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Measles elimination in Italy: projected impact of the National Elimination Plan

P. MANFREDI[1], J. R. WILLIAMS[2], M. L. CIOFI DEGLI ATTI[3]* AND S. SALMASO[3]

[1] *Dipartimento di Statistica e Matematica Applicata all'Economia, Università di Pisa, Pisa, Italy*
[2] *Department of Infectious Disease Epidemiology, Division of Primary Care & Population Health Sciences, Faculty of Medicine, Imperial College London, London, UK*
[3] *Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute, Istituto Superiore di Sanità, Roma, Italy*

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SUMMARY

A mathematical model was used to evaluate the impact of the Italian Measles National Elimination Plan (NEP), and possible sources of failure in achieving its targets. The model considered two different estimates of force of infection, and the possible effect on measles transmission of the current Italian demographic situation, characterized by a below-replacement fertility. Results suggest that reaching all NEP targets will allow measles elimination to be achieved. In addition, the model suggests that achieving elimination by reaching a 95% first-dose coverage appears unlikely; and that conducting catch-up activities, reaching high vaccination coverage, could interrupt virus circulation, but could not prevent the infection re-emerging before 2020. Also, the introduction of the second dose of measles vaccine seems necessary for achieving and maintaining elimination. Furthermore, current Italian demography appears to be favourable for reaching elimination.

INTRODUCTION

Compared to other European countries, Italy is a long way from achieving the European WHO target of elimination of indigenous measles by 2010 [1]. In fact, measles vaccination coverage rates have always been low in Italy, with a national average of only 56% in children aged 12–24 months in 1998 [2]. Despite significant achievements in subsequent years, with an increase in the national coverage to 77% in 2003 [3], and despite several supplementary vaccination activities conducted locally in many regions [4], vaccination coverage rates are still a long way from the levels required to interrupt transmission, i.e. 95% by 2 years of life [5]. In addition, the Italian health system is decentralized, and each region has the responsibility of implementing measles vaccination policies. As a consequence, large differences in vaccination coverage between regions have been observed [2], lower coverage areas being located mainly in southern Italy, where large measles epidemics occurred during 2002–2003 [6].

Since the interruption of measles transmission can be achieved at the national level only with coordinated and uniform actions throughout the country, in 2002–2003 a National Elimination Plan (NEP) has been developed jointly by the Regional Health Authorities, the National Institute of Health and the Ministry of Health [7]. NEP key strategies to achieve measles elimination in Italy include improving routine coverage with one dose of measles–mumps–rubella

* Author for correspondence: Dr M. L. Ciofi degli Atti, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Roma, Italy. (Email: ciofi@iss.it)

(MMR) vaccine by 24 months of age to $\geqslant 95\%$, catch-up of unvaccinated children during other routine immunization activities; i.e. polio booster dose in the third year of life, and diphtheria–tetanus–acellular pertussis (DTaP) booster dose at 5–6 years of age, conducting a national 'catch-up' vaccination campaign for children aged 6–13 years during 2004–2005, and achieving and sustaining a high routine coverage with a second routine dose of MMR vaccine among children aged 5–6 years, administering the MMR vaccine simultaneously with the DTaP booster dose included in the national schedule.

In order to evaluate the likely impact of the NEP on measles transmission, a mathematical model was developed. The objectives of the model were to evaluate whether the achievement of the NEP targets would bring success in achieving measles elimination, and the effect of possible failures in achieving one or more of the NEP targets. In order to take into account the current Italian demographic situation, characterized by a below-replacement fertility from 1976 onwards [8], until the present state of very low fertility (i.e. a total fertility rate close to 1·2 since the beginning of the 1990s) [9], with the sustained ageing of the population as a main consequence, a 'realistic demography' variant of the standard deterministic model [10] was also developed. This article reports the main results obtained under the different assumptions considered.

METHODS

The epidemiological model

Measles transmission dynamics in Italy were modelled by a deterministic MSEIR (maternal antibody protection–susceptible–exposed–infective–recovered) age-structured model [10], with age-related force of infection (FOI).

Two distinct assumptions on the underlying population dynamics were considered. The first one (D1) assumes a stationary population dynamics, as in most modelling work on measles in modern industrialized countries [11, 12]. The second assumption (D2) aimed to mirror the current Italian demography: fertility rates were derived from 1951–2000 national data [source: National Institute of Statistics (ISTAT)], and ISTAT national life-tables for years 1980–1982 were used to mirror mortality rates. Under this 'realistic demography' scenario, we made the assumption of continuation after 2002 of the current demographic pattern. The model does not include seasonal forcing. Further details are presented in the Appendix.

