Ageing populations and childhood infections: the potential impact on epidemic patterns and morbidity

John R Williams1,2 and Piero Manfredi2

Background Population decline, arising from below replacement fertility and possibly giving rise to substantial changes in age distribution, is a feature of many industrialized developed countries; Italy is one of the most notable European examples. The potential influence of this phenomenon on prevalence of chronic non-infectious disease is well known, but little attention to date has been paid to the impact on severe disease due to childhood infections in those cases where control is insufficient to achieve elimination.

Methods A transmission dynamics model incorporating realistic demography is used to investigate the possible impact of population decline and ageing and suboptimal vaccination uptake on the age distribution of incidence of measles infection and of consequent mortality. Data from Italy is used to parameterize the model.

Results Population ageing in the absence of vaccination is shown to reduce per capita incidence of infection but also to increase average and upper quartile ages at infection. The effect is substantially enhanced by significantly suboptimal vaccination uptake, when disease-induced mortality has, for a period, the potential to exceed that in the absence of vaccination.

Conclusions Although a substantially increased burden from chronic non-infectious disease has frequently been proposed as a consequence of population decline, there is also potential for an increase in morbidity and mortality from measles and other childhood infectious diseases, particularly where vaccine uptake is substantially below the optimum. Rubella is highlighted as a particular cause for concern. This work also has implications for less-developed countries.

Keywords Age distribution, childhood infections, fertility, health transition, health planning, immunization programs, Italy, mathematical model, measles, non-linear dynamics, population decline, population dynamics, rubella, theoretical models, vaccination coverage

A widespread fall in fertility has been observed in many so-called ‘industrialized developed countries’ (IDC) with consequent population decline and ageing.1 As is well recognized, this presages increased prevalence of chronic non-infectious diseases (e.g. ref. 2). To date, however, it appears that little regard has been paid to the impact of this phenomenon (sometimes termed the ‘second demographic transition’3) upon incidence of childhood infections and corresponding morbidity.

It has been argued that the drop in fertility associated with the ‘first demographic transition’ from rapidly growing to approximately constant population size was, through a consequential increase in average age at infection, associated with decreased mortality from childhood infections.4 It may seem strange, therefore, to consider an ageing population as a potential cause for concern in relation to such infections. However, it should be recalled that the description ‘childhood...
infectious diseases' was acquired simply as a result of historic average ages at infection resulting from interactions at the time between demography, the epidemiology or ecology of these infections, and their inducement of lasting immunity following recovery.\(^5\) The present onset of a period of significant demographic change in IDC and other countries has the potential to strongly influence these interactions and warrants further investigation.

For a specific disease the age-related per capita incidence of infection among susceptible individuals (i.e. the force of infection [FOI]), may vary over time. It is strongly influenced by patterns of contact between age groups and by population age distribution.\(^5\) Using the example of measles in Italy, the question addressed here is to what extent age distribution of infection is influenced by the process of population ageing. This is an important issue because of the observed linkage between increasing age on infection and measles morbidity and mortality, so with more infections in higher age groups increased numbers of deaths and serious disease may follow (Figure 1 shows age-related measles mortality data (diamond markers) from Black\(^6\) and a fitted curve, combining initial exponential decay with a logistic curve; c.f. also Eichner\(^7\) ). Although here measles is considered, the conclusions apply with similar force to other childhood infections, mutatis mutandis.

While there is a safe and effective vaccine against measles, high vaccination rates are required to achieve elimination. To date many countries, including Italy, have fallen far short of such a target.\(^8\) By reducing annual per capita infection risk, the introduction of vaccination is itself expected to increase average age at infection,\(^5\) although this effect is, clearly, transient where vaccine uptake is sufficiently high to achieve elimination.

Among IDC, Italy has experienced one of the most dramatic declines in fertility and potentially a very rapidly ageing population (Figure 2) (other examples are Spain and some Central and Eastern European countries\(^3\) ). Thus Italy serves as a useful laboratory for considering epidemiological effects of these processes. Here we investigate their potential influence on age at infection using a transmission dynamics model incorporating age structure\(^5\) and which is capable of realistic representation of Italian demography. We demonstrate, both in the particular case of Italy and more generally, that potential effects on age distribution of infection are quite dramatic, with consequent significant increases in morbidity and mortality. It is anticipated that similar, more or less dramatic, effects would be shown for other infections, with or without the presence of vaccination.

