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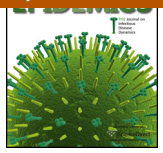

The effects of demographic change on disease transmission and vaccine impact in a household structured population

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ABSTRACT

The demographic structure of populations in both more developed and less developed countries is changing: increases in life expectancy and declining fertility have led to older populations and smaller households. The implications of these demographic changes for the spread and control of infectious diseases are not fully understood. Here we use an individual based model with realistic and dynamic age and household structure to demonstrate the marked effect that demographic change has on disease transmission at the population and household level. The decline in fertility is associated with a decrease in disease incidence and an increase in the age of first infection, even in the absence of vaccination or other control measures. Although large households become rarer as fertility decreases, we show that there is a proportionate increase in incidence of disease in these households as the accumulation of susceptible clusters increases the potential for explosive outbreaks. By modelling vaccination, we provide a direct comparison of the relative importance of demographic change and vaccination on incidence of disease. We highlight the increased risks associated with unvaccinated households in a low fertility setting if vaccine behaviour is correlated with household membership. We suggest that models that do not account for future demographic change, and especially its effect on household structure, may potentially overestimate the impact of vaccination.

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1. Introduction

The demographic structure of a population is a key determinant of patterns of contact and hence of infectious disease spread, with implications for the design of effective control measures. Households in particular are recognised as an important focus of disease transmission, due to the duration and intensity of contacts occurring within them (Hope-Simpson, 1970). Over time, demographic processes such as birth, death, aging, marriage and divorce modify age and household structure. During the 20th century, the populations of more developed countries experienced demographic changes—increases in life expectancy and decreases in fertility—that have led to older populations living in smaller households. Drivers of these demographic changes include improvements to public health, and social and economic transformation associated with the growth of urban industrial societies (Livi-Bacci, 1997). Similar trends are occurring, at differing rates, among less developed countries. Understanding how changes in the demographic structure of a population affect disease transmission is a necessary step towards the design of more effective strategies for disease control (John, 1990; Manfredi and Williams, 2004).

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Mathematical models can help improve our understanding of how infectious diseases spread and inform decision making about how they can be controlled (Anderson and May, 1992; Keeling and Rohani, 2007). To capture the full impact of changes in demography on disease spread, a model must represent age and household structure, as well as how these evolve over an extended period of time. Compartmental models of disease transmission that include either age *or* household structure are well established (Hethcote, 2000; Hall and Becker, 1996; House and Keeling, 2009). However, combining both age *and* household structure in a single model is challenging due to the combinatoric growth in the number of compartments required to capture variations in household composition and disease status. An assumption of many existing models is that population structure exhibits an age distribution that does not change over time (*i.e.*, it is demographically stable). While reasonable over short time frames, for example a single influenza season, this assumption is clearly unrealistic when considering the long term dynamics of an endemic disease, or the long term impacts of vaccination programs. Models that incorporate demographic processes have been proposed, but typically assume either stationary or exponentially growing populations (John, 1990), and only rarely include household structure (Glass et al., 2011). Models that do incorporate non-stationary age structure have demonstrated significant implications for both patterns of disease and the effectiveness of vaccine programs (Manfredi and Williams, 2004; Finkenstädt and Grenfell, 2000; Williams and Manfredi, 2004; Gao and Hethcote, 2006; Iannelli and Manfredi, 2007; Cummings et al., 2009; McDonald, 2012; Merler and Ajelli, 2014; Liu et al., 2014; Marziano et al., 2015).

An alternative approach is individual based models, which explicitly simulate each member of a population together with their demographic characteristics, social contacts and disease status. These models allow much greater flexibility in representing the heterogeneity present in real populations. They have been used for simulating outbreak scenarios in realistically structured (*i.e.*, containing both age and household structure) static and dynamic populations (Eubank et al., 2004; Ferguson et al., 2005; Ajelli and Merler, 2009; Guzzetta et al., 2011; Silhol and Boëlle, 2011). To date, these models do not explicitly capture the long-term impact of demographic changes to both age and household structure that underpin the contact patterns most relevant to disease transmission.

We have previously described a parsimonious individual based model of household structure and dynamics capable of simulating a range of non-stationary demographic scenarios (Geard et al., 2013). Here we use this model to show how demographic processes alter the age and household structure of a population, and the effects this has on patterns of contact, disease transmission and vaccine impact.

