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Estimating measles transmission potential in Italy over the period 2010-2011

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Abstract

Background. Recent history of measles epidemiology in Italy is characterized by the recurrence of spatially localized epidemics.
Aim. In this study we investigate the three major outbreaks occurred in Italy over the period 2010-2011 and estimate the measles transmission potential. The epidemics mainly involved individuals aged 10-28 years and the transmission potential, measured as effective reproduction number – *i.e*. the number of new infections generated by a primary infector – was estimated to be 1.9-5.9.
Results. Despite such high values, we found that, in all investigated outbreaks, the reproduction number has remained above the epidemic threshold for no more than twelve weeks, suggesting that measles may hardly have the potential to give rise to new nationwide epidemics.
Conclusion. In conclusion, the performed analysis highlights the need of planning additional vaccination programs targeting those age classes currently showing a higher susceptibility to infection, in order not to compromise the elimination goal by 2015.

Key words
- measles
- transmission potential
- Italy
- reproduction number

INTRODUCTION

In September 2010, Member States in the WHO European Region set themselves 2015 as the new target date for eliminating measles and rubella [1]. However, even if Europe is on the way to measles elimination, the virus is currently still circulating in most European countries [2]. For instance in 2011, more than 15 000 cases were recorded in France, with a monthly maximum of 3726 cases in March, 5181 cases were reported in Italy, 4015 in Romania and more than 1000 cases were reported in Spain, Germany and the UK [2]. Moreover, from July 2013 to June 2014, 7116 cases were reported from 30 EU/EEA countries conducting measles surveillance. Germany, Italy and the Netherlands accounted for 77.3% of the cases in this period and 6 European countries reporting outbreaks (Spain, The Netherlands, Belgium, Latvia, Czech Republic and Sweden) [3]. This generates serious concerns about the possibility of reaching the target within 2015 [4].

A single-antigen measles vaccine was introduced in Italy in 1976: measles-mumps-rubella (MMR) vaccine has been recommended since the early 1990s. Initially, a single dose of a measles-containing vaccine was recommended for children aged 15 months. Later, in 1999, the age of administration of the first dose (of MMR vaccine) was lowered to 12 months. From 1999 the Ministry of Health recommended the Regional Health Authorities to actively offer the MMR vaccine free of charge and to administer a second dose of MMR vaccine in regions that had reached a coverage level of 80% or higher for the first dose [5]. Since 2003, a National Plan for the Elimination of measles and congenital Rubella was implemented and recommended two doses of MMR vaccine in all regions: the first dose at 12-15 months and the second at the age of 5-6 years or 11-12 years. Moreover the Plan requested to all Regions in Italy (21) in an extra-ordinary effort to perform a catch-up vaccination program using all occasion of contact of children (who had not yet received the two recommended MMR vaccine doses) with vaccination services, including a campaign aimed at inviting all school age children in primary and lower secondary schools [5].

At the time of measles vaccine introduction, the coverage for the first dose was only 6%, and then the level quickly increased until remaining around 90% in the last 5 years [6], while for the second dose it increased from about 51% in 1999 to about 75% from 2006 to nowadays [5]. Such vaccination effort led to a substantial decrease of measles incidence and to a dramatic change in its epidemiology. In fact, Italy is no more subject to large nationwide epidemics and, in recent years, measles dynamics were characterized by the occurrence of

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several spatially localized outbreaks ranging from a few cases up to more than a thousand cases [7].

Factors concurring to this increase include suboptimal routine vaccination coverage (< 95%) that cause large numbers of susceptible adolescents and young adults born in the 1980s and 1990s, when measles vaccine uptake was very low and the second dose had not yet been introduced.

Adolescents and young adults have been frequently affected in outbreaks in recent years, but there continue to be high levels of susceptibility in these age groups [6].

Incidence varied greatly among geographical regions, and factors such as local epidemiology and accumulation of susceptible groups, but also difference in underreporting, may account for these differences [7].

The present study aims to better understand the dynamics of recent local outbreaks (*e.g.*, in terms of final impact, timing and age distribution of cases) and to estimate the current measles transmission potential in Italy, in order to give insights for the design of adequate immunization plans in such a way to speed up the elimination goal by 2015.

