Università degli Studi di Pisa
Dipartimento di Statistica e Matematica
Applicata all'Economia

Report n. 226

Population decline and population waves: their impact upon epidemic patterns and morbidity rates for childhood infectious diseases. Measles in Italy as an example

Piero Manfredi – John R.Williams

Pisa, Giugno 2002

- Stampato in Proprio –

Via Cosimo Ridolfi, 10 - 56124 PISA - Tel. Segr. Amm. 050 945231 Segr. Stud. 050 945317 Fax 050 945375
Cod. Fisc. 80003670504 - P. IVA 00286820501 - Web http://statmat.ec.unipi.it/ - E-mail: dipstat@ec.unipi.it

Population decline and population waves: their impact upon epidemic patterns and morbidity rates for childhood infectious diseases. Measles in Italy as an example[1]

Piero Manfredi[1], John R. Williams[2]

[1](corresponding author) Dipartimento di Statistica e Matematica Applicata all'Economia, Università di Pisa, Via Ridolfi 10, 56124 Pisa, ITALY

[2]Department of Infectious Disease Epidemiology, Division of Primary Care & Population Health Sciences
Faculty of Medicine, Imperial College of Science, Technology and Medicine
Norfolk Place, London W2 1PG, U.K.

Paper submitted for the Conference on

"Mathematical modelling of population dynamics"

24-28/06/2002, Bedlewo (Poland)

Summary
Most contributions in the field of mathematical modelling of childhood infectious diseases transmission dynamics has concentrated on stationary or exponentially growing populations. In this paper we show that the transition to sustained below replacement fertility (BRF since now on) recently observed in a number of western countries, Italy as a major example, can be characterised by severe non equilibrium conditions in the age distribution of the population, which in turn may significantly impact on epidemic patterns and levels of age related morbidity.

[1] Paper written within the research project "Epidemiologia delle vaccinazioni in Italia", national coordinator S. Salmaso (ISS).

Introduction

As regards the control of childhood infectious diseases, measles as a major examples, one usually has in mind two basically distinct patterns, e.g. those typical of developed countries (characterised by an average age at infection in urban areas around 4-6 years in the pre-vaccination era, and by little contribution to mortality by the disease) versus the developing world (a smaller average age at infection in urban areas, around 2-3 years in the pre-vaccination era, and therefore a much smaller vaccination window, and finally a significant mortality burden by the disease). These two types of patterns correspond to two peculiarly different social and demographic environments.

Most of the available mathematical modelling of childhood infectious diseases transmission dynamics used for public health purposes has modelled these different demographic environments by resorting to two highly stylised hypothesis, e.g. stationary (in total numbers and age structure) populations, aimed at representing population evolution in the developed world, and (quickly) exponentially growing populations, hopefully mimicking least developed countries (for an extensive discussion see Anderson & May 1991, and references therein).[2]

The analysis of the equilibrium relationships in both models leads to great epidemiological insight on the relations between fundamental epidemiological parameters, especially parameters governing social interactions between individuals (mixing parameters) and on the required eradication efforts. Moreover, by resorting to simulation it is possible to investigate the consequences of different immunization programmes.

Clearly stationary plus exponentially growing populations do not exhaust the possible forms of population dynamics. For instance the transition to sustained below replacement fertility (BRF since now on) recently observed in a number of western countries, Italy as a major example, has not yet been considered from the point of view neither of theoretical nor of practical epidemiological modelling. The fact that BRF is going to represent the rule of demographic evolution in a part of the western world is certainly worth of consideration by itself for practical modellers, who will have to necessarily take BRF into account in their epidemiological models if they want to be consistent with reality. From the theoretical point of view, the case of BRF populations does not seem, to our mind, to be of interest just for its long term equilibrium outcomes (long term population decline plus a somewhat "old" age distribution, this is just the opposite of what one finds in the model for developing countries). More interesting appears the fact that in many cases BRF has implied severe non equilibrium conditions in the age structures of the involved populations. These non equilibrium conditions may, in situations characterised by sub-optimal vaccination coverages (and even without vaccination), significantly impact on epidemic patterns and levels of age related morbidity. This aspect is not of little relevance: unstable demographic patterns with aging is a general feature of the demographic evolution of all those developing countries now in their process of fertility transition.

A further important point which arises from a highly unstable demographic environment is the need, if one aims to match observed epidemiological patterns, for embedding realistic population dynamic patterns into our mathematical models. Indeed, in presence of significant demographic instability it would be rush to place confidence in results without keeping demographic factors under control.

In this paper we use a standard age structured mathematical model for measles embedding realistic (e.g. actually observed fertility and mortality) demography to investigate measles transmission dynamics and scenarios for control under conditions of population instability caused by BRF using the example of Italy. A related purpose of the paper is that of characterising the effects played by the peculiar demographic environment which Italy is presently experiencing, in relation with the

---

[2] It is to be pointed out, however, that "stationary" versus "exponentially" growing populations are to be intended as "proxies" for a more complex set of differences involving also the spatial distribution of the population, its distribution by age and family size, etc. At a greater detail other modelling strategies commonly adopted in order to emphasise differences between developed versus developing countries concern human mortality: it is typical (Anderson & May 1991) to use Type II (constant death rate) mortality for developing countries, and Type I (death rate equal to zero up to a maximal age and infinity thereafter) mortality for the developed ones.

WHO targets. Though our paper systematically uses Italy as an example, our results have probably a wider scope.
The present paper is organised as follows. In section 2 we discuss the demographic situation of Italy as a major example of a country with BRF. Section 3 briefly describes the mathematical model used. Section four reports some results from our main scenario of epidemic control under continuation of below replacement fertility. A discussion of the critical points follows in section 5.