Force of infection

The FOI has been defined as follows [13, 14]:

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

where β_{ij} are the age-related transmission rates in contacts between susceptibles in age group i and infectives in age group j, $Y_j(t)$ is the number of infectious individuals in age group j at time t, and $n(t)$ the total population. With regards to social behaviour, we have considered the following five age groups, which correspond to the main school grades in Italy: very young children of 0–2 years, pre-school children of 3–5 years, primary schoolchildren of 6–10 years, secondary schoolchildren of 11–18 years, and adults aged $\geqslant 19$ years.

The choice of equation (1) has been motivated as follows: (*a*) under the assumption of a stationary population dynamics (D1) equation (1) is equivalent to the traditional bilinear formulation $\lambda_i(t) = \sum_{j=1}^{m} \beta_{ij} Y_j(t)$; (*b*) under assumption D2 of realistic demography, equation (1) allows a feedback of the changing age distribution of the population on the risk of infection. In particular, in a condition of sustained population ageing, equation (1) allows a long-term decline of the overall risk of infection due to the increased relative frequency of contacts with older people, which might encompass effects such as that of the decreased family size (e.g. decline in intra-family transmission). Thus, as further discussed in the Appendix, the choice of FOI1 allows not only consideration of the traditional case of stationary demography, but also to roughly bound the potential decline in transmissibility that is possibly caused by a situation of sustained population ageing.

In order to consider the maximal variation in the pre-vaccination FOI, we adopted as an upper bound the 'EURO' FOI estimated by Edmunds et al. [15], by pooling pre-vaccination data from some European countries.

As a lower bound we took the FOI computed from Italian case reports for years 1951–1976 (source: ISTAT), by preliminarily estimating the levels of under-reporting at the regional level and then correcting regional figures, in order to obtain a corrected age distribution of cases at the national level [16].

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Table 1. *EURO and IT forces of infection for measles, and corresponding values of R_0 and p_c under default mixing* (*vaccine efficacy is assumed to be 100%*)

	Force of infection by age group (%/year)						
	0–2 yr	3–5 yr	6–10 yr	11–18 yr	19+ yr	R_0	p_c
EURO	12	28	40	20	10	9·8	91%
IT	8	17	31	19	6	6·3	86%

Mixing patterns

Pre-vaccination mixing patterns were estimated from both FOIs by using WAIFW ('Who Acquires the Infection From Whom') matrices, using the standard technique assuming stationarity [10], and using the 'default' (DEF) configuration [15]:

$$\mathrm{DEF} = \begin{pmatrix} \beta_1 & \beta_1 & \beta_1 & \beta_1 & \beta_5 \\ \beta_1 & \beta_2 & \beta_4 & \beta_4 & \beta_5 \\ \beta_1 & \beta_4 & \beta_3 & \beta_5 & \beta_5 \\ \beta_1 & \beta_4 & \beta_5 & \beta_3 & \beta_5 \\ \beta_5 & \beta_5 & \beta_5 & \beta_5 & \beta_5 \end{pmatrix}.$$

DEF-type matrices assign a dominant role to transmission in school and pre-school ages, and appear a reasonable representation of pre-vaccination contact patterns in western Europe.

Alternative types of mixing, e.g. proportionate and 'preferred' mixing [14], and 'diagonal' mixing [15] were also considered, and a sensitivity analysis of the model output to such alternative mixing was also conducted. Since results did not add much insight to the results found by the baseline 'default' assumption, they are not reported in this article.

Table 1 reports the values of both the EURO and the Italian (IT) FOIs by the age group considered in this study, jointly with the associated values of the basic reproduction ratio R_0 [17] under 'default' mixing and the related critical coverages for routine vaccination at 15 months of age, when assuming a 100% vaccine efficacy ($p_c = 1 - 1/R_0$).

Vaccination coverage

Vaccination against measles in Italy began in 1976, and MMR was introduced in 1991. Average national vaccination coverage data were obtained by available yearly routine regional reports, and from *ad-hoc* studies conducted in years 1985 [18], 1993 [19], 1998 [2] and 2003 [3]. The estimated vaccination coverage from 1976 to 2003 is shown in Figure 1.

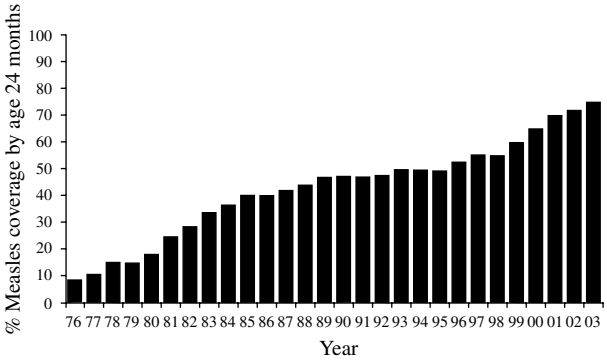

Fig. 1. Estimated measles vaccination coverage by 24 months of age. Italy, 1976–2003.

