



Estimating the clinical impact of introducing paediatric influenza vaccination in England and Wales[☆]

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ABSTRACT

Influenza causes a significant burden of disease each year in England and Wales, with the young and the elderly suffering the greatest burden. Children are recognised as playing an important role in the dissemination of the influenza virus. This study examines the population impact of implementing a programme of paediatric vaccination.

A dynamic transmission model was used to simulate the impact of vaccination programmes with varying levels of coverage across pre-school and school age children. These analyses suggest that vaccinating as few as 50% of 2–18 year olds could result in a substantial reduction in the annual incidence of influenza related morbidity and mortality across the population. Herd immunity may extend this protection to the young and the elderly. It is assumed that such programmes would be implemented in concert with the current strategy of vaccinating the elderly and younger at risk groups with an inactivated vaccine.

In England and Wales, paediatric vaccination of two to eighteen year olds reduced the estimated number of general practice consultations, hospitalisations and deaths arising from influenza A and B infections by up to 95%. This translates into an annual average reduction of approximately 52,000, 1500 and 1200 events, respectively.

A policy of paediatric vaccination could significantly reduce the clinical burden of influenza in England and Wales, in all age groups, with the added value of herd immunity helping to protect the young and the elderly who are at highest risk of complications.

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1. Introduction

Influenza is a highly infectious disease affecting 5–15% of the overall population worldwide [1] every year, predominantly in the autumn and winter season in temperate regions. Incidence rates are highest in children, especially in congregate settings with rates of up to 50% in children attending day care centres [2]. The burden of influenza in children is substantial, with frequent primary care (general practice) consultations in children under the age of 2 years [3] and in school age children [3,4], as well as a high hospitalisation rate in young children [3,5–7]. As children are thought to be the principal transmitters of influenza in the community [2,8,9], adequate childhood vaccination may efficiently disrupt the transmission and spread of influenza in the population, leading to the

indirect protection (herd immunity) of close household contacts and of the wider community, including vulnerable risk groups with chronic underlying medical conditions and the frail elderly.

Individuals at risk of influenza related complications include those with chronic respiratory, heart, liver or kidney disease, and the immunosuppressed, as well as all individuals over the age of 64 years [10].

Although at risk individuals are currently targeted for seasonal vaccination in England and Wales and a number of other European countries, vaccination rates in most countries are suboptimal although coverage of the elderly is often better than that of clinical risk groups [11,12]. A recent survey has shown that vaccination rates in the elderly differ considerably across Europe [12], being highest in the UK (70.2%) and lowest in Eastern European countries such as Poland (13.9%). Furthermore, evidence is accumulating that vaccination of the elderly with an inactivated vaccine offers only partial protection. Reported estimates of vaccine effectiveness vary widely in the elderly, ranging from 20% to over 50% [13,14].

Vaccination rates in individuals with a chronic medical condition considered at a high risk of developing complications due to influenza are also low, ranging from 56% in the UK to 11% in Poland.

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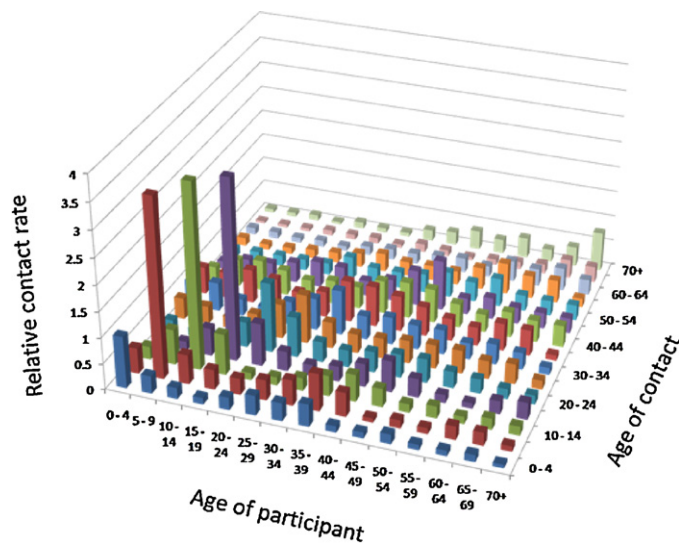


Fig. 1. Who Acquires Infection From Whom (WAIFW) matrix for Great Britain, as derived by the POLYMOD study [16] for both physical and non-physical contacts.

Vaccination rates have increased marginally over the last few years. Non-vaccinated individuals constitute a hard to reach group. In those EU member states where vaccination rates are low due to the absence of funding, childhood vaccination may be an attractive option. Provided adequate coverage is achieved, not only will children be protected but herd immunity could offer protection to at risk groups across the age ranges.

2. Aims and objectives

The aim of this paper is to estimate the potential clinical impact of paediatric influenza vaccination in England and Wales. Specific objectives were to develop a demographic model of England and Wales, to capture the population structure over time, and to create a dynamic transmission model simulating the transmission of influenza and the current influenza vaccination policy. A set of risk functions were developed to translate the incidence of infection into clinical outcomes. The resulting model was used to estimate the impact of vaccinating pre-school and school aged children with a live attenuated influenza vaccine. Clinical impact was quantified as the mean annual number of averted influenza infections and the related general practice consultations, hospitalisations and deaths, over a 15-year time horizon.

3. Methods

3.1. Demographics and age dependent mixing

The model adopts a realistic age structure (RAS), starting with population data for England and Wales in 1980, provided by the Office for National Statistics (ONS). These data are single year of age stratified population numbers [15]. Individuals within the model are aged on a monthly basis. Mortality from causes other than influenza starts from age 65 and thereafter is assumed to be a constant risk, corresponding to a mean life expectancy of 25 years for individuals aged 65 (Table 1).

Individuals in different age groups mix with one another as defined in a UK specific age stratified contact matrix developed by the POLYMOD study [16]. Such matrices are usually referred to as 'Who Acquires Infection from Whom' (WAIFW) contact matrices (Fig. 1) and provide a relative measure of the frequency of contact between individuals of different or similar ages.

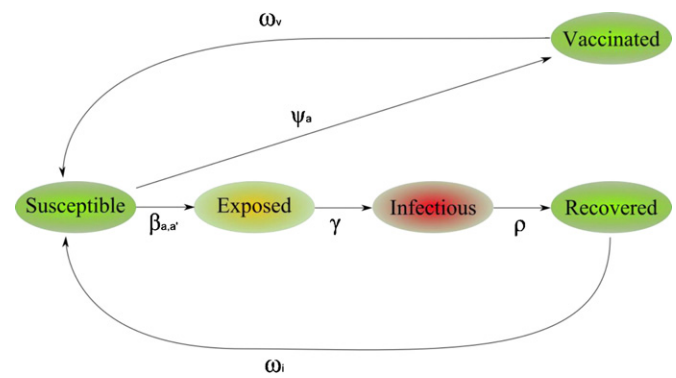


Fig. 2. The structure of the age stratified influenza SEIRS model. These compartments represent the infection status of the population and do not relate to clinical presentation. Infected individuals may or may not be symptomatic. ψ_a is the age dependent rate of vaccination. See Table 1 for a list of the remaining parameters.

3.2. Dynamic transmission model

An influenza transmission model was developed, building on an approach set out previously [17]. For the purposes of this model, influenza is assumed to occur as two sub-types of influenza A (e.g. H1N1 and H3N2) and as influenza B. All subtypes are assumed to be immunologically distinct and to occur every two years, with the A subtypes alternating to give an annual peak in incidence between week 40 and week 20 of the following year.

The dynamic transmission model subdivides the population into 5 subgroups, the Susceptible, Exposed, Infectious, Recovered and Vaccinated populations (Fig. 2). This stratification is based on the influenza virus infection status of members of the population and not on clinical presentation. A set of linked differential equations (see Appendix A) describes the flow of individuals between these subgroups and the system is solved numerically using a fourth order Runge–Kutta method with adaptive step control [18].

Exposed (latently infected) individuals are assumed to be infected for an average of 2 days before becoming infectious [19]. They remain infectious on average for a further 2 days [19], during which time the intensity and duration of viral shedding is assumed to be uniform across the age bands.

Once an individual has recovered from infection, they are assumed to be immune to reinfection with the same subtype. This immunity wanes over time as a result of the combined effects of a gradual decline in immunological memory and antigenic drift on the part of the virus. The resulting duration of protection was assumed to last for 6 and 12 years for influenza A and influenza B, respectively [17].

3.3. The basic reproductive rate

The basic reproductive rate (R_0) is defined as the number of secondary infections arising from one primary infection in a totally susceptible population [20,21]. Using data from past pandemics, R_0 for influenza has been estimated to range from 1.6 to 3.9 [22,23]. A value for the transmission coefficient was chosen, corresponding to a conservative R_0 of 1.8, calculated using the dominant eigenvalue of the next generation matrix [24,25].

3.4. Seasonality

The incidence of influenza follows a marked seasonal pattern. Peak incidence was assumed to occur on December 22 and to reach a minimum on June 23. The magnitude of the basic reproduction number at the peak of influenza incidence compared to baseline was set to 1.43 [17].

Table 1
Outline of the parameters used in the transmission model.

Parameter	Value	Source/comment
Transmission coefficient $\beta_{a,a'}$	3.99×10^{-08}	Chosen to give a mean R_0 of 1.8 [22]
Mean duration of latency $1/\gamma$	2 days	Based on volunteer challenge studies [19]
Mean duration of infectiousness $1/\rho$	2 days	Based on volunteer challenge studies [19]
Mean duration of natural immunity $1/\omega_i$	Influenza A: 6 years Influenza B: 12 years	The duration of protection is likely to be variable. These values are consistent with the observed dynamics of influenza and are consistent with those used by Vynnycky et al. [17]
Mean duration of vaccine induced immunity $1/\omega_v$	Influenza A: 6 years Influenza B: 12 years	Assumed to be equal to natural immunity, unless stated otherwise
Seasonal forcing	1.43	The maximum factor by which R_0 differs from the mean [17,52]. Assumed to be sinusoidal, see text
Annual birth rate	621,300/year	Number of live births per year [15]
Influenza independent mortality rate μ_a	0 for age < 65 years 1/25 years for age > 64 years	Assumed to be zero up to the age of 64. Thereafter, is assumed to be constant [53]

3.5. Imported influenza

In order to capture the influenza dynamics that are observed in England and Wales, the model population had to be seeded each year with new infectious influenza cases [17]. Annually a total of 100 cases were introduced into each one year age band between the ages of 5 and 50 years. Children under 5 years old are less likely to be the first individuals infected in an epidemic [26]. Adults over 50 years of age also tend not to be the first infected, due to pre-existing immunity to circulating strains.

