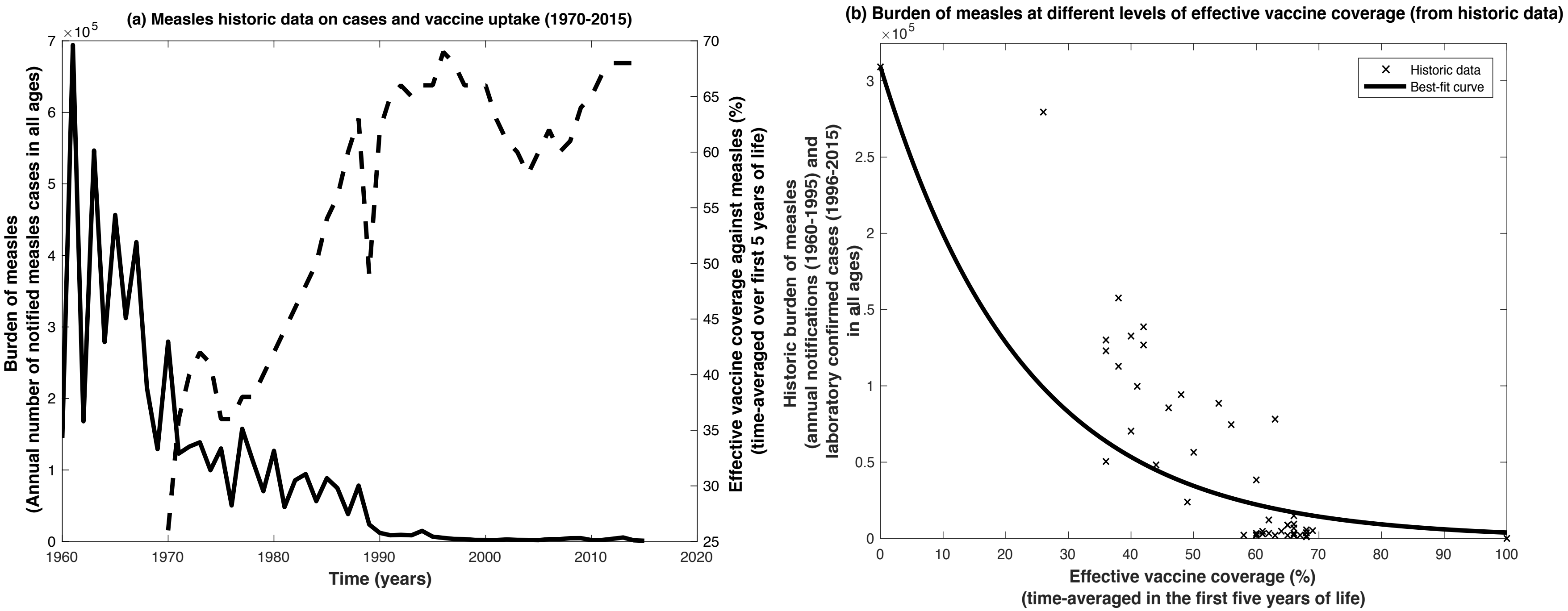

Figure A10 (a)-(b): (a) Projections of historic burden of measles as a combination of annual notifications (1960-1995) and laboratory confirmed measles (1996-2015)(solid line) and effective vaccine coverage against measles (calculated combining the historic uptake values of measles vaccine and the vaccine product efficacy using method in A 3.4 -dashed line) (b) Combining the data from (a) we project the burden of measles at different levels of effective vaccine coverage ('x') and fit a best-fit curve using Curve Fitting Toolbox in MATLAB (solid line, with $R^2 = 0.9765$).

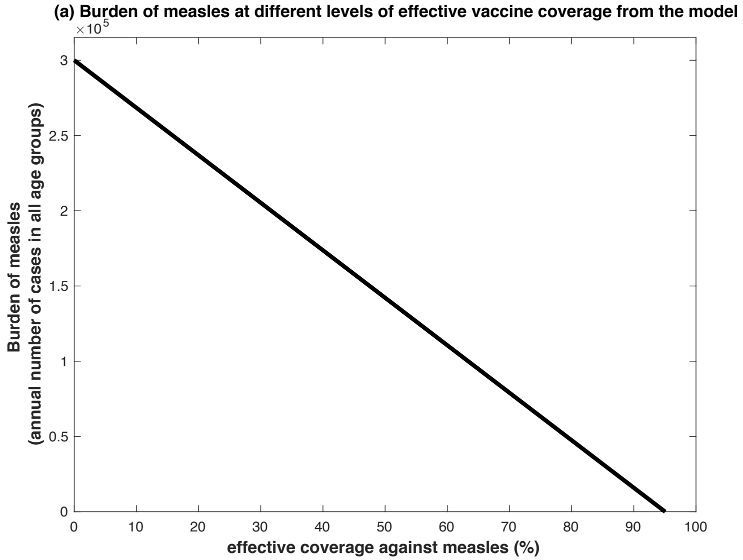

Figure A11: Projections from a mathematical model of the burden of measles at different levels of effective coverage against this disease.

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A.11 Mumps

Mumps is an acute viral disease caused by paramyxovirus and spread by airborne or droplet transmission [1]. Before the introduction of the measles, mumps and rubella (MMR) vaccine in 1988, mumps occurred commonly in school-age children and was the commonest cause of viral meningitis in children [1,2]. Moreover, more than 85% of adults had evidence of previous mumps infection and mumps was the cause of 1200 hospital admissions each year in England and Wales [2].