2. The model

We model a population of individual people characterised by their age, sex, and the household in which they currently reside. Over time, people are born, age, enter into and leave couples and households, and eventually die. The dynamics of these demographic processes are parameterised using age- and sex-specific mortality and fertility rates, and calibrated against observed patterns of household formation and dissolution (see Supplementary information for detail). By choosing appropriate rates, a variety of demographic scenarios can be simulated, including stable, exponentially growing, and non-stationary populations (Geard et al., 2013). Here we focus on a population moving from a high to a low fertility setting, using current and historical Australian census and survey data to calibrate our model. The key demographic trends included are an increase in life expectancy and a decrease in birth rate, together with social factors such as an increase in the average age of childbearing and an increase in the rate of couple separation.

This demographic model is overlaid with a Susceptible, Infectious, Removed disease transmission model, with contact and transmission simulated in the community and household settings. As our primary focus is the role of household transmission, we aggregate contacts occurring outside of the household—in locations such as schools, workplaces and public spaces—into a matrix of age-specific community contact rates. We assume these contact rates to be age-assortative; that is, people are more likely to come into contact with others of a similar age to themselves (Mossong et al., 2008). These contact rates are derived from the age structure of the population and empirically observed activity levels (Hethcote, 1996; Mossong et al., 2008) (see Supplementary information for detail). Within the community, we make the standard assumption for large populations that transmission is frequency dependent. As the age structure of the population evolves over time, we recalculate the community contact rates at five yearly intervals. Contacts occurring within households are determined directly by the structure of the model population. Here we assume tha all individuals within a household mix equally with one enother, irrespective of age. The degree to which household transmission is frequency or density dependent is not well-established—and most likely varies by disease (van Boven et al., 2010)—and can be varied within the model.

Thus, the probability of a susceptible person in age class i becoming infected in a given time step (here, 1 week) depends on the prevalence of disease in their household and in the broader community, and is given by $1 - e^{-\lambda_{i,N_H}}$, where the force of infection λ_{i,N_H} on an individual in age class i, in a household of size N_H is given by

$$\lambda_{i,N_H} = q_h \frac{I_H}{(N_H - 1)^{\alpha}} + q_c \sum_j \eta_{ij} \frac{I_j}{N_j} \tag{1}$$

where q_h and q_c are transmission coefficients for household and community transmission, I_H and N_H are, respectively, the number of infectious people and the total number of people in the susceptible person's household, α specifies the degree to which household transmission is frequency ($\alpha = 1$) or density ($\alpha = 0$) dependent, η_{ij} is the average number of community contacts between a person in age class i and people in age class j, and I_j and N_j are, respectively, the number of infectious people and the total number of people in age class j. In addition to endemic transmission, we also allowed for the importation of infection from sources external to the population. At each time step, a susceptible individuals could become infected from an external source with a small probability.

In this study, we parameterised the demography of our population model based on historical Australian census and survey data from 1910 to 2010 (Australian Bureau of Statistics, 2008, 2009, 2010a,b; de Vaus, 2004; Wilkins et al., 2011) (see Supplementary information for detail). As data were only available on the average size of households in the Australian population in 1910, initial household size distributions were estimated using a zero-truncated Poisson distribution (Jennings et al., 1999). The model is stochastic, and each scenario was simulated 10 times; unless otherwise noted, results reported represent means and standard deviations across each set of simulations. Starting populations for all simulations were created by running the model for 200 years, using the earliest available demographic rates, to reach an endemic disease equilibrium. Final population sizes in each simulation were approximately 225,000. Importation of cases from an external source (equivalent to 5×10^{-6} cases per person per week on average) was used to prevent epidemic fade-out due to stochasticity. The model is implemented in Python and source code is available from http://bitbucket.org/ngeard/simodd-pub.

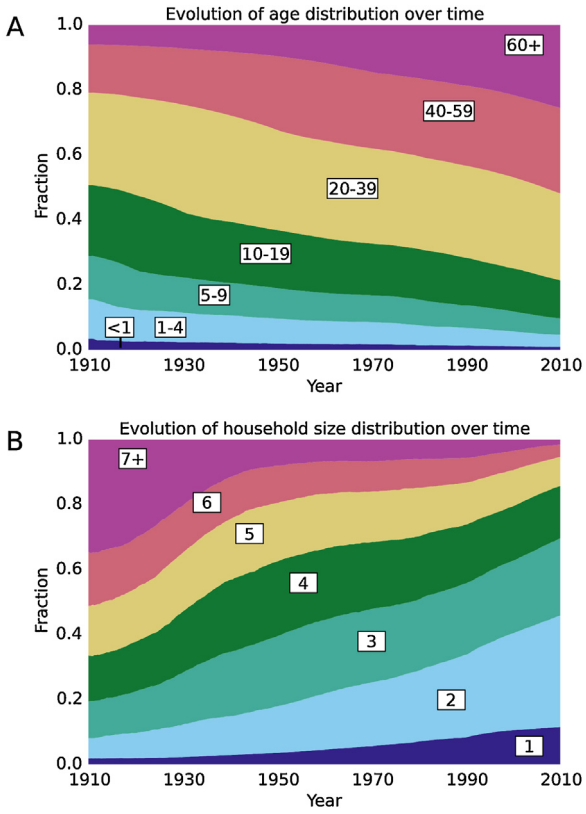

Fig. 1. The evolution of (A) age distribution (years) and (B) household size distribution of a simulated population over 100 years, showing the demographic shift towards an older population living in smaller households.