Below replacement fertility, population instability, aging: an overview of some realistic population dynamics facing public health modellers

Below replacement fertility, as defined by a Total Fertility Rate (TFR) sustainedly less than the "replacement" level *2.1*, initiated in Italy in 1976. Moment TFR have been steadily declining thereafter reaching level *1.2* in 1994 and remaining more or less constant in the past *7* years. The long term argument suggests that if BRF should continue in the future, then, by assuming unchanging (female) fertility and mortality rates at their 1996-1998 levels, our population would achieve the very "old" stable age distribution reported in fig. 1. Such age distribution would be achieved by 2020-2030. Moreover, Lotka's intrinsic rate is r_0=*-0.0181*, a very large decay rate, implying a high long term pace of exponential decline with halving time around *38.3* years.[3]

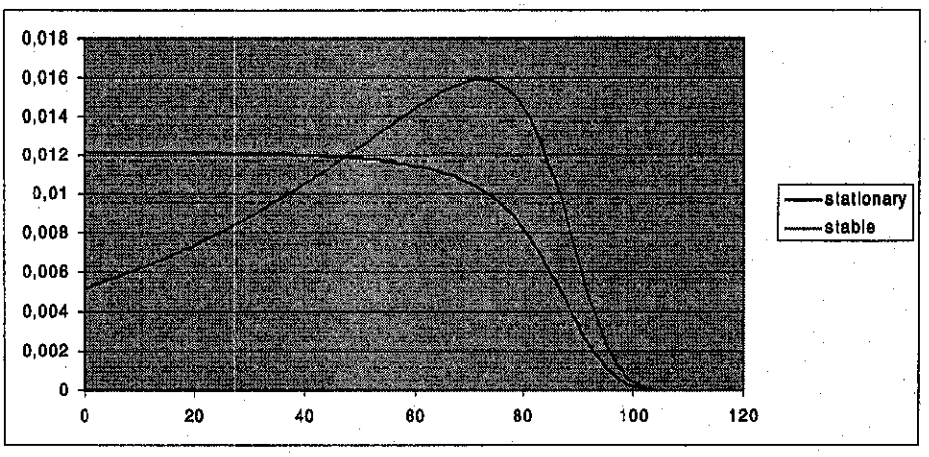


Fig. 1. Long-term stable age distribution implied by the Italian 1996-98 vital rates and the corresponding stationary population implied by the 1996-98 life table

Another significant feature of the long term regime implied by the continuation of BRF is (fig. 2) the distribution of age at chilbearing, which is characterised by an average around *30.5* years. This may become extremely relevant for rubella transmission dynamics, especially in presence of sub-optimal vaccination coverages.

[3] For what concerns the actual Italian population we notice however that it has not yet start declining, despite 25 years of BRF, due to the joint action of the inertial effect of its initially "young" age distribution, and of significant migration flows initiated around 1985.

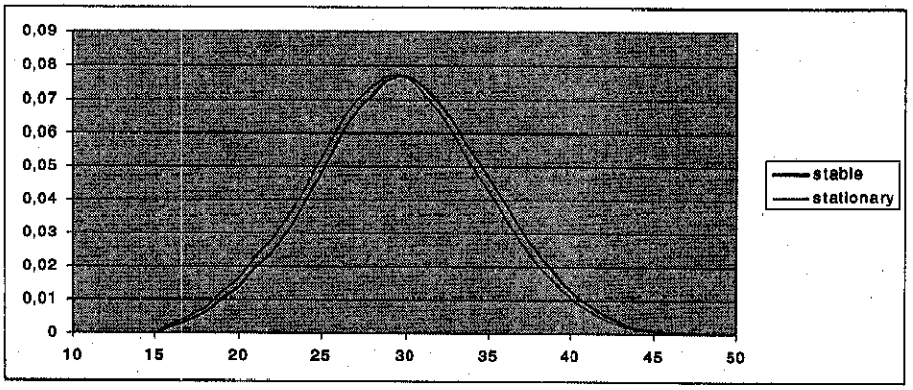


Fig. 2. Distribution of age at chilbearing in the long term stable population.

What confidence do we place in the continuation of sustained BRF in the future, e.g. how likely are scenarios based on the assumption of continuation of BRF against alternative scenarios postulating a fertility relapse ? From the theoretical point of view the major problem is whether the "one child" society might be considered some sort of social optimum (that would mean a possibly stable equilibrium point for the society as a whole) or not. In a recent study on countries with "lowest low fertility" (LLF), Kohler, Billari and Ortega (2002) have listed the major determining factors of LLF. They suggest that is hard to see in current data clear indication of sharp reversal, or at least of interruption, in the present trends. In any case it is clear that if LLF should continue for few years still, so that the age distribution of the Italian population will be sufficiently close to its limiting form, then even a sharp reversal in fertility.

Fig. 3 reports the number of births (which surely is the most important input from the demographic system to the epidemiological one, as long as we are concerned with childhood infections with long-term immunity) predicted for Italy by our mathematical model on the period 1951-2100. For the time window 1951-2000 the predicted trajectory very closely follow the observed one (not reported in the figure), as we would expect given that we have used observed fertility and mortality rates. The trajectory shows both the baby-boom in the sixties and the subsequent period of sustained low fertility. For the time window 1951-2100 figure 3 bifurcates into two distinct trajectories which correspond to two distinct scenarios, e.g. i) continuation of BRF with fertility rates constant at their 1996-98 levels (the declining branch), and ii) relapse of a regime of stationarity (TFR = 2.1 around 2015) followed by a regime of slow growth. Scenario i) ends in its long term regime of exponential decline (predicted also theoretically, as vital rates are kept constant after 1998).