In the model, we considered that first measles vaccination is administered at the age of 15 months, as recommended since 1979. In order to take into account the catch-up activities conducted during the 1990s in many regions [4], we added to the model a 5% catch-up immunization of susceptible children in the age group 1–9 years, conducted for years 1990–1994. Vaccine efficacy (VE) was set at 95%, and it was assumed that vaccination offers life-long immunity.

Other model parameters

We assumed that all infants are protected from measles infection by maternally derived antibodies for the first 6 months of life on average, after which they become susceptibles. After infection with measles virus, individuals pass through a latent, non-infectious phase with an average duration of 7 days, and then become infective. The average duration of the infectious period was set to 7 days, after which individuals are considered immune for the rest of their life.

Modelling strategy and simulation

The model was run with the purpose of investigating the likely impact of the Italian measles elimination plan, and the possible effects of failure in some of

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Table 2. *Description of the vaccination scenarios considered in the model*

Scenario	Vaccination coverage (%) by immunization activities			
	1st dose by 24 months of age	School-age campaign	Catch-up at other immunization activities	2nd dose
Best (B)	95	95	95	95
1st dose (D)	95	0	0	0
Catch-up (CU)	95	95	95	0
Suboptimal catch-up (CU1)	95	95	80	0
Moderate failure (MF)	80	80	80	0
Worst (W)	80	60	0	0
Worst with 2nd dose (W2)	80	60	0	75
Realistic (R)	90	60	95	60

its goals. Given the focus on the elimination target, we use as an indicator the effective reproduction ratio (ERR, often referred to as R), which expresses the average number of secondary cases generated for each primary cases in a partly immune population. Therefore, if ERR is higher than 1, an epidemic may occur, whereas if it is below 1, measles transmission should be interrupted.

Under epidemic conditions the ERR indicates the actual rate of increase of measles infection per generation of infection. It is computed at each moment of time as the dominant eigenvalue of the next generation matrix under the age distribution of susceptibles predicted by the model. The ERR is thus, also, a measure of the epidemic potential which is incorporated, at each moment of time, in the current age profile of susceptibility, conditionally to the assumed mixing patterns. Therefore, under circumstances of elimination (e.g. situations in which the virus is temporarily non-circulating, as in most of our subsequent scenarios) the ERR is a suitable indicator of the potential for infection outbreaks/persistence after re-introduction of cases [11].

As regards simulation, we chose the year 1951 as the initial time motivated by the fact that in 1951 the first post-war Italian population census was held, thus providing a reliable initial age distribution of the population. The model was then run until 2020, analysing eight scenarios based on different performance of the NEP objectives.

The best scenario assumes that all targets of the NEP will be reached, i.e.:

- 95% first-dose coverage by 24 months of age, achieved for children of the 2001 birth cohort onwards.
- 95% first-dose coverage achieved in older unvaccinated children through catch-up conducted during routine immunization activities (i.e. polio booster dose in the third year of life, and DTaP booster dose at 5–6 years of age).
- 95% coverage achieved in all school-aged children during a national vaccination campaign targeting children aged 6–13 years during 2004–2005. During the campaign, vaccination will be offered to all unvaccinated children, as well as to children previously vaccinated with one dose only.
- 95% second-dose coverage among children aged 5–6 years, achieved for children of the 2002 birth cohort onwards (i.e. from 2007).

In the model, all these vaccinations were assumed to be independent. The other scenarios consider different types of failure in reaching these targets, and are summarized in Table 2.

For each scenario, the model was run for each of the four assumptions that are obtained by crossing the two assumptions on the underlying demography (D1 *vs.* D2) with the two assumptions on the FOI (EURO *vs.* IT), giving a total of 32 scenarios.

In particular, the EURO/D1 represents the worst case in term of the required elimination efforts, since the FOI is higher (EURO), and is not affected by population change. Conversely, IT/D2 represents the most favourable case, because it assumes that the FOI is the lower one (IT), and is further decreased by the process of ageing of the Italian population, according to the mechanism embedded in equation (1). Finally EURO/D2 and IT/D1 should represent intermediate situations.

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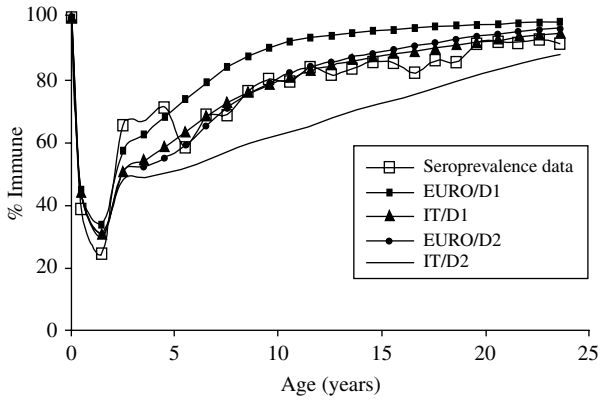

Fig. 2. Proportion of individuals immune to measles by age observed by seroprevalence data, and predicted by the model under its various assumptions.