Routine immunisation against mumps started in 1988 as a combined measles-mumps-rubella (MMR) vaccine. In October 1996, a two-dose MMR schedule was introduced based on the findings that a single dose of a mumps-containing vaccine confers between 61% and 91% (78% average) protection against mumps, whereas the two doses vaccine has 87% efficacy against mumps infection [3].
Following the implementation of the routine mumps vaccination in the period 1989-1999 the burden of mumps in England and Wales dropped dramatically, but since 1999, there has been a considerable increase in confirmed mumps cases. Most of these cases have occurred in adolescents

or young adults who were too old to have been offered MMR when it was introduced in 1988 or to have had a second dose when this was introduced in 1996 [1]. They had not previously been exposed to natural mumps infection as children and so remained susceptible. In late 2004, a further increase in clinically diagnosed and confirmed mumps infections was observed. The vast majority of confirmed cases were in those born between 1980 and 1987 and outbreaks occurred mainly in higher education institutions.

This burden of mumps in England and Wales is quantified by Public Health England by the total number of laboratory confirmed cases of mumps and is publicly available for the period 1996-2015 [4,5]. We plot this burden for all ages in Figure A12(a) (solid black curve). Historic levels of uptake for the mumps vaccine are reported in [6,7] and EMC reports the efficacy of the MMR vaccine against mumps to be 64% after one dose and 87% after 2 doses. We use these values and utilise the method from section A3.4 to determine the averaged over the first 5 years of life effective vaccine against mumps and plot this in Figure A12(a) (dashed curve).

To correlate the burden of mumps with the effective coverage of the mumps vaccine we can use SIR models such as [8] or [9]. The development of such models is not complicated, but the parametrisation and the calibration to settings such as England requires more time than available within the timescale of this project. After discussion with experts within PHE and LSHTM we decided that linking historic data is sufficient to quantify the relationship between mumps burden and effective vaccination levels in England.

Combining the results from Figure A12(a) we project the burden of mumps at different levels of effective coverage against mumps (Figure A12(b)). We note that in addition to the data from Figure A12(a) we used the constraint of around 500 cases per 100,000 population in the pre-vaccine era from [12]. This scales to 265,000 cases of mumps at 0% effective coverage against mumps or 232,730 cases when rescalled for England only [1]. We used the Curve Fitting Toolbox in MATLAB to find a decreasing function that best fits this data and determined that the best fit was the exponential function $y = 1920 * e^{-1.369*x}$ with $R^2 = 0.9966$.

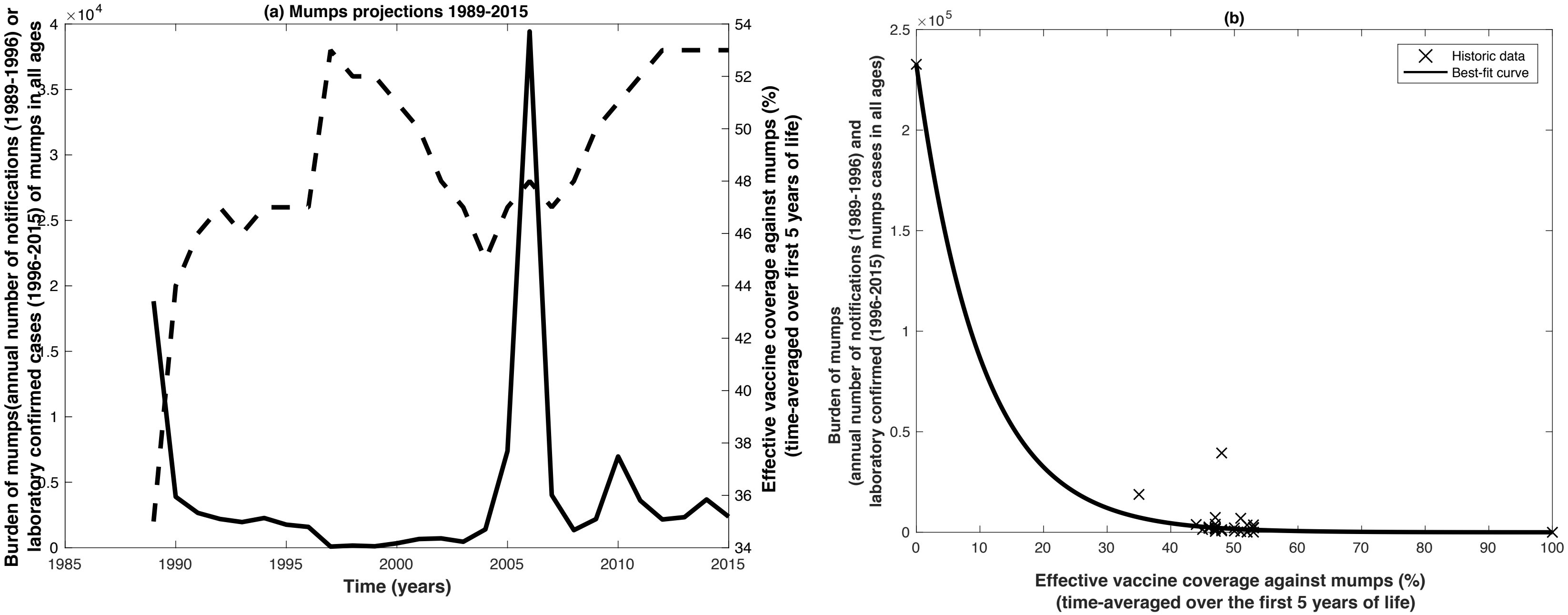

Figure A12(a)-(b). (a) Projections over time of the historic (1996-2015) burden of mumps (solid line) and historic (1996-2015) levels of (time-averaged over the first 5 years of life) effective vaccine coverage (dashed line) using publicly available data. (b) Combining the historic data from (a) and assuming around 232,730 mumps cases pre-vaccination we project the burden of mumps at different levels of EC of mumps vaccine. In (b) The data ('x') are fitted to an exponential function in MATLAB (solid line) that gives the best fit to the data with $R^2 = 0.9966$.