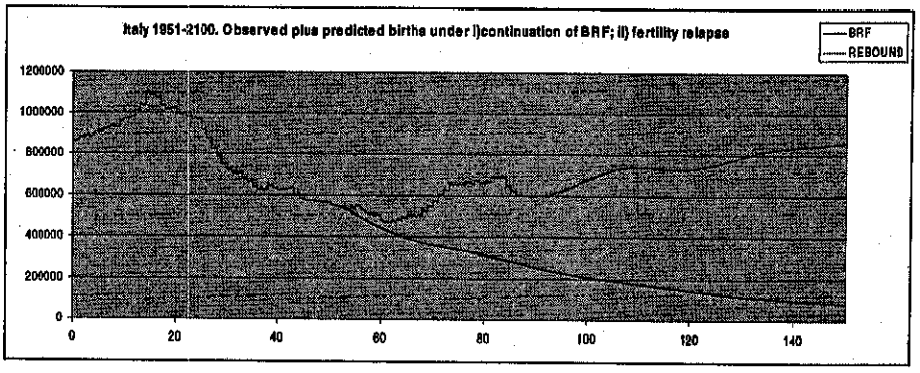


Fig. 3. Observed and predicted births under two different scenarios.

Scenario ii) is alternative to the continuation of BRF and is based on the "optimistic" view (for instance Bongaarts (1999)) by which further decline as well as continuation of the present low levels of fertility are unlikely, because, apart the effects of biases in moment TFR, it is well

documented (for instance by european FFS data, Bongaarts 1999) that couples in most post-transitional societes "...plan to have about two children" (ibidem, 256).
The two scenarios i) and ii) previously introduced represent, from the standpoint of control of childhood diseases, two significantly different demographic environments. The effects implied by scenario i), which is our major concern here, are also well illustrated in fig. 4, reporting the predicted dynamics of the Italian population in some selected age groups under scenario i). Fig. 4 shows well the inertial effect of age structure leading to aging of the overall population. It is to be noticed that aging of the population is a phenomenon that pertains exclusively to the transient phase which characterises the achievement of the long term stable regime and not to the long term regime by itself (as clear from Lotka's theorem of mathematical demography).

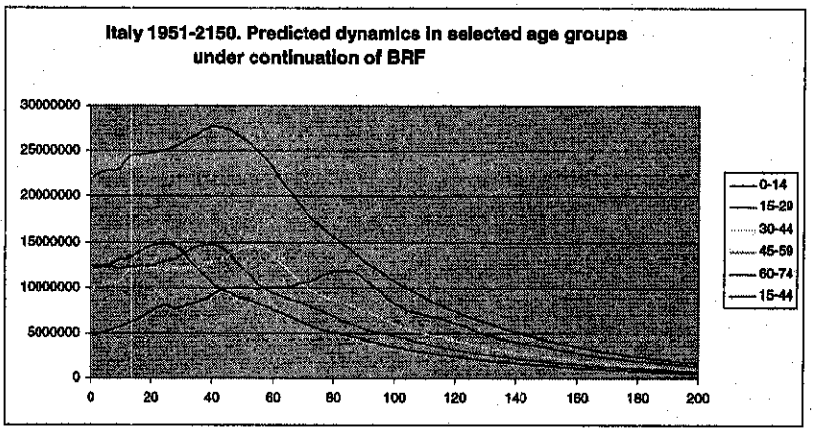


Fig. 4. Time evolution of selected age groups under continuation of BRF

Scenarios i) and ii) are based on reasonable boundary assumptions, at least as long as we postulate a "closed" population, as typical in standard epidemiological models. In particular i) reflects the feeling that fertility will not further decline.
A final point concerns the fundamental assumption of a closed population. In very recent times, e.g. since 1985-1990, Italy has started to host significant immigration flows, and demographers have been very much concerned with immigration as a tool against depopulation and aging caused by sustained lowest low fertility (Manfredi & Valentini 2000, Billari et al. 2000). Systematic investigation of scenarios including international immigration as well are developed in Manfredi & Williams 2002.

Materials and methods

The mathematical model

We use a MSEIR (maternal antibody protection → susceptible → exposed → infective → removed) age structured mathematical model for measles with age related force of infection. The force of infection was modelled according to an age structured "true mass action" (De Jong et al. 1994, Hethcote 1999), of the form

$$\lambda(a,t)=\frac{\int_0^\infty \beta(a,a')Y(a',t)da'}{\int_0^\infty n(a,t)da}=\frac{\int_0^\infty \beta(a,a')Y(a',t)da'}{n(t)} \qquad (1)$$

Under the common assuption of piece-wise constant transmission rates over broad age groups (1) looks as

$$\lambda_i(t)=\frac{\sum_{j=1}^{m}\beta_{ij}Y_j(t)}{n(t)} \qquad (2)$$

This choice appears to be the more consistent one in a regime characterised by population instability.[4] In particular it allows for a stable age distribution by infective state in the long term regime of stable decline which follows under scenario 1 (contrary to bilinear "pseudo" mass action, as adopted in Anderson & May 1991, or Louie et al. 1994), see the appendix.
Mixing patterns were estimated by means of standard techniques (Anderson & May 1991) from pre-vaccination measles data. Such estimates were based on two broadly different assumptions on the force of infection (FOI) of measles: a "low" assumption, estimated from available Italian data from the pre-vaccination era, and a "high" assumption, borrowing the so called "EURO" FOI estimated by Edmunds et al. (2001) for some european countries with reliable data. In particular the "low" FOI was estimated by preliminarily estimating the levels of under-reporting at the regional level, and then correcting regional figures, in order to achieve a corrected age distribution of cases at the national level (Williams & Manfredi 2002, Manfredi & Williams 2001). This "low" FOI is denoted as the ICN-UR[5] FOI in what follows. The "low" and the "high" FOI's were systematically used with the purpose to build low and high epidemiological scenarios (hopefully bounding true epidemiological patterns).
In contrast to standard approaches, we have considered, in order to match the model to observed data, realistic demography, e.g. the model is simulated under observed fertility and mortality for the time window 1951-2001.