Validation of the model

The model was validated by comparing the susceptibility profiles predicted for the years 1996–1997 under the different model assumptions with the seroprevalence data obtained in the same years. These data were obtained from a national survey conducted during 1996–1997, when 3182 samples were collected from residual sera of routine laboratory testing, in 18 out of 20 Italian regions [20].

Given that the susceptibility profiles predicted by the model are simply projections by a fully deterministic model, and no stochastic assumptions were specified, a formal quantification of the goodness of fit provided by the four different assumptions would not be appropriate, and has not been performed.

RESULTS

The susceptibility profiles predicted by the model and the observed measles seroprevalence are shown in Figure 2. Overall, the EURO/D1 assumption (i.e. high FOI, and stationary demography) seems to lead to a systematic overestimate of the observed serological profile, whereas the IT/D2 (i.e. low FOI, and realistic demography) leads to a systematic underestimate of the observed profile, suggesting that EURO/D1 and IT/D2 assumptions provide upper and lower bounds to true epidemiological outcomes. By contrast, the IT/D1 and the EURO/D2 assumptions provide a quite satisfactory fit. Nevertheless, the observed proportion of children from 2 to 5 years of age immune to measles in 1996–1997 is higher than predicted by the model, under all assumptions considered.

Figures 3 and 4 report the predicted impact of NEP under the different scenarios considered, for the various assumptions on FOI and demography adopted. Under Best (B) scenario, the ERR which was in excess of 1 before 2003, quickly goes below 1, and remains well below the value of 1 until 2020 under all assumptions considered.

The effect of a policy based on first dose only

Under First-dose (D) scenario, which assumes the achievement of a 95% coverage for the first routine dose by 2005, but no catch-up activities or second-dose administration, the ERR remains persistently below 1 only under IT/D2 assumptions, while persistent epidemics will continue to occur under EURO/D1, with an estimated inter-epidemic period up to 5 years.

The impact of catch-up activities, in absence of a second dose

The Catch-up (CU) scenario, which assumes the achievement of a 95% coverage both for routine first-dose and catch-up activities, but no second-dose administration, allows rapid interruption of measles circulation (i.e. ERR below 1 achieved by 2004) under all assumptions considered. Nevertheless, the ERR is predicted to exceed the unit threshold by 2009 in the EURO/D1 case, in 2017 under the IT/D1 assumption, and in 2020 in the EURO/D2 scenario. By contrast, the ERR is predicted to remain persistently below 1 only in the IT/D2 case.

Suboptimal catch-up (CU1) scenario illustrates the consequences of failures in achieving high coverage in the supplementary catch-up activities (80% instead of 95%). The ERR is predicted to again exceed unity by 2007 in the EURO/D1 case, and respectively by 2015 and 2018 under IT/D1 and EURO/D2 assumptions, while it remains persistently below 1 only in the IT/D2 case.

If only 80% coverage rates are achieved in both routine and catch-up activities [Moderate failure (MF scenario)], a serious worsening occurs, as the ERR is predicted to once again exceed unity from 2 years (EURO/D1) to 5 years (EURO/D2) earlier, compared to the CU1 scenario.

Under Worst (W) scenario, which assumes 80% in routine coverage, 60% coverage in school-aged children during the campaign, but no supplementary catch-up and second-dose activities, measles circulation might not be interrupted in the EURO/D1

