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Original article

Estimating age-stratified measles susceptibility using the screening method: an example from 2018–21 measles resurgence in Brazil

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Abstract

Objectives **Characterizing susceptibility profiles across age groups and administrative units is essential for targeted vaccination and control of resurgent vaccine-preventable diseases like measles, but is often limited by the lack of historical vaccination records.**

Methods **We proposed a methodology based on the screening method that uses routine surveillance data, such as case age and vaccination status, along with an estimate of vaccine effectiveness, to estimate age-stratified susceptibility to a vaccine-preventable disease.**

Results **Applying this method to the 10 most affected Brazilian municipalities by measles resurgence in 2018–21, we signal municipalities that have a population immunity below the herd immunity threshold, along with the age groups with the largest susceptible cohorts. Some municipalities show an overall large susceptibility, while others concentrate susceptible individuals in the age cohorts >20 years, as a result of past low vaccine coverage.**

Conclusion **The proposed methodology is a low-cost tool to estimate susceptibility using readily available surveillance data, allowing for identification of susceptible age cohorts, even in the absence of historical vaccination data. The results obtained offer actionable insights for designing vaccination strategies in Brazil as well as similar epidemiological contexts, as the methodology can be easily applied on similar datasets.**

Keywords measles, screening method, susceptibility

Introduction

A recent resurgence of vaccine-preventable diseases (VPDs) like measles[1–3] has been observed worldwide because of overall population immunity gaps. This is a result of multiple factors such as growing vaccine hesitancy[4,5] and a decrease in vaccination coverage after the COVID-19 pandemic.[6,7]

In this context, understanding population susceptibility and immunity against measles, as well as other VPDs, is an imperative yet difficult task. Although serological surveys are particularly resource-demanding, one possible source of information is administrative vaccination coverage data, which indicate the proportion of a target population that was vaccinated in a given year and region. However, for this reason, vaccination coverage values alone can be misleading as high vaccination coverage does not equal overall high populational immunity. First, because this would neglect the role of primary and secondary vaccine failure. Furthermore, as target populations are well-defined, particularly in terms of age, coverage only provides information on specific groups. As coverage can also be heterogeneous in time, being high during certain periods and low during others, differences in susceptibility across birth cohorts are expected. For instance, this is the case with several VPDs, whose coverage was undermined by the COVID-19 pandemic.[6,8,9] In addition, vaccination coverage is usually calculated using routine vaccination data, thus forfeiting the role of supplementary vaccination activities, such as catch-up campaigns, or leading to unexpected reported coverage values (e.g. >100%).[10] Moreover, for some age cohorts or administrative units, time series of vaccination coverages or vaccine doses applied may be unavailable. For example, coverage and dose data from Brazil for the measles, mumps, and rubella (MMR) vaccine are publicly available starting in the early 2000s.[11]

In the current study, we propose a method to estimate age-stratified immunity proportions of a population by using an adaptation of the screening method, an epidemiological tool for calculating field vaccine effectiveness (VE). Our methodology uses routinely collected surveillance data, such as the number of cases of a disease, aggregated by age group and vaccine status, along with literature estimates of VE. As an example, we use the data of the 10 municipalities with the most measles cases during 2018–21 in

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Brazil, and we estimate their age-stratified susceptibility. The obtained estimates are heterogeneous among age groups and municipalities, with several cities shown to be below or very near the herd immunity threshold (HIT).

Materials and methods

Screening method

The screening method[12,13] is used in epidemiology to estimate VE from data on cases of a disease in a population where the proportion of the vaccinated population is known. The basis for this method is the standard formula for VE, given by

$$VE = 1 - \frac{PCV}{1 - PCV}\frac{1 - PPV}{PPV}, \quad (1)$$

where PCV is the proportion of cases that are vaccinated and PPV is the proportion of the total population that is vaccinated. In the context of vaccine introduction, this proportion can be directly related to the proportion of the population that is immune. Therefore, if both of these quantities are known, it is possible to estimate VE. However, if VE is known, this equation also allows for an estimation of PPV, by rewriting it as

$$PPV = \frac{1}{1 + (1 - VE)\left(\frac{1}{PCV} - 1\right)} \quad (2)$$

Finally, stratifying by age it is possible to obtain PPV(i), that is, the proportion of immune individuals for an age group i. In order to do this, we adopt a value for VE of ∼90% for all age groups, as is often reported.[14–17] It is worth noting that PPV(i) is different from vaccination coverage. Vaccination coverage is usually calculated as the number of doses administered over the target population in a given time period. Thus, it provides information on the immunization status of this particular target population. Conversely, PPV(i) is a measure of the immune status of the population, and is calculated considering different age groups, instead of only a given target population. Furthermore, PPV(i) reflects the immune status, rather than only immunization status, therefore taking into account possible acquisition of immunity by infection as well as vaccine failure.