Data
Age structured case notification data at the regional level from both the pre-vaccination era (1951-1976) and the post-vaccination era (1977-1998) were provided by ISTAT.
Vaccination against measles in Italy initiated in 1976. Unfortunately the vaccination being only recommended and not compulsory, coverages remained for quite a long while at disappointingly low levels. The apparent lack of availability of good data on vaccination is also disappointing.
The very few available data on vaccination coverages were used here to interpolate some "reasonable" national time profile of routine vaccination coverages used in the simulations.
Data on fertility and mortality rates at the national level are obtained from published national statistics (Istat, several sources).

Results

We basically deal here with the "continuation of BRF" scenario, which is the more interesting for the purposes of the present paper. The model was simulated, using year 1951 as initial time, under observed fertility and mortality for the time window 1951-2001, and by continuing the BRF assumption thereafter. The choice start of 1951 as initial time was motivated by the fact that at 1951 the first post-war population census was held, and of course by the need for matching the predictions of the model against some pre-vaccination data.

---

[4] A more rigorous approach may be based on the definition:

$$\lambda_i(t) = \sum_{j=1}^{m} b_{ij} C_i p_{ij} \frac{Y_j(t)}{n_j(t)}$$

traditionally used for STD's, where C_i=contact rate in group i, p_{ij}=mixing fraction of i-individuals with j-individuals, b_{ij}= infectivity rate. Taking $b_{ij}=b$ (a constant infectivity rate) one gets the equilibrium relation $\lambda_i = \sum_{j=1}^{m} \left(\frac{b C_i p_{ij}}{n_j} \right) Y_j$ which conforms to (2) in the main text under the identification $\beta_{ij} = \frac{b C_i p_{ij}}{n_j}$. The results provided by this alternative formulation are however only slightly different. Of course these two alternatives do not provide the "final answer" to the point.

[5] The acronym stands for Italy Case Notifications (corrected for spatial) Under Reporting.

A major problem was the selection of a suitable initial age distribution by epidemiological state, the problem being of course that in presence of severe demographic instability the choice of initial conditions could matter a lot. Fortunately our simulation suggest that in a time span of around 25/30 years, i.e. from the initial time until the beginning of the post-vaccination era (1976), initial conditions are sufficiently well forgotten with a sufficiently good synchronisation of oscillations *for a very wide range of initial distributions,* as illustrated in fig. 5. (Giampaolo Scalia Tomba pointed out to us that such a result is a sort of *weak ergodic* behaviour for a "demographically perturbed" epidemiological system: we do not know at present any type of theoretical results, estending demographic weak ergodic theorems to epidemiology, on which to rely for supporting our simulation).

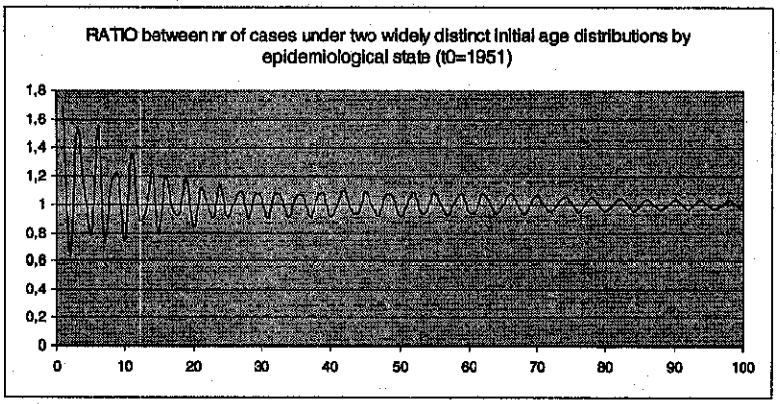


Fig. 5.

Once the predictions from the the model are compared with actual data (we do not report here such "validation results", which are extensively discussed in a broader paper in preparation, Manfredi & Williams 2002b), the model seems to match observed patterns quite well, in the sense that our two boundary assumptions on the force of infections allow to bound observed epidemiological trends quite well (whereas the use of a "standard" stationary population model for "developed countries" provided much more unsatisfactory "fit" of observed patterns, therefore suggesting that the use of realistic demography in some cases may significantly improve the confidence in our results).

Scenarios for measles without vaccination

A first set of scenarios for measles was constructed by explicitly assuming no vaccination. The main question attacked here could be rephrased as follows: "how could have the "natural history" (e.g. in absence of vaccination) of measles in Italy been under a severely unstable demographic environment characterised by a baby-boom (1965-1970) and subsequently by the initiation and indefinite continuation of BRF" ? Here we report results under one of the more plausible forms of mixing matrices, e.g. the "default" mixing used by Edmunds et al . (2001), but our results are broadly confirmed for a wide range of mixing patterns compatible with the estimated FOI's.

