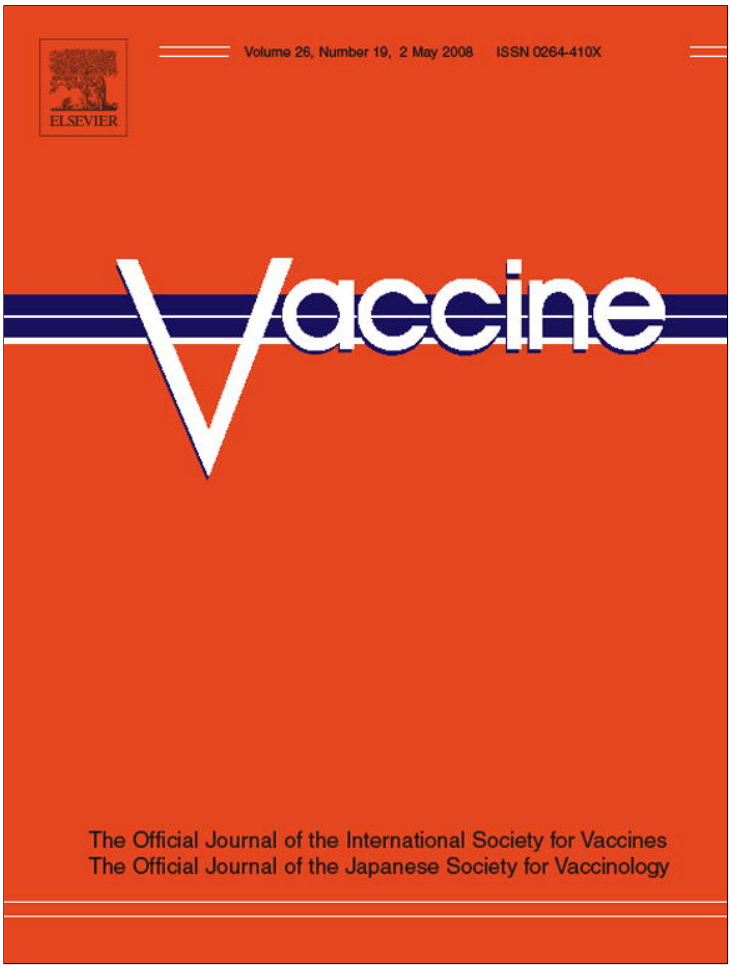

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Dynamics and control of measles in Portugal: Accessing the impact of anticipating the age for the first dose of MMR from 15 to 12 months of age

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Summary The all-time low incidence of measles in Portugal in the recent years, raises questions regarding whether the disease has been eliminated, the role of recent control measures, and the epidemiological consequences of the rise in the proportion of newborns to vaccinated mothers, as opposed to those born to mothers who acquired immunity by natural infection. We estimate the vaccination coverage against measles in Portugal on a cohort-by-cohort basis, and incorporate this information into an age-structured seasonally-driven mathematical model aimed at reproducing measles dynamics in the past decades. The model reproduces documented trends in disease notifications and the serological profile of the Portuguese population, as estimated by a recent National Serological Survey. We provide evidence that the effective reproduction number (R_e) of measles has been driven below 1 in Portugal, and that sustained measles elimination is crucially dependent upon the maintenance of a high (>95%) coverage with the MMR I vaccine in the future. If the vaccination coverage decreases to levels around 90% the anticipation of the first dose of the MMR I from 15 to 12 months of age, will ensure that R_e remains below 1.

Introduction

Over the past 5 years, the incidence of measles in Portugal has declined to an all-time low. Between 2002 and 2005, a total of 24 suspected cases of measles were notified to the Portuguese authorities [1], corresponding to an annual

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incidence of <0.6 cases per million individuals. This follows a strategy put into place against measles that included a two-year catch-up vaccination campaign (1998—1999), the anticipation of the age of the second dose of the measles-mumps-rubella vaccine (MMR II) from 11—13 to 5—6 years old (since January 2000), and the maintenance of a high level of immunization coverage by routine vaccination, as documented by the National Serologic Survey [2] conducted in 2001—2002. Portugal thus appears to be on track to fulfill the 2010 measles elimination target set by WHO [3].

Nevertheless the high transmissibility of measles poses a significant challenge to any attempt to eliminate it. Recently, measles re-emerged in the European Region of the WHO, including countries that had already achieved good levels of measles control [4—8]. Most cases occurred in non-immunized individuals that either failed vaccination or were too young to be vaccinated, usually children younger than 15 months of age [4—6]. The building of a susceptible pool of these infants is of particular concern, as a disproportionate number of measles-associated deaths occur in children under the age of routine immunization [9,10].

The resurgence of measles in the United States of America, between 1989 and 1991, provides an outstanding example. During this epidemic, the epidemiology shifted dramatically from school-aged to preschool children [11]. Infants below 15 months of age were not yet eligible for vaccination and, despite comprising only 2% of the general population, accounted for 24% of the 55,622 cases reported. Sixty percent of measles related deaths occurred among preschool children [11,12]. Other examples of outbreaks among the very young have been recently reported in Europe. In a cluster of 580 cases in south London, between December 2001 and May 2002, 40% were aged under 12 months [4]. At La Rioja, Spain, where vaccine coverage was estimated to be 96.3% at 15 months of age, 13 out of the 18 confirmed cases of measles that took place in 2005—2006, were in children aged under 15 months [5].

Previous studies have indicated that infants whose mothers acquired immunity to measles by vaccination, have increased susceptibility to clinical measles, as compared to infants born to mothers who have been exposed to the wild virus [12]. This is in agreement with evidence for a faster seroprevalence decay of passively acquired maternal antibodies in unvaccinated infants born to vaccinated mothers, as compared to those whose mothers had measles [13—16]. As the proportion of mothers who have been vaccinated increases over the years in the current vaccination era, so does the proportion of children who should respond to the measles vaccine at younger ages [14]. As a consequence, in January 1994 the routine age for MMR I vaccination in the USA was lowered from 15 months to between 12 and 15 months [17]. Recently, concern has also been raised in Europe regarding this issue [3,5] and, accordingly, the Portuguese authorities are contemplating to anticipate the age of MMR I from 15 to 12 months old by the time the proportion of newborns from vaccinated mothers exceeds 50%.