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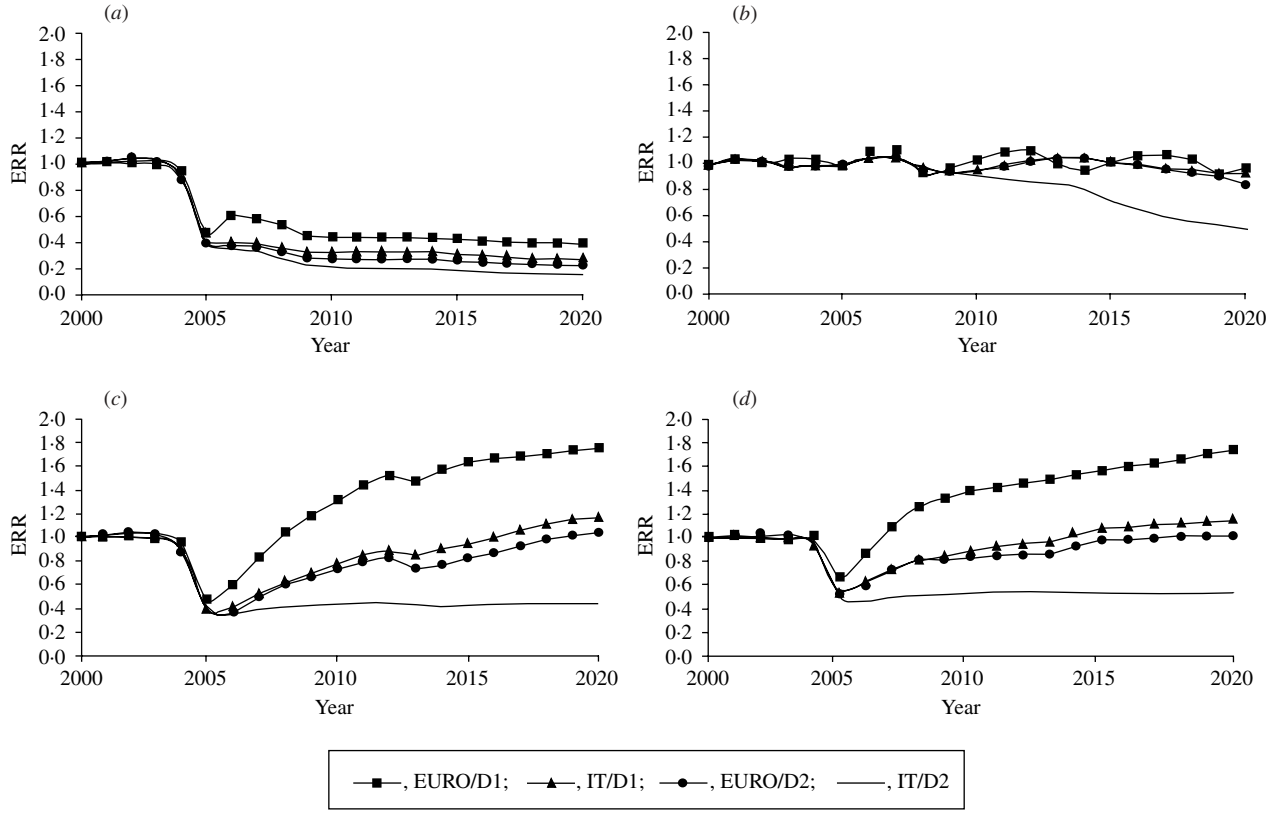

Fig. 3. Effective reproduction ratio predicted under (*a*) best scenario; (*b*) first-dose scenario; (*c*) catch-up scenario; (*d*) suboptimal catch-up scenario. Italy, 2000–2020.

case, and large epidemics (the first one predicted for 2007–2008) could continue to occur. In the other cases, the ERR goes below 1 in 2004, but exceeds again the unit threshold by 2007 under IT/D1 and EURO/D2 assumptions.

The impact of the second dose

Results from the Worst with 2nd dose (W2) scenario show that by achieving a 75% second-dose coverage from 2007 onwards, the ERR is persistently below 1 after 2008, under all the assumptions considered.

The Realistic (R) scenario assumes, compared to W2, a higher coverage for first-dose (90%), and for catch-up activities (95%) other than the school-age campaign, and is associated with a lower second-dose coverage (60%) and the same coverage for the school-age campaign (60%). This scenario causes ERR to persistently remain below 1 even under all the assumptions considered.

DISCUSSION

In this study, a deterministic mathematical model has been used to evaluate the ability of the recently approved Italian National Plan [7] to achieve and maintain measles elimination, and to assess which are the vaccination parameters to which the outcome of NEP is more sensitive.

The results suggest that reaching all NEP targets will be largely sufficient in achieving elimination. Nevertheless, given the history of measles vaccination in Italy, where 25 years have been needed in order to reach a national routine coverage of 77% [3], we considered different scenarios, where different degrees of failure in the achievement of NEP targets were taken into account. Our findings suggest that elimination by means of a first-dose programme, even reaching the target levels (95%), appears to be unlikely, the conduct of catch-up activities, reaching high vaccination coverage could interrupt virus circulation, but could not before 2020 prevent the infection re-emerging, and the introduction of the second dose thus seems necessary for achieving elimination and maintaining it.

It should also be noted that the 'Worst' scenario suggests that an inability to raise first-dose coverage beyond 80%, which is more than has ever been achieved in Italy, jointly with a limited success in