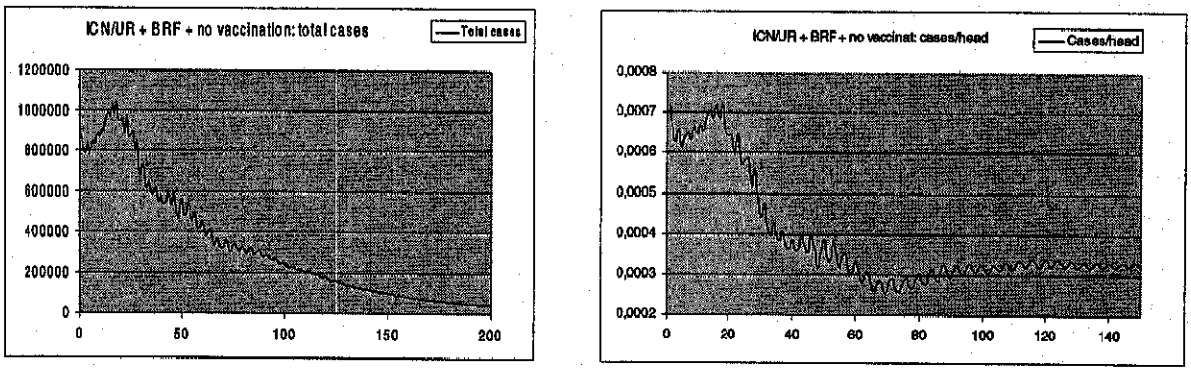


Fig. 6a,b. Total and standardised cases under the BRF scenario

As illustrated in fig. 6a the total number of measles cases steadily declines after the peak corresponding to the baby-boom (1965-1970), whereas (6b) the number of cases per head steadily declines only over the whole unstable phase characterised by population aging, and stabilises when the long term stable age distribution is finally achieved.

A striking point is the extent of the "control effect" on the disease played by population aging (rather than, purely, population decline: it would be a trivial fact). This effect is well evident from fig. 7, reporting the time paths of the average ages at infection under both the "low" (ICN-UR) and the high (EURO) FOI's considered in this paper.

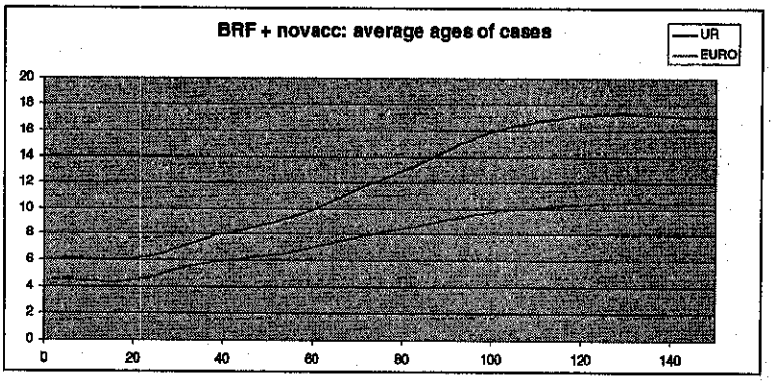


Fig. 7. Time paths of the average ages at infection.

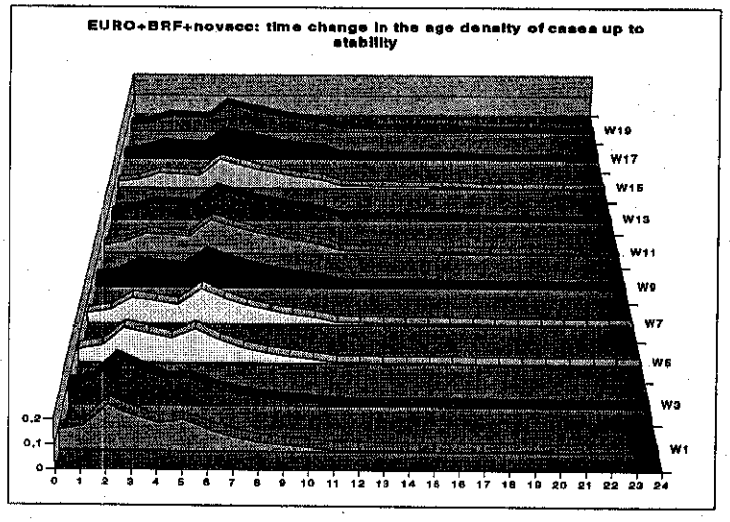


Fig. 8

Under both assumptions on the underlying force of infection the average age increases by a factor around 2,5. This effect would not exist at all under a pure "stable" population decline in which the declining population has already achieved its stable age distribution (this is evident from the long term flat dynamics of the average ages at infection, once the stable age distribution is achieved). It is therefore a major consequence of the transient process of population aging due to the initial unstable phase.
This control effect is evident also from fig. 8, reporting the "time-film" of the overall age distribution of cases under the high FOI. The formal explanation of such a control effect is understandable from equation (1), which is suggestive, by just recalling the shape of the long term age distribution of fig.1 compared to the standard "flat" stationary age distribution, of the potentially relevant effects played by the process of population aging for the dynamics of the disease (more deep considerations are developed elsewhere).
Two major remarks arise at this stage.
The first remark is of course that an unstable regime of population aging may play a role of control of the disease, quite similar to vaccination (and in fact both effects essentially act through reducing recruitment of susceptibles). The fact that control becomes easier as times goes on is not counterintuitive. One simple manner for "proving" this fact is the following. One can consider different windows of time, and compute for each of these, by using standard epidemiological techniques, the related forces of infection from the predicted data. One will then observe a steady decline, as time goes up, in both the FOI's and the corresponding values of R0, and therefore in the amount of effort needed to eradicate the disease. This seems to be a good new, if the target is eradication (see the discussion for the possible limits of the present analysis).
We also notice that this transient phase of demographic instability is magnified here by the heritage of the baby-boom (causing severe istability), but it would exists even under more "neutral" initial conditions.
The second remark is concerned with the fact that this further control factor, probably not considered by public health policy makers, could magnify "perverse" effects of vaccination once vaccination is introduced, especially if vaccination coverages are maintained at sub-optimal levels, as it seems to have been the rule in Italy in the past 25 years (national coverage in 1998 around 55%, but with huge heterogeneity at the spatial scale, AAVV 1998). In this case one could fear that the joint action of continued sub-optimal vaccination plus aging could significantly impact upon age related morbidity, a problem that is of serious concern for measles and rubella. Again the role of the initial demographically unstable phase could be important (for instance population aged 30-45 at risks of serious complications by both measles and rubella starts to decline only by 2010, see fig. 4). This motivates the investigation of the next set of scenarios.