We investigate the current epidemiological situation of measles in Portugal, focusing on whether recent vaccination strategies created conditions for measles elimination. We estimate vaccination coverage along cohorts and input this information into an age-structured PSEIR (protected-susceptible-exposed-infected-recovered) mathematical model, where the ''protected'' category keeps track of newborns from vaccinated, unvaccinated non-susceptible, and unvaccinated susceptible mothers.

The model is aimed at revealing the most important aspects of measles dynamics in Portugal in the recent past, but we also investigate how future scenarios of measles control are effective at ensuring sustained measles elimination. In particular, we show that, for a narrow region of vaccination coverage around 90%, the anticipation of the recommended age for the first dose of the vaccine, from 15 to 12 months, is crucial to maintain the effective reproduction number below 1 and thus, preventing measles outbreaks. For higher levels of vaccination coverage however, it contributes to hamper the building of a pool of susceptible children younger than vaccination age, decreasing the likelihood that imported cases result in small clusters among that age group. We also show that the success in sustaining measles elimination is crucially dependent on the maintenance of a very high vaccination coverage with the MMR I.

Data and methods

Past-vaccination strategies and vaccine data

Vaccination against measles in Portugal started in 1973, with a major catch-up campaign aimed at children under 10 years old. The campaign lasted until 1977 with 650,000 vaccines being delivered throughout. Routine vaccination started in 1974, with a single-dose at 15 months of age. In 1987, the monovalent measles vaccine was replaced by the MMR I and, in late 1990, the second dose (MMR II) was introduced in the routine calendar for children between 11 and 13 years old. In 1998, the forecast of an upcoming measles outbreak from time series analysis [18] prompted health authorities to conduct a two step catch-up campaign for unvaccinated children. This second campaign targeted ages 15—59 months in 1998 and ages 6—18 years old in 1999. In 2000, further analysis [19] led authorities to anticipate the recommended age of the MMR II to 5—6 years old.

The number of vaccines delivered every year, has been published by the Portuguese National Institute of Statistics [20] with varying age groups over time. Previous attempts to estimate vaccination coverage in Portugal [21,22], were based upon the ratio between vaccines given during the second year of life and estimates of the standing population at the same age. By not following cohorts, these estimates miss the combined impact of campaigns with routine vaccination and disregarded vaccination with the MMR II.

In order to estimate vaccination coverage along cohorts, we have separated vaccines by age, following a procedure similar to the one by Fine and Clarkson [23]:

1. Vaccines given to age group 0—4 years old:
   In years 1974—1977, 1979—1982, and 1986—1990, there is information available on the number of vaccines by age. These records show that before 1988, less than 80% of the vaccines were given between 12 and

Table 1 Proportional distribution per year of the 650,000 vaccines given during the 1973—1977 vaccination campaign

Scenario	Vaccine distribution				
	1973	1974	1975	1976	1977
1	2/7	2/7	1/7	1/7	1/7
2	5/15	4/15	3/15	2/15	1/15
3	4/8	1/8	1/8	1/8	1/8

24 months of age. After 1989, the percentage given at 12—24 months rose above 80%, indicating a tendency to vaccinate closer to the recommended age of 15 months. Whenever necessary, we have thus disaggregated vaccines by age, in years before 1989, following the percentages 2.6%, 65.8%, 18.4%, 7.9% and 5.3% for ages 0, 1, 2, 3, and 4 years old, respectively. In 1989 and later years, we have used the percentages 2.6%, 89.5%, 2.6%, 2.6% and 2.6% for the same ages.

2. Vaccines given to age group 5—10 years:
   We have assumed that the majority of children were vaccinated between 5 and 7 years, as they are required to present the vaccination booklet at registration for the first school grade. Vaccines were thus distributed by age, attributing a weight of 2/8 to ages 5, 6, and 7 and 1/8 to ages 8 and 9.
3. Vaccines given to age group 11—16 years old were uniformly distributed by ages. It is assumed that these ages received MMR II, whereas ages 1—10 received MMR I.

There is no information available regarding the break up of the 650,000 vaccines given in the 1973—1977 campaign by year and age, so we have considered three plausible scenarios of vaccine distribution throughout this period which are described in Table 1.

Vaccination coverage

Vaccination coverage with the MMR I is the cumulative proportion of vaccinated individuals along each cohort, estimated as follows,

$$VC = \frac{\sum_{i=0}^{10}[v_i - \frac{v_i}{n_i}d_i]}{N_0 - \sum_{i=0}^{10} d_i} \quad (1)$$

For each cohort, the number of vaccines, v_i, given to children in yearly age groups $i = 0, 1, 2, \ldots 10$, was added up to give the total number of vaccinees at age i. As the cohort ages, its initial number of individuals, N_0, diminishes because of deaths, d_i. We denote the number of children alive at age j by $n_j = N_0 - \sum_{i=0}^{j} d_i$. A proportion of deaths $\frac{v_i}{n_i}d_i$, is subtracted from those who were vaccinated, assuming that the likelihood of dying is independent of the vaccination status. To estimate the vaccination coverage with the MMR II, Eq. (1) was adapted to ages between 11 and 16 years old.

Epidemiological model

Basic structure

The transmission dynamics of measles was modelled by a deterministic PSEIR (protected by maternal antibodies, susceptible, exposed, infectious, recovered) age-structured model [24,25], where the protected compartment has been split into two, one for newborns to vaccinated mothers and another for newborns to mothers who became immune by contact with the wild virus; newborns to susceptible mothers enter directly into the susceptible compartment. Individuals are classified into cohorts, where each cohort consists of children born at the beginning of the school year (starting 1st of October). The age of all children is incremented by one year at the end of the school year (30th September). The mean number of births per year, life expectancy and the fertility function used in the model (Table 2), were estimated from Portuguese data [26,27]. Epidemiological parameters (Table 2), were drawn from the literature [28]. Markowitz et al. [14] demostrated that 98% of children born from vaccinated mothers had a serological response to measles vaccine at 12 months of age, compared with 83—90% of children born from naturally immune mothers. Assuming an exponential decay of antibodies, these percentages can be accounted by, respectivelly, a maternal mean antibody duration of, approximately 3 and 6 months.