---

**Figure 1** Curve fitted to data of Black\(^6\) on age-specific risk of dying from measles

**Figure 2** Italian demography: (a) births per capita (crude birth rate) in the years 1950–1996; (b) 1951 population age distribution; (c) projected age distribution for the year 2002 (most recent census: 2001)
programmes. Additionally, important effects resulting from changing demography may also be expected to be observed in so-called ‘developing’ or ‘less developed countries’ (LDC).

Materials and Methods

Data

Italian measles notification data (Figure 3a) provided a standard against which to measure model ability to capture Italian measles epidemiology. The FOI for each age group was estimated using pre-vaccination age-related incidence data from Italy. Because of substantial under-reporting of measles cases in Italy, data corrected for under-reporting9 was used. Yearly age-related fertility rates from 1951 to 1996 were provided by the Italian National Institute of Statistics (ISTAT); ISTAT also provided the 1951 Italian population age distribution used as the starting point for model simulations (Figure 2b). Since 1996 fertility rates have remained quite stable so, in the projection, it was assumed that they remained at 1996 levels. To distinguish between effects particular to the Italian demographic environment, and those which may be generalized, hypothetical population data were also used, characterized by an initially flat (Type I) age distribution. In this latter population fertility rates were kept either at replacement level throughout or at ‘replacement’ for the first 30 years followed by decay over the ensuing 40 years to constant ‘below replacement’ levels. For this generalized population, fertility rates were uniform across age groups at all time points. ISTAT mortality data for the period 1970–1980 were used to derive age-related mortality rates kept constant throughout the simulation period, a reasonably plausible representation of mortality over this period.

Vaccination

Within the Italian public health system measles vaccination is classified as ‘Recommended’ rather than ‘Compulsory’. Partly for this reason the extent of data on measles vaccination coverage in Italy is quite limited,10 although strenuous attempts are being made to improve this record and at the time of writing it is understood that a new Measles Elimination Plan (MEP) is due to be announced. A plausible vaccination profile, reconstructed from the limited available data, has been used here (Figure 3b) as significant errors in this estimate are unlikely to affect the general conclusions drawn from this work. Starting in 1976, this cohort vaccination profile was applied at age 1.5 years to both the Italian and generalized model populations; 95% efficacy and 6 months mean maternal antibody duration were assumed; for future years it was assumed vaccination continued at 1997 levels. Other model simulations were also carried out assuming that (1) a high level of vaccination had been achieved from 1997 onwards (increasing by 5% each year to 95%), and (2) no vaccination had been given at any time (i.e. 0% coverage for all years).

Model

A standard compartmental and age-structured deterministic transmission dynamics model5,11 was employed incorporating natural history of measles, and the flow of susceptibles to the exposed class was governed by the FOI and the specified contact pattern (Appendix). The model also incorporated realistic demography in terms of Italian initial age distribution, yearly changes in age-related fertility rates, and age-related mortality. By this means observed numbers of births in Italy since 1950 (Figure 2a) were closely mirrored by model outputs (not shown).

Results

Figure 4 shows model results in terms of incidence of infection for both Italian (Figure 4a) and generalized populations (Figure 4b) for ‘moderate’ (i.e. estimated) and ‘high’ vaccination profiles; the scenario with no vaccination is also shown. Model results shown here for ‘moderate’ vaccination in Italy (Figure 4a) correspond broadly to corrected historic incidence data (Figure 3a) in terms of magnitude, timing, and shape. Results for the generalized population (Figure 4b) also bear strong similarities to ‘Italian’ results if additional ‘noise’ is ignored (a result of loss of damping through replacement of age-related fertility with uniform rates and the substitution of an initial uniform age distribution).5 In both cases, as predicted by theory,5 introduction of vaccination generates an increase in inter-epidemic period. If vaccination continues at moderate levels, decline in incidence ceases. This is followed in later years by a significant increase, more noticeable in the ‘Italian’ population. With the ‘high’ vaccination profile, incidence rapidly declines to negligible levels. In complete absence of vaccination, in both populations, there is still significant decline in per capita
incidence to an approximately constant lower level. This effect arises from interaction between the change in age distribution, induced by population decline, and the moderation in FOI with age. However these results, being aggregated over age, do not make clear how experience of infection changes with age under these scenarios.