3. Results

3.1. Effects of demographic change on population structure and mixing behaviour

The demographic changes modelled here have a marked effect on population structure. Using historic demographic rates, the median age of the model population increases from 23 to 40 years (Fig. 1A), while mean household size decreases from 4.5 to 2.6 people (Fig. 1B), comparable to both the increase in median age from 22 to 37 years and reduction in mean household size from 4.5 to 2.6 that have been observed in the Australian population during the 20th century (Hugo, 2001). In turn, these shifts affect how people mix in a population. As the population ages, the relative proportion of community contacts that are made with adults increases for all age groups (Fig. 2A,B). With data-driven assumptions about rates of household formation and dissolution, we can also infer how patterns of household contact change as fertility declines (Fig. 2C,D). As households become smaller, the overall level of contact occurring in this setting decreases and patterns of contact between age groups change. In particular, children have less contact with siblings and relatively more with their parents.

3.2. Effect of demographic change on disease dynamics

For our baseline scenario, we chose parameters corresponding to a highly transmissible "measles-like" illness. The duration of infection for each case was sampled from an Erlang distribution ($k=5$, $\mu=2$) with a mean duration of 2 weeks, roughly equivalent to the generation time of measles (Finkenstädt and Grenfell, 2000). Community and household transmission coefficients ($q_c=0.01$ and $q_h=0.8$) were chosen such that a randomly selected individual in a fully susceptible population would infect around 17 individuals in total, and 80–100% of their household. We assume that household transmission is frequency dependent ($\alpha=1$), but also explore the effect of density dependent household transmission. As described above, a key feature of our model is the inclusion of realistic household structure. To establish the independent effect of household mixing on disease dynamics during the shift to a low fertility setting, we compared our baseline scenario to a scenario in which there was no household transmission ($q_h=0$), and community transmission was re-calibrated to ensure that a randomly selected individual in a susceptible population would still infect around 17 individuals ($q_c=0.017$).

Incidence of disease decreases over the 100 year period simulated, from approximately 25 to 10 cases per 1000 people annually, in the absence of any vaccination (Supplementary information, Fig. S1A). This decrease in incidence occurs at an equivalent rate in simulations both with and without household mixing, suggesting that declining fertility, rather than change in household structure, is the key driver. As the prevalence of disease in the population falls, it takes longer for a susceptible child to be exposed to infection, and the average age of infection increases from approximately 4.5 to 10.5 years with households and approximately 9 years without households (Supplementary information, Fig. S1B). The decrease in incidence was observed irrespective of whether frequency or density dependent household transmission was used, as could be expected given the high transmissibility associated with the household setting (Supplementary information, Fig. S2).

While overall disease incidence is similar with or without households, the inclusion of household mixing has a stronger effect on the distribution of incidence by age (Fig. 3A,B), reducing incidence in infants and children aged less than 5 years. Children in both scenarios make an equivalent number of daily contacts; however, the inclusion of household structure alters who these contacts are with. Fewer contacts are made with the general pool of predominantly susceptible children in the community, and more are made with household members, including parents, who by virtue of their age are more likely to be immune and hence pose a lower risk. This difference in incidence by age is more pronounced in the low fertility setting (Fig. 3B). Smaller households typically contain a greater proportion of adults, which intensifies the potential "cocooning" effect of households.

Disease incidence increases with household size, both with and without household mixing (Fig. 3C,D). Larger households are more likely to have experienced recent birth events and hence more likely to contain susceptible infants. The relationship between incidence and household size is stronger in the low fertility setting (Fig. 3D). That is, even as large households become less common in the population (Fig. 1B), the relative risk of infection associated with being born into them (compared to smaller households) is greater.

The increased risk associated with large households in the low fertility setting is a consequence of changes to patterns of susceptibility in households. In the high fertility setting, disease prevalence is also high and the average age of infection is low. Thus, each child born into a household will tend to be infected before the birth of their younger siblings. By the time subsequent children are born to a household, their older siblings will already have been infected and acquired immunity, so there will be limited opportunity for onward transmission within the household. In contrast, in the low fertility setting, when disease prevalence is lower and the average age of infection is higher, there is a longer window of opportunity for households to accrue additional children prior to the introduction of disease. In high fertility households, this delay enables the accumulation of greater numbers of susceptible children prior to a household outbreak (Fig. 4A).