The model keeps track of daily changes between epidemiological compartments within each cohort, due to disease transmission, disease recovery, and vaccination. The latter was input based on our estimates of vaccination coverage along cohorts, following the methodology described above, and attempting the three campaign scenarios in Table 1. Mathematically, the model is represented by a set of ordinary differential equations (Appendix A), one for each compartment.

Transmission rates

The model incorporated age-dependent force of infection and seasonality driven by the school calendar. The contact patterns of four age groups (0—4, 5—10, 11—20, >20) are described by the ''Who Acquires Infection From Whom'' (WAIFW) matrix [28] presented in the Appendix A. These age groups roughly correspond to the main school grades in Portugal: preschool (0—4 years old), primary school (5—10 years old), secondary school (11—20 years old), and adults. The structure of the matrix embodies the opinion that the main route of transmission for measles is whithin the school playground or classroom. There is a unique coefficient, $b(2)$, describing the presumed high transmission among susceptible and infectious individuals of age group 5—10 and other coefficients, $b(1)$ and $b(3)$, for contacts among individuals less than 20 years old while the older age group is described as likely to acquire infection from a wider range of age groups. This structure was used in Schenzle [24] and in Anderson and May [28] to model measles notification data in England and Wales before the introduction of mass vaccination. Following previous authors [24,25,28], we have assumed that the contact rate within the 5—10 age group depended upon the school calendar. Transmission attained a maximum in school days and a minimum in weekends and holidays. We have also assumed that the contact rate in the

Table 2 Values of demographic and epidemiological parameters used in the model

Parameter	Symbol	Value	References
Number of newborns		126,666 per year	[26,27]
Life expectancy		75 years	[26,27]
Mean duration of latency	$1/\sigma$	8 days	[28,29]
Mean duration of infectiousness	$1/\upsilon$	5 days	[28,29]
Mean duration of passive immunity due to measles infection	$1/m$	6 months	[14,30]
Mean duration of passive immunity due to vaccine-induced immunity	$1/p$	3 months	[14,30]

5—10 years old group was always equal or greater than that in the 0—4 years old group.

In Portugal, notification reports of measles started in 1987, 14 years after the beginning of mass vaccination, rendering the direct estimation of the force of infection from notifications unfeasible. To circumvent this problem, we have initially approximated the transmission rates by numerical values derived from estimates of the basic reproduction numbers used to characterize the transmission dynamics of measles in England and Wales (case 1 in Table 3) [24]. The age-specific basic reproduction number, $R_{0,i}$, is defined as the average number of secondary infections (in all age classes) generated by one primary case in the ith age class, when the population is wholly susceptible [28]. With this definition,

$$R_{0,i} = \sum_{j=1} \frac{N_0}{\nu} \beta_{ji} (a_j - a_{j-1}) \quad (2)$$

where N_0 is the number of newborns, ν is recovery rate from the infectious state, and the a_j are bounds on discrete age classes. The transmission coefficients β_{ji} are the elements of the WAIFW matrix, and represent the probability per unit time of an effective contact of individuals in age group i with individuals in age group j. Eq. (2) can be simplified by limiting the number of distinct elements in the WAIFW matrix, namely, by setting it symmetric, such that $\beta_{ji} = \beta_{ij}$ and assuming equal contact rates among selected age groups [24,28].

Assuming that the pattern of R_0 variation with age has not been too different across European countries [31], we have adopted the $R_{0,k}$ values 4.5, 9.0, 3.5, and 3.0, respectively, for preschool children, primary school children, adolescents, and adults, which have been used in Schenzle [24] for England and Wales. We have then calculated four corresponding numerical values for the transmission parameters, β_k, that satisfy that baseline $R_{0,k}$ vector. Furthermore, we have considered nine additional plausible $R_{0,k}$ sets (Table 3) that are slight modifications of the baseline vector, gathering a total of ten possible $R_{0,k}$ sets that were used to access the sensitivity of model results.

Table 3 Values for $R_{0,k}$ and the corresponding b_k values

Case	$R_{0,k}$	$b_k(10^{-6})$
1 [a]	4.5, 7, 3.5, 3	0.26, 1.05, 0.10, 0.063
2	4.5, 5, 3.5, 3	0.26, 0.41, 0.10, 0.063
3	4.5, 12, 3.5, 3	0.26, 2.63, 0.10, 0.063
4	4.5, 10, 3.5, 3	0.26, 1.99, 0.10, 0.063
5	4.5, 8, 3.5, 3	0.26, 1.36, 0.10, 0.063
6	6, 9, 3.5, 3	0.49, 1.44, 0.10, 0.06
7 [b]	5, 9, 3.5, 3	0.33, 1.60, 0.10, 0.06
8	7, 9, 3.5, 3	0.65, 1.28, 0.10, 0.06
9	6, 9, 5, 3	0.37, 1.32, 0.22, 0.06
10	4.5, 9, 4, 3	0.22, 1.64, 0.14, 0.06

[a] Base line values given in Schenzle [24].
[b] Parameter values selected for Portugal.

The model was run for each $R_{0,k}$ set until reaching equilibrium. Those sets yielding sustained 2—3-year epidemic cycles, typical of measles in absence of mass vaccination [32], were then selected. The vaccination campaign was allowed to start both in epidemic and non-epidemic years.