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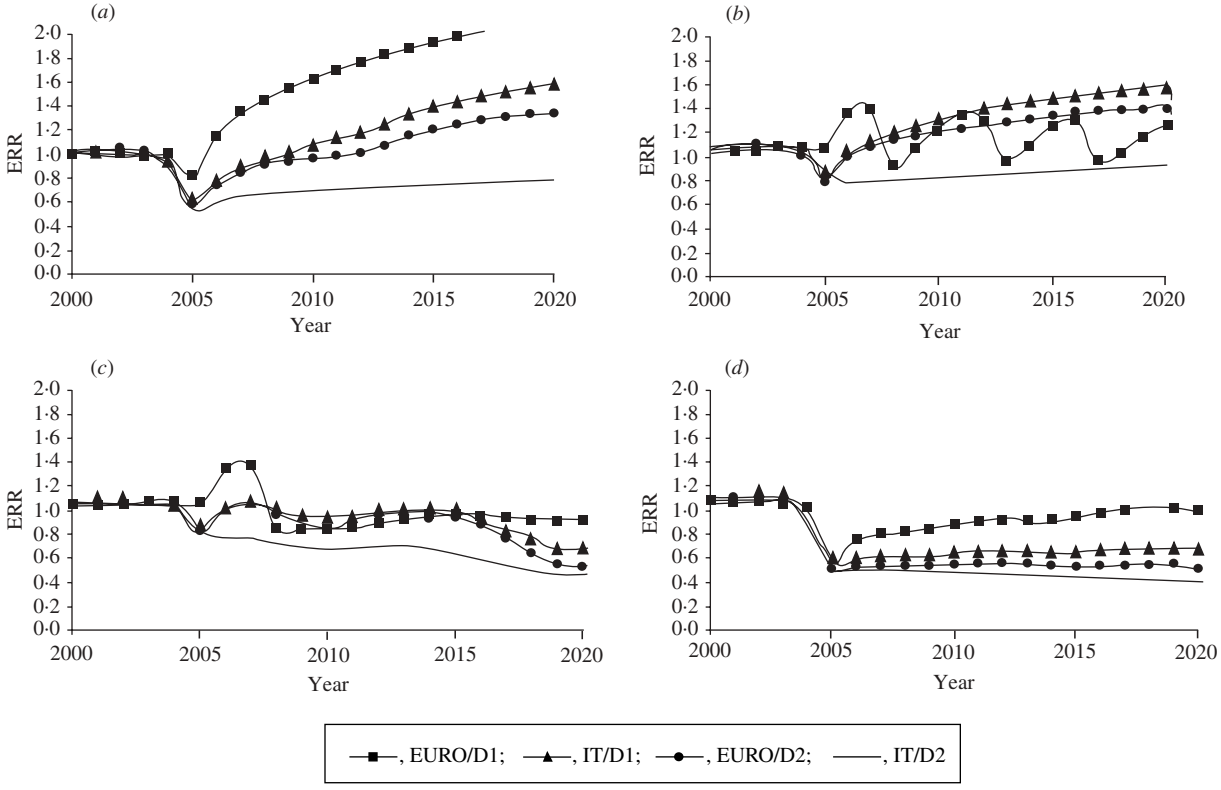

Fig. 4. Effective reproduction ratio predicted under (*a*) moderate failure scenario; (*b*) worst scenario; (*c*) worst with second dose scenario; (*d*) realistic scenario. Italy, 2000–2020.

catch-up activities and no second dose, would expose the NEP to serious risk of failure, with persistent epidemics continuing to occur. Thus, the increase of routine first-dose coverage remains a major priority.

Among different scenarios considered, we defined as 'Realistic' the one that combines the achievement of 90% first-dose coverage with a limited success in the school-age campaign, 95% coverage rate of catch-up of unvaccinated children during other routine immunization activities, and a 60% second-dose coverage. It is reassuring that, in our results, this scenario allows us to reach elimination under all assumptions considered.

The study has a number of limitations. First, a serious problem in the modelling of measles in Italy is the uncertainty surrounding the true FOI [15]. To take into account this uncertainty, in our model we have considered two different assumptions, derived respectively from European and national data [15, 16]. The implied values of R_0 obtained from estimated FOIs are in line with some modelling studies [10], despite being smaller compared to others [12]. Nevertheless, any progress in our knowledge of the true FOI would allow us to reduce the uncertainty in our scenarios.

In the model we also considered some possible effects caused by the current process of demographic change, with decreased fertility and increasing ageing of the population. To bound true epidemiological patterns, four different cases (EURO/D1, EURO/D2, IT/D1, IT/D2) have been considered. In this manner we feel that we have taken in consideration both the maximal variation in the pre-vaccination FOI, and also the maximal effects of the demographic trend on the FOI itself.

According to our results, the assumptions that consider realistic demography scenarios (EURO/D2 and IT/D2) appear to be much more favourable towards reaching elimination. Such assumptions predict a long-term decline in the overall FOI, which might well be a consequence of sustained population ageing, for instance through the reduction in the average family size that should significantly affect the risk of intra-family transmission. Nevertheless, if population ageing decreases the overall FOI, thereby making measles elimination easier, it could also emphasize the perverse outcome of suboptimal

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vaccination coverage, namely the increase in number of measles infections acquired at older age, causing an increase in the number of serious measles cases and deaths [21].

A second limitation of the study is that our model does not take stochasticity into account. This for instance prevents us from saying whether an average value of ERR close to 1, such as ERR = 0·98, has a large chance of causing an epidemic. However, it should be emphasized that informing public health choices is the primary aim of this modelling work, by providing indications of the dynamics in play in the process rather than the making of precise predictions.