3.6. Model validation

As a check for coding errors and of the model's structure and numerical solution, the RAS model was independently recoded as a set of partial differential equations (PDEs) and run using the baseline set of parameter values for influenza A. Firstly, numerical solutions of the RAS model and the PDE model were compared visually. Secondly, the PDE model population was assumed to mix in a homogeneous fashion and the model was integrated over age to derive an ordinary differential equation (ODE) system in time only. An equilibrium analysis was performed on the ODE system and the numerical solution was compared with that of the PDE system integrated over time. Thirdly, the PDE model was considered at the time-independent equilibrium, resulting in a set of ODEs in age. This system was solved numerically and compared with the equilibrium age profile generated from the full PDE system. The details of this analysis are included in Appendix B.

The simulated age stratified proportion of the population infected was checked for face validity against corresponding data from the Tecumseh study performed in 1978 [27,28]. The Tecumseh data should only be considered as a rough guide as the data are old and probably underestimate the proportion infected, especially in young children [27]. Additionally, population density and mixing patterns are likely to have changed over the intervening years.

3.7. Risk functions and clinical outcomes

In order to translate incident infections into clinical outcomes, the model was used to estimate the mean annual number of new influenza infections, prior to the introduction of any new interventions. An estimate of the annual number of each clinical outcome was taken from a previous study of the burden of influenza [3]. Dividing the mean annual number of each outcome by the mean annual number of infections provided an age stratified estimate of the probability of a new infection leading to a general practice consultation, hospitalisation or death.

The burden of influenza was measured using the age stratified mean annual number of general practice consultations, hospitalisations and deaths over 15 years, from 2009 to 2024 (Appendix A).

3.8. Current practice

Current practice in England and Wales involves vaccinating everyone over the age of 65 years and anyone between 6 months and 64 years of age in a defined risk group [29] with a trivalent inactivated vaccine (TIV). This policy was introduced in 2000.

Vaccine induced immunity was assumed to last for the same duration as natural immunity, with successfully vaccinated individuals transferring directly from the susceptible to the vaccinated subgroup. Vaccination was assumed to have been completed annually by August 31. Simulated coverage rates (the proportion of the population vaccinated) were based on data published by the Health Protection Agency for England and Wales [29,30]. The efficacy of TIV was based on prior publications [13,31,32] (Table 2).

3.9. Impact of paediatric vaccination

Paediatric vaccination scenarios were constructed combining current practice with strategies to immunise, with a live attenuated influenza vaccine (LAIV), pre-school age children, aged 2–4 years old, on their own or in combination with school age children, aged 5–18 years old. The efficacy of LAIV in children from 2 to 18 years of age was assumed to be 80% [32,33].

Coverage rates for LAIV of 10%, 50% and 80% were explored in each scenario. It was assumed that in those age groups targeted for paediatric vaccination, LAIV was used exclusively, with TIV vaccination of at risk individuals in the rest of the population remaining

Table 2
The percentage efficacy [13,31,32] and uptake of TIV in England and Wales assumed by the model (Health Protection Agency data, www.HPA.org.uk, accessed 22nd January 2010).

Age groups in model	% Efficacy	% Uptake in total population
0–<1	60%	0.1%
1–<2	60%	0.1%
2–<5	60%	1.4%
5–<11	60%	1.4%
11–<19	60%	1.4%
19–<50	75%	5.6%
50–<65	75%	5.6%
65+	50%	73.5%

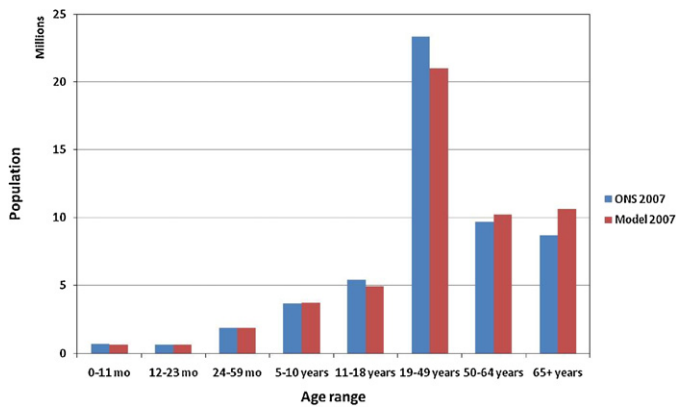


Fig. 3. Age distribution of the population of England and Wales in mid 2007, as estimated by the Office for National Statistics (<http://www.statistics.gov.uk/>, accessed 19th May 2010) and by the RAS model used in this analysis.

unchanged. The impact was quantified in terms of the mean annual number of averted incident infections, general practice consultations, hospitalisations and deaths, over 15 years from 2009 to 2024.

3.10. Sensitivity analyses

A one-way sensitivity analysis was performed on the key parameters in the model. Briefly, the impact of varying these parameters on the cumulative incidence of infection per 100,000 population between 1995 and 2020 was estimated, assuming current practice combined with 80% LAIV coverage of children from 2 to 18 years of age.

The parameter variations were:

- the removal of seasonal forcing
- annual seeding reduced from 100 to 10 infections per year class
- R_0 values of 1.4 and 2.2
- Homogeneous mixing, maintaining an R_0 of 1.8 by adjusting the transmission coefficient
- Homogeneous mixing, leaving the transmission coefficient unchanged
- Mixing based on the “physical contact only” UK POLYMOD matrix, rather than the “all contacts” matrix, maintaining an R_0 of 1.8 by adjusting the transmission coefficient
- Mixing based on the “physical contact only” UK POLYMOD matrix, rather than the “all contacts” matrix, leaving the transmission coefficient unchanged
- Allowing vaccination to start on 1st September and gradually increase, achieving the final coverage level on the 16th December
- The duration of vaccine induced immunity reduced to half that of natural immunity

In addition to the one-way sensitivity analysis, two alternative scenarios were examined, along with a multi-way extreme value analysis and a simulation to explore the impact of a mismatched vaccine year. Full details are given in [Appendix A](#).

4. Results

4.1. Demography

The simulated England and Wales population size and age structure over 30 years, taking the population in 1980 as a starting point, was seen to increase and age in line with population data from the Office for National Statistics ([Fig. 3](#)).

4.2. Temporal dynamics of infection

The simulated impact of current practice, introduced in 2000, on the quarterly incidence of influenza ([Fig. 4](#)) produces an initial fall in incidence followed by a partial rebound to a stable cycle with annual peaks below those prior to the introduction of the new policy. This is observed with both influenza A and B, and is consistent with the observed dynamics of laboratory confirmed influenza.

The simulated introduction of paediatric vaccination in 2009 produces a further reduction in incidence that is more pronounced at higher levels of vaccination coverage and for influenza B.

The annual incidence of influenza A exceeded that of influenza B and vaccination at a given level of coverage had a greater impact on the incidence of influenza B, than influenza A. Both these observations are consistent with the longer duration of natural immunity to B.

The consequence of each paediatric vaccination scenario, relative to current practice, can be summarised by the mean annual number of averted influenza infections, over the 15-year time horizon of the model.

4.3. Averted infections

Targeting two to eighteen year olds, the mean annual numbers of averted incident infections of influenza A over the 15 years of model simulation were 1.6 million, 4.3 million and 4.9 million at coverage rates of 10%, 50% and 80% respectively. These represent a percentage reduction of 32%, 84% and 96% respectively. The corresponding figures for influenza B were 0.67 million (56%), 0.97 million (81%) and 1.1 million (90%).

Targeting paediatric vaccination at the more restricted age range of pre-school age children (2–4 years of age) at a coverage rate of 80% reduced the mean annual incidence by 1.8 million (36%) and 0.8 million (64%) for influenza A and B respectively.

Vaccinating 10% of 2–18 year olds is predicted to prevent, on average, 1 million influenza A and B infections per year in those vaccinated, with herd immunity preventing, on average, a further 1.2 million (<2 years: 0.08 million; 19–49 year: 0.8 million; 50–64 years: 0.3 million; 65+ years: 0.07 million) ([Fig. 5a](#)).

Increasing vaccination coverage in 2–18 year olds to 50% would prevent a mean of 2.3 million influenza A and B infections per annum in this age group and a further 3 million as a result of indirect protection (<2 years: 0.2 million, 19–49 year: 2 million, 50–64 years: 0.7 million, 65+ years: 0.2 million).

The model suggests that only modest additional gains would be made by further increasing vaccine coverage to 80% in 2–18 year olds, preventing an average of approximately 2.4 million influenza A and B infections per annum in this age group, with indirect protection preventing a further 3.5 million infections (<2 years: 0.2 million, 19–49 year: 2.3 million, 50–64 years: 0.8 million, 65+ years: 0.2 million).

A high level of vaccination coverage (80%) of pre-school age children aged two to four years is estimated to prevent a similar number of infections as 10% coverage of 2–18 year olds, with an annual average of 0.2 million infections prevented in the target age group and herd immunity averting a further 2.4 million (<2 years: 106,000; 5–18 years: 1 million; 19–49 year: 840,000; 50–64 years: 310,000; 65+ years: 75,000).

4.4. Progression from infection to clinical outcomes

The predicted probability of an influenza infection leading to a general practice consultation was approximately 30% in children under five years old. This fell to approximately 10% in five to sixty-four year olds, before rising to approximately 50% in people over sixty-four years of age.