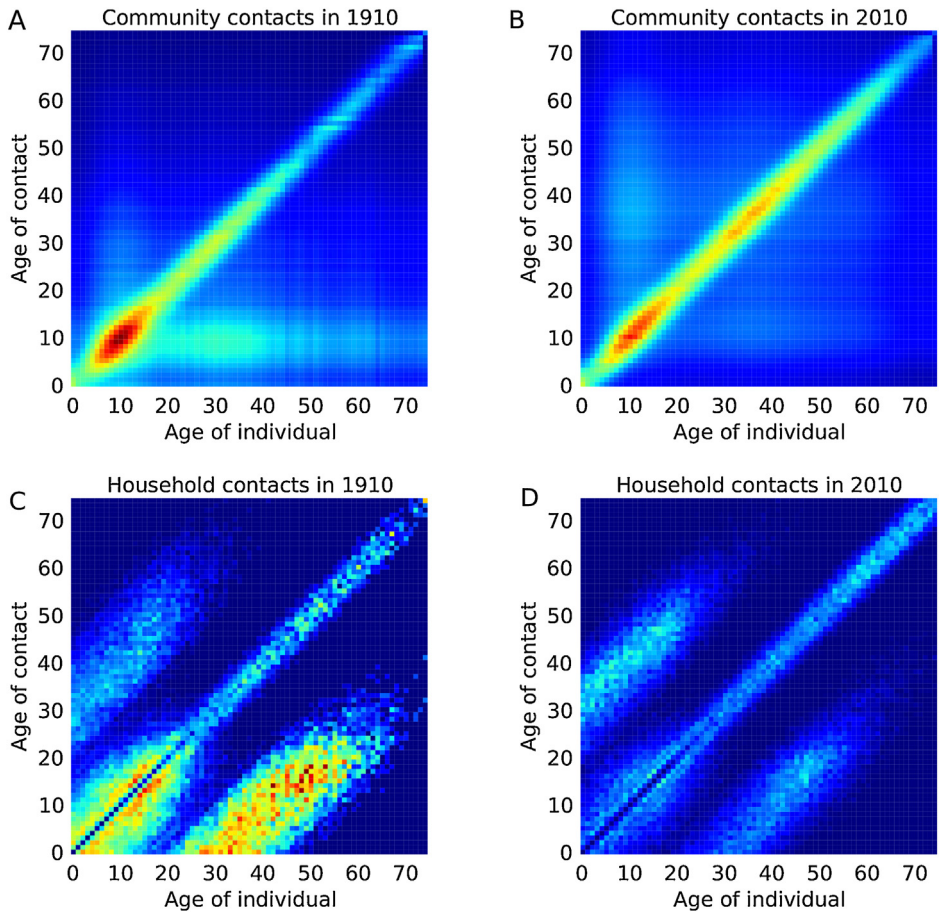

Fig. 2. Contact matrices from a sample simulation run showing age-specific rates of contact in the community (A and B) and households (C and D) in the high (A and C) and low (B and D) fertility settings. The contacts of individuals aged 75–100 years have been binned. Equivalent colour scales are used for each pair (A,B and C,D) of matrices. Community contact is age-assortative, and changes in the matrix structure over time reflect the shift towards an older population. The household contact matrices show age-assortative contact between couples and among siblings, as well as inter-generational contact between parents and children. Changes in the matrix structure reflect the shift towards households containing fewer children.

The presence of multiple susceptible children in a household poses two risks. First, there are more opportunities for disease introduction arising from contact between a susceptible household member and infection in the wider community. Second, the clustering of susceptible children provides ideal conditions for onward transmission within the household. Indeed, the proportion of cases for which the source was a household member increases with household size, and also over time (Fig. 4B). Thus, in the low fertility and low prevalence setting, more cases will occur in larger households than might be expected, given their relative scarcity in the population.

It is important to note that population-level observations can be misleading as a guide to disease dynamics within households. Over the entire population, the level of transmission within the household appears to remain constant or even decrease slightly over time (Fig. 4B, dashed line). However, for a case occurring in a household of a particular size, the probability that the source of infection is a household member actually increases over time, for households of *all* sizes (Fig. 4B, solid lines). The apparently contradictory population-level trend reflects the demographic shift towards smaller households (Figure 1B), which experience lower levels of transmission within the household.