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A.12 Rubella

Rubella is a mild disease caused by a togavirus and spread by droplet transmission [1]. Often a rash is a symptomatic of the disease but it can be fleeting and maybe not be specific to rubella, this making clinical diagnosis often unreliable. Before the introduction of routine rubella immunisation, rubella occurred commonly in children, and more than 80% of adults had evidence of previous rubella infection [2]. Rubella is dangerous in pregnancy where it may result in fetal loss or in congenital rubella syndrome (CRS) characterised with multiply defects of the fetus. To prevent rubella infection in pregnancy, immunisation against rubella was introduced in the UK in 1970 for pre-pubertal girls and non-immune women of childbearing age. In October 1988, this vaccine was replaced with a combined immunisation against measles, mumps and rubella (MMR) vaccine and included in the routine childhood vaccination programme administered at 12 months of age. In October 1996, a second dose of the MMR vaccine was also included as part of the routine childhood immunisation programme in the UK and is given at around 40 months of age.

A considerable decline in rubella in young children followed the introduction of the MMR vaccine, with a concomitant fall in rubella infections in pregnant women – from 167 in 1987 to one in 2003 [1]. Annual confirmed laboratory cases of rubella for England and Wales for all ages are reported for the period 1996-2015 [3]-[4] and we plot these rescaled for England in Figure A13(a) (solid curve).

The historic uptake levels of this vaccine in England and Wales is publicly available for the period 1989-2015 [5-6]. The efficacy of the rubella-containing vaccine as used in the UK confers around 95 to 100% protection against rubella [1] and EMC reports 99% and 99.9% protection against rubella after one and two doses of the vaccine respectively. We will use these values and combine it with the reported historic uptake level of the vaccination against rubella utilising the method from section A 3.4 to derive the time-averaged effective vaccine coverage against rubella over the first 5 years of life and plot it in Figure A13(a) (dashed line).

In Figure A13(b) (as ‘x’) we combine these publicly available historic data on rubella burden and effective vaccine coverage against rubella from Figure A13(a). In addition, we use the number of notified rubella cases in 1988 from [7] as the burden of rubella pre-vaccination – so that at 0% EC we assume there to be around 227,270 cases of rubella. Furthermore, we assume that at 100% effective coverage rubella will be diminished. Using the Curve fitting toolbox in MATLAB we determine that the exponential function $= 41.27 * e^{-1.903*x}$ is the best-fit to this data with $R^2 = 0.9986$.

The current burden of rubella in England is low with only one cases confirmed between Jan-Sep 2016, 5 in 2015 and 1 in 2014 [4,5,8]. This suggests that the high-uptake levels of the MMR vaccine are able to control rubella burden and there is no need to apply mathematical models and explore how this vaccine imp-act can be improved. We note that in the past mathematical models for rubella transmission and vaccination have been developed and used to explore the impact of different vaccine scenarios and in different settings (e.g. [9-11]). But if we were to use any of these for the purposes of our study, or if we indeed developed a new model we would need to refit it to current England data and this was not feasible within the timescale of this project. Hence, we will use the historic data (Figure A13(b)) for our projections.