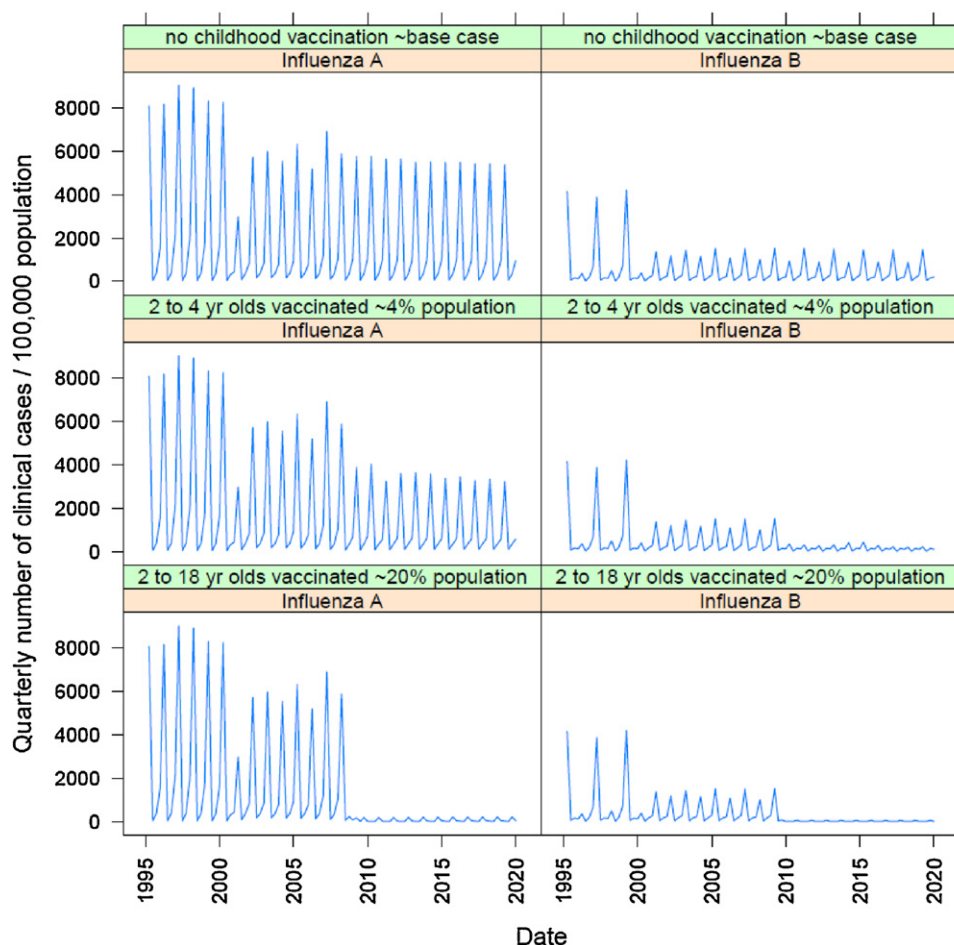


Fig. 4. The estimated quarterly annual incidence of clinical cases per 100,000 population for influenza A (left hand panel) and influenza B (right hand panel). The top row simulates current practice, with vaccination of risk groups and the elderly with TIV commencing in 2000. The middle row assumes 80% of all 2–4 year olds are vaccinated with LAIV from 2009, on top of current practice. In the bottom row, the target group is expanded to cover 2–18 year olds, with the same 80% coverage rate with LAIV from 2009, on top of current practice.

The corresponding predicted probabilities for hospitalisations show a similar pattern, with children under the age of five years experiencing a higher annual risk than in individuals who are five to sixty-four years old; 0.7% in children under five years old vs. 0.002% in those five to ten years old, rising to 0.2% in adults who are fifty to sixty-four years old. The annual probability of hospitalisation is highest in those over sixty-four years old, at approximately 8%.

The predicted probability of infection leading to death was under 0.001% in children under eleven years of age, rising to approximately 0.07% in fifty to sixty-four year olds. The corresponding risk of death increased considerably in the over sixty-four year olds, to approximately 9%, although the greater part of this risk is likely to be concentrated in the oldest individuals.

4.5. Averted clinical outcomes

Paediatric vaccination of two to eighteen year olds, at coverage rates of 10%, 50% and 80%, reduced the simulated mean annual number of general practice consultations resulting from influenza A and B infections in the entire population by 310,000 (37%), 690,000 (84%) and 790,000 (95%) respectively. Corresponding figures for hospitalisations were 8000 (34%), 19,000 (78%) and 23,000 (94%) and for deaths were 6000 (33%), 15,000 (76%) and 18,000 (94%).

An 80% coverage of 2–4 year olds reduced the mean annual number of consultations, hospitalisations and deaths in the entire population by 360,000 (44%), 10,000 (40%) and 7000 (36%).

Vaccinating 10% of two to eighteen year olds is predicted to avert an annual mean of 140,000 general practice consultations in this age group and a further 160,000 in the wider population, as a result of indirect protection (<2 years: 25,000; 19–49 years: 75,000; 50–64 years: 25,000; 65+ years: 36,000) (Fig. 5b).

Increasing coverage of 2–18 year olds to 50% significantly increases the mean annual number of consultations averted, with 310,000 prevented by vaccination in the target age group and herd immunity preventing 390,000 more (<2 years: 56,000; 19–49 years: 187,000; 50–64 years: 60,000; 65+ years: 82,000).

Further increasing the coverage to 80% of 2–18 year olds results in diminishing returns reflecting the pattern of infection, annually preventing a mean of 330,000 consultations in those age groups receiving the vaccine and herd immunity averting 463,000 additional consultations (<2 years: 63,000; 19–49 years: 223,000; 50–64 years: 74,000; 65+ years: 103,000).

The corresponding figures for 10% coverage of 2–4 year olds were 185,000 consultations prevented in the targeted age groups, with indirect protection averting a further 180,000 (<2 years: 32,000; 19–49 years: 80,000; 50–64 years: 28,000; 65+ years: 39,000).

The skewed nature of the probability of hospitalisation or death with age, once infected with influenza, is apparent in the number of these outcomes averted by paediatric vaccination.

Within those age groups targeted, vaccination of 10% of 2–18 year olds is estimated to prevent an annual mean of approximately

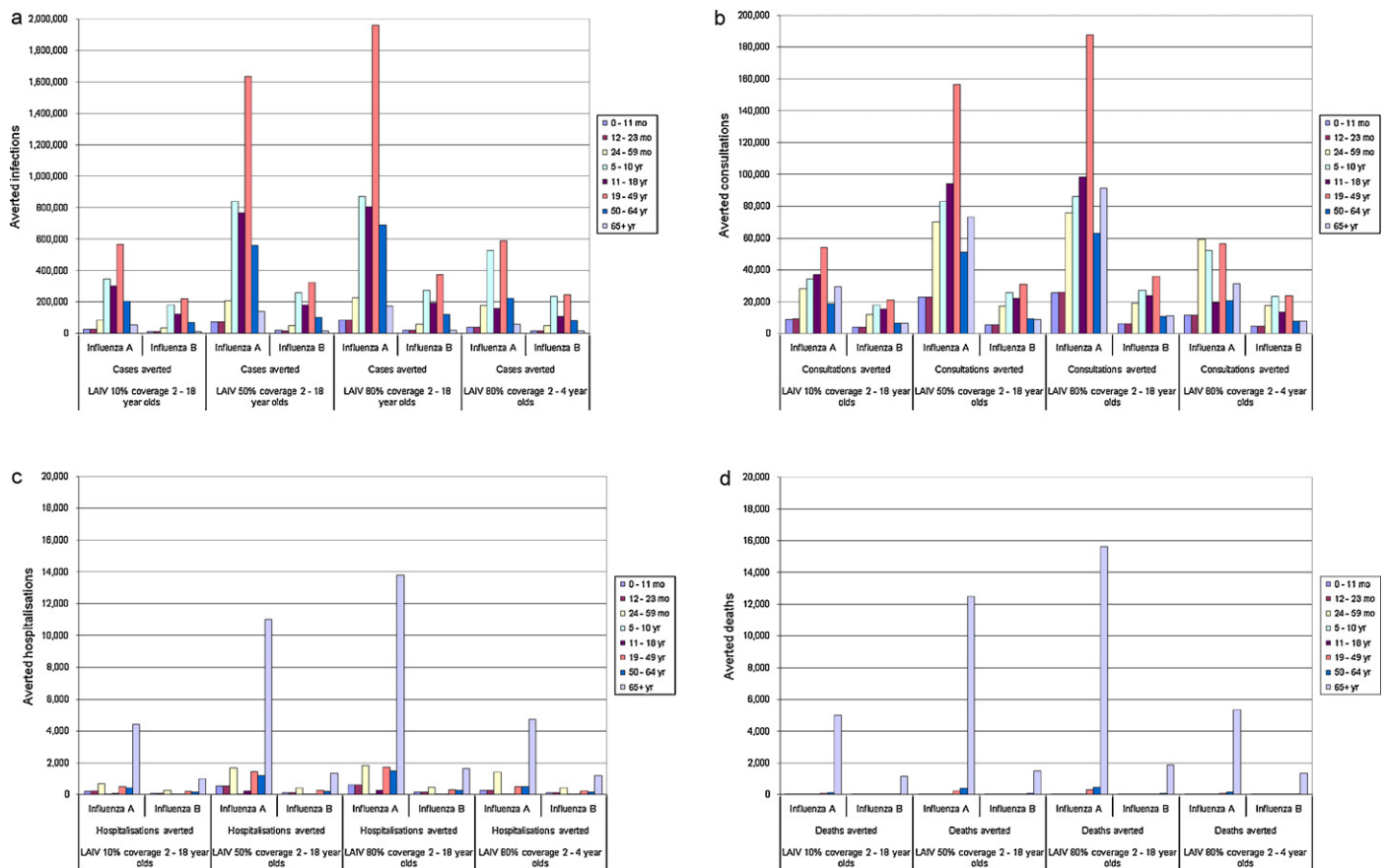


Fig. 5. (a) The estimated mean annual number of *averted* infections between 2009 and 2023 by age group, relative to current practice. The first three panels illustrate the impact, on influenza A and B, of vaccinating 2–18 year olds with LAIV, at coverage rates of 10%, 50% and 80% respectively. The final panel illustrates the impact of targeting the more restricted age range of 2–4 year olds with LAIV at an 80% coverage rate. (b) The estimated mean annual number of averted General Practice consultations between 2009 and 2023 by age group, relative to current practice. Intervention scenarios as for part figure a. (c) The estimated mean annual number of averted hospitalisations between 2009 and 2023 by age group, relative to current practice. Intervention scenarios as for part figure a. (d) The estimated mean annual number of averted deaths between 2009 and 2023 by age group, relative to current practice. Intervention scenarios as for part figure a.

1000 hospitalisations (Fig. 5c) and fewer than 20 deaths (Fig. 5d). Herd immunity in the remaining population would prevent 7300 hospitalisations and 6500 deaths, of whom 5400 (74%) and 6100 (95%) respectively are in the elderly over 64 years of age.

At 50% coverage of 2–18 year olds, the model predicts that 2400 hospitalisations and approximately 40 deaths per year would be prevented in the targeted age groups, with indirect protection in the remaining population averting a further 16,800 hospitalisations and 14,700 deaths of whom 12,300 and 14,000 respectively are in the elderly.

Vaccinating 80% of 2–18 year olds is estimated to prevent 2600 hospitalisations and 40 deaths in those targeted and to indirectly avert 20,700 hospitalisations (15,400 in 65+ year olds) and 18,400 deaths (17,500 in 65+ year olds).

4.6. Validation

The PDE model produced simulations of the temporal dynamics of infection and the equilibrium age distribution that were very close to those generated by the ODE model (Appendix B for full details). Exact correspondence would not be expected, as the models are structurally different.

The pattern in the proportion of the population that is infected by age is consistent with that observed in the Tecumseh studies in the 1970s [27], particularly for influenza A (Fig. 6a). The simulated peak incidence of influenza B in school aged children corresponds well with these data, however, in the older age classes the model

predicts a prevalence of infection that is approximately 5% higher than the Tecumseh data (Fig. 6b).

4.7. Sensitivity analysis

The sensitivity analysis outlined in Appendix A demonstrates that, while the number of averted case is influenced to varying degrees by changes in the parameter values, the qualitative results are robust, with paediatric vaccination likely to result in a substantial number of averted primary care consultations, hospitalisations and deaths.