Figure 5 shows, for the 'Italian' population, how proportions of young school-age children and adults remaining susceptible to infection change through time under assumptions of (1) no vaccination and (2) continuing 'moderate' vaccination. In each case proportion susceptible increases through time, but for young children (Figure 5: 2 upper lines), vaccination reduces the demographically driven increase in proportion susceptible; for adults (2 middle lines) the effect is reversed with vaccination increasing the susceptible proportion. Overall relative increase in susceptibility is much greater for both adult scenarios. These effects are broadly similar for the generalized population with below replacement fertility and are not shown. When the same vaccination scenarios are applied to a generalized population with constant population size and age distribution, the increase in susceptibility is some four or five times less.

A more worrying picture emerges, if the combined impact of demographic change and 'moderate' vaccination on age distribution of cases is considered. Figure 6 suggests that over the next 25 years, in the absence of any vaccination, the (moment) upper quartile age of cases in the 'Italian' population would rise from around 8 or 9 years to about 13 or 14 years. At historic ('moderate') vaccination levels, Figure 6 also suggests that the median age of cases has already increased from around 5 years to 10 years (recently published data gives some support to this observation)\(^1\); this median would reach about 18 years of age after a further 25 years. Corresponding upper quartile ages are approximately 7 years, 17 years, and 35 years of age, with these measures continuing to increase substantially in the ensuing period. A similar pattern is seen for the generalized population, albeit with slightly smaller age increases. Figure 6 shows the contrast between these results and those with constant population size (i.e. replacement fertility) where, with 'moderate' vaccination, the change in percentile measures is minimal.

Morbidity and mortality from measles infection is strongly age-related. By combining this age-related risk of mortality (Figure 1) with the projected age distribution of cases, a snapshot can be constructed of possible future patterns of
mortality under scenarios of no vaccination and sub-optimal (‘moderate’) vaccination (Figure 7). The important result shown suggests that although incidence is much lower under ‘moderate’ vaccination and initially accompanied by a decline in mortality and morbidity, there is potential for mortality and morbidity to substantially increase in ensuing years. Indeed, for a period, this may reach levels in excess of those under the ‘no vaccination’ scenario. Fewer deaths are occurring at younger ages but these are more than compensated by the increase in deaths of mature adults.

**Discussion**

Much attention has been paid to transmission dynamics of measles over the past 20 years (e.g. refs 13–16 among many others). Nevertheless it is believed this is the first published work to address the effect on measles dynamics of projected population decline in the ‘developed’ world.

Distinct patterns of fertility well below replacement are now widespread in Europe. These first became evident in Southern Europe, i.e. Italy, Spain, and Greece, in the 1980s and later, in the late 1990s, were seen in Central and Eastern Europe, where decline has been more sudden and rapid. The continuation of this process is likely to lead to population ageing, whose effects are already apparent. One effect of this process is increased skewing of the population age distribution towards higher ages. The endpoint of this process, assuming fertility remains broadly unchanged from current levels, is that the shape of the age distribution tends to stabilize over a period of some decades at unchanged from current levels, is that the shape of the age distribution tends to stabilize over a period of some decades at unchanged from current levels. This is of course subject to the proviso that vaccination (in combination with the level of infection-based immunity) which is important as a determinant of epidemiological contact patterns. Although the contact pattern will also determine the evolution of age distribution of infection through time. Here the change in FOI with age has been estimated from Italian data and the contact pattern is one used elsewhere for modelling European childhood infections (e.g. refs 5, 22). However, the possibility remains that changes in population age distribution with time may themselves influence epidemiological contact patterns. Although the contact pattern employed here provides a satisfactory starting point, this also warrants further investigation. Qualitatively the projected changes in age distribution of infection described here are fully consistent with theory, although their magnitude may at first sight appear somewhat surprising. (Similar changes were observed, albeit to a lesser degree, when simulations were repeated with a higher FOI corresponding to that described in Edmunds et al. [not shown].)

Continued circulation of measles infection relies on a sufficiently large pool of susceptibles to sustain it. Thus, rather than annual variations in vaccine uptake, it is the cumulative build-up of vaccine-based immunity (in combination with the level of infection-based immunity) which is important as a determinant of age distribution of susceptibility, and hence of infection over the longer term. Although a specific vaccination scenario has been employed here, to a greater or lesser degree, comparable results would be obtained from a wide range of cohort vaccination profiles. This is of course subject to the proviso that vaccination was significantly below uptake levels for elimination; these are recently been argued that this first transition may now be relatively quickly followed by a further transition to population decline, mirroring that described above, with further consequences for measles dynamics, and those of other infections. These issues will be dealt with in more detail in a forthcoming publication.