Scenarios with vaccination

Consistently with the last remark we now add vaccination to our model, in the form of routine vaccination, e.g. vaccination administered to cohorts of newborn babies. A time profile of routine vaccination coverage at the national level was reconstructed by collating the few available data (fig. 9), suggesting a coverage rate around 55% at the national level by 1997. We only investigate here the effects of the continuation, during the full time span of our scenarios, of the level achieved by 1997.

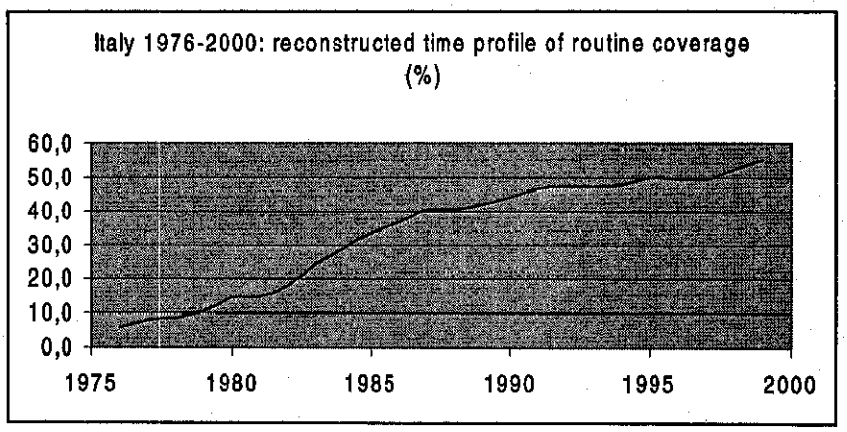


Fig. 9

We report some illustrative results under the "low" FOI only.[6] Fig. 10a reports the time path in the total number of susceptibles. The striking predicted increase is the sum of two effects, namely Schenzle's effect (Schenzle 1984), predicting possible increase in numbers of susceptibles as a consequence of sub-optimal vaccination coverages, and that due to demographic instability. Fig. 10b reports the pattern of increase of the average age at infection. By 2025-2030, when the peak in the number of susceptibles is achieved, the predicted average age at infection is around 25. The extent of the increase is striking compared to the level expected on the basis of the simple formula $A_V=A/(1-p)$ (Anderson % May 1991) relating, in a homogeneous mixing model, the average age at infection in the pre- and post-vaccination regime following the adoption of a vaccination programme consisting in the immunization of a constant fraction p of newborn babies.

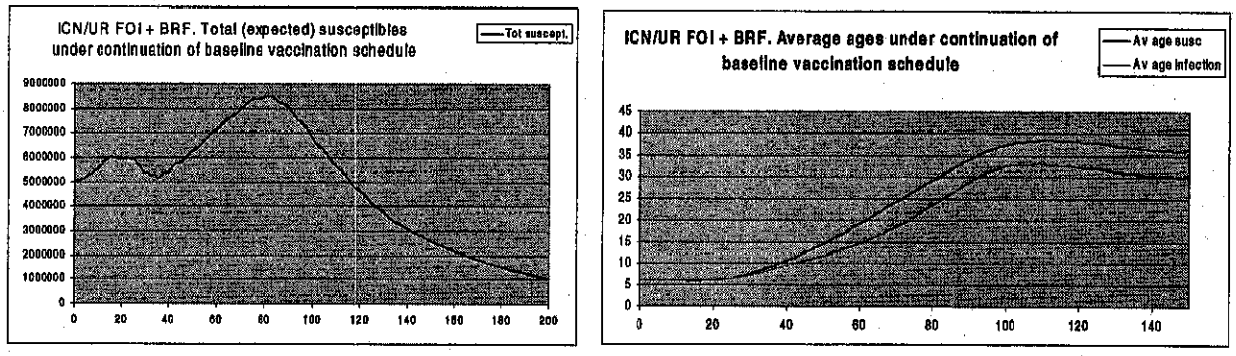


Fig. 10a,b

Fig. 11 reports the time path expected for the number of cases, exhibiting the achievement by 2020 of a plateau (compared to the previous period), which is maintained for around 20 years. The sub-optimal immunization programme is exactly pushing the infection from the smaller young age groups to the relatively larger higher age groups which emerge as a consequence of the aging process.

[6] The "low" FOI appears also indicative, at least partly, of rubella patterns (Edmunds et al. 2001).

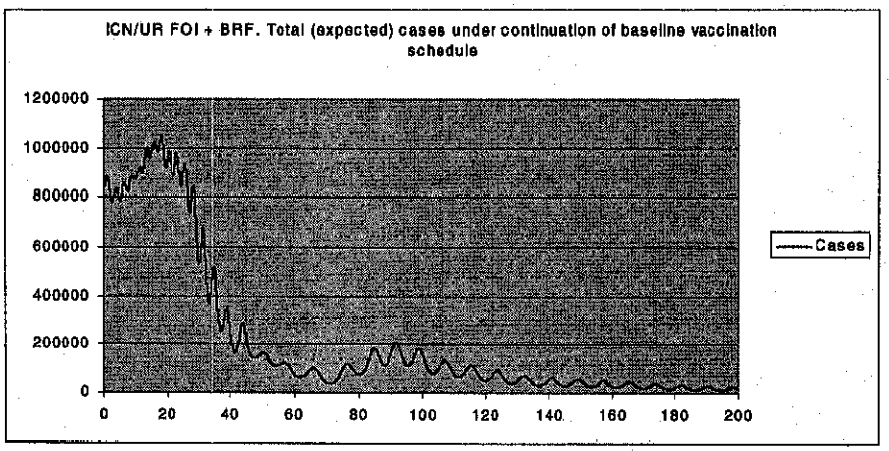


Fig. 11.