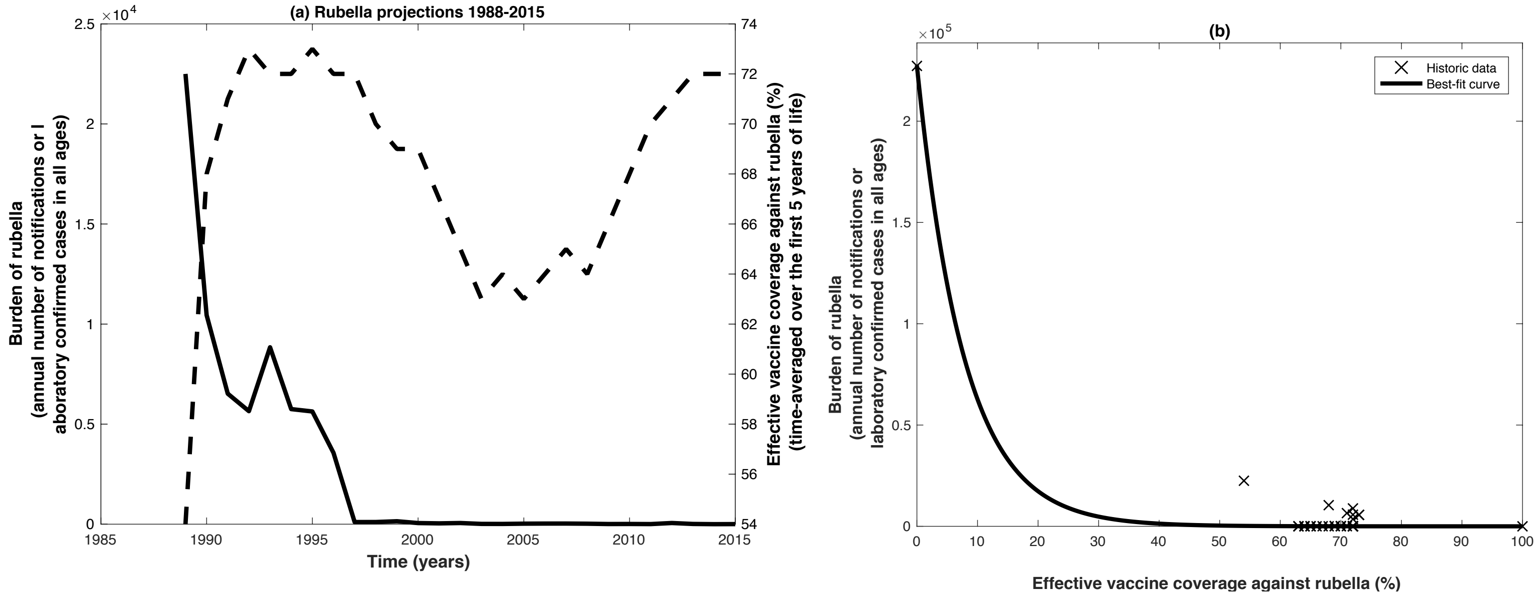

Figure A13(a)-(b). (a) Projections of the historic (1996-2015) burden of rubella (solid line) and historic effective coverage against rubella (as time-averaged over the first 5 years of life using the method from A 3.4) (dashed line) rescaled to England using the dat1 from [3]-[7]. (b) Combining the data from (a) (plotted as 'x') and subject to constraints at 0% and 100% EC, we project the burden of rubella at different levels of time-averaged over the first 5 years effective coverage against rubella. The data ('x') are fitted to an exponential function with $R^2 = 0.9986$.

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A.13 Pneumococcal disease

Pneumococcal infections are caused by the Streptococcus pneumoniae bacteria with more than 90 different serotypes and categorised as invasive and non-invasive pneumococcal diseases [1]. Non-invasive pneumococcal infections (e.g. bronchitis, otitis media (ear infection) or sinusitis) occur outside major organs or the blood and tend to be less serious. Invasive pneumococcal infections (e.g. septicaemia (blood poisoning), osteomyelitis (infection of the bone), pneumonia or meningitis) occur inside a major organ or the blood, are serious infections and represent the biggest burden from pnemococcal.

Vaccination against pneumococcal stereotypes is the most effective way of preventing invasive pneumococcal disease (IPD) cases. Routine vaccination against pneumococcal in England and Wales started in September 2006 with a 7-valent pneumococcal conjugate vaccine (PCV7) [1]. This vaccine offered protection against 7 pneumococcal serotypes and its' introduction was informed by a dynamic transmission model parametrised using IPD data and following PCV7 introduction in the USA [2]. The model predicted over time elimination of the IPDs with sufficiently high uptake of the vaccine and minimal serotype replacement [2]. However, the actual experience in England and Wales post PCV7 suggested a more aggressive serotype replacement [3,4] and additional modelling analysis was undertaken based on the first three years of PCV7 programme [5]. It predicted that the long-time reduction in IPDs is due to replacement of the PCV7 serotypes with other serotypes [5]. As a consequence, a 13-valent pnemococcal vaccine (PCV13), covering against additional 6 replaced serotypes, replaced the PCV7 vaccine within the routine childhood vaccination programme in the UK from Sep 2010. Further modelling analysis of the impact of PCV13 on both serotypes replaced by PCV7 and PCV13 as well as on the overall number of pneumococcal IPD followed [6]. Results of this analysis suggest a continual vaccination with pneumococcal conjugate vaccine is necessary to prevent a dramatic increase in pneumococcal IPD cases. Furthermore, the model in [6] suggested that replacement of PCV7 with PCV13 would induce biggest overall decrease in IPD cases, but the absolute level of IPD decline will depend on the replacement level of additional serotypes.

As well as continual vaccination with PCV13 in children under 2 years old, since 2007, a pneumococcal polysaccharide vaccine (PPV) offering protection against 23 pneumococcal serotypes is recommended to healthy adults over 65 years of age. We note that this PPV vaccine is not suitable for children under 2 years old as it offers poor antibodies response in this age-cohort [1].

Public Health England (PHE) undertakes enhanced surveillance of the annual IPD cases in different age cohorts and both for strains that are covered with the PCV13 as well as those that are not [7]. The annual number of IPD cases is available as figures and we used these graphs to extract the number of IPD cases, for all strains, across all ages between the period 2007-2015. We re-plot these in Figure A14 (a) (full line).