In addition to fertility, migration and mortality are the other demographic processes affecting population size and composition. Patterns of mortality in the ‘developed world’ correspond reasonably well to the constant age-related ‘Italian’ rates used here, so that applying rates applicable to other European countries would not be expected to influence results significantly. However, in the case of the ‘developing’ world, where reductions in mortality arising from improvements in health care may interact in many cases with increasing premature mortality resulting from human immunodeficiency virus (HIV)/AIDS, models using mortality rates that do not change over time may not suffice. Here net mortality may evolve in a much more complex way, necessitating more realistic representation if demographic patterns are to be mirrored satisfactorily. In contrast to mortality, the potential impact of migration on European demographic patterns is less clear and the degree to which migration may influence age distribution of measles infection is a question that warrants further research. However, unless both age distribution and that of infection within the immigrant population were markedly different from those in the host population, it would be expected that quite substantial population movements would be needed to affect its age distribution of infection.

Clearly the pattern and magnitude of trends in specific demographic processes, i.e. fertility, mortality, and migration, will influence the age distribution of infection. Additionally, assumptions about contact patterns between age groups and changes in FOI with age which are intrinsic to a given model will also determine the evolution of age distribution of infection through time. Here the change in FOI with age has been estimated from Italian data and the contact pattern is one used elsewhere for modelling European childhood infections (e.g. refs 5, 22). However, the possibility remains that changes in population age distribution with time may themselves influence epidemiological contact patterns. Although the contact pattern employed here provides a satisfactory starting point, this also warrants further investigation. Qualitatively the projected changes in age distribution of infection described here are fully consistent with theory, although their magnitude may at first sight appear somewhat surprising. (Similar changes were observed, albeit to a lesser degree, when simulations were repeated with a higher FOI corresponding to that described in Edmunds et al. [not shown].)

Continued circulation of measles infection relies on a sufficiently large pool of susceptibles to sustain it. Thus, rather than annual variations in vaccine uptake, it is the cumulative build-up of vaccine-based immunity (in combination with the level of infection-based immunity) which is important as a determinant of age distribution of susceptibility, and hence of infection over the longer term. Although a specific vaccination scenario has been employed here, to a greater or lesser degree, comparable results would be obtained from a wide range of cohort vaccination profiles. This is of course subject to the proviso that vaccination was significantly below uptake levels for elimination; these are...
notoriously difficult to achieve through cohort vaccination alone. Additional vaccine-based immunity may be achieved through delivery of a second dose later in childhood, or by supplementing cohort vaccination with campaign programmes, either on a single (‘catch up’) or a repeated (‘pulse’) basis. The Italian MEP comprises a programme combining some of these additional measures. The potential influence of the population ageing scenarios described here on the likely success of the MEP will be considered in a subsequent publication.

While age-structured models of the type used in this work provide a reasonably satisfactory representation of epidemic trends, to achieve more precise representation suitable for informing detailed policy decisions, more sophisticated models are desirable (e.g. those of Babad, Ferguson et al. etc). Nevertheless it is argued that the results described above do provide a valid qualitative description of the impact of population decline on the age distribution of infection.

This work specifically focuses on the effect of population decline and sub-optimal vaccination on the age distribution of measles infection, and highlights a consequent risk of an increase in measles-related morbidity and mortality. However, the work also constitutes a more general warning of the need not to lose sight of the implications of population decline for other infectious diseases in which mortality and morbidity increase with age. Varicella is one example, but rubella, in particular, stands out as posing a particular threat, with the potential for a large proportion of cases to occur in the fertile age range with a consequent substantial increase in cases of congenital rubella syndrome; this issue needs to be urgently addressed.

The onset of population decline and ageing has led, quite rightly, to increasing emphasis on chronic non-infectious diseases. Such dangers must increase the urgency and importance of monitoring age-related experience of infection through seroprevalence surveys and, where vaccines do exist, of achieving and maintaining high levels of vaccination cover.

Acknowledgements

John Williams was funded under a project grant from the Italian Ministry of Universities and Scientific Research; Piero Manfredi was funded by the Italian Ministry of Health. We thank Stefania Salmaso, Marta Ciofi degli Atti, John Edmunds, Eugene Cleur, and the anonymous referees for valuable comments and suggestions.

Appendix

The deterministic measles transmission dynamic model used in this work can be described in the form of the following partial differential equation system whose solution was effected using a Fortran 77 computer program.