5. Discussion

This study builds on previous influenza transmission modelling [17] which examined the potential impact of paediatric influenza vaccination on the incidence of disease and mortality in England and Wales but did not formally analyse or quantify the potential implications for GP consultations, hospitalisations and deaths. The concepts drawn from that paper were the use of waning immunity to simulate antigenic drift and the annual seeding of the population with new infectious individuals.

This manuscript extends the analysis to look at the impact of paediatric vaccination on clinical outcomes: GP consultations, hospitalisations and deaths, and encompasses both the trivalent inactivated vaccine and a live attenuated vaccine that has recently been licensed for use in Europe.

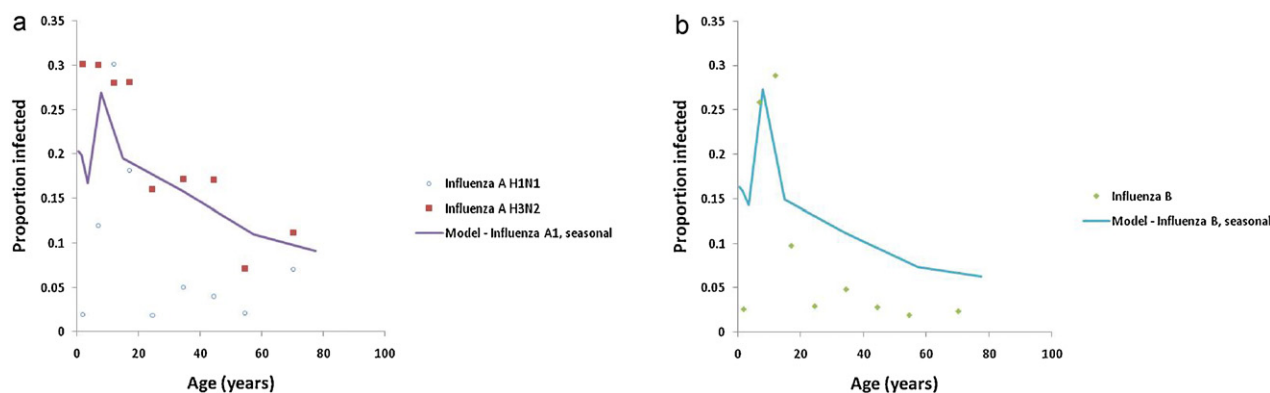


Fig. 6. (a) The observed proportion of the population infected with influenza A in Tecumseh 1967–8 [27] and as predicted by the RAS model. A1 refers to a single influenza A sub-type. Specific sub-types were not explicitly modelled, so A1 could be H1N1 or H3N2. (b) The observed proportion of the population infected with influenza B in Tecumseh 1977–8 [27] and as predicted by the RAS model.

This analysis demonstrates that paediatric influenza vaccination has the potential to significantly reduce the clinical burden of influenza in England and Wales. The estimated proportion of infections prevented across the entire population is consistent with previous modelling estimates [17,34].

Children under the age of 5 years, and in particular those under 2 years, experience the highest annual rate of general practice consultations and hospitalisation per 100,000 population [3] and therefore stand to benefit from a programme of paediatric vaccination, even if they themselves are not vaccinated.

Children are believed to be efficient transmitters of the virus, for a number of reasons [2,8,9]. There is some evidence for more intense and prolonged shedding of the virus in children [35,36] and for frequent contacts between children and between children and adults [16]. Disrupting this transmission by vaccinating children may have the additional effect of protecting the wider community through the indirect protection offered by herd immunity [37,38].

The simulated effect of indirect protection is apparent in, for example, the age stratified number of averted influenza infections (Fig. 5a). Where pre-school and school age children are vaccinated, the model suggests that the greatest number of averted infections is in the 19–49 year old age class, consistent with available data [39]. Averted infections are predicted in all age classes, including the very young and the elderly who are at greatest risk of hospitalisation and death. This is further reflected in the number of general practice consultations, hospitalisations and deaths avoided across the age ranges, with the elderly in particular protected from hospitalisation and death. It is of note that these gains would be achieved by targeting an age group (2–18 year olds) that make up approximately 20% of the population.

The greatest increase in the number of infections averted occurs when increasing coverage from 10% to 50%, suggesting that higher rates of coverage may produce diminishing returns. This is especially true when the target age range is restricted. An 80% coverage of 2–4 year olds results in a comparable number of averted cases to 10% coverage of 2–18 year olds.

The quantitative details of the simulations were found to vary depending on the parameter values chosen, particularly the value of those parameters with a direct bearing on the basic reproductive rate, such as the transmission coefficient and the age stratified pattern of population mixing. The qualitative pattern was, however, robust, with the largest number of primary care consultations averted in 19–49 years olds, as well as in children over one year of age and the elderly. Paediatric vaccination is estimated to prevent up to 95% of hospitalisations and deaths resulting from influenza, 74% and 95% of which, respectively, occur in the elderly. As infections that lead to hospitalisation are those with the highest

level of morbidity and have the greatest impact on the health service, the indirect effects of vaccination have the potential to influence the overall effectiveness and cost-effectiveness of a paediatric vaccination programme. The cost-effectiveness of paediatric vaccination strategies will be addressed in a separate paper.

There has been some debate as to the strength of the indirect protection effects associated with influenza vaccination [40], however a recent randomised controlled study to quantify these effects has been completed in 3273 children of 36 months to 15 years of age in 49 Hutterite colonies in Alberta, Saskatchewan, and Manitoba, Canada [41]. A total of 947 were vaccinated against influenza using TIV and 2326 community members received a hepatitis A vaccination as a control. At a mean TIV coverage rate of 83% (range, 53–100%), indirect protection of non-recipients of the influenza vaccine had a protective effectiveness of 61% (95% confidence interval, 8–83%; $P = .03$). The overall protective effectiveness (direct and indirect protection) was estimated to be 59% (95% CI, 5–82%; $P = .04$). Bearing in mind that this randomised controlled study was over a single season, used TIV rather than LAIV and targeted a slightly narrow age range, the estimate of indirect protection is consistent with that estimated in this paper.

The long-term impact of vaccination on the dynamics of influenza transmission depends in part on the degree of cross protection between different strains, imparted by the vaccine. This analysis has highlighted the potential importance of herd immunity in preventing influenza in high risk groups. A long-term programme of vaccination may, however, alter the breadth of this herd immunity.

The influenza virus evolves away from the herd host immune protection by a process of antigenic shift and drift [42,43]. Each individual host immune system comprises a repertoire of immunities to strains that had previously infected that individual. This natural immunity is long term and has some level of cross-protection against strains not previously experienced by that individual. Thus the natural herd immunity of a population is based on the collective experience of influenza over the last 50 years and is cross-protective to varying degrees against other related strains as well.

It can be assumed that vaccine induced immunity is less cross-protective and possibly shorter lived than natural immunity, although studies of the duration of immunity in naturally exposed individuals and from time series data have proved inconclusive [44,45]. If an effective seasonal influenza vaccination strategy were in place for 50 years, the herd immunity of the population will comprise the collective experience of annual influenza vaccination over the last 30 or so years (as the immunity from 30 to 50 years will have waned and natural infection would have been rare). This new

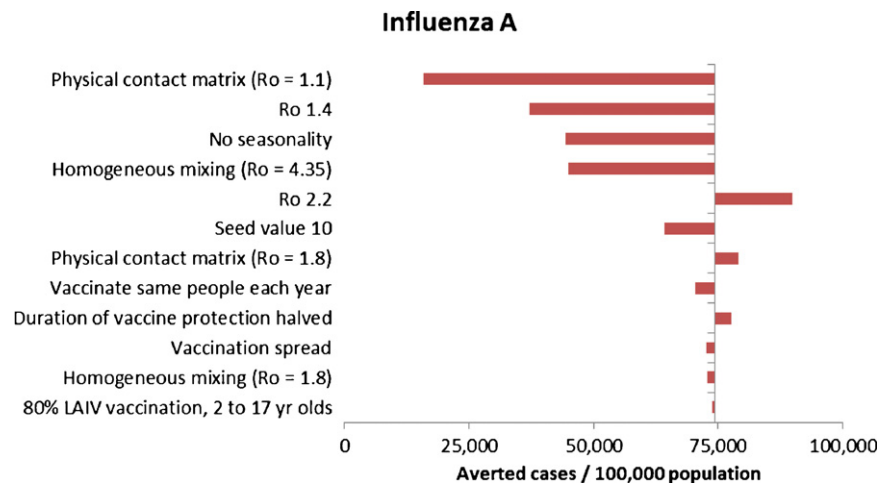


Fig. A1. Sensitivity of the cumulative number of averted influenza A cases per 100,000 population, from 2009 to 2020, to changes in the model parameter values, relative to the estimated 74,295 averted by vaccinating 80% of all 2–18 year old children with LAIV in addition to current practice.

herd immunity will be at a high level, but its antigenic scope may be narrower than the natural herd immunity counterpart, possibly leading to an increased susceptibility to strains that have undergone antigenic drift or shift.

Strains that have undergone antigenic shifts have the potential to cause pandemics, as was observed in 2009. These emerging strains typically infect and cause morbidity in younger individuals than those responsible for seasonal influenza [46,47]. With the emergence of A(H1N1)v following the 2009 pandemic, this shift in the age distribution of infection towards younger individuals is likely to increase the direct benefits of paediatric vaccination.

The temporal dynamics of influenza infection further illustrate the need to assess influenza vaccination strategies over an extended time horizon. Following the introduction of a new programme of vaccination, the incidence of infection would be expected to follow a well recognised pattern [48,49]. There is an initial drop in incidence, called the honeymoon period, brought about by the addition of protection arising from immunisation to the existing naturally acquired immunity. The resulting fall in incidence leads to a reduction in naturally acquired immunity, allowing a partial rebound. Infection incidence then settles into a new suppressed cycle. This pattern is consistent with the observed pattern of laboratory confirmed influenza in England and Wales.

While the temporal pattern of influenza incidence is consistent with the available observed data, the lack of recent population wide data on infection incidence and prevalence is a limitation to modelling influenza transmission. The collection of good quality population level data on the incidence and prevalence of influenza infection would help to reduce uncertainty when calibrating such models. However, alternative analyses of the impact of vaccination policies, which fail to account for the dynamic nature of transmission, risk seriously underestimating the potential effects of such policies.

A further weakness in the model is the inconclusive nature of data on the duration of vaccine induced immunity as well as on that arising from natural infection. Should the duration of vaccine induced immunity be significantly shorter than its naturally arising counterpart, then the impact of paediatric vaccination would be reduced.