The more interesting things are illustrated in fig. 12,13. Fig. 12 puts together the time path of total cases under the "low" FOI in absence of any immunisation programme (i.e. the path reported in fig. 6a) with the time path of fig. 11, drawn under the continuation of the current immunization programme. Fig. 12 illustrates that there will a long time interval, starting at 2015, in correspondence of which, due to the aforementioned effects, the effectiveness of the current program in preventing cases will be minimal.

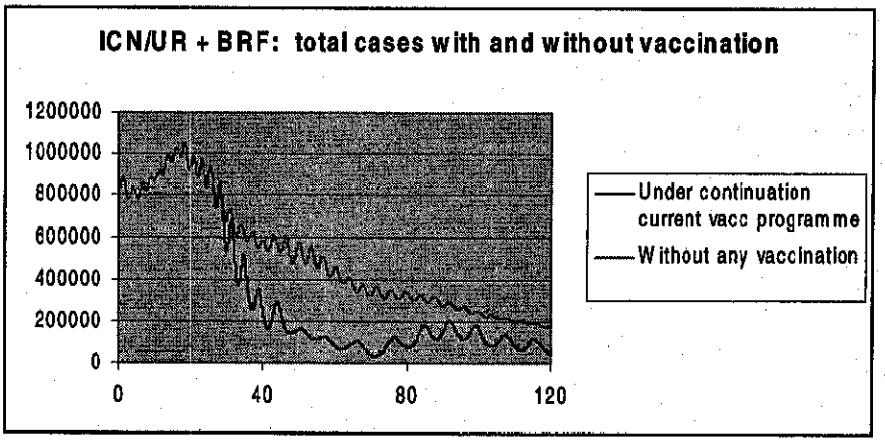
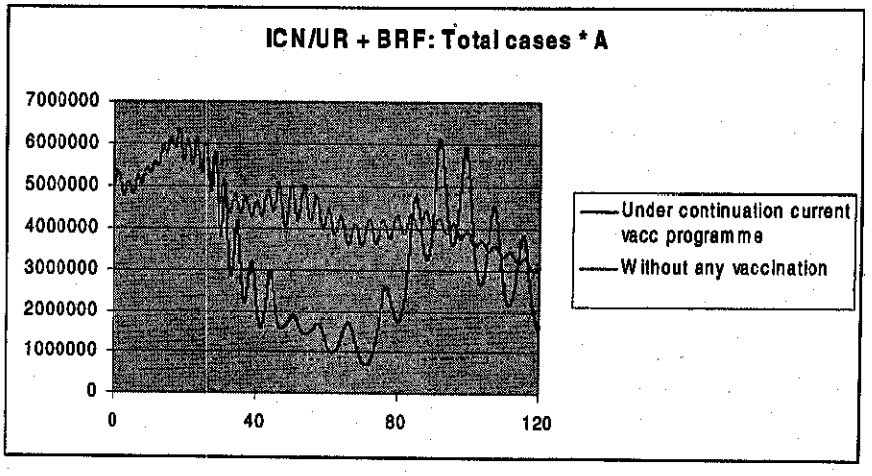


Fig. 12

Fig. 13 summarises, by a very rough measure, e.g. the product between the predicted number of cases and the average age at infection, the corresponding extent of the possible perverse effect of vaccination.



Discussion

The paper has investigated scenarios for the control of measles in a regime of transient (but severe) demographic instability due to the onset and continuation of sustained below replacement fertility. This was done by means of a standard age structured epidemiological model with realistic demography. Our results suggest that the aging process which characterises the transitional phase can have two major effects: i) it may reduce the amount of vaccination effort required for eradicating the disease; ii) it may significantly magnify the perverse impact of vaccination in terms of the burden of severe age related morbidity.

From the public health point of view our work seems therefore to suggest that, in the case of Italy, it is extremely important to quickly improve present sub-optimal coverage levels. This choice could successfully take profit of the possibly easier conditions under which planning eradication, and avoid a possibly sad epoch, possibly starting by 2015-2020, in which the big expected aging wave could magnify the perverse effects of vaccination, and lead to a heavy burden of serious illnesses. There seems therefore to be a "favourable moment" during which planning measles eradication efforts, consistently with WHO general planning.

These considerations apply not only to measles but all childhood diseases, in particular to mumps and rubella as well. We also notice that the "favourable moment for eradication" could be lost by the relapse of fertility: a new birth wave would restore less favourable conditions.

We very briefly suggest here some main critical points of the present work.

A first point concerns the adopted form of the force of infection: though important theoretical considerations make "true mass action" preferable to other forms, caution, and therefore more work, should be used for actual public health epidemiological modelling.

A second point is the need for a more extensive exploration of alternative forms of mixing (Manfredi & Williams 2002).

A third point is the lack in the model (just because this is the common choice, see also Anderson & May 1991, not because it is unrelevant) of any type of mixing restraints. But quickly aging (as, by the way, quickly growing) "one child per family" populations, as the Italian one, experience significant dynamical changes leading to old long term age distributions which are very different from traditional "flat" stationary populations commonly adopted in standard epidemiological modelling for developed countries. All this could imply significant changes in the relevant mixing pattern not purely explainable through the dependency of the force of infection by the age structure of the population as expressed by formulas as (A5) in the appendix.

Finally, the demographic scenarios considered here do not consider immigration, which is a further important point. Its implications are deply investigated in a paper in preparation.

References

A.A.V.V. (1998), ICONA: indagine nazionale sulla copertura vaccinale infantile, Rapporto ISTISAN 98/33.

Anderson R.M:, May R.M. (1991), *Infectious diseases of humans: dynamics and control*, Oxford University Press, Oxford.

Bongaarts J.(1999), Fertility decline in the developed world: where will it end ? *American Economic Review*, 89,2, 256-260.