Model validation

The model was validated by several criteria. First, transmission parameters were selected to yield sustained incidence oscillations with an inter-epidemic period of 2—3 years. Second, measles incidence simulated by the model was compared with case-notifications available in Portugal for the period 1987—1997; attention was particularly directed to (i) the model's ability to reproduce three epidemic peaks known to have occurred in 1984—1985, 1988—1989, and 1993—1994, and (ii) the ability to reproduce the five-fold increase observed in case-notifications, between pre-epidemic and epidemic peaks. Third, the distribution of seropositives by age predicted by the model in 2001, was compared with the results of the National Serologic Survey conducted in Portugal for 2001—2002. Fourth, seasonality coefficients (mean deviation between monthly incidence and overall mean) predicted by the model were compared with case-notification seasonality. Finally, we have compared the incidence by age in epidemic years predicted by the model with notifications by age in the 1988—1989 and 1993—1994 epidemics. The selection of epidemic years for comparison is meant to avoid the noise associated with under-reporting and false positives, both known to be more pervasive in inter-epidemic periods [33].

Effective reproduction number

The effective reproduction number, R_e, is defined as the actual mean number of secondary cases produced by a typical infectious individual in the population. If measles is in endemic equilibrium, one expects $R_e \approx 1$, as each case produces on average one other case, whereas if the infection is driven to elimination, one expects R_e to be consistently below 1. Mathematically, R_e is the largest eigenvalue of the following matrix [34,35]:

$$\mathrm{Diag}(S)G \quad (3)$$

where Diag(S) is a matrix with the proportion of susceptible per age group in the main diagonal and $G = [g_{ij}]$ is the so-called next generation matrix. The elements g_{ij} can be decomposed as

$$g_{ij} = \frac{\beta_{ij}}{\upsilon} \quad (4)$$

where υ is the instantaneous rate of recovery from infectiousness, $1/\upsilon$ is the average duration of the infectious period (with type I mortality), and β_{ij} is the transmission coefficient. In the simulations, R_e was computed on a daily basis, by building the (4×4) matrix in Eq. (3) and extracting its largest eigenvalue.

Control scenarios

We have examined the likely contribution of the 1998—1999 catch-up campaign to the elimination of indigenous measles in Portugal, and simulated realistic scenarios of measles control, in order to determine which are likely to sustain measles elimination. In particular, we have explored the ongoing vaccination coverage with the MMR I, either at 90% or 95%, assuming that individuals effectively immunized by vaccination stay lifelong immune. Vaccination coverage with the MMR II was simulated at 10% and 70% of those that remained susceptible. We have also examined how important it is to anticipate the recommended age of the MMR I from 15 to 12 months of age. Vaccine efficacy is assumed to be of 95%.

Results

Vaccination coverage

The number of vaccines against measles given in Portugal increased over the years, since vaccination begun in 1973 (Fig. 1), with peak uptakes observed shortly after 1985, 1989, and 1994, probably a reaction to the epidemic outbreaks that took place in those years. The number of MMR II doses decreased since its introduction (Fig. 1). Nevertheless, as the effort to accurately target the recommended 11—13 year olders improved, estimates of MMR II coverage at 12 years old increased from about 20% in the 1979 cohort to above 40% in subsequent cohorts (Fig. 2). It has not been possible to determine what percentage of those that received the MMR II were already immune by either vaccination or infection.

In the years following the introduction of mass vaccination, the number of vaccines was much smaller than the number of newborns, but this ratio changed around 1989 (Fig. 1). Accordingly, at 2 years of age the vaccination coverage of the 1975 cohort was around 20%, but coverage gradually increased in subsequent cohorts, reaching 80% in the 1989 cohort and remaining above this value thereafter. Children in cohorts born before 1987 were vaccinated at ages older than recommended and consequently, at 7 years of age, the cumulative coverage of these cohorts almost doubled the cumulative coverage at 2 years of age (Fig. 2). Vaccination coverage with the MMR II, as accessed at 12 years of age, remained at low levels, varying between 20% and 60% between 1991 and 2000 (cohorts 1979—1988). An unknown proportion of individuals were already immune by the time they took the MMR II, so the additional coverage of susceptibles brought about by the MMR II should be yet lower.

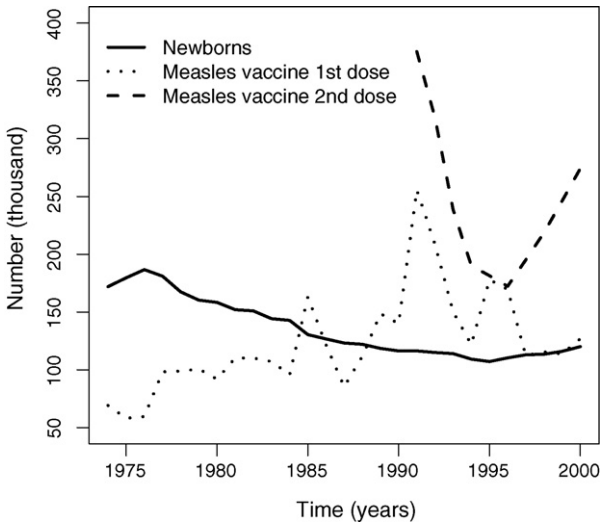

Figure 1 Number of vaccines against measles given between 1974 and 2000 (dashed lines) and number of newborns per year over the same time period (full line). We assume that first dose vaccines are given to children less then 11 years old and second dose vaccines are given to children between 11 and 16 years old.