While multiple studies have shown the indirect benefit (herd immunity) in adults through vaccinating children against influenza [41,50,51], each of these studies used different study designs resulting in variability in the estimated benefits. Additional studies comparing real world dynamics of influenza transmission against dynamic models are of interest.

This analysis demonstrates the complex and inter-related nature of factors influencing the evaluation of paediatric influenza vaccination. While there remains uncertainty in many of the parameters, the qualitative picture emerging suggests that paediatric vaccination may result in substantial benefits to children, as well as to those at risk of influenza related complications and to the elderly.

Appendix A.

A.1. Demography

Underlying this analysis is a realistic age structured (RAS) demographic model that simulated the population of England and Wales from 1980 through to 2024. The starting data derives from national population statistics, collated by the Office for National Statistics (ONS, <http://www.statistics.gov.uk/>, accessed 6th January, 2009).

Individuals are born and the population is aged at the end of each month:

$$P_m = 51,775 \quad \text{for } m = 0$$

$$P_m = P_{m-1} \quad \text{for } m = 1-1200 \text{ months}$$

where P_m is the number of individuals of age m (in months) in the population.

Natural mortality attributed to all causes other than influenza is applied as a continuous function:

$$\frac{dP_a}{dt} = \mu_a P_a(t)$$

$$\text{for } a = 0-65 \text{ years, } \mu_a = 0$$

$$\text{for } a = 66-100, 1/\mu_a = 25$$

A.2. Transmission model

The dynamic transmission model compartmentalises the population solely on the basis of individual's age and their immunological and influenza infection status. These compartments are composed of Susceptible, Exposed (latently infected), Infectious, Recovered and Vaccinated individuals. It is assumed that a proportion, that is less than 100%, of infectious individuals are symptomatic and that all symptomatic individuals are at some point infectious.

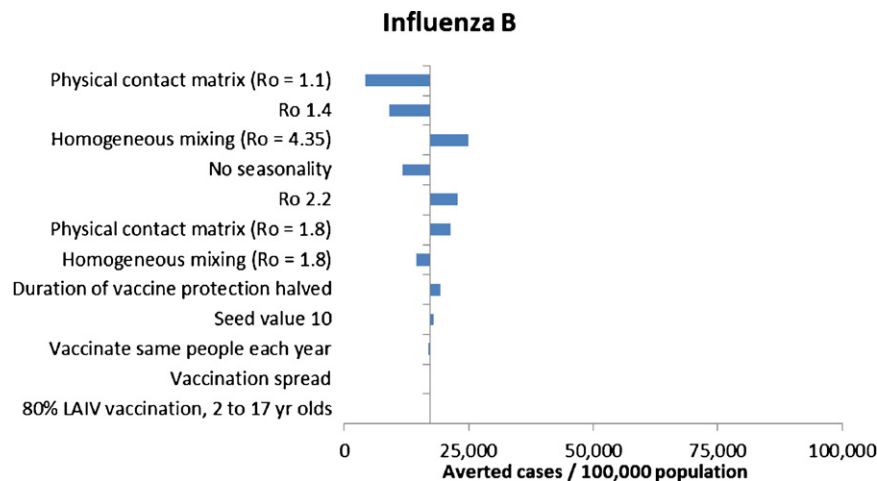


Fig. A2. Sensitivity of the cumulative number of averted influenza B cases per 100,000 population, from 2009 to 2020, to changes in the model parameter values, relative to the estimated 17,220 averted by vaccinating 80% of all 2–18 year old children with LAIV in addition to current practice.

The flow of individuals between each of the compartments, including the dynamics of influenza transmission, progression and recovery, are described by the following set of linked differential equations, for $a = 0, 1, 2, \dots, 100$ years of age:

$$\frac{dS_a}{dt} = \omega_v V_a(t) + \omega_i R_a(t) - S_a(t)[\mu_a + \psi_a + \lambda_a(t)]$$

$$\frac{dE_a}{dt} = \lambda_a(t) S_a(t) - E_a(t)[\mu_a + \gamma]$$

$$\frac{dI_a}{dt} = \gamma E_a(t) - I_a(t)[\mu_a + \rho]$$

$$\frac{dR_a}{dt} = \rho I_a(t) - R_a(t)[\mu_a + \omega_i]$$

$$\frac{dV_a}{dt} = \psi_a S_a(t) - V_a(t)[\mu_a + \omega_v]$$

where ω_v and ω_i are the rate of loss of vaccine induced and naturally acquired immunity respectively. The natural death rate is given by μ_a , the average latent period by $1/\gamma$ and the duration of infectiousness as $1/\rho$. The age dependent vaccination rate is signified by ψ_a and $\lambda_a(t)$ represent the age dependent force of infection in the model

$$\lambda_a(t) = z(t) \sum_{a'} \beta_{a,a'} I_{a'}(t)$$

where $\beta_{a,a'}$ is the transmission coefficient describing the rate of contact and probability of transmission from individuals of age a' to those of age a . The term $z(t)$ is a sine wave function emulating the seasonal fluctuation in the force of infection:

$$z(t) = 1 + q \cdot \sin\left(\frac{2\pi(t-p)}{365}\right)$$

where t is the number of days since the start of the simulation, q controls the amplitude and p the phase of the wave.

These first order ordinary differential equations were numerically solved using a fourth-order Runge–Kutta method with adaptive step control [18].

The dynamic transmission model was programmed in Fortran and the outputs saved in comma delimited text format for subsequent import into Microsoft Excel for graphical presentation.

A.3. Averted infections

The number of infections averted by the instigation of a programme of paediatric vaccination was used as the basic outcome measure from the dynamic transmission model.

The incidence of influenza A infection for age group i on day d , z_{di} , is given by

$$z_{di} = \int_T^{T+1} \sum_{a=j}^{j'} \lambda_a(t) \cdot S_a(t) dt$$

that is the sum of incident cases from time T at the start of day d to the start of the following day at time $T+1$, in age group i that encompasses the years of age, a , from j to j' . The number of incident cases of age a , at time t , is the product of the force of infection, λ_a and the number of susceptible individuals, S_a .

The total number of incident cases, Z_i in age group i between the 1st January 2009 ($d = 10,585$) and 31st December 2023 ($d = 16,059$) was calculated as

$$Z_i = \sum_{d=10,585}^{16,059} z_{di}$$

Let the total incident cases by age group under the current practice be Z_i and the corresponding number in an alternative scenario be Z'_i .

The averted number of infections in age group i , A_i is therefore

$$A_i = Z_i - Z'_i$$

Corresponding figures were calculated for influenza B.

A.4. Sensitivity analysis

A.4.1. One way

A one-way analysis was carried out to establish the sensitivity of the estimated cumulative number of averted cases per 100,000 population, from 2009 to 2020, to changes in the model's parameters, when summed over all age groups (Table A1 and Figs. A1 and A2).

The effect of seasonal fluctuations in the transmission of the virus was removed by setting the forcing function to zero, resulting in a reduction in the number of averted case of 40% and 32% for influenza A and B respectively. Reducing the seeding term to 10, from 100, had relatively little effect on averted cases, reducing the number of influenza A cases by 14% and B cases by 5%.

Changes in the basic reproductive rate had the greatest impact on the number of averted cases. Increasing R_0 from 1.8 to 2.2 resulted in an increase in the number of averted cases, of approximately 20% and 30% for influenza A and B, respectively. Reducing

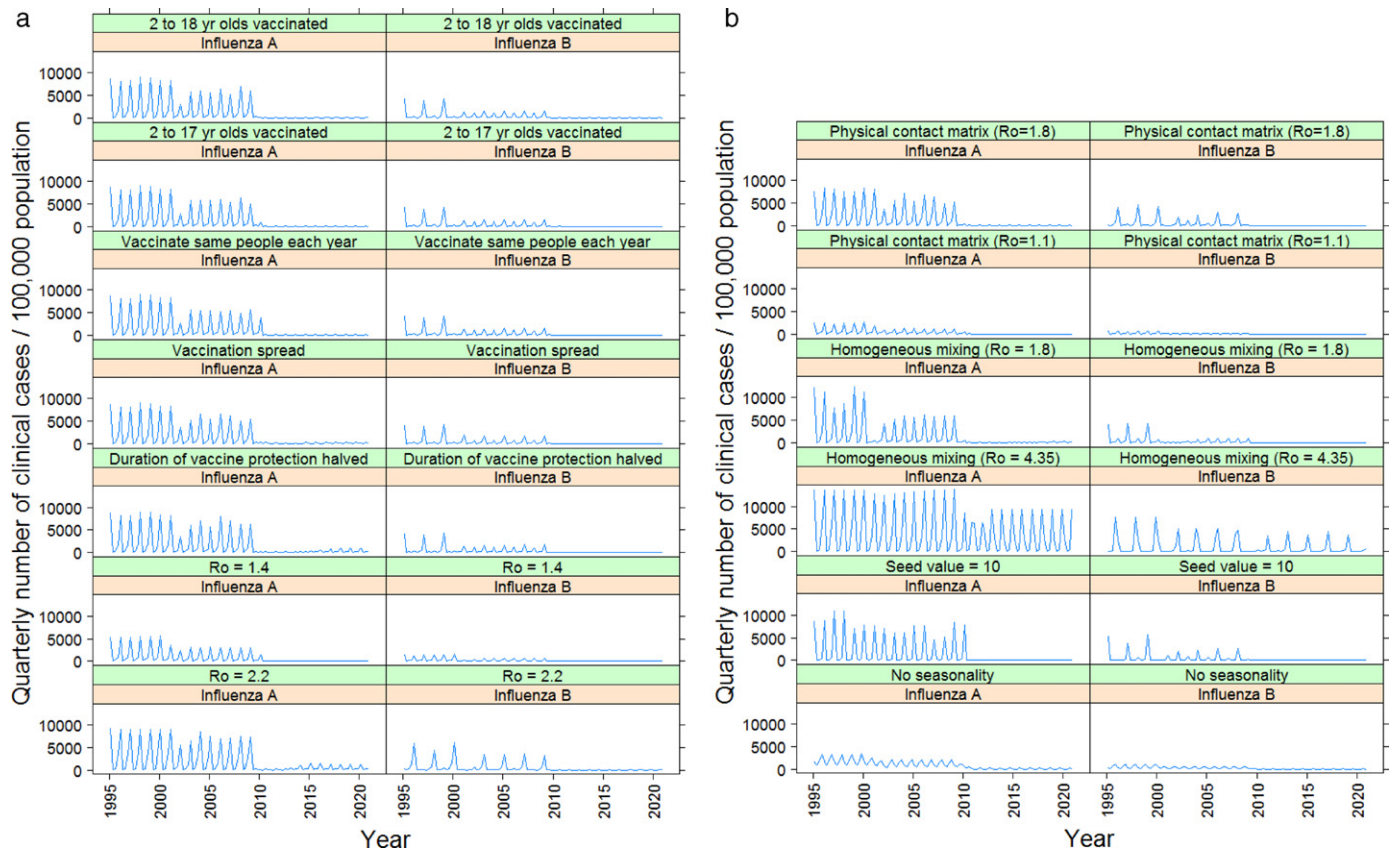


Fig. A3. (a) Sensitivity of the temporal pattern of incidence to changes in model parameters. The traces on the top row are the reference (standard) and assume 80% LAIV coverage of 2–18 year olds. Vaccination of the elderly was simulated to have commenced in September 2000 and paediatric vaccination added in September 2009. (b) Sensitivity of the temporal pattern of incidence to changes in model parameters assuming 80% LAIV coverage of 2–17 year olds. See Fig. 3a for reference traces.