METHODS

Measles surveillance system in Italy

The Italian measles surveillance system has been previously described [7, 8]. Measles has been statutorily notifiable in Italy since 1934. An enhanced surveillance system was introduced in 2007 to improve timeliness, completeness of case reporting, and case investigation, including laboratory confirmation of diagnosis [8]. Briefly, according to this system, physicians are required to report all suspected measles cases to the local health authorities within 12 hours. For each suspected case, the local health authorities are required to carry out an epidemiological investigation, including obtaining specimens for laboratory confirmation and genotyping and to complete a standard measles notification form, which is then to be sent to regional health authorities. The regional authorities forward the forms immediately to the Ministry of Health and to the Infectious Diseases Epidemiology Unit of the National Center for Epidemiology Surveillance and Health Promotion of the National Institute of Health.

Cases are then classified as probable, possible and confirmed at national level using the European Union case definition [9]. Cases classified as "non cases" on the basis of the laboratory investigation were excluded from the analysis.

To investigate measles transmission potential in Italy, we analyze cases on the three largest epidemics reported to the national surveillance system over the period 2010-2011 from 3 Region and Autonomous Provinces (Lazio, PA of Trento and PA of Bolzano) [7, 8]. The Lazio experienced two outbreaks in the considered period [10]; however in this article we consider only the epidemic occurred in 2010. Data were extracted from the surveillance system database in April 2013.

Mathematical model

A population will rarely be totally susceptible to an infection in the real world. To such aim, we make use of the concept of effective reproduction number (*R*), which is defined as the average number of secondary cases per infectious case in a population made up of both susceptible and non-susceptible hosts and represents a measure for the transmission potential of an infectious disease.

In fact, the basic reproduction number is the average number of secondary cases generated by a typical index case in a fully susceptible population. The effective reproduction number, the one considered in our work, accounts for reduced transmissibility due to the presence of a large fraction of protected individuals in the population (typical of childhood diseases when a large fraction of adults is immune). Reproduction numbers are key parameters because they are related to the final size of the epidemic. Basically, if the reproduction number is lower than 1 the epidemic goes extinct, otherwise an epidemic outbreak can be observed and the final size will be proportional to the reproduction number itself.

The estimation procedure we use for computing the maximum value of *R* is widely adopted in the literature [11-16] and can be briefly described as follows:

a) Given the intrinsic uncertainty in all notification data, we use a Poisson distribution having mean equal to the weekly number of reported cases to generate 10 000 simulated time series of measles weekly cases.
b) For each time series, we estimate the exponential growth rate of the epidemic *r* by fitting a linear model to the logarithm of the number of new cases in the three-weeks time window showing the largest growth rate [16].
c) We model measles transmission flow as follows: susceptible individuals can acquire the disease (and enter in the latent stage) through contact with infectious individuals during both prodromal and exanthema phase; before recovering an infected individual undergoes latent, prodromal and exanthema phases, lasting on average 10, 4 and 4 days, respectively [17]. Given this model, the following relation between the effective reproduction number *R* and the exponential growth rate *r* holds [18]:

$$R = 1/\left[(1-k)\frac{\omega}{\omega+r}\frac{\gamma}{\gamma+r} + k\frac{\omega}{\omega+r}\frac{\gamma}{\gamma+r}\frac{\delta}{\delta+r}\right],$$

where $1/\omega$, $1/\gamma$ and $1/\delta$ represent the average duration of latent, prodromal and exanthema phases, respectively, and *k* represents the fraction of cases generated by a primary infector during the exanthema phase, and consequently (1-k) refers to the fraction of cases generated during the prodromal phase – we explore *k* in the range 10%-50% as no precise information is available. We decide to use this range (10%-50% during the exanthema phase) to explore a very large range of possibilities but we also assume that transmission is lower during the exanthema phase (in this phase, individuals are assumed to stay at home and thus can infect less individuals with respect to the prodromal phase). This is why we assume 50% as upper limit for the proportion of cases during the exanthema phase.