Incidence and model validation

The simulation results were very sensitive to the set of basic reproduction numbers adopted. Only the set number 7 (Table 3), when combined with scenario 1 of the vaccination campaign (Table 1), produced incidence patterns resembling measles epidemiology between 1987 and 1998 (Fig. 3). There is a good match between simulated incidence and notifica-

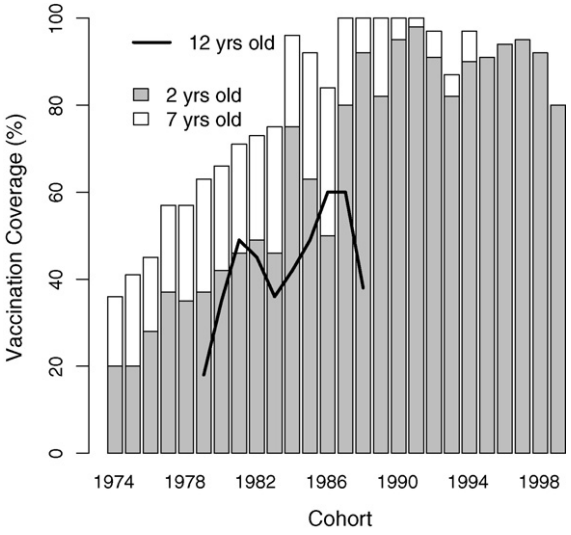

Figure 2 Vaccination coverage of the 1974—1998 cohorts with the MMR I at 2 and 7 years old (bars), and with the MMR II at 12 years old (dark line).

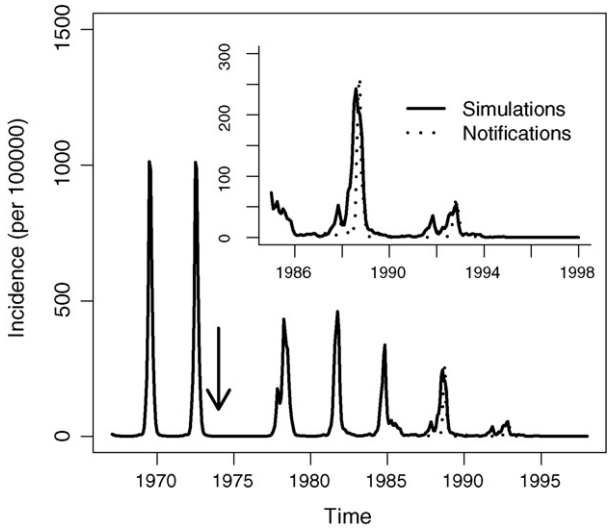

Figure 3 Incidence of measles per month for the period between 1967 and 1998, resulting from the model (full line), and from notifications multiplied by a factor of 7 (dashed line). The arrow points the beginning of mass vaccination.

tions when the latter are amplified by a factor of seven. This can be considered an estimate of the degree of sub-notification of measles and it is coincident with a previous estimate of the sub-notification of chickenpox in Portugal [36].

The simulated ratio between incidence in pre-epidemic and epidemic peaks, both in 1989—1990 and in 1993—1994, was 1:6.8. This is not too different from the 1:5.5 ratio calculated directly from measles notifications. The model was also able to reproduce the distribution of measles cases by age group, as observed in a comparison with notifications of the 1988—1989 (11,791 notifications) and 1993—1994 (3230 notifications) epidemics (Fig. 4 A), and in a comparison with the distribution of seropositives estimated by the National Serological Survey (NSS) conducted in 2001—2002 (Fig. 4B). The NSS was based on a sample of 851 individuals older than 2 years old, attending a network of health-care clinics present throughout the 18 districts of mainland Portugal.

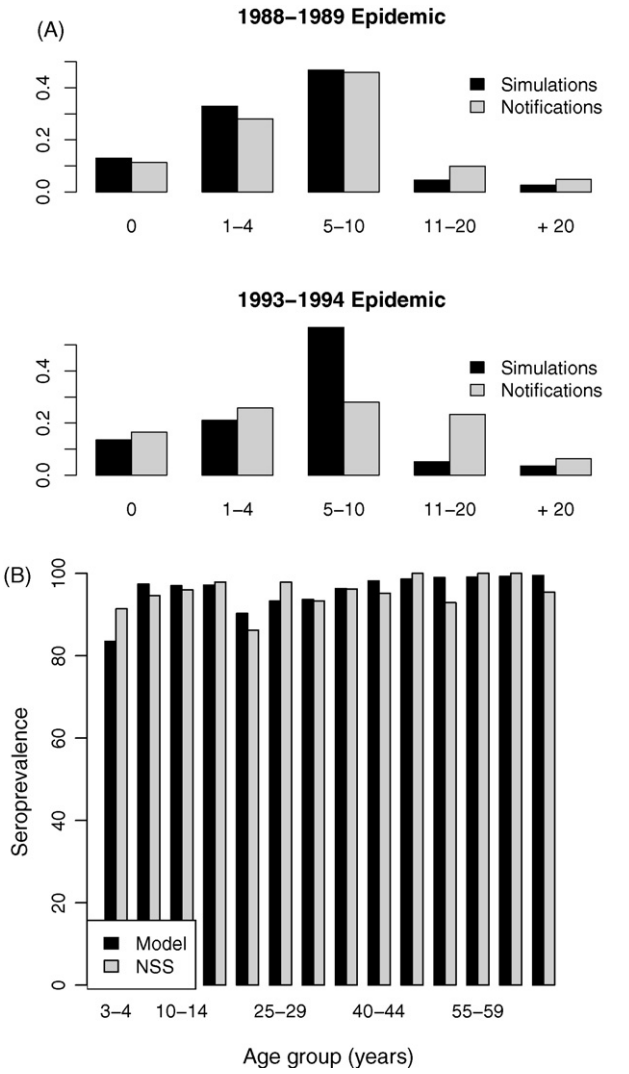

Figure 4 (A) Distribution of measles cases by age class from notifications and from the model in the epidemics of 1988—1989 and 1993—1994. (B) Distribution of seropositives by age class in the NSS and in the model in 2001. The NSS, conducted in 2001—2002, was based on a sample of 851 individuals older than 2 years old, attending a network of health-care clinics present throughout the 18 districts of mainland Portugal.

Impact of vaccination strategies

Fig. 5 presents the changing epidemiology of measles by age (0—15 years old), between 1967 and 2000, as predicted by the model. Before mass vaccination, the susceptible pool was concentrated in 0—5 year olders, with the majority of people being already immune by 7—8 years old. Oscillations in the pool of susceptibles, due to the accumulation of susceptible newborns and their consumption by epidemics, is represented in the lower part of Fig. 5 by the widening and narrowing of the whitish spots. The grey spikes extending to the top right in the figure, represent cohorts with higher proportions of susceptibles within the 0—15 age range. With the introduction of mass vaccination in 1974, the whitish areas decrease gradually and susceptibility concentrated increasingly in newborns too young to be vaccinated.