Measles data

Data on individual measles cases in Brazil during 2018–21 were obtained for analysis through the DataSUS website[18] from the Ministry of Health of Brazil. Among other fields, each individual case is accompanied by data on country and municipality of residence, and reports the date of first symptom onset and vaccination status (when known). It is worth clarifying that vaccination status is declared by patients and only includes data on whether a person is vaccinated or unvaccinated, or whether they ignore their vaccination status. That is, it does not include any information on the number of doses received.

Estimates of the population pyramids of municipalities, which are necessary to compute the proportion of susceptible individuals given the calculated susceptibility per age group, were obtained from the DataSUS—Tabnet website from the Ministry of Health.[19]

Uncertainty estimation

In order to quantify uncertainty in immunity estimates, two main uncertainty sources were considered: population sampling and VE uncertainty. For the former, we considered that the number of individuals per age group that were immunized were sampled as part of a binomial process in a population N(i) equal to the number of cases and with a probability of success (being vaccinated) given by the empirical PCV(i). The variance obtained for the number of cases on vaccinated individuals per age group $N_c(i)$ was propagated to obtain an uncertainty estimate for PCV(i), and then the same process was carried out to obtain an estimate of this effect on the computed PPV(i) values. Regarding VE, we considered that $VE = (90 \pm 5)\%$[20] and propagated this uncertainty onto an uncertainty value for PPV(i). Both of these uncertainties were considered in order to calculate the total uncertainty for PPV(i).

It is worth noting, that to use Equation (2), information on the vaccination status of all patients is needed. Because there were patients for which this information was missing, we calculated population immunity under two scenarios. First, the scenario labelled as 'Full', which corresponds to considering that all those individuals for which the vaccination status was unavailable were vaccinated. This is a rather optimistic scenario, albeit a realistic one, due to high historical vaccine coverage. Second, the scenario labelled as 'Half' corresponded to assuming that one-half of the patients with unknown vaccination status were vaccinated and that the other half were not. As per Equations (1) and (2), higher proportions of vaccinated individuals (PCV) result in higher values of estimated immune proportions. Thus, the 'Full' scenario is expected to produce more optimistic estimates of immunity when compared with the 'Half' scenarios and with other scenarios yielding lower PCV values. Even if more pessimistic scenarios are possible, the 'Half' scenario is considered realistic, as 60% of cases with a known vaccination status in the selected municipalities are declared as unvaccinated.

Other potential sources of uncertainty, such as self-reporting of vaccination status, are not considered, as their suitable quantification would require non-available information and would thus rely on ad hoc assumptions. In particular, under-reporting is not taken into account, as measles is non-endemic and of compulsory notification in Brazil, thus we expect the under-reporting rates to be negligible. Misclassification is also neglected, as confirmed cases follow the final classification criteria of the Notifiable Diseases Information System (*Sistema de Informação de Agravos de Notificação*, SINAN).

Results

Analysis of cases in Brazil

During 2018–21, there were 39 594 cases of measles in Brazil, 42 of which resulted in death. The vast majority of cases were in patients residing and being infected in the country, with only 108 cases in non-residents and 381 cases known to have not been infected in Brazil. That means that, even although measles probably was introduced from abroad, as shown by the time series of Figure 1, transmission quickly became local. Several sources in the literature point to an ongoing outbreak of measles in Venezuela in 2018 as being one of the sources of this reintroduction,[21–23] particularly through genomic analysis.[24,25]