3.3. Interactions between demographic change and vaccination

Demographic context can affect vaccine impact (Metcalf et al., 2011), and both changing demography and vaccination have contributed to observed reductions in disease such as measles (Merler and Ajelli, 2014). To ascertain the effect of household structure on vaccination, we compared two control scenarios to the baseline scenario described above. Each control scenario introduced vaccination in year 60 of the simulation, corresponding to the era when uptake of childhood vaccination against disease such as measles and pertussis became widespread in Australia. In the *individual* vaccination scenario, each infant born after vaccine introduction had an independent probability v of being vaccinated and receiving lifelong immunity. In the *household-based* vaccination scenario, the probability of vaccination was evaluated at the household level, recognising that the vaccine status of children from the same household is likely to be correlated (Smith et al., 2004). In this scenario, the first infant born into a household after vaccine introduction was vaccinated with probability v. Thereafter, subsequent infants born into a household were vaccinated only if their older siblings were. Across the population, an equal proportion of infants were vaccinated in both scenarios.

The simulated vaccine interventions further reduce population susceptibility, with associated impact on disease incidence (Fig. 5A,B). However, the impact of the vaccine intervention depends critically upon our assumptions about the households that vaccinated people belong to. If children born to the same household share vaccination status (as in the household-based vaccination scenario), then the reduction in incidence is less than if the decision to vaccinate is made independently for each child, across a range of coverage levels (Fig. 5C). The additional disease burden under the

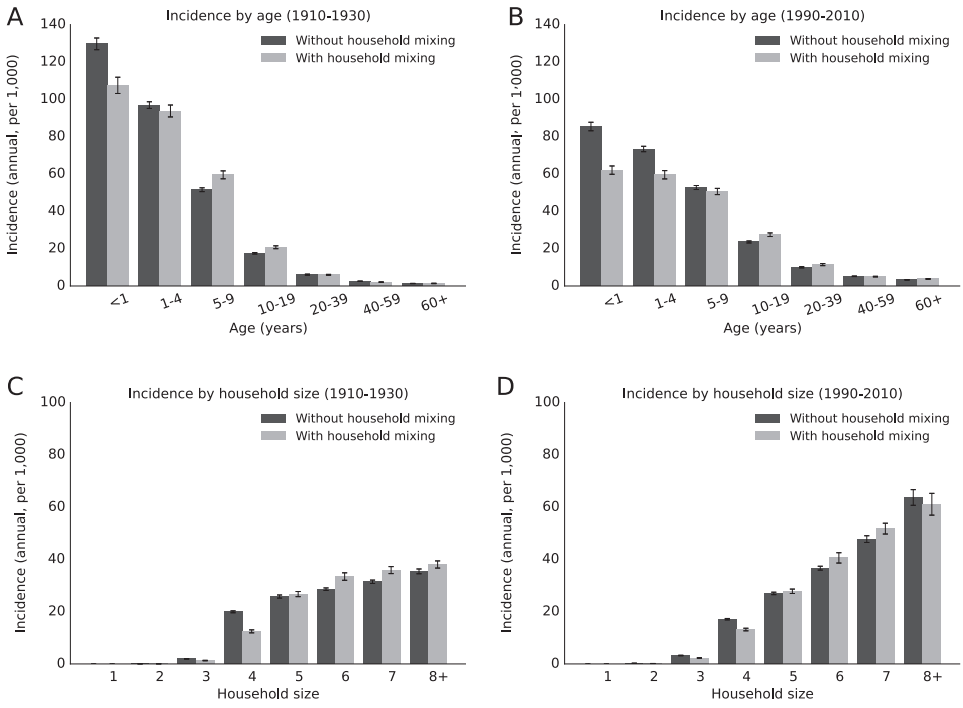

Fig. 3. Incidence with and without household mixing by age group (A and B) and household size (C and D) in the high (A and C) and low (B and D) fertility settings. Error bars show standard deviation over 10 independent simulation runs. With household mixing, infants and young children benefit from the "cocooning" effect of households, particularly in the smaller households that predominate in the low fertility setting. However, while large households are rarer, the relative risk of infection associated with being born into them is greater.

household-based vaccination scenario is evident across age classes but is greatest in younger age groups, who may be most likely to experience severe disease (Fig. 5D).

These differences are a consequence of the effect that each vaccination scenario has on the distribution of susceptibility across households. Vaccinating children at random, irrespective of the household they belong to, reduces the size of susceptible clusters across households of *all* sizes, reducing the risk of disease introduction and onward transmission (Supplementary information, Fig. S3). In contrast, vaccinating children by household reinforces the clustering of susceptibility observed in the low fertility setting, particularly among larger households (Supplementary information, Fig. S4). Randomly targeted vaccination is unlikely to ever be a realistic policy option (House and Keeling, 2009); however, these results illustrate the potential for a vaccine's impact to be overestimated if household clustering is not accounted for.