R_0 to 1.4 from 1.8 reduced the number of averted cases by approximately 50% in both cases.

The sensitivity to the value of the basic reproductive rate is reflected in changes resulting from alterations to the pattern of population mixing. If mixing is assumed to occur randomly between individuals of different ages (homogeneous mixing), while maintaining the same viral propensity to transmit (constant transmission coefficient) then the basic reproductive rate increases to 4.35 and the number of averted influenza A cases falls by 39%. A similar effect in the opposite direction is observed for influenza B, with an increase of 44%. If, however, the transmission coefficient

is adjusted to maintain an R_0 of 1.8, then a more modest fall is observed in the number of cases averted with both influenza A and B (2% and 15% respectively).

If mixing is based on the “physical contact only” POLYMOD matrix [16], rather than the “all contacts” matrix, then the number of averted cases falls by 78% for influenza A and 75% for influenza B. This large fall is predominantly the result of R_0 being reduced to 1.1 leading to fewer cases of influenza. Consequently, there are fewer cases to prevent. Adjusting the transmission coefficient to maintain an R_0 of 1.8 resulted in an increase in the number of influenza cases averted rather than a fall, of 6% for influenza A and 24% for B.

As the rate of vaccine uptake in the population may vary, this analysis assumes that all vaccinations are delivered before the start of the influenza season. Relaxing this assumption to allow for a more gradual uptake, starting on the 1st September and continuing to the 16th December made less than a 3% difference to the number of cases averted.

As the duration of vaccine induced immunity is often shorter than that of natural immunity, its duration was reduced to half that arising from a natural infection. This too produced only marginal differences in the numbers of cases averted (5% and 13% for influenza A and B, respectively).

A.4.2. Scenario analysis

On the 1st February 2011, the European Commission granted marketing authorisation to a nasally administered LAIV, for the prevention of seasonal influenza in children aged 2–17 years of age. In order to estimate the impact of reducing the target age range by one year, the model was rerun, simulating the vaccination of this target group and the cumulative number of averted cases per 100,000

Table A1

The cumulative number of averted influenza cases per 100,000 population between 2009 and 2020, summed over all age groups. See text for a description of the scenarios.

Averted cases/100,000 population over 12 years		
Scenario	Influenza A	Influenza B
80% LAIV vaccination, 2–18 yr olds	74,295	17,220
80% LAIV vaccination, 2–17 yr olds	73,740	17,076
Homogeneous mixing ($R_0 = 1.8$)	72,778	14,581
Vaccination spread	72,525	17,053
Duration of vaccine protection halved	77,689	19,389
Vaccinate same people each year	70,406	16,976
Physical contact matrix ($R_0 = 1.8$)	78,971	21,339
Seed value 10	64,107	17,999
$R_0 = 2.2$	89,820	22,665
Homogeneous mixing ($R_0 = 4.35$)	44,950	24,854
No seasonality	44,354	11,756
$R_0 = 1.4$	37,060	9151
Physical contact matrix ($R_0 = 1.1$)	15,795	4279

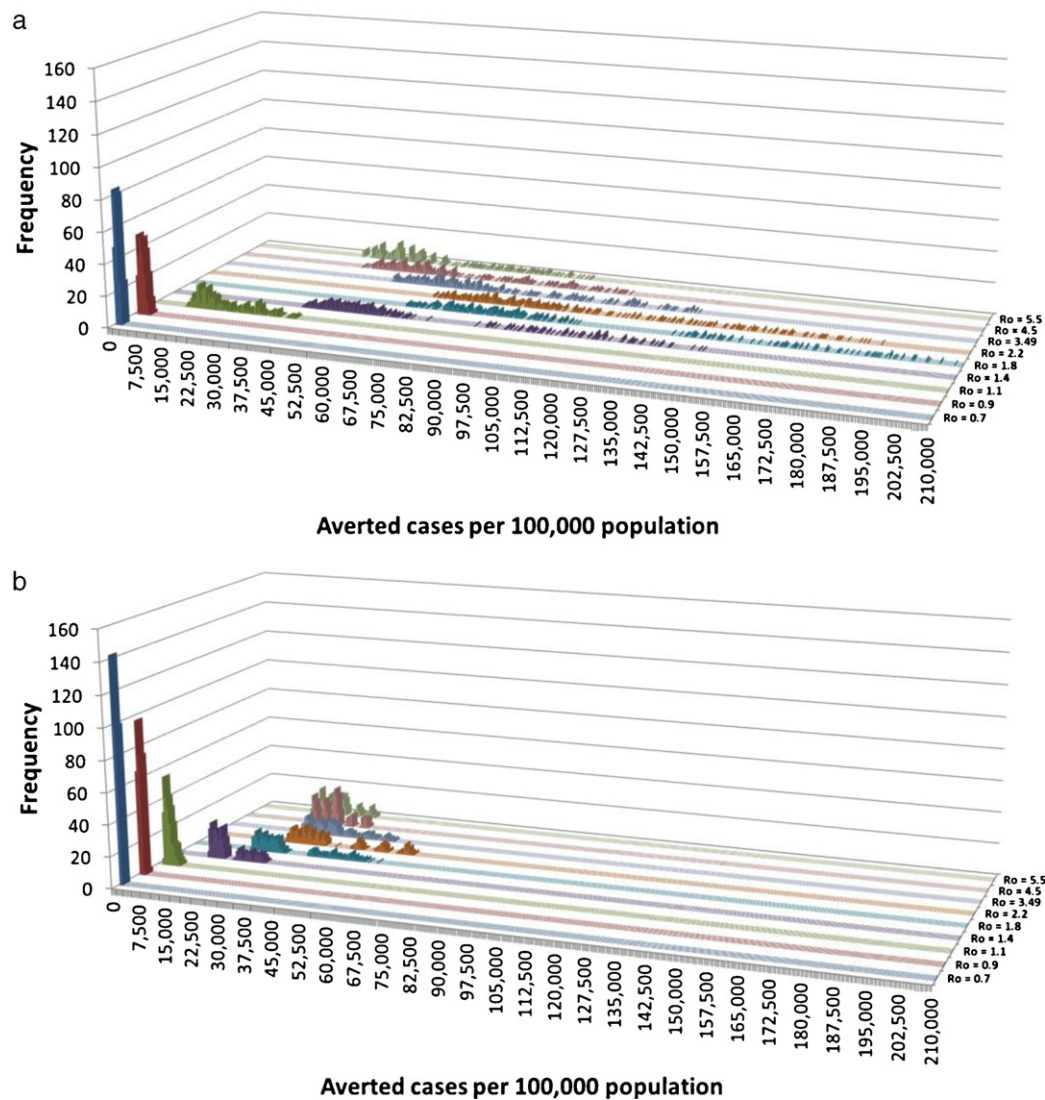


Fig. A4. (a) Simulated distribution of averted influenza cases per 100,000 population caused by influenza A, stratified by R_0 and generated by the extreme value analysis (see text for details). (b) Simulated distribution of averted influenza cases per 100,000 population caused by influenza B, stratified by R_0 and generated by the extreme value analysis.

population over 12 years, calculated in the same way as for the one way sensitivity analysis. This resulted in a fall in the number of cases averted of 0.7% for influenza A and 0.8% for influenza B.

The model assumes that a random selection of individuals are vaccinated each year, however, it is also possible that the same individuals return each year to be vaccinated. Assuming a duration of vaccine induced protection of 6 years against influenza A, this would result in a reduction in the cumulative proportion of children protected from 64% to 40%. Vaccine coverage was lowered to 18% in the model, to reflect this reduction, and the cumulative number of averted cases per 100,000 population over 12 years calculated as above. This resulted in a reduction in the number of cases averted of 5% and 1% for influenza A and B respectively.

A.4.3. Temporal dynamics

The impact of these parameter changes on the temporal dynamics of influenza A and B varied considerably (Fig. A3). Removing seasonal forcing resulted in the dynamics being driven by annual seeding, a reduction in which led to an increase in the inter-epidemic period.

Reducing R_0 also reduced the peak quarterly incidence of cases. A higher R_0 increased peak incidence and made its reduction via

vaccination harder. Allowing the population to mix randomly had a similar effect, resulting from the associated increase in R_0 , from 1.8 to 4.35. Reducing the transmission coefficient to compensate for this increase returns the dynamics to a pattern similar to that seen simulating current practice, except for an extended honeymoon period.

Basing the mixing matrix on the “physical contact only” POLY-MOD matrix [16] while constraining R_0 to a value of 1.8 had very little impact on the dynamics of influenza A. The inter-epidemic period of influenza B was increased by vaccinating the elderly, as was the peak incidence, however, incidence was suppressed to very low levels by LAIV.

Allowing for a more gradual increase in vaccination had little effect, as did assuming the same individuals were vaccinated each year, while halving the duration of vaccine induced immunity allowed the peak annual incidence of influenza to increase.

A.4.4. Extreme value analysis

A multi-way sensitivity analysis was performed by defining a low, expected and high value for the key parameters and running simulations for every possible combination. For n variables there are 3^n combinations. For each combination, an influenza

Table A2

The estimated effect of a mismatched vaccine on the number of clinical outcomes in the 2015/16 influenza season, relative to the same season with a matching vaccine.