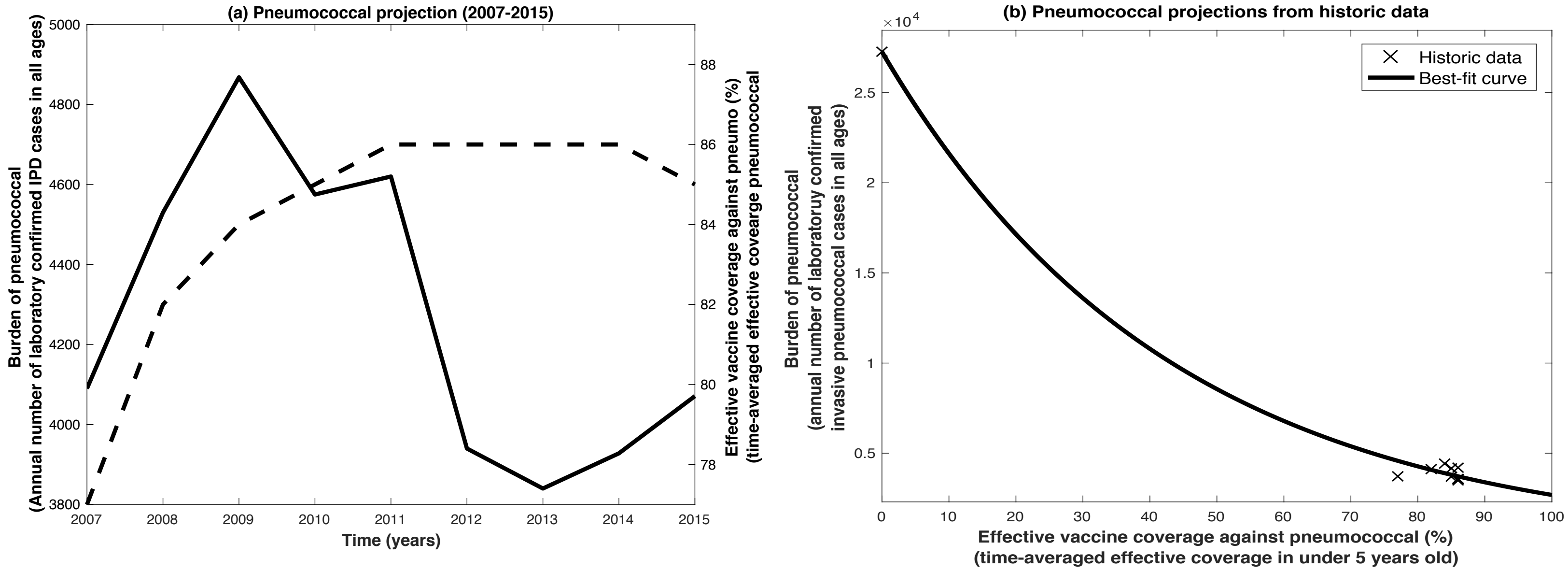
The uptake level of the pneumococcal conjugate vaccine at 12 months and at 2 years of age for England and Wales is reported for the period 2007-2015 in [8,9]. We use these values, combined with the vaccine efficacy (94.8% against all strains as per Table S1), and employ the method from A.3.4 to calculate the time-averaged effective coverage against IPD in under 5 years old. This is plotted for the period 2007-2015 in Figure A14(a) (dashed curve).

In Figure A14(b) we combine the historic data from Figure A14(a) (plotted as ‘x’) to determine a relationship showing the decline in pneumococcal burden with increased effective vaccine coverage against pneumococcal disease. In discussion with epidemiological experts, we use the constrain that pre-vaccination there were around 30,000 IPD cases annually in England and Wales (rescalling to England only to be consistent across all disease). Using this as a constraint at 0% effective vaccine coverage (defining the pre-vaccine level of IPD) we use the MATLAB Curve fitting Toolbox we to determine the best fit curve to the data to be the exponential function $y = 4718e^{-0.6197x}$ with $R^2 = 0.9965$ as shown in Figure A14(b).

Projections from a mathematical model

Within the timescale of this work it was not feasible to use the established mathematical model for pneumococcal disease transmission and vaccination from [6] as the authors (Y.Choi, personal communication) were at the time undertaking re-calibration of the model to the most recent IPD data. Instead, we collaborated with Matt Keeling's modelling team at Warwick University (Tinevimbo Shiri, personal communication) who recently developed and calibrated to most-recent data (until 2015) a mathematical model to evaluate the impact of 13 strain-vaccine against pneumococcal diseases (PCV13) on the current pneumococcal burden. This is an individual-based model and a preview of it is available in [11] and the related website. The full paper is currently in preparation and including the numerical code (in absence of equation for an IBM model) here will deduct from the novelty of that work, and is therefore not included. For the purpose of our work the calibrated model was simulated by Tinevimbo Shiri and the incidence number of invasive pneumococcal diseases (IPDs) at different levels of effective coverage of the PCV13 vaccine (as an average in under 5 years old) was projected. From these incidence values, we calculate the annual number of IPDs by using the population mid-point estimates from 2015 (i.e. 57.9 million people in England (from [12])). The model projected data is shown in Figure A14(c)('x'). We utilized the Curve fitting toolbox in MATLAB to derive the curve that best fits the points to be the exponential function $y = 405.5e^{-3.172x} + 1035e^{-0.1854x}$ with $R^2 = 0.9879$).

For the purpose of this project we could use either the curve from Figure A14(b) or A14(c). Since our intention was to employ results from mathematical models where possible, we have decided to use the curve from Figure A14(c).


(a) Pneumococcal projection (2007-2015)
Burden of pneumococcal
(Annual number of laboratory confirmed IPD cases in all ages)
Effective vaccine coverage against pneumo (%)
(time-averaged effective covearge pneumococcal
Time (years)
5000
4800
4600
4400
4200
4000
3800
88
86
84
82
80
78
2007
2008
2009
2010
2011
2012
2013
2014
2015
(b) Pneumococcal projections from historic data
×10^4
Historic data
Best-fit curve
Burden of pneumococcal
(annual number of laboratoruy confirmed
invasive pneumococcal cases in all ages)
2.5
2
1.5
1
0.5
0
10
20
30
40
50
60
70
80
90
100
Effective vaccine coverage against pneumococcal (%)
(time-averaged effective coverage in under 5 years old)