Another critical aspect is that the adopted model is spatially homogeneous and thus disregards geographical variation in vaccine coverage, that is well documented in Italy [2, 3] and which allowed the epidemics observed in southern Italy in 2002 and 2003 [6]. The adoption here of an average national vaccination coverage is a simplification which represents a reasonable starting point and, additionally, is broadly consistent with 1996–1997 serological data. Nevertheless, the proportion of children from 2 to 5 years of age immune to measles in 1996–1997 is higher than predicted by the model, perhaps because of an increase in routine coverage observed in several Italian areas since mid-1990s [3]. In order to reduce the geographical differences in measles susceptibility observed in the 1990s [20], it is crucial that the school-age campaign is successful in achieving uniformly high coverage rates.

Although the present paper only focused on measles, there is an important point regarding the expected outcome of the plan for rubella and mumps, since the use of MMR has the advantage of providing control for these infections as well. Nevertheless, failure in achieving NEP targets can create perverse outcomes; this is particularly so for rubella where a suboptimal programme, by reducing but not eliminating risk of infection, may result in more infections occurring during women's fertile years and an increase in cases of congenital rubella syndrome [22]. Using a model with standard demography, Edmunds et al. have explored these issues for a number of European countries, including Italy, and highlighted the important role of supplementary rubella vaccination of schoolgirls [23]. These considerations, further complicated by strong variation in patterns of infection and vaccination between regions, mean that the need for careful design and thorough implementation of the NEP in combination with effective surveillance becomes even more critical for congenital rubella control.

APPENDIX. The mathematical model for measles

The model

As stated in the Methods section, the model for measles used in the paper is a MSEIR (maternal antibody protection–susceptible–exposed–infective–recovered) model for childhood diseases. The epidemiological variables representing densities of individuals in the epidemiological states MSEIR are usually indicated as MXHYZ [10]. In particular, let $M(a, t)$, $X(a, t)$, $H(a, t)$, $Y(a, t)$, $Z(a, t)$ respectively denote the densities of individuals which are newborn and thus protected by maternal antibody, susceptibles, exposed (e.g. infected but not yet infectious), infective and recovered of age a at time t. The model is described by the following system of partial differential equations [10, 14]

$$\begin{aligned}
\delta M(a,t) &= -(\mu(a,t)+d)M(a,t)\\
\delta X(a,t) &= dM(a,t)-(\mu(a,t)+p(a,t)+\lambda(a,t))X(a,t)\\
\delta H(a,t) &= \lambda(a,t)X(a,t)-(\mu(a,t)+\sigma)H(a,t)\\
\delta Y(a,t) &= \sigma H(a,t)-(\mu(a,t)+v)Y(a,t)\\
\delta Z(a,t) &= \varphi(a,t)X(a,t)+vY(a,t)-\mu(a,t)Z(a,t),
\end{aligned} \tag{A 1}$$

where $\delta = (\partial/\partial a + \partial/\partial t)$ is the 'population ageing' operator, plus the boundary conditions:

$$\begin{aligned}
&M(0,t) = B(t) - X(0,t);\\
&X(0,t) = \int_0^\infty m(a,t)X(a,t)\mathrm{d}a;\\
&H(0,t) = 0;\ Y(0,t) = 0;\ Z(0,t) = 0,
\end{aligned} \tag{A 2}$$

where $B(t)$ denotes the total births at time t, $X(0, t)$ the births of susceptibles, $m(a, t)$ and $\mu(a, t)$ respectively denote the fertility and mortality rates at age a (which are assumed time dependent but converging for $t \to \infty$ to some age-independent form $\mu^*(a)$ and $m^*(a)$, in order to allow the onset of a stable age distribution in the long term, σ the rate of transition from the infected to the infective state, v the recovery rate, $p(a, t)$ the age-specific vaccination rate (which is set to zero in the pre-vaccination era). The total population by age

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$n(a, t) - M(a, t) + X(a, t) + H(a, t) + Y(a, t) + Z(a, t)$ obeys the partial differential equation:

$$\begin{aligned} \delta n(a,t) &= -\mu(a,t)n(a,t) \\ n(0,t) = B(t) &= \int_0^\infty n(a,t)m(a,t)\mathrm{d}a \\ n(a,0) &= \psi_0(a). \end{aligned} \tag{A 3}$$

The functional form of the FOI

The FOI was modelled as by McLean & Anderson [13] and Hethcote [14]

$$\begin{aligned} \lambda(a,t) &= \frac{\int_0^\infty \beta(a,a')\,Y(a',t)\mathrm{d}a'}{\int_0^\infty n(a,t)\mathrm{d}a} \\ &= \frac{\int_0^\infty \beta(a,a')\,Y(a',t)\mathrm{d}a'}{n(t)}, \end{aligned} \tag{A 4}$$

where $Y(a, t)$ denotes the density of infectious individuals aged a at time t, $n(t)$ the total population, and $\beta(a, a')$ the (age-related) transmission rates. Equation (A 4) takes the form of equation (1) in the text under the assumption of piece-wise constant transmission rates.