Starting from the original weekly number Xt of cases

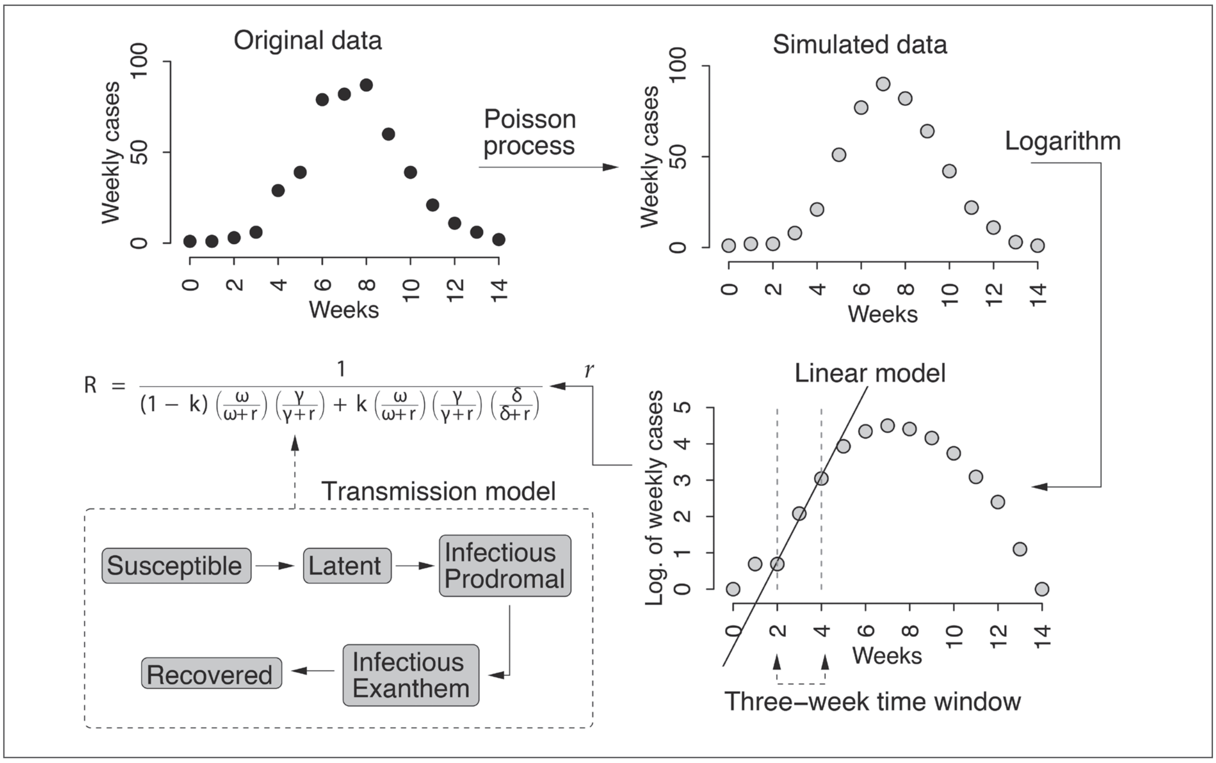

Figure 1
Graphical representation of the performed epidemiological analysis. In order to guarantee the stability of the results, the procedure is repeated 10 000 times.