		Matched 2015/16 season	Mis-matched 2015/16 season	Difference
Current practice	GP consultations	793,006	937,376	144,370
	Hospitalisations	23,638	30,926	7287
	Deaths	18,726	25,686	6959
Current practice + 50% LAIV coverage in 2–18 year olds	GP consultations	55,812	103,624	47,812
	Hospitalisations	1995	4087	2092
	Deaths	1633	3507	1874

A simulation was run with and without paediatric vaccination and the number of averted cases of symptomatic influenza calculated per 100,000 population between 1995 and 2020, assuming current practice combined with 80% LAIV coverage of children from 2 to 18 years of age. The procedure was then repeated for influenza B. Including all 18 model parameter would have required $3^{18} = 387,420,489$ simulations and taken just over 12 years to complete. In order to be achievable, the following parameters were chosen to vary:

- The transmission coefficient (corresponding to R_0 of 1.4, 1.8 and 2.2)
- The number of infectious cases seeded into the population each year (50, 100, 150)
- The duration of natural immunity (influenza A: 5 years, 6 years, 7 years; influenza B: 11 years, 12 years, 13 years)
- The duration of infectiousness (1 day, 2 days, 5 days)
- The percentage of infected individuals that experience symptoms (55%, 64%, 73%)
- The latent period (1 day, 2 days, 3 days)
- The duration of vaccine induced immunity (Flu A: 3 years, 6 years, 7 years; Flu B: 6 years, 12 years, 13 years)

The distribution of results for both influenza A and B (Fig. A4a and b) display a high peak at low numbers of cases averted. This peak corresponds to values of R_0 below or close to 1. As a results, there are few cases of influenza and so correspondingly few to prevent. As R_0 increases to 1.8, so does the mean number and spread of averted cases. In these simulations, while the virus has the potential to spread, it is still well controlled by paediatric vaccination. Once R_0 increases above 1.8, influenza transmission becomes increasingly difficult to control using paediatric vaccination and the number of averted cases begins to fall.

At a R_0 of 1.8, the base case values of 74,295 and 17,220 averted cases per 100,000 population for influenza A and B lie at the lower end of the simulated distribution, suggesting that our estimates are conservative.

A.4.5. Mismatched vaccine year

In order to explore the potential impact of a mismatched vaccine, two additional simulations were run, in which vaccine efficacy was assumed to be reduced by a factor of 5/8 during the 2015/16 season. The first corresponded to current practice, vaccinating risk groups and the elderly with TIV at efficacies of 38% (6 months–18 years of age), 47% (19–64 years) and 31% (over 64 years). The second simulated paediatric vaccination, in addition to current practice with reduced TIV efficacy as above, with LAIV administered to 50% of 2–18 year olds at an efficacy reduced by 5/8 to 50% [54,55].

Comparing these simulations of a mismatched vaccine in the 2015/16 influenza season with previous simulations of the same season with a matching vaccine, current practice resulted in an estimated additional 145,000 GP consultations, 7300 hospitalisations and 7000 deaths. Corresponding figures for current practice plus LAIV were 48,000, 2000 and 1800, respectively (Table A2).

Appendix B.

The RAS model (as used in the main text) is written as a set of PDEs and the baseline set of parameter values is used to validate the model structure and numerical solution. Firstly, numerical solutions of the RAS model and the PDE model were compared visually. Secondly, the PDE model was assumed to have homogeneous mixing and was integrated over age to derive an ODE system in time only. An equilibrium analysis was performed on the ODE system and the numerical solution was compared with that of the PDE system integrated over time. Thirdly, the PDE model was considered at the time-independent equilibrium, resulting in a set of ODEs in age. This system was solved numerically and compared with the equilibrium age profile generated from the full PDE system.

B.1. Parameter set for model verification and comparison

A single parameter set was used for the RAS, PDE and ODE models for verification purposes.

Parameter	Units	Description
$3.99E-08$	day^{-1}	Transmission coefficient
-101	Days	Offset in days – for seasonality sine wave
100	Count	Number of infectious cases seeded into age bands 5–50 each year
6	Years	Duration of natural immunity
0.43	None	Seasonal forcing
2	Days	Infectious period
51,775	Count	Live births per year
2	Days	Latent period

Annual seeding occurs on the 1st September each year.

B.2. The PDEs

$$\frac{\partial S}{\partial t} + \frac{\partial S}{\partial a} = \omega R(a, t) - S(a, t)[\nu(a) + \lambda(a, t)]$$

$$\frac{\partial E}{\partial t} + \frac{\partial E}{\partial a} = \lambda(a, t)S(a, t) - E(a, t)[\nu(a) + \gamma]$$

$$\frac{\partial I}{\partial t} + \frac{\partial I}{\partial a} = \gamma E(a, t) - I(a, t)[\nu(a) + \rho]$$

$$\frac{\partial R}{\partial t} + \frac{\partial R}{\partial a} = \rho I(a, t) - R(a, t)[\nu(a) + \omega]$$

$$\lambda(a, t) = \tau \sum_{j=1}^c \left[m_{ij} \int_{A(j-1)}^{A(j)} I(a, t) da \right]$$

$$\text{for } a \in (A(i-1), A(i)), i = \{1, \dots, c\}$$

$$S(0, t) = \mu(t)$$

$$\nu(a) = \begin{cases} 0 & \text{for } 0 \leq a < 65 \\ \frac{1}{25} & \text{for } a \geq 65 \end{cases}$$

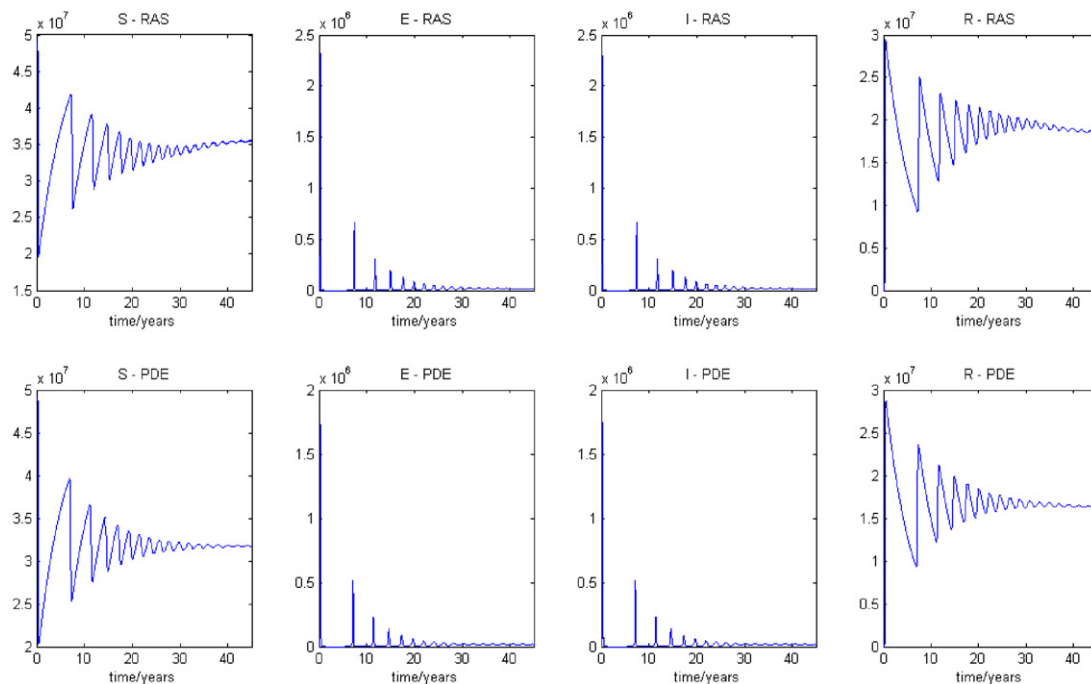
where: $\mu(t)$ is the time dependent birth rate of the population; $\nu(a)$ is the age dependent mortality rate; m_{ij} are elements of the contact matrix divided by the element in position (1,1); c is the number of age categories; τ is a factor that transforms the contact levels into transmission rates, $A(c-1)$ and $A(c)$ are the lower and upper

age limits respectively of age class c . The all contacts mixing matrix [16] was used.

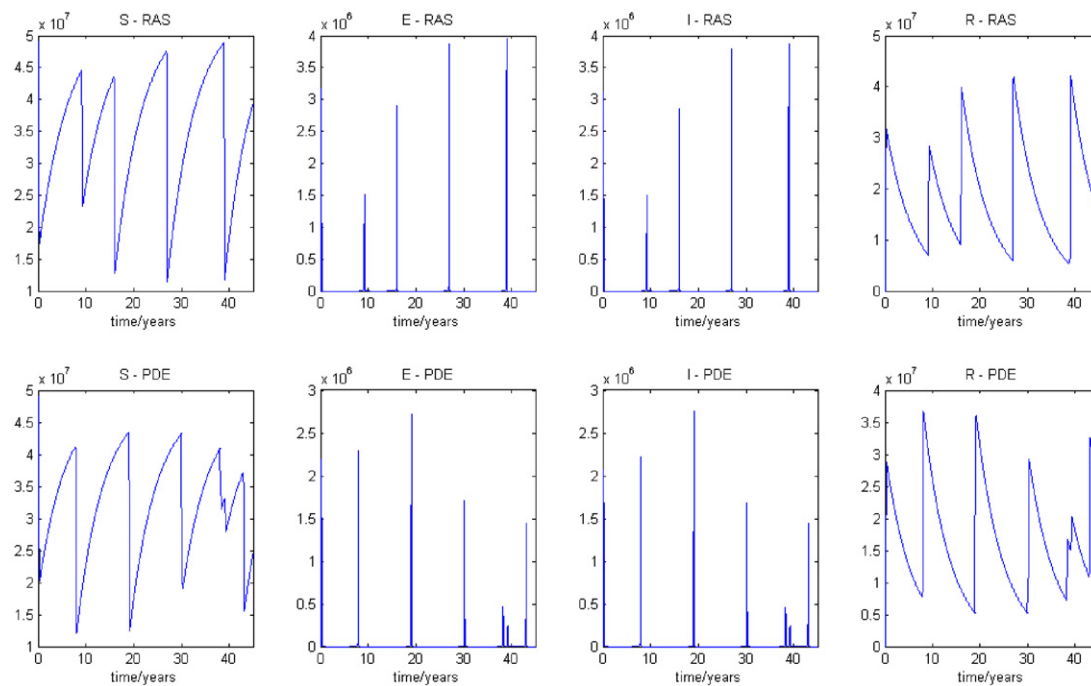
The above equations were solved numerically using the escalator boxcar train method [56], written in matlab, to obtain age distributions varying in time. The PDE model output was compared to the RAS model output for a given set of parameters to verify the

RAS code. The following graphs represent the RAS and PDE model outputs for no seasonality or annual seeding, seasonality and no annual seeding, no seasonality but annual seeding and seasonality and annual seeding respectively. The outputs are similar but not identical. This is to be expected since the RAS model is not structurally identical to the PDE model.