In the simulations, the effective reproduction number exhibit damped oscillations around 1 until 1998 (Fig. 6). We find that in absence of the 1998—1999 catch-up campaign, R_e would not have decreased enough to avoid a return to 1 and measles would have remained endemic in Portugal. The model shows how the 1998—1999 campaign pulled R_e to values around 0.4 in 2000—2001 and how its evolution in the future depends on the vaccination coverage achieved (Fig. 6). Once R_e became systematically lower than 1, an MMR I coverage < 90% is too low to guarantee $R_e < 1$, given an MMR II coverage of only 10% of those who are susceptible at 6 years old (either due to MMR I failure or because they were never vaccinated or infected). In spite of the progress so far made to control measles, a very high vaccination coverage (>95%) with the MMR I is still the most effective way to maintain herd immunity in Portugal to a level where R_e stays below 1. The simulations also indicate that these results are little influenced by whether the recommended age for the

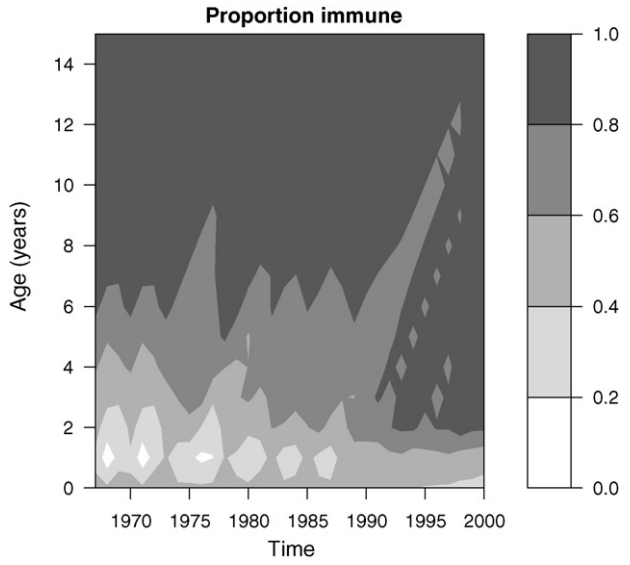

Figure 5 Evolution between 1967 and 2000 of the proportion of immune individuals since birth to 15 years old (simulated by the model).

MMR I remains at 15 months or is anticipated to 12 months of age (Fig. 7) unless vaccination coverage is near 90%.

The ratio between newborns to vaccinated mothers versus newborns to naturally immune mothers has been rising steeply since the late 1980s (Fig. 8). We estimate that by 2011 it should hit 50%, an estimate that is little sensitive

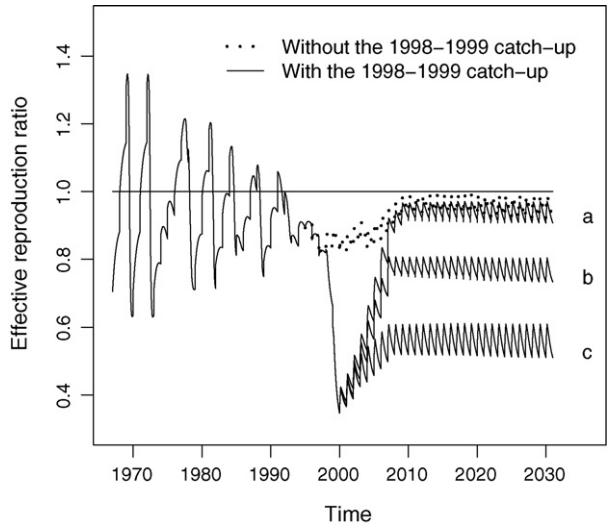

Figure 6 Simulated evolution of the effective reproduction rate R_e for measles in Portugal. Values of R_e from 1967 to 2000, based on estimates of real vaccination coverages in the model. The simulation shows that in absence of the 1998—1999 catch-up campaign, R_e would have not remained well below 1. After 2000, R_e is simulated under different vaccination scenarios. Full line curves follow the catch-up campaign and represent different coverages with MMR I and II, respectively, (a) 9% and 10%, (b) 95% and 10%, (c) 95% and 70%. Dashed lines illustrate the same three scenarios, from top to bottom, if the catch-up campaign had not taken place.

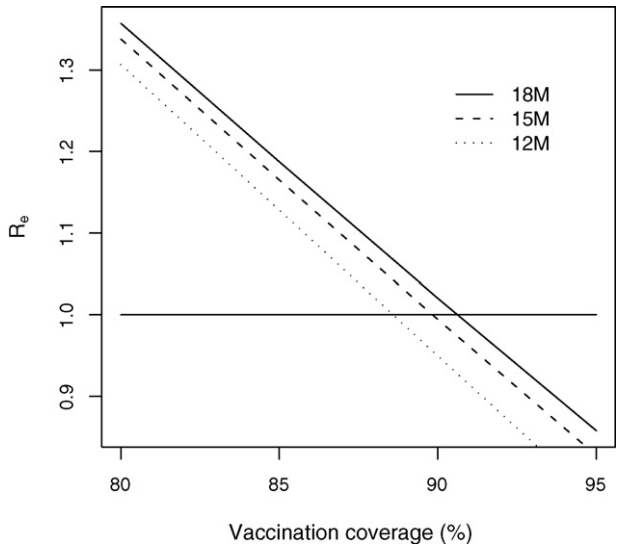

Figure 7 Relation between the effective reproduction number and different levels of vaccination coverage when the age for MMR I is 18 months (full line), 15 months (dashed line) or 12 months old (dotted line). Simulations corresponds to the case where 60% of newborns are born to vaccinated mothers.

to assumptions concerning vaccination coverage with the MMR I so long as it remains within realistic limits (more than 90—98%). Given the shorter duration of passive immunity in newborns to vaccinated mothers, more infants less than 15 months old will experience a larger period during which the titer of maternal antibodies falls below a protective level. At 10 months of age, for example, the prevalence of susceptible children is expected to increase from 87% to 93% and 96%, respectively in the cohorts of 1998, 2010, and 2028.