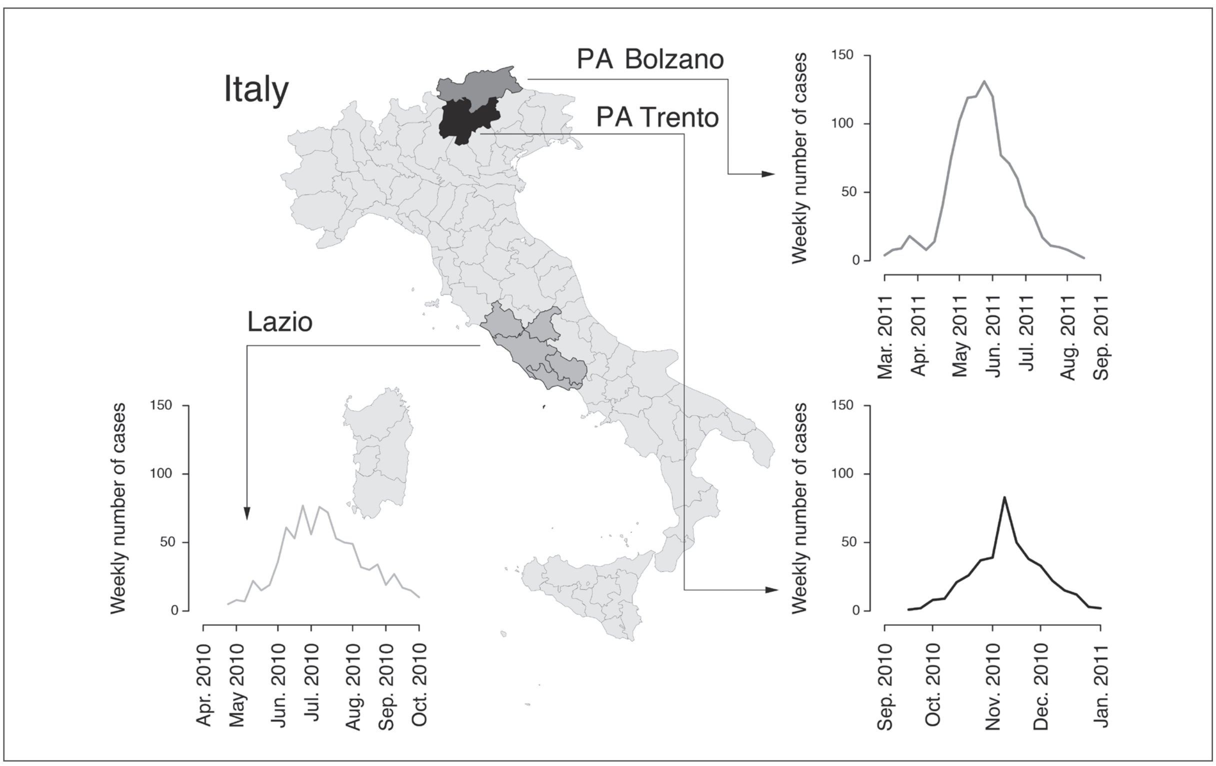

Figure 2
Spatial location and weekly number of cases reported to the national surveillance system. Only the three major epidemics occurred in Italy over the period 2010-2011 are shown.

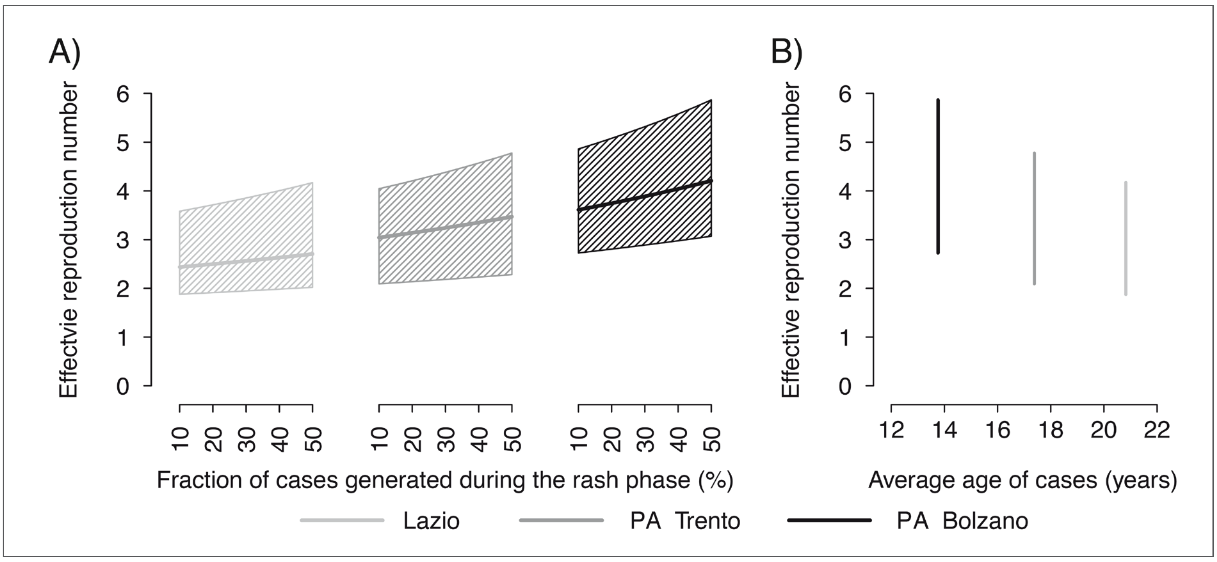

Figure 3
Estimated effective reproduction number. Panel A) Estimated maximum value of the effective reproduction number as a function of the fraction of cases generated during the exanthema phase, for the epidemic in Lazio (left), PA Trento (center) and PA Bolzano (right). Solid lines represent averages, shaded areas represent 95% CI. Panel B) Estimated range for the maximum value of effective reproduction number plotted against the average age of the reported cases during the epidemic in Lazio (light grey), PA Trento (grey) and PA Bolzano (dark grey).