4. Discussion

Demographic change can have a profound impact on the structure of populations, and consequently on mixing patterns, and the spread and control of infectious diseases. Here we have used an individual based model with evolving age and household structure to explore the effects of demographic change on mixing behaviour and disease dynamics. In agreement with existing age-structured models (Manfredi and Williams, 2004; Ferrari et al., 2013; Merler and Ajelli, 2014), lower fertility levels lead to reduced incidence at the population level and an increase in the average age at infection, even in the absence of vaccination and other factors.

However, because our model explicitly includes households, it also demonstrates how changes in a population's demography affect mixing behaviour and disease incidence at the sub-population level, and it is here that we make three important and perhaps surprising observations. First, even a relatively simple model of contact that includes just household and community locations can produce contact matrices (Fig. 2) that recapture key features of empirically observed contact patterns: high levels of household mixing within age groups, corresponding to interactions among siblings (in younger age groups) and between couples (in older age groups), and secondary "wings" reflecting inter-generational contact between parents and children (Mossong et al., 2008). As populations age and smaller households become more common, the relative contribution of adults to mixing in the household setting increases, both among adults, and between adults and children. The increase in relative contribution of adults to mixing behaviour in the low fertility setting accords with recent observations of the importance of adults as sources of infection in children (Schellekens et al., 2005; Jardine et al., 2010). Second, even as large households become less common in a population, the risk of infection associated with being born into these households increases (Fig. 3D). In the low fertility setting, lower disease prevalence provides increased opportunity for susceptible children to accumulate in large households (Fig. 4A). These susceptible clusters increase both the opportunity for infection to enter a household, and the potential size of the resulting outbreak when it does. Finally, the impact of vaccination will be reduced if vaccine status is correlated within households (Fig. 5), as observed in previous studies of populations with static household structure (Ball and Lyne, 2002; House and Keeling, 2009). The persistence of susceptible clusters in non-vaccinating households allows higher levels of endemic transmission compared to a scenario in which unvaccinated children are distributed at random in a population. Given the important role of parents in vaccination decisions, both psychological and environmental factors support the likelihood of shared vaccine status among siblings (Luman et al., 2003; Smith et al., 2004).

A major challenge when modelling historical disease scenarios is the absence of data to parameterise mixing behavior, and interpret how changes in the age structure of a population will translate into patterns of contact (Manfredi and Williams, 2004; Merler and Ajelli, 2014). Studies aiming to quantify mixing behaviour related

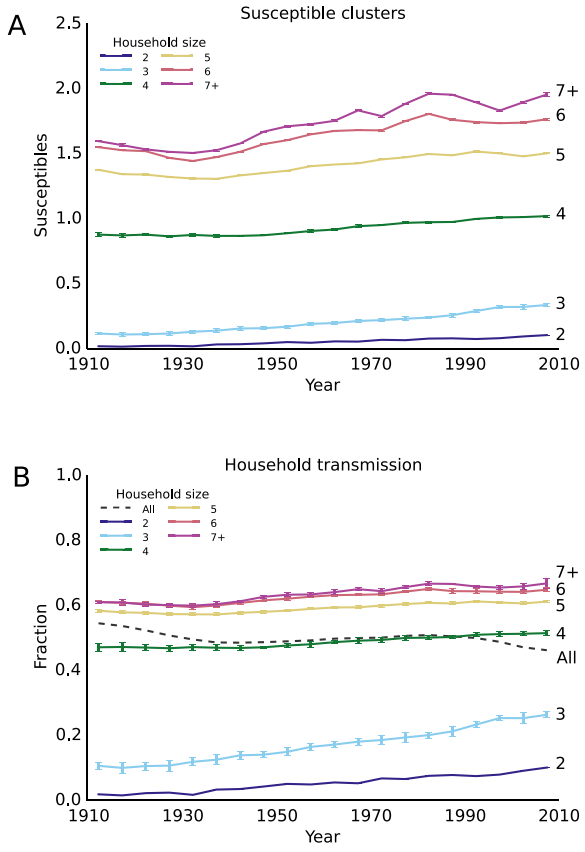

Fig. 4. Patterns of susceptibility and transmission within households during the shift from a high to low fertility setting. Each series shows mean values and standard deviations across 10 independent simulation runs. (A) The average number of susceptible people in a household at the time of disease introduction (excluding the index case) by household size; (B) the proportion of infections for which the source was a household member, over the whole population (dashed line), and by household size (solid lines), estimated using the relative force of infection acting from community and household sources in Eq. (1). Overall, larger households accumulate larger susceptible clusters between outbreaks, and experience higher levels of within household transmission. Clustering of susceptibility and household transmission increases in households of all sizes.