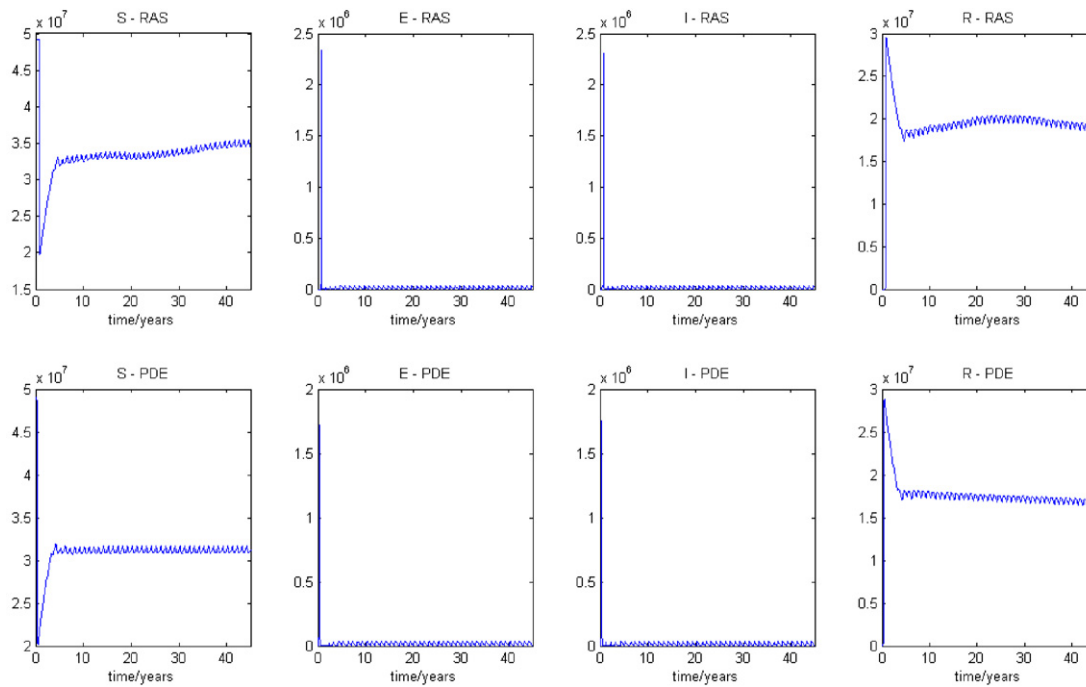
No seasonality and no annual seeding:



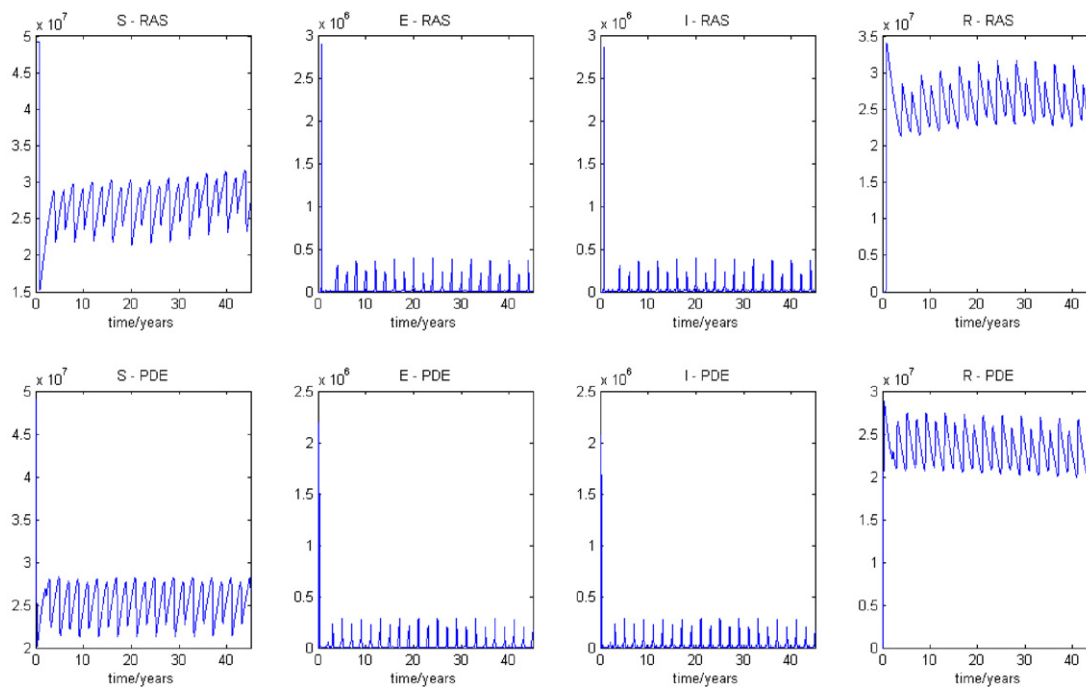
Seasonality and no annual seeding:



No seasonality but annual seeding:



Seasonality and annual seeding:



ODEs in time: The output was compared to the solution of the homogeneous mixing equivalent set of ordinary differential equations (ODEs) in time derived from integrating the PDEs with respect to age to obtain the following equations.

$$\begin{aligned}\frac{dS}{dt} &= \mu N + \omega[N - S(t) - E(t) - I(t)] - S(t)[\mu + \lambda(t)] \\ \frac{dE}{dt} &= \lambda(t)S(t) - E(t)[\mu + \gamma] \\ \frac{dI}{dt} &= \gamma E(t) - I(t)[\mu + \rho] \\ \lambda(t) &= \beta I(t)\end{aligned}$$

We assume homogeneous mixing by giving β as τ multiplied by the mean of m_{ij} . There are two equilibria the trivial disease free equilibrium and the non-trivial disease present equilibrium.

$$\begin{pmatrix} S^* \\ E^* \\ I^* \end{pmatrix} = \begin{pmatrix} N \\ 0 \\ 0 \end{pmatrix} \text{ or } \begin{pmatrix} \frac{(\gamma + \mu)(\rho + \mu)}{\beta\gamma} \\ \frac{(\rho + \mu)(\omega + \mu)[\gamma\beta N - (\rho + \mu)(\gamma + \mu)]}{\gamma\beta[(\rho + \mu)(\omega + \mu) + \gamma(\rho + \mu + \omega)]} \\ \frac{(\omega + \mu)[\gamma\beta N - (\rho + \mu)(\gamma + \mu)]}{\beta[(\rho + \mu)(\omega + \mu) + \gamma(\rho + \mu + \omega)]} \end{pmatrix}$$

Jacobian matrix:

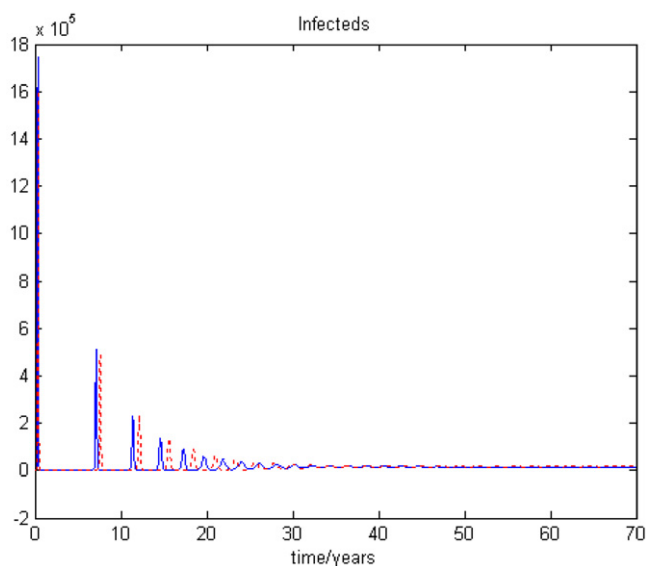
$$\begin{pmatrix} -\beta N I^* - (\omega + \mu) & -\omega & -\beta S^* - \omega \\ \beta I^* & -(\gamma + \mu) & \beta S^* \\ 0 & \gamma & -(\rho + \mu) \end{pmatrix}$$

Define the basic reproduction number

$$R_0 = \frac{\gamma\beta N}{(\gamma + \mu)(\rho + \mu)}$$

The trivial disease free equilibrium becomes unstable when the basic reproduction number is greater than unity. An approximation for the basic reproduction number based on the time independent ODE system and the baseline set of parameter values is 1.5. This value is close to that estimated from the RAS model using the next generation matrix.

The following graph represents a comparison between the PDE model output (solid blue) for infectious individuals compared with that produced from a numerical solution of the ODE system in time (dashed red). The outputs are similar but not identical since the ODE model does not include heterogeneous contacts.



ODEs in age: The time independent equilibrium age distributions can be obtained from the full PDE system by equating the derivatives with respect to time to zero.

Let

$$X = \begin{pmatrix} S^*(a) \\ I^*(a) \\ E^*(a) \\ R^*(a) \end{pmatrix}$$

and

$$J(a, k) = \begin{pmatrix} -\Lambda(k) - v(a) & 0 & 0 & \omega \\ \Lambda(k) & -\gamma - v(a) & 0 & 0 \\ 0 & \gamma & -\rho - v(a) & 0 \\ 0 & 0 & \rho & -\omega - v(a) \end{pmatrix}$$

where

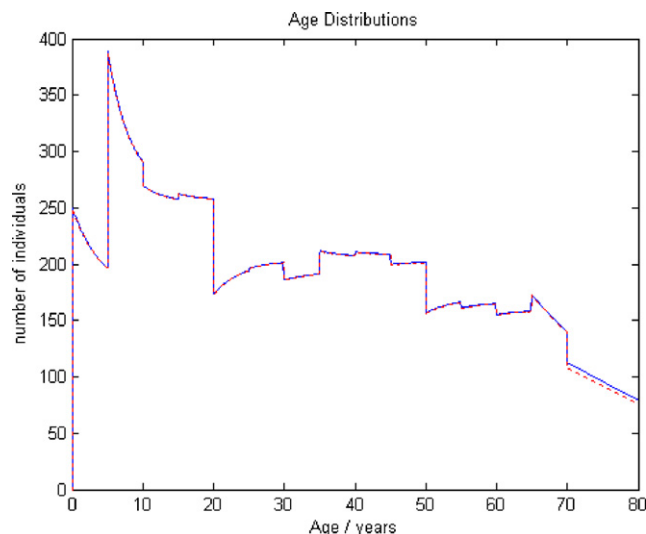
$$\Lambda(k) = \tau \sum_{j=1}^c \left[m_{kj} \int_{A(j-1)}^{A(j)} I(a, t) da \right]$$

Then solve $(dX/da) = J(a, k)X$ to obtain

$$X(a) = X(A(k-1)) \exp[J(a, k)(a - A(k-1))] \text{ for } A(k-1) \leq a \leq A(k), k = (1, \dots, c)$$

This is a piecewise solution of a linear system in each age class using the vector Λ . However the vector Λ involves a sum over all ages. Therefore, the distributions $X(a)$ can be obtained by using an initial guess for Λ , solving the system and recalculating Λ and repeating this process until the solution converges.

The following graph shows the equilibrium age distribution of infected individuals predicted from the PDE model (solid blue) and the ODE system in age (dashed red). These outputs should be and are very similar since the method for calculating this distribution should predict the equilibrium age distribution of the PDE model with numerical but not structural error, and within 70 years, the PDE model has visibly reached this equilibrium.



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