If vaccination coverage decreases to levels around 90%, anticipation of the age from 15 to 12 months of age should decrease R_e below 1 and avoid outbreaks. For higher levels of vaccination coverage, if indigenous measles remains absent,

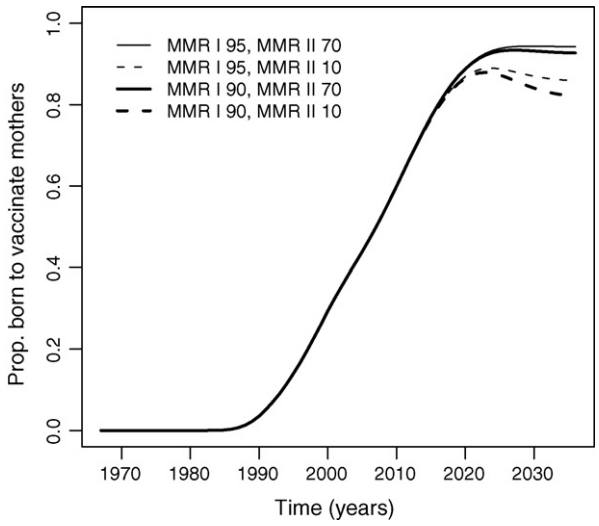

Figure 8 Evolution between 1967 and 2036 of the proportion of newborns born to vaccinated mothers. Proportions were calculated based on model simulations where different vaccination coverages are considered.

the system will reach a state where every newborn child will be born either to a vaccinated or to a susceptible mother. In such a limit situation, the anticipation of the age of MMR I from 15 to 12 months of age should decrease the number of susceptible infants per day in about 25% (assuming Type I mortality and average duration of passive immunity of 3 months). We have found that this is not an important determinant for sustained measles elimination in Portugal, but it would reduce the likelihood of infants being involved in localized outbreaks triggered by imported cases of measles.

Conclusions

The vaccination coverage in Portugal increased consistently since 1974, as the number of vaccines given over time increased and the yearly number of newborns decreased (Fig. 1). Vaccination coverage per cohort, evaluated at 2 years of age, was estimated to rise from about 20% in 1974 to current levels at about 95% (Fig. 2). The peak vaccine uptakes observed shortly after 1985, 1989, and 1994 (Fig. 1), probably in reaction to the epidemic outbreaks that took place those years, are also a likely consequence of the new vaccination schemes introduced in 1987 (monovalent vaccine was substituted by the MMR) and 1990 (the two-dose scheme began).

The age-structured seasonally-forced model presented here, has the capability to reconstruct the epidemiological patterns of measles incidence in Portugal during the most recent decades, given the appropriate set of basic reproduction numbers and plausible assumptions about how vaccination was distributed over ages and time. The model reproduces the pre-vaccination 3-year inter-epidemic period, which had previously been reported from time series analysis of deaths by measles [32], as well as the major outbreaks that took place in 1984—1985, 1988—1989, and 1993—1994. As expected, the absolute number of cases over time, predicted by the model, is much larger than the number of measles notifications reported to authorities in Portugal. Indeed, the model suggests that notifications underestimate the number of cases by a factor of seven. This figure is coincident with the conclusion by Fleming et al. [36] that chickenpox incidence is seven times higher than the number of notifications reported by the Portuguese sentinel surveillance network.

The distribution of seropositives by age (>2 years old) produced by the model is in good agreement with results of the NSS based on blood samples collected in 2002 (Fig. 4B). Both show that the most prominent pool of susceptibles is in the 1978—1982 cohorts (20—24 years of age in 2002), with an estimate of 10% and 14% susceptibles, respectively, in the model and in the NSS. Cohorts from 1974, the year that correspond to the introduction of vaccination, until 1983 were shown to have low vaccination coverages (Fig. 1) which allied to smaller outbreaks (Fig. 3) cause this increase in susceptibility. Nonetheless, during the years from 1974 to 1977, there was supplementary vaccination due to the catch-up campaign held between 1973 to 1977, making this cohorts less susceptible then the 1978 to 1982 ones.

The model indicates that the 1998—1999 catch-up campaign, put into place by health authorities to avoid an outbreak projected for 1999—2000, created conditions to bring the effective reproduction number of measles to values continuously below 1. The simulations thus support the claim that the reduced notification of suspected cases of measles in Portugal since 2002, and the absence of laboratory confirmed cases, is a consequence of the interruption of indigenous measles transmission in Portugal since the late 1990s.

Outbreaks linked to imported cases are likely to continue to occur as long as measles remains endemic in parts of the world. Importations to well immunized countries will affect susceptible infants and previously vaccinated individuals whose immunity may not be complete. The capacity to keep imported cases from triggering endemic disease resurgence, is very much dependent on our ability to maintain a very high level of vaccination coverage (>95%) with the MMR I. This conclusion remains valid, irrespective of whether the vaccine is given at 12 or 15 months, and is little sensitive to changes in realistic levels of vaccination coverage with the MMR II. It is also in agreement with previous theoretical results on how crucial it is to keep high levels of first-dose coverage in two-dose vaccination schemes against childhood diseases [19].

The anticipation of the age of the MMR I has a significant impact on global transmission levels for a narrow band of vaccination coverage around 90%. Below this level of vaccination R_e will be above 1 irrespective of whether the age for MMR I is anticipated or not. Also if the level of vaccination coverage is above this band the reproduction number is always below 1. This result differs from other authors [37] who considered the contact rate in the first age group (0—4 years old) the lowest one. In our case this is the second highest contact rate, which is in accordance with the high rates of attendance of very young infants (from 4 months old) to daycare centers in Portugal.