Billari F., Manfredi P., Valentini A. (2000), Macro-demographic effects of the transition to adulthood: multistate stable population theory and an application to Italy, *Mathematical Population Studies*, 9,1, 33-63.

De Jong M., Diekmann O., Heesterbeek H. (1994), How does transmission of infection depend on population size?, in Mollison D. (ed.), Epidemic Models, Cambridge University Press, 84-94.

Edmunds WJ. Gay NJ., Kretzchmar M., Pebody RG., Wachmann H (2001), The pre-vaccination epidemiology of measles, mumps and rubella in Europe: Implications for modelling studies, *Epidemiology & Infection*, 125(3):635-650.

Kohler H.P. Billari F.C., Ortega J.A. (2001), Towards a theory of lowest-low fertility, MPIDR WP 2001-032.
Louie K., Roberts M.G. Wake G.C. (1994), The regulation of an age-structured population by a fatal disease, *IMA Journal Math. Applied in Medicine & Biology*, 11, 229-244.
Manfredi P., Valentini A. (2000), Populations with below replacement fertility and immigration: theoretical considerations and scenarios from the "Italian laboratory", *Rivista Internazionale di Scienze Sociali*, 108, 1, 61-94.
Manfredi P., Williams J.R. (2001), To what extent can inter-regional migration perturb local endemic patterns? Estimating measles incidence and under-reporting rates in the Italian regions, WP 187 Dip. Statistica e Matematica Applicata all'Economia, Università di Pisa, submitted to Epidemiology and Infection.
Manfredi P., Williams J.R. (2002), Measles in Italy: scenarios from several options on vaccinations and demography, in preparation.
Istat 1950-1996, Annuari di Statistiche sanitarie, Istat, Roma.
Istat 1950-1998, Annuari di Statistiche demografiche, Istat, Roma.
Schenzle D. (1984), An age-structured model of pre- and post-vaccination measles transmission, *IMA Journal Math. Applied in Medicine & Biology*, 1, 169-191,
Williams J.R., Manfredi P., Salmaso S., Ciofi M. (2001), Heterogeneity in regional notification patterns and its impact on aggregate national case notification data: the example of measles in Italy, WP 216 Dip. Statistica e Matematica Applicata all'Economia, Università di Pisa, submitted to Epidemiology and Infection.

Appendix. The "reference" mathematical model

The mathematical model simulated in the paper is a standard SEIR-type model for childhood diseases. Let $X(a,t)$, $H(a,t)$, $Y(a,t)$, $Z(a,t)$ respectively denote the numbers of susceptibles, exposed (e.g. infected but not yet infectious), infective and recovered individuals of age a at time t. The model is described by the following balance PDE's (Anderson & May 1991):

$$\begin{aligned}
\delta X(a,t) &= -(\mu(a,t)+\lambda(a,t))X(a,t) \\
\delta H(a,t) &= \lambda(a,t)X(a,t)-(\mu(a,t)+\sigma)H(a,t) \\
\delta Y(a,t) &= \sigma H(a,t)-(\mu(a,t)+\nu)Y(a,t) \\
\delta Z(a,t) &= \nu Y(a,t)-\mu(a,t)Z(a,t)
\end{aligned} \qquad \text{(A.1)}$$

where $\delta = \left(\frac{\partial}{\partial a}+\frac{\partial}{\partial t}\right)$ denotes the usual "population aging" operator along population characteristics, plus the boundary conditions

$$X(0,t)=B(t)(1-p(t)) \;;\; H(0,t)=0 \;;\; Y(0,t)=0 \;;\; Z(0,t)=0 \quad \text{(A.2)}$$

where

$$B(t)=\int_0^\infty n(a,t)m(a,t)da$$

In (A.1)-(A.2) $\mu(a,t)$ is the mortality rate at age a (assumed time dependent), $\lambda(a,t)$ the force of infection faced by susceptibles aged a, σ the rate of transition from the infected to the infective state, ν the recovery rate. Moreover $n(a,t) = X(a,t)+H(a,t)+Y(a,t)+Z(a,t)$ denotes the total population, $B(t)$ the birth function, $m(a,t)$ the fertility rate, which is assumed to be time dependent, $p(t)$ the routine vaccination coverage for newborn babies (which is assumed to be indetically zero in the pre-vaccination era). The force of infection is defined as follows:

$$\lambda(a,t)=\frac{\int_0^\infty \beta(a,a')Y(a',t)da'}{\int_0^\infty n(a,t)da}=\frac{\int_0^\infty \beta(a,a')Y(a',t)da'}{n(t)} \qquad \text{(A3)}$$

where $\beta(a,a')$ are the transmission rates between age groups a and a'.
In the case of no vaccination, under scenario i) considered in the paper, e.g. continuation of BRF with unchanging fertility and mortality, the model is postulated to have a long term dynamics characterised by an unchanging demography. This implies that in such a case a stable age distribution by age and epidemiological state exists. Such a stable age distribution characterises the long term regime of the system. The stable regime is characterised by the time independent FOI

$$\lambda(a)=\int_0^\infty \beta(a,a')y(a')c(a')da' \qquad \text{(A.4)}$$

where $y(a)$ is the infective fraction at equilibrium ($=Y(a/n(a))$, and $c(a)$ denotes the stable age distribution of the population in the stable long term regime:

$$c(a)=\frac{e^{-ra}p(a)}{\int_0^\infty e^{-ra}p(a)da} \qquad \text{(A.5)}$$

where r denotes the intrinsic rate of population decay (because we are assuming BRF) in the asymptotic regime, and $p(a)$ the survival function postulated for the long term dynamics of the model. The equation (A.4) is suggestive, by just recalling the shape of the long term age distribution of fig.1 compared to the standard "flat" stationary age distribution, of the potentially relevant effects played by the process of population aging for the dynamics of the disease.