to the transmission of respiratory illness were first conducted in the 1990s (Edmunds et al., 1997; Wallinga et al., 1999). The POLYMOD study provided one of the largest data sets on patterns of contact hitherto gathered (Mossong et al., 2008) and has, as a consequence, become a *de facto* standard for parameterising models of disease spread. However, while broad in scope (covering eight European countries), POLYMOD captures social behaviour in a specific geographic and temporal context, and it is arguably inappropriate to use in earlier time periods or for populations with different social structures. Recent studies in urban and rural regions of China (Read et al., 2014), Thailand (Stein et al., 2014) and Vietnam (Horby et al., 2011) are starting to improve our understanding of how contact patterns vary across different societies and cultures.

Furthermore, the contact matrices used in compartmental models also typically do not capture variation in the intensity of mixing in different settings, although a recent method for constructing matrices directly from demographic data does allow contacts occurring in different locations to be weighted (Fumanelli et al., 2012). Compartmental models also fail to capture the heterogeneity of mixing behaviour within a given age group that arises from the household setting. An entry in a contact matrix describes the *average* level of contact between people in two age classes. However, the real contact patterns of two adults of the same age will be very different if, for example, one lives alone while the other lives with a partner and children. From the other perspective, households of the same size will have very different contact patterns depending on the age of their members. For example, three-person households could consist of two young parents with a newborn infant, two older parents whose youngest child has yet to leave home, or a single parent with two school age children. In each case the mixing behaviour and disease risk are likely to differ.

The individual based model described here addresses these challenges by explicitly simulating how mixing behaviour arises from the demographic structure of populations. Age and household size distributions are often available, or can be estimated, for historical populations. Drawing on census and survey sources, our model enables us to estimate mixing behaviour in a way that captures both a natural and important way in which populations cluster and mix within heterogeneous groups (households), as well as plausible patterns of interaction between those groups, defined in terms of the age-specific patterns of community contact of each of their members. Our model focuses on the changes wrought by demographic change on age and household structure. However, it is likely that, during the 20th century, other social factors would have influenced mixing behaviour, such as changing patterns of travel, work participation and childcare. In the absence of historic contact data, we have assumed that the total number of community contacts that a person makes has remained constant over time, such that all changes to contact patterns are a result of changing age and household structure, and that community contacts are independent of household size. In its current form, our model balances the complexity necessary to produce the household dynamics associated with changing demography against parsimony in choice of model parameters.

Similarly, we have modelled an infection with "measles-like" characteristics in order to illustrate how changes to a population's demographic structure affect the spread of disease. Calibration against historical data could enable more specific predictions about particular diseases, but such calibration efforts must confront two challenges. First, as demonstrated here and elsewhere (Merler and Ajelli, 2014; Marziano et al., 2015), the dynamics of an infectious disease are dependent on the demographic trajectory of a population. The data, both demographic and epidemiological, required for calibration of disease transmission in the presence of demographic instability are scarce, particularly for historical time periods. Second, historical data that are available can be biased by understanding of disease characteristics at the time of their collection. For example, in the pre-vaccine era, pertussis infection in adults was not commonly recognised, and historic measurements of disease prevalence are likely to underestimate true incidence (Gunning et al., 2014).

Our findings demonstrate the potential for changes in population's demography to affect its experience of disease, with significant interactions between fertility rates and the household size distribution. This important context must be appreciated when interpreting the past and likely future impact of vaccine strategies. Experience with the combined measles, mumps and rubella vaccine has shown that vaccination programs can have unintended long term effects, such as the potential for decreased levels of maternal immunity among children born to vaccinated mothers (McLean, 1995; Waaijenborg et al., 2013). Our model further highlights the contribution of changes in population structure to the long-term impact of vaccines. The ability to track patterns of disease and susceptibility at the household level is particularly important when evaluating vaccine strategies that explicitly target households in an effort to provide local herd immunity for young infants, such as maternal immunisation and cocooning (Coudeville et al., 2008). We have used the model described here to compare the effectiveness of alternative antenatal and postnatal vaccination strategies (Campbell et al., submitted for publication).