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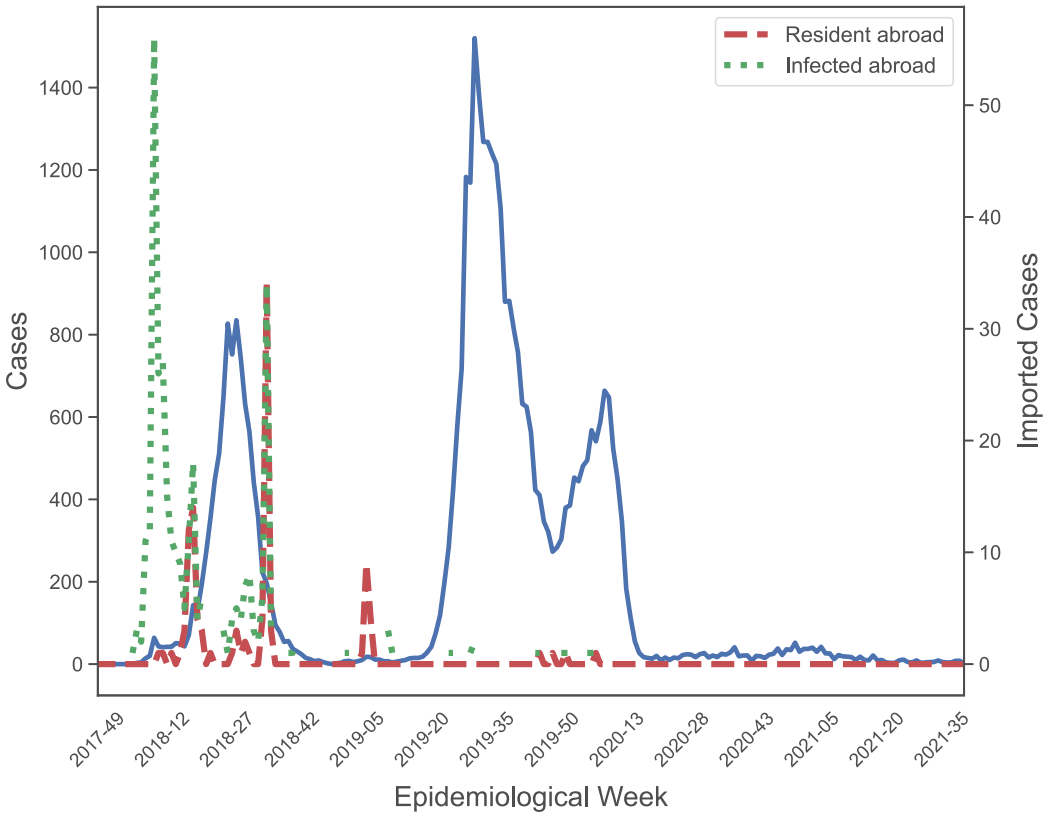

Figure 1 Total cases registered in Brazil per epidemiological week in the period 2018- 2021 (blue filled line, left axis). Also, cases from non-residents (resident abroad) and cases infected abroad (red dashed and green dotted lines, values on right axis).

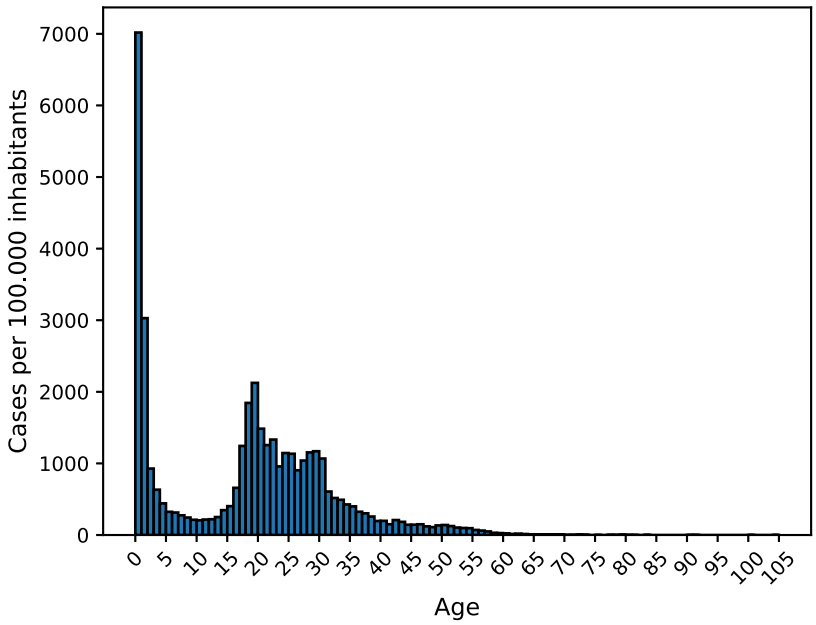

Figure 2 Histogram of ages of people that were reported as measles cases in the period 2018–2021 in Brazil.