Models of vaccine preventable diseases are mostly built in two main steps: (*a*) estimation of mixing parameters, which are the more critical epidemiological parameters. According to the standard approach [10] this step is usually carried out by determining such parameters from pre-vaccination data (infection or serological) on the assumption that stationarity prevails, e.g. that pre-vaccination data reflect an underlying equilibrium situation as regards epidemiological (and demographic) variables; (*b*) evaluation of the impact of different immunization programmes on the assumption that the mixing parameters estimated from the pre-vaccination era do not change as we progressively move in the post-vaccination era.

In most instances step (*b*) is conducted by also assuming that the demographic environment is fully stationary over time, e.g. that the population is unchanging in both total numbers and age distribution.

In this study, we have conducted step (*a*) following the standard approach assuming stationarity. As regards step (*b*) we have considered two distinct possibilities, e.g. the case labelled D1 in the paper, which considers a stationary demography, as in most applied epidemiological work, and the case labelled D2, considering 'realistic demography'. More detailed, case D2 uses observed demographic rates for the period until 2003, while for the period post-2003 we have assumed the continuation in the future of the current demographic situation (as typically done as baseline scenario in most official demographic projections) which would, in the Italian case, lead to sustained population ageing and decline. Now, as far as we assume demographic stationarity (Assumption D1) the choice of the functional form of the FOI does not matter for either steps (*a*) and (*b*). Consider for instance – for any given estimate of the pre-vaccination FOI – the following functional forms:

$$\text{FOI1:}\quad \lambda_i(t) = \sum_{j=1}^{m} \frac{\beta_{ij} Y_j(t)}{n(t)},$$

$$\text{FOI2:}\quad \lambda_i(t) = \sum_{j=1}^{m} \frac{\beta_{ij} Y_j(t)}{n_j(t)},$$

$$\text{FOI3:}\quad \lambda_i(t) = \sum_{j=1}^{m} \beta_{ij} Y_j(t),$$

where FOI1 denotes the form in equation (1) of the methods, FOI2 is reported by Anderson & May [10], in their equation (13.62), and FOI3 is the traditional bilinear mass action formulation, which is extensively used in ref. [10], and in all subsequent modelling efforts assuming demographic stationarity.

If the population is perfectly stationary over time, in total numbers and age distribution, then the three previous forms lead, by properly rescaling the β coefficients, to the same outcomes. This can be checked by the fact that the constant population terms $n_j(t)$ in FOI2, and $n(t)$ in FOI1 may be incorporated in the coefficients β_{ij}, by making formally indistinguishable the three expressions. Thus, as regards the two cases EURO/D1 and IT/D1 considered in the study, the use of FOI1 is an application of the standard approach.

By contrast, for assumption D2, the unstable demography leads to significant changes in both total numbers and age distribution of the population, that are differently handled by FOI1, FOI2, FOI3.

The first two authors of the present article have investigated the impact of regimes of sustained demographic instability, as the demographic transition observed in the western world since the eighteenth century and currently in most developing countries, and the transition to sustained low fertility now

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observed in Italy, on the epidemiology of childhood diseases. This has been done by comparing, for standard patterns of mixing, the outcomes of FOI1 and FOI2 which represent different relationships between age structure and contacts; FOI3 has not been considered because it leads to unsatisfactory results for exponentially evolving populations, as eventually approached in the long term in our case D2.

They found that whereas under FOI2 no major quantitative effects of demographic instability are predicted to occur compared to the stationary case, under FOI1 the non-equilibrium circumstances peculiar to the transition to sustained low fertility might significantly alter the underlying epidemiological conditions. For instance, in the absence of vaccination, population ageing leads, under FOI1, to a decline in transmission. Such results are not surprising: FOI1 allows, contrary to FOI2, a significant feedback of the changing age distribution of the population on the FOI.

In fact, FOI1 leads to large, but reasonable, quantitative effects that we felt could be taken as a bound to the maximal variation in transmission caused by a regime of demographic instability.

Model simulation

Under assumption D2 the demographic evolution was simulated over the period 1951–2050. The population age distribution observed in the 1951 census (the first post-war Italian population census) was used as initial age distribution. Observed fertility and mortality rates were used in order to closely mirror observed demographic trends. In particular, for fertility we used the yearly national time-series of observed fertility rates for 1951–2000, whereas for mortality we used the national life-tables estimated for 1980–1982, taken as representative of observed mortality in the period at hand. After 2000 the model is simulated according to the scenario of low fertility by assuming unchanging fertility at the levels observed during 1996–2000, and unchanging mortality. The initial age distribution by epidemiological state in 1951 was generated by preliminarily running the model in a stationary population until equilibrium was achieved, and then taking such equilibrium age distributions as initial distributions at 1951. The model was simulated by solving numerically the involved partial differential equations by means of a Euler's first-order method along characteristics, with time step $h = 3{\cdot}5$ days.

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