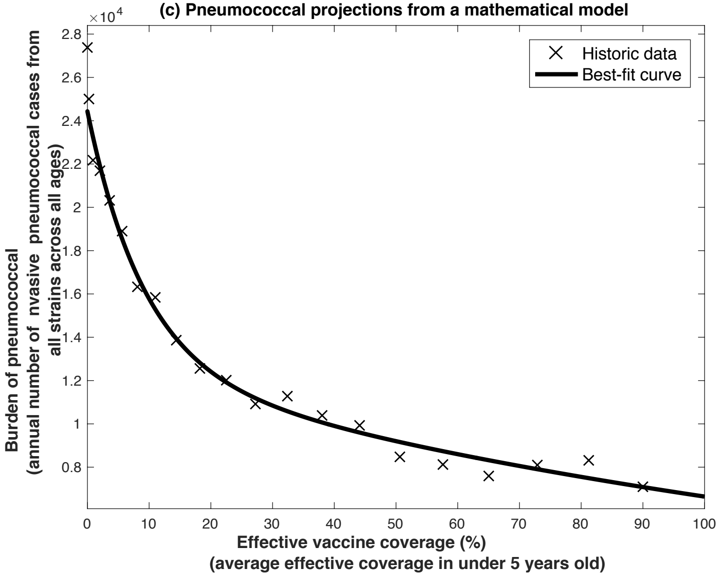


Figure A14(a)-(c). (a) Projections of the historic (2007-2015) burden of pneumococcal disease (solid line) and the effective vaccine coverage against pneumococcal disease (2007-2015). The effective vaccine coverage is calculated using the method from A.3.4 and shown as a dashed line in (a). (b) Combining the historic data from (a) (as 'x') with a constraint of 27,273 IPD cases in England in the pre-vaccine era (i.e. at 0% effective coverage), we fit an exponential function (solid line) as the best-fit to the data with $R^2 = 0.9965$. (c) Projections of the incidence of invasive pneumococcal disease at different levels of effective vaccine coverage in under 5 years old from the mathematical model in [11]. The data ('x') are fitted to an 2nd order exponential function with $R^2 = 0.9879$.

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A.14 Neisseria Meningitides Group C (Men C) & Meningitides Group B (Men B)

Meningococcal disease occurs as a result of a bacterial infection by Neisseria meningitides. There are to date 12 identified capsular groups, A, B, C, E, H, I, K, L, W, X, Y, and Z, of which groups B, C, W and Y have historically been the most common in the UK [1].

Meningococcal transmission is by aerosol, droplets or direct contact with respiratory secretions of someone carrying the organism and usually requires frequent or prolonged close contact. The most common presentation of the meningococcal infection is either as meningitis or bacterial septicaemia, or a combination of both [2].

In England and Wales, the incidence of meningococcal disease is highest in children under five years of age, with a peak incidence in infants under one year of age [1]. There is a secondary peak in incidence in young people aged 15 to 19 years of age [2].

Large epidemics of meningococcal disease are mostly caused by capsular group A and coincided with each of the two World Wars, with reported over 12,000 annual meningococcal notifications in England and Wales [1]. After WWII, disease levels declined but meningococcal epidemics associated with capsular group B (Men B) were evident between 1972 and 1975 and in 1985. An epidemic associated with the capsular group C (Men C) started in 1995 and ended with the introduction of the Men C vaccination in the UK from November 1999 [1].

In the next two sections, we use publicly available data and/or established mathematical models to project the burden of both Men C and Men B in all ages at different levels of effective vaccine coverage against these diseases over the first 5 years of life.

A14.1 Men C projections from the available data

Following the epidemic associated with the capsular group C (Men C) from 1995, a vaccine against Men C was introduced in England and Wales in November 1999 [1]. Initially, this Men C conjugate vaccine was given within the routine childhood immunisation programme along with a catch-up campaign for older children, adolescents and young adults up to 18 years and in January 2002, the campaign was extended to include all adults less than 25 years of age [1]. Following the Men C vaccination campaign, the number of reported and laboratory confirmed Men C fell by over 90% in all age groups immunised to around 30-40 annual number of cases [3-5]. It also fell by around 66% in non-vaccinated groups due to herd immunity. The current burden of Men C is low with Men C infections causing only 2 deaths in children and young people under 20 in the last 5 years, compared to 78 deaths in the single year before the vaccine against Men C was introduced [3,6].

Public Heath England collects annual numbers of laboratory confirmed invasive meningococcal cases stratified by capsular group and age: they are publicly available for the period 1998/99-2015/16 [6]. We use these reported values to quantify the burden of Men C in all ages in England and plot this over the period 1998-2015 in Figure A15(a) (solid curve).

The reported uptake levels of the Men C vaccine for the period 2000-2015 are publically available in [7,8]. The efficacy of the two-dose Men C vaccine was estimated to be 98–100% [9,10] in agreement to the EMC reported value of 100% (as per table S1). Taking the efficacy of the Men C vaccine to be 100%, and using the historic level of Men C vaccine uptake from [7,8] we calculate the time-averaged historic effective coverage against Men C over the first 5 years of life using the method from A3.4. We plot these values as the effective vaccine coverage against Men C annually for the period 2000-2014 in Figure A15 (a)(dashed line).

To determine the relationship between the decline in Men C burden in all ages with increased effective vaccination against Men C over the first 5 years of life, we use data from Figure A15(a) together with two constraints: the annual number of Men C cases pre-vaccination (giving us a constraint at 0% effective vaccine coverage) and elimination of Men C at 100% effective vaccinations coverage. Since vaccination has reduced the number of Men C cases by over 90%, bringing them down to 30-40 a year in all ages as reported in [3-5], we can scale this up to approximate that in the pre-vaccination era (i.e. at 0% effective coverage) there will be around 3500 annual Men C cases in all ages. The best fit to the historic data is the declining exponential function $y = 64.07e^{-1.073*x}$ with $R^2 = 0.9975$ as shown in Figure A15(b)(solid line).

We note that there is an established model for Men C vaccination in England [5] but this model is currently being calibrated to the most recent data (C.Trotter, personal communication) and as such was not available within the timescale of this project to determine a relationship between Men C burden and effective vaccine coverage against Men C. There are plans to undertake this analysis in future.