observed at time t, we simulate different time series of data Yt by sampling, at each time t, from a Poisson distribution of mean Xt, to account for stochastic effects. The time window depends on the duration of the analyzed outbreak and may vary from region to region.

In *Figure 1* a graphical representation of the above described procedure is shown. In addition, in order to estimate the effective reproduction number over the entire course of the epidemic, the same method can be applied to each three-weeks time window of the epidemic [14, 19]. Finally, the uncertainty of our estimates of the transmission potential is obtained by combining the uncertainty in both the reporting system and *k*. Specifically, *R* ranges we present refer to the upper 95% CI of *r* combined with the larger value of *k* and to the lower 95% CI of *r* combined with the lower value of *k*. The algorithm was implemented in the statistical package R [20].

RESULTS

Over the period 2010-2011 Italy experienced three major measles epidemics. The first one spread from mid April 2010 until October 2010 in Lazio (Central Italy): the total number of cases reported to the surveillance system is 910, the average age is 20.8 years and 50% of cases are aged 14-28 years. The Lazio region experienced an outbreak also in 2011 [10], however, in this article we consider the epidemic occurred in 2010. The second epidemic spread from mid September 2010 until the end of December 2010 in the Autonomous Province of Trento (PA Trento, Northern Italy): the total number of reported cases is 400, the average age is 17.4 years and 50% of cases are aged 13-21 years. The third one spread from mid March 2011 until mid August 2011 in the Autonomous Province of Bolzano (PA

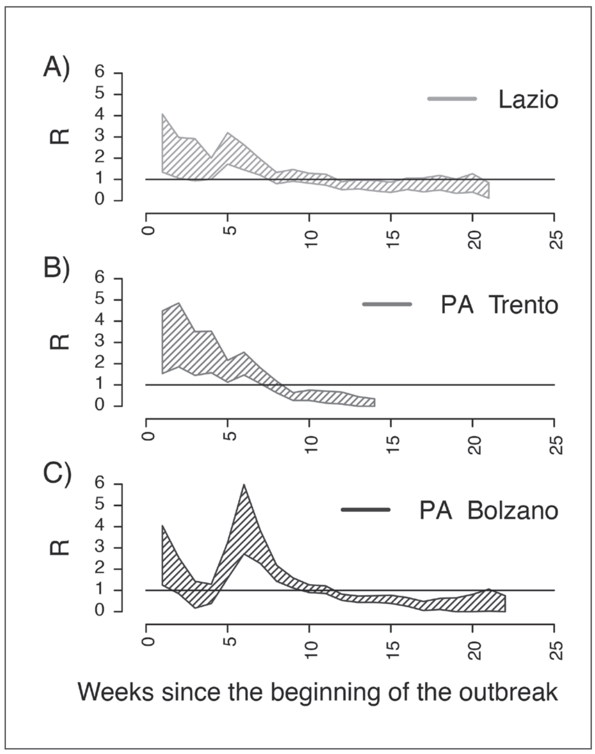

Figure 4
Effective reproduction number over time. Panel A) Estimated range of the effective reproduction number over time during the epidemic in Lazio. Panel B) Estimated range of the effective reproduction number over time during the epidemic in PA Trento. Panel C) Estimated range of the effective reproduction number over time during the epidemic in PA Bolzano.
The horizontal line represents the epidemic threshold R = 1; R at week t is computed by considering the three-weeks moving window from t - 1 to t + 1.