The state variables represent respectively the numbers (at any given age and time) of individuals susceptible to infection \( X \), latently infected \( H \), infectious \( Y \), recovered \( Z \), and immunised \( V \). Model rate parameters are \( d \) (decay of maternal antibody), \( \mu(a) \) (age-related mortality), \( \gamma \) (recovery), with age-specific fertility \( \phi(a) \) (Source: MacLean & Anderson

\[ \frac{dM}{da} + \frac{dM}{dt} = -(d + \mu(a))M(a, t) \]

\[ \frac{dX}{da} + \frac{dX}{dt} = dM - (\nu(a)\lambda(a, t) + \mu(a))X(a, t) \]

\[ \frac{dH}{da} + \frac{dH}{dt} = \lambda(a, t)X(a, t) - (\sigma + \mu(a))H(a, t) \]

\[ \frac{dY}{da} + \frac{dY}{dt} = \sigma H(a, t) - (\gamma + \mu(a))Y(a, t) \]

\[ \frac{dZ}{da} + \frac{dZ}{dt} = \gamma Y(a, t) - \mu(a)Z(a, t) \]

\[ \frac{dV}{da} + \frac{dV}{dt} = \nu(a)X(a, t) - \mu(a)V(a, t) \]

\[ \lambda(a, t) = \frac{\int_{0}^{\infty} \beta(a, a')Y(a', t)da'}{\int_{0}^{\infty} n(a', t)da'} \]

Births are represented by the following boundary condition:

\[ M(0, t) = \int_{0}^{\infty} \phi(a)n(a, t)da \]

where

\[ n(a, t) = M(a, t) + X(a, t) + H(a, t) + Y(a, t) + Z(a, t) + V(a, t) \]

Table 1a specifies the form of the age-related transmission matrix (the ‘Who acquires infection from whom’, or WAIFW, matrix). \( \beta_{ij} \) values for the WAIFW matrix are derived from the estimated FOI using the method described by Anderson & May. The \( \beta_{ij} \) values correspond to the continuous \( \beta(a, a') \) in the expression for \( \lambda \). Table 1b shows these estimated FOI values.

### Table 1

#### (a) Age-related transmission matrix

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>0–1</th>
<th>2–4</th>
<th>5–10</th>
<th>11–17</th>
<th>18–74</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>( \beta_1 )</td>
<td>( \beta_1 )</td>
<td>( \beta_1 )</td>
<td>( \beta_1 )</td>
<td>( \beta_1 )</td>
</tr>
<tr>
<td>2–4</td>
<td>( \beta_2 )</td>
<td>( \beta_2 )</td>
<td>( \beta_4 )</td>
<td>( \beta_3 )</td>
<td>( \beta_3 )</td>
</tr>
<tr>
<td>5–10</td>
<td>( \beta_1 )</td>
<td>( \beta_4 )</td>
<td>( \beta_1 )</td>
<td>( \beta_1 )</td>
<td>( \beta_1 )</td>
</tr>
<tr>
<td>11–17</td>
<td>( \beta_1 )</td>
<td>( \beta_3 )</td>
<td>( \beta_3 )</td>
<td>( \beta_3 )</td>
<td>( \beta_3 )</td>
</tr>
<tr>
<td>18–74</td>
<td>( \beta_2 )</td>
<td>( \beta_5 )</td>
<td>( \beta_5 )</td>
<td>( \beta_5 )</td>
<td>( \beta_5 )</td>
</tr>
</tbody>
</table>

#### (b) Force of infection (FOI) values estimated from incidence data

<table>
<thead>
<tr>
<th>Age range</th>
<th>FOI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>0.077</td>
</tr>
<tr>
<td>2–4</td>
<td>0.158</td>
</tr>
<tr>
<td>5–10</td>
<td>0.290</td>
</tr>
<tr>
<td>11–17</td>
<td>0.181</td>
</tr>
<tr>
<td>18–74</td>
<td>0.062</td>
</tr>
</tbody>
</table>
KEY MESSAGES

- The impact of population ageing is not confined to chronic disease but also affects incidence of childhood infections.
- Measles incidence is reduced by population ageing but the age at infection increases.
- Increased deaths from measles may result from suboptimal vaccination coverage interacting with population ageing to further increase age at infection.
- The results indicate that population ageing increases the importance of eliminating vaccine preventable diseases of childhood.

References