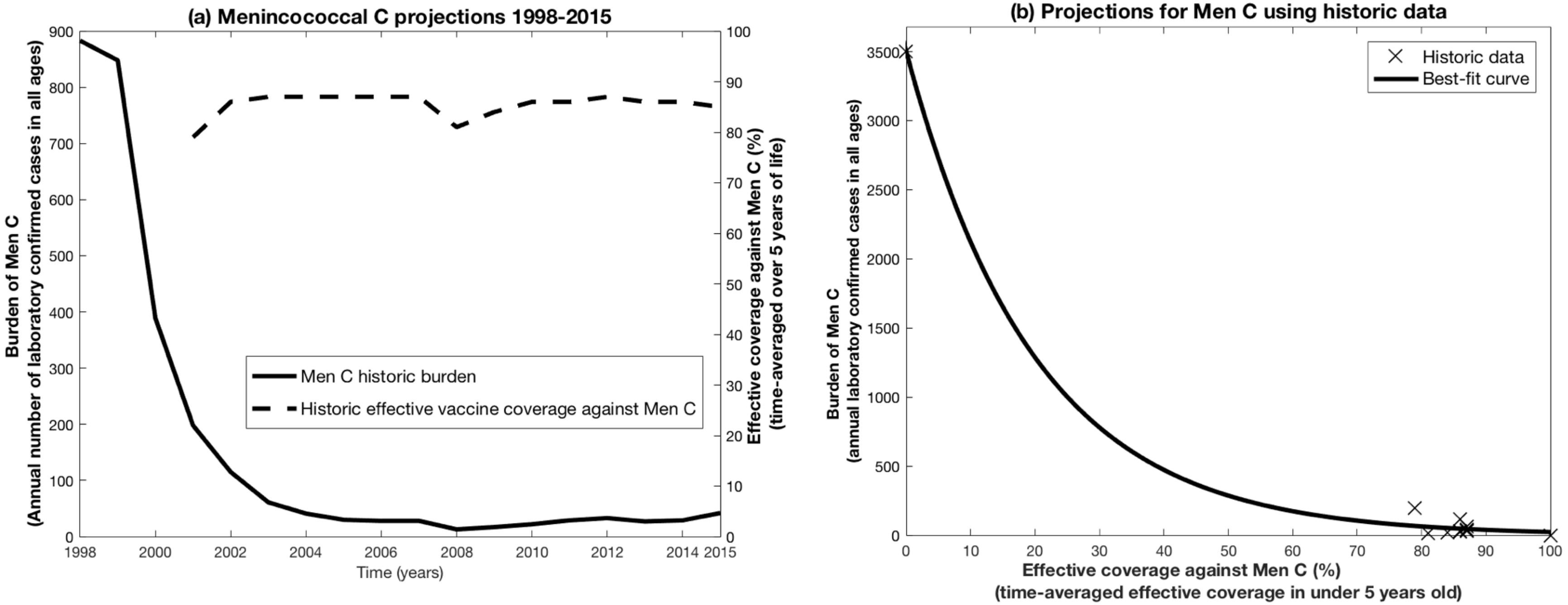

Figure A15(a)-(b): (a) Publicly available historic data on the annual burden of Men C in England (as laboratory confirmed cases of Men C in all ages) over the period 1998-2015 (full line) and the effective vaccine coverage against Men C in England (as time-averaged effective coverage calculated using the method in A3.4) over the period 2000-2015. (b) Combining the data from (a) (and plotted as 'x' in (b)) we fit a curve to determine the relationship between the annual burden of Men C across all ages and effective vaccine coverage against Men C. We use the Curve Fitting Toolbox in Matlab and determine that an exponential function (solid line) is the best fit with $R^2 = 0.9975$.

A14.2 Men B projections from the available data

Vaccination against Men C in England and Wales has been very effective in reducing the burden of Men C, and since 2009 capsular group B has been responsible for around 85% of all meningococcal cases in England and Wales [6]. To reduce this burden, in January 2013, a four-component meningococcal B (4CMenB) vaccine was authorised for use by the European Medicines Agency and in August 2015 4CMenB was added to the routine UK childhood immunisation schedule [1].

The number of invasive meningococcal cases stratified by capsular group and age are reported by Public Health England annually and are available for the period 1998/99-2015/16 in [6,14]. We use this dataset to extract the annual number of invasive Men C cases in all ages and explicitly in children under 5 years old and plot these in Figure A16(a).

The reported uptake of the Men B vaccine over the first year of Men B vaccination in England and Wales was 95.8% at 1st dose and 94.3% for the two-dose vaccine [11]. Since vaccination against Men B started recently, there are not sufficient number of historic data points to correlate historic burden with effective coverage against Men B. Instead, we will apply a dynamic transmission model calibrated to historic data on Men B hospitalisation and incidence rates for England and Wales. This model was developed and calibrated to England and Wales data by Hannah Christensen (University of Bristol) in [12] and further applied in [13]. The model is a dynamic age-stratified SIR model and was instrumental in evaluating the potential impact of the Men B vaccine before it was routinely included in the UK childhood vaccination in the UK. The model is able to project the number of all meningitis cases, hospitalisation and deaths in children under 5 years old.