Bolzano, Northern Italy): the total number of reported cases is 1110, the average age is 13.8 years and 50% of cases are aged 10-17 years. Epidemic profiles and the spatial location of the outbreaks are shown in *Figure 2.*

The exponential growth rate is estimated to be 0.56 (95% CI: 0.37-0.90), 0.75 (95% CI: 0.45-1.02) and 0.91 (95% CI: 0.65-1.22) per week for the epidemic in Lazio, PA Trento and PA Bolzano, respectively. This leads to an effective reproduction number in the range 1.9-4.2, 2.1-4.8 and 2.7-5.9 for the epidemic in Lazio, PA Trento and PA Bolzano respectively (see *Figure 3A*). Moreover, we find that the estimated value of *R* increases as the average age of reported cases decreases (see *Figure 3B*).

Finally, as shown in *Figure 4*, in the three epidemics the effective reproduction number remains above the epidemic threshold (R = 1) for less than twelve weeks since the beginning of the outbreak.

DISCUSSION

Two main conclusions can be drawn from our epidemiological analysis. First, at a local scale the current measles transmission potential can still be high, giving rise to spatially localized outbreaks. Specifically, we estimate the maximum value of the effective reproduction number to be in the range 1.9-5.9, during the three largest epidemics occurred over the period 2010-2011. This range is remarkably above the unit; however, it is lower than that observed during the 70s in Italy [21], when the country experienced nationwide epidemics.

Moreover, data show that in the three major epidemics *R* is estimated to be above the epidemic threshold for less than twelve weeks since the beginning of the outbreak. This common pattern suggests that, given the current immunization level in the Italian population, measles has no more the potential to give rise to nationwide epidemics, however, it should be considered that simultaneous local outbreaks can derive by a unique "index case".

Second, the analysed epidemics mainly involved adolescents and young adults. This suggests that the ages that are currently more susceptible to measles infections lie in the range 10-28 years, mainly as a consequence of the ongoing children immunization program which is leading to a remarkable drop in the number of yearly cases and to an increase in the age at infection.

Nonetheless, our analysis reveals that infections in lower ages are associated to larger values of the effective reproduction number, suggesting that measles has the capability to better spread in children than in the other age classes. It should be noted that the lower average age of cases reported in the PA Bolzano is due to the lower vaccine coverage for measles among children at 24 months of age (72.4%) with respect to the average national coverage (90.1%). In fact, vaccination coverages in Italy are quite variable across regions: for instance, in 2011 measles vaccine coverage at 24 months of age ranged from 72.4% of the PA of Bolzano (Northern Italy), to 82.5% in Calabria (Southern Italy), to more than 92% in Puglia (Southern Italy), Piedmont (Northern Italy), Marche and Tuscany (Central Italy) [5].

Our study as others study relying on surveillance data has a potential limitation due to a certain degree of underreporting. Since the introduction of the enhanced surveillance system in Italy in 2007 [8], reporting and completeness of cases is improved, however we cannot exclude the possibility of a certain degree of underreporting. In late 90s and early 2000s, on the basis of data reported by a sentinel surveillance system relying on paediatricians (SPES), measles incidence was estimated to be 10 times greater than incidence estimated through the statutory notifications [22, 23]. Thus, for the Lazio region, data from the National enhanced surveillance system have shown a total of 910 cases in 2010 compared to the 1054 cases (incidence rate of 18.4 x 100 000) reported by Regional Public Health Authorities [10], that is well below the 10 times degree of underreporting previously recorded.

In 2011, the Italian Ministry of Health published a new national elimination plan approved by the State-Regions collegial body (Conferenza Stato Regioni), which means that all 21 regions have committed to the objectives and strategies included in the plan [24]. The plan, which includes all components of the WHO elimination strategy, comprises also specific measures to be considered in case of an outbreak (*i.e.* isolation of cases and vaccination of close contacts). However, since several local outbreaks are still ongoing in Italy [3], in order not to jeopardize the elimination goal by 2015, there is an urgent need of vaccination strategies aimed at covering those age classes (mainly adolescents and young adults) that are currently more susceptible to the disease.

Surely additional immunisation efforts (*e.g* new catch-up campaign) should be considered for susceptible groups above described: this call for new modelling studies for evaluating the effectiveness of targeted vaccination strategies. An intriguing hypothesis would be to reinforce the two-dose vaccination program currently in place by offering the vaccine, only for one year, in lower and upper secondary schools in order to immunize the 11-16 age brackets. As a matter of fact, optimisation of vaccination programme design can be greatly facilitated through insights gained from the mathematical modelling of measles transmission dynamics [25].

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Conflict of interest statement

None to declare.

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