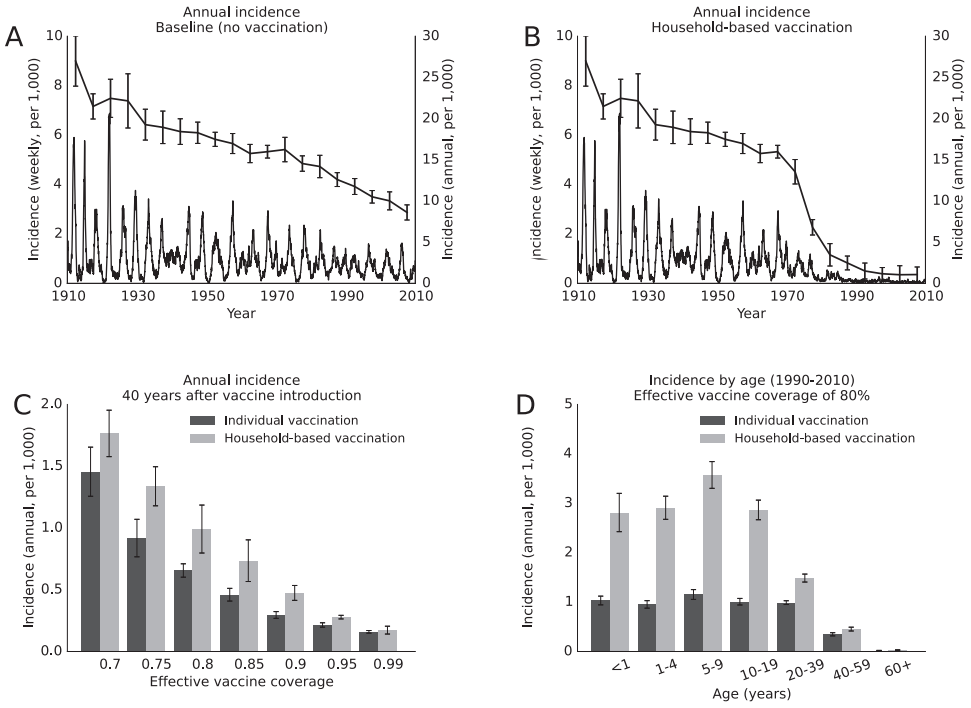

Fig. 5. Combined impact of vaccination and demographic change on annual disease incidence. Annual incidence for the baseline scenario with no vaccination (A), and the household vaccination scenario (B), with 80% of children receiving effective vaccination. Also shown are weekly incidence plots for a pair of representative simulation runs (left axis). (C) Vaccine impact in 2010, after 40 years of vaccination, for varying levels of effective vaccine coverage under individual and household vaccination scenarios. (D) Disease incidence by age group, aggregated over the final 20 years of simulation, for 80% coverage under individual and household vaccination scenarios.

Households, and their changing structure, could also help in understanding of vector borne diseases. For example, it has been demonstrated that an observed decrease in prevalence and accompanying increase in average age of dengue hemorrhagic fever in Thailand can be accounted for by changes in birth and death rate (Cummings et al., 2009). However, household clustering of dengue cases has been observed, particularly in rural settings (Getis et al., 2003). Households are also an obvious foci for control measures such insecticides and screening, suggesting that it may be worth exploring the possible impact of future changes in household structure.

In countries with established vaccination programs, our results highlight how the correlation of vaccination status within households can exacerbate the formation of susceptible clusters. We might expect the risk of outbreaks to be further heightened if under-immunisation is associated with larger households, and if these households are geographically co-located. Evidence of this heightened risk can be seen in measles outbreaks occurring among the large family groups prevalent in ultra-orthodox communities in Jerusalem (Stein-Zamir et al., 2012). The recent development of a global Vaccine Confidence Index suggests that addressing trust in vaccination is a challenge that transcends political and cultural boundaries (Larson et al., 2015).

Finally, our results highlight the importance of considering future demographic trends when evaluating the introduction of vaccine programs to new countries. It is clear that the decision to introduce a new vaccination program into a country must take into consideration the local factors that may affect it's success. Rubella vaccination is a canonical example, where the benefits associated with vaccination must be balanced against the risks that insufficient coverage may lead to an increase in average age of infection, resulting in an increase in congenital rubella syndrome (Lessler et al., 2013). Previous studies have focused on the role played by changes in age structure that result from declining fertility (Gao and Hethcote, 2006; Metcalf et al., 2012), but the implications of broader changes in contact patterns have been less frequently considered. The simulations reported here have focused on a vaccine introduced at an advanced stage of demographic transition. Some less developed countries are likely to experience similar patterns of demographic change in the future. If these countries follow a similar path to that experienced by more developed countries, disease incidence may reduce even in the absence of vaccination, but clustering of unvaccinated sub-populations will pose ongoing challenges to control and elimination.

Authors' contributions

NG contributed to the conception and design of the study, performed the experiments, analyzed the data and wrote the manuscript. KG, JMM, ESM, KBK and JM conceived and designed the study and analyzed the data. MJK contributed to interpretation of the data. All authors contributed to critical revision of the manuscript and have seen and approved the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.epidem.2015.08.002.

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