For the purposes of this project this model was run by H.Christensen (University of Bristol) varying the level of vaccine uptake between 10-100%. The efficacy against Men B was 83.6% in under 5 years old (as used in [13] and also from the subtext in Table S1). The model projected the annual number of all meningitis cases in under 5 years old. To translate this to number of meningitis cases in all ages we used the statistics from [14] to calculate that on average 56% of all historic meningitis cases occur in under 5 years old so we adjusted the model projected numbers accordingly. Furthermore, we translated this number of all meningitis cases to number of Men B cases only, by using the statistics from [6] to determine that on average 78% (for 1999/00-2013/14 inclusive; range=[50%,90%]) of all historic meningitis cases are of Men B type. Again, we adjusted the number of cases accordingly. Finally, for the pre-vaccination levels, we used the historic data on the number of Men B cases from [6] to calculate an average annual number of Men B cases in under 5 years old (between 1999-2014), and again translated this to annual number of Men B cases in all ages pre-vaccination in England. In Figure A16(b) we plot these values (as 'x') to represent the burden of Men B at the different levels of effective coverage against Men B. We used the Curve fitting Toolbox in Matlab to fit a decreasing function to this data and determined that the best-fit curve was the exponential function $y = 308.5e^{-2.976*x} + 1151e^{-0.009822*x}$ with $R^2 = 0.9983$.

We note that analogous analysis using the model projected number of meningitis cases in under 5 years old combined with statistics on the data from [6] and [14], can be used to project the burden (as number of cases in all ages) of Men C. However, this will only account for Men C vaccination with Bexsero and not with other vaccines (e.g. the combined Men C/Hib vaccine) and hence, as we discussed in the previous subsection, we instead used the historic data for the Men C projections.

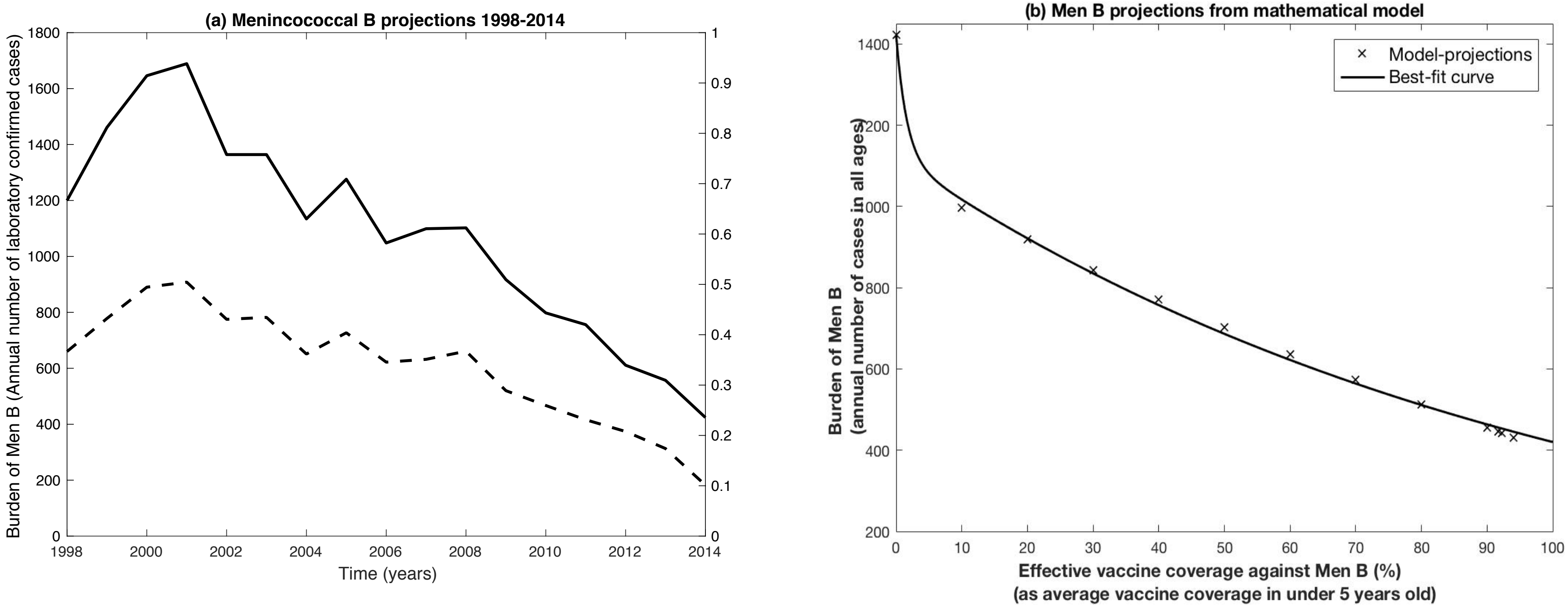

Figure A16(a)-(b): (a) Projections of the annual burden of Men B in all ages (solid line) and in children under 5 years old (dashed line) in England. (b) Projections of the annual burden of Men B across all ages at different levels of effective coverage against Men B. The points ‘x’ in here are generated by applying the established model from [12,13], which are then fitted to a decreasing an exponential function (solid line) as the best-fit curve with $R^2 = 0.9983$.

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Infectious disease	Model used for burden projections	Data used for burden projections	Historic data available for burden projections	
			Notified annual number of cases	Laboratory confirmed number of cases
Polio		X	1966-2015	
Diphtheria		X	1966-1985	1986-2015
Tetanus		X	1966-2015	
Pertussis		X	1966-2015	
Measles		X	1960-1995	1996-2015
Mumps		X	1989-1995	1996-2015
Rubella		X	1989-1995	1996-2015
Men C		X		1989-2015
Men B	X			1989-2015
Rotavirus	X			2000-2016
Pneumococcal	X			2007-2015
Hib	X			1990-2014

Table S3: Summary of the methods used to project disease burden (historic data or model projections) per disease, across the 12 diseases included in the current childhood immunisation programme in the UK.