In conclusion, Portugal is expected to remain free of endemic measles transmission if the present social and demographic conditions are maintained and levels of vaccination coverage with the MMR I remain above 95%, together with timeliness in the application of the recommended schedule. The greatest threat to measles elimination in countries like Portugal is reduced compliance with vaccination in face of a false sense of security created by absence of publicized outbreaks over the years. The longer the community goes without circulating measles virus, the more strict public health officials must be in handling imported cases and fighting the tendency to lower defences against what might become perceived as a disease of the past to the eyes of health workers and the general public.

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Appendix A. Model description

We have used an age-structured model with six epidemiologic compartments: maternally protected newborns, split

into newborns to vaccinated mothers (M) and newborns to naturally immune mothers (P), susceptibles (S), exposed (E), infectious (I), and recovered (R) individuals. Newborns enter cohorts defined by the academic year (1st October to 30th September), moving altogether to the next year of age at the beginning of a new academic year. A total of 75 cohorts were initiated with $n_0 = 126,666$ newborns. Those born to susceptible mothers enter directly into the susceptible compartment, whereas newborns with passive immunity enter the appropriate maternally protected compartment. The model keeps track of daily changes of individuals between epidemiological compartments throughout the year, using a 4th order Runge—Kutta approximation. The simplified model equations used throughout the whole school year are formalized as

For $i = 0, 1$

$$\frac{dP_i}{dt} = -pP_i$$
$$\frac{dM_i}{dt} = -mM_i$$
$$\frac{dS_0}{dt} = -\lambda(a,t)S_0 + pP_0 + mM_0$$
$$\frac{dS_1}{dt} = -\lambda(a,t)S_1 + pP_1 + mM_1 - \varphi_1 S_1$$

for $i = 2, \ldots, 74$

$$\frac{dS_i}{dt} = -\lambda(a,t)S_i - \varphi_i S_i$$

else, for $i = 0, \ldots, 74$

$$\frac{dE_i}{dt} = \lambda(a,t)S_i - \sigma E_i$$
$$\frac{dI_i}{dt} = \sigma E_i - \upsilon I_i$$
$$\frac{dR_i}{dt} = \upsilon I_i$$
$$\frac{dV_i}{dt} = \varphi_i S_i$$

Initial conditions are defined every year as:

$$P_0 = n_o - \left(\sum_i f_i S_i + \sum_i f_i V_i\right)$$
$$M_0 = \sum_i f_i V_i$$
$$S_0 = \sum_i f_i S_i$$

Also,

$$E_0(0) = I_0(0) = R_0(0) = V_0(0) = 0 \quad \text{and}$$
$$P_i(0) = M_i(0) = S_i(0) = E_i(0) = I_i(0) = R_i(0) = V_i(0) = 0$$

After running the differential equations for 365 days, the initial values are update as:

$$P_1(0) = P_0(365)$$
$$M_1(0) = M_0(365)$$

For $i = 2, \ldots, 74$

$$P_i(t) = M_i(t) = 0$$

and for $i = 1, \ldots, 74$

$$S_i(0) = S_{i-1}(365)$$
$$E_i(0) = E_{i-1}(365)$$
$$I_i(0) = I_{i-1}(365)$$
$$R_i(0) = R_{i-1}(365)$$
$$V_i(0) = V_{i-1}(365)$$

Here m and p are the rates of loss of protection by maternal antibodies in newborns to, respectively, vaccinated and naturally immunized mothers. Individuals leave the susceptible compartment either by vaccination at rate φ_i, that depends on age a and time t, or by infection at a rate defined by the force of infection $\lambda(a,t)$. Once infected, individuals become latent and then infectious at rate σ, recovering from infectiousness at rate υ. Individuals who become immune, either by vaccination or natural infection, are assumed to stay immune lifelong. Numerical values for the parameters are listed in Table 2.

The force of infection is defined by the function,

$$\lambda(a,t) = \sum_{a=1}^{4} b(a) I(a,t) \tag{A.1}$$

where $b(a)$ is the age-related transmission rate (number of contacts per unit time). $I(a,t)$ is the number of infectious individuals in age group a at time t. Age groups are defined as 0—4, 5—10, 11—20 and more then 20 years. The force of infection depends on the WAIFW (Who Acquires the Infection From Whom) matrix, a way of representing assumptions about how individuals mix among ages [24,28]. We have used a WAIFW matrix that conveys the common opinion that the main route of transmission takes place in primary schools (5—10 years old children). The structure of the WAIFW matrix was defined as in Schenzle [24] and Anderson and May [28],

$$\text{WAIFW} = \begin{pmatrix} b(1) & b(1) & b(3) & b(4) \\ b(1) & b(2) & b(3) & b(4) \\ b(3) & b(3) & b(3) & b(4) \\ b(4) & b(4) & b(4) & b(4) \end{pmatrix}$$

There is a unique coefficient ($b(2)$) describing the transmission among susceptible and infectious in age group 2 and there are two other coefficients, $b(1)$ and $b(3)$, for the contacts among individuals aged less then 21 years; whereas adults are described as being likely to acquire infection from a wider range of age groups. We further use a symmetry relation, indicating that individuals in age group j make contact with individuals in age group i at the same rate as individuals in the latter group make contact with those in the former. Transmission in the 5—10 age group, $b(2)$, takes a minimum value (equal to $b(1)$) every Sunday, during Christmas holidays (23rd of December to January the 7th), Easter holidays

(11th to 25th of April) and during the summer holidays (14th of July to the 7th of October). The set of values used for the WAIFW matrix elements are in Table 3.

The adopted structure fits the pattern found by Del Valle et al. [38] when studying contact patterns that determine the transmission of air born diseases.

To compute the number of newborns through time as a function of women's age, we have used the fertility function f_i estimated for Portugal in 1994 [26], defined as the average number of children per women at age i.

We assumed that all individuals die as they reach the age of 75 years (type I mortality).

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