It is also interesting to analyse how cases were distributed in terms of the ages of patients, as measles is known as a childhood disease. From the histogram of the ages of individual cases in Figure 2, it is possible to distinguish two age groups most affected by measles during this period: unvaccinated children aged <1 year and people in the 15–40 years age range. The latter should, in theory, be vaccinated with at least one MMR dose, according to regulations from the Brazilian Ministry of Health.[26]

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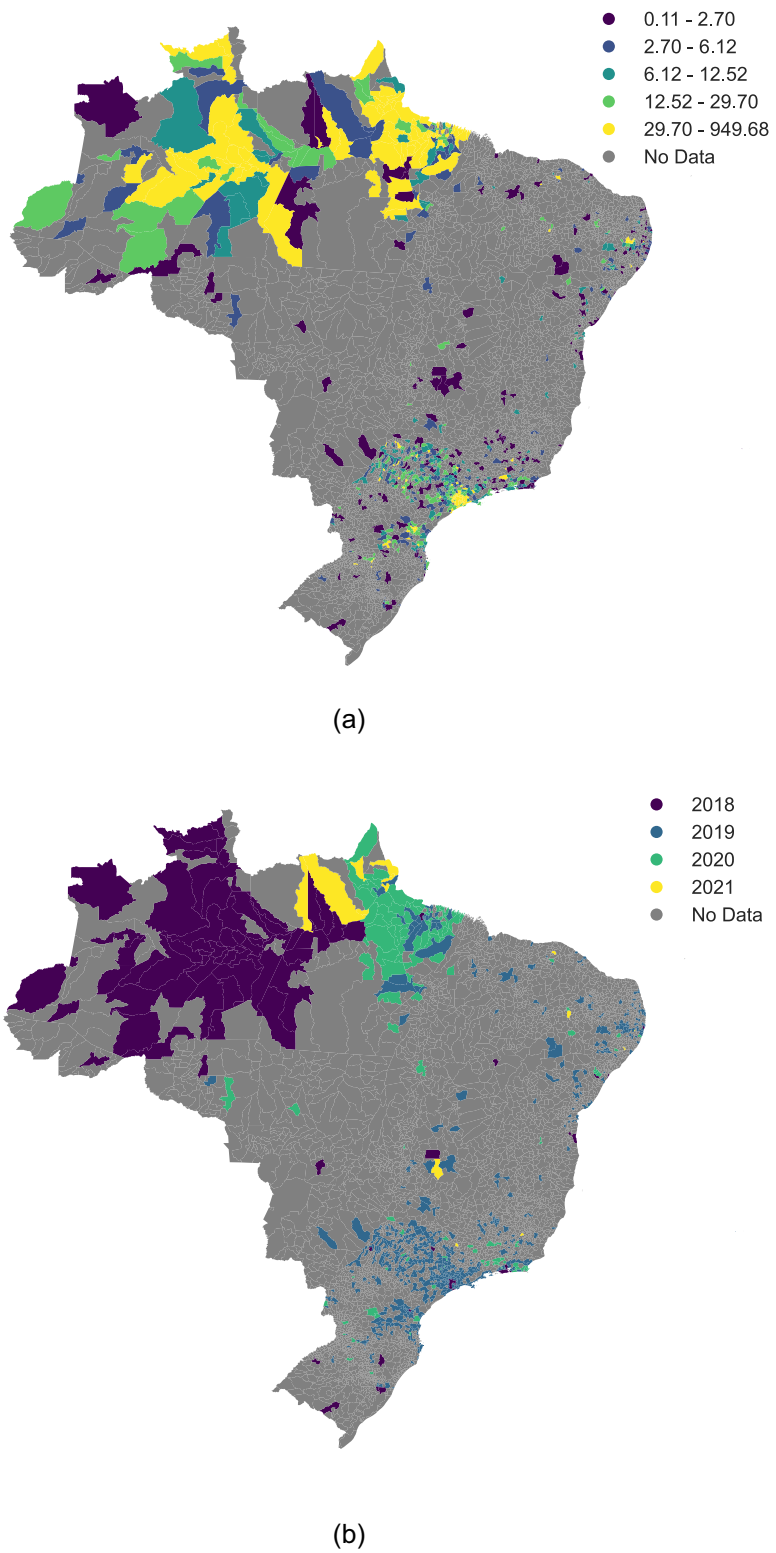

Figure 3 (a) Map of number of cases per 100.000 inhabitants in each Brazilian municipality in the period 2018–2021. (b) Map of symptom onset year of the first case detected in each Brazilian municipality.

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Table 1 Cases, incidence per 100 000 inhabitants, and the proportion of susceptible individuals, S_0, in each city computed from the coverage values calculated, assuming that either all ('Full' scenario) or one-half ('Half' scenario) of the individuals with unkown vaccination status are unvaccinated.

Municipality	Cases	Incidence	S_0 ('Full') (%)	S_0 ('Half') (%)
São Paulo	9812	79.1	6.3 (1.2)	9.8 (1.8)
Manaus	7164	317.6	21 (3)	25 (4)
Belém	1436	95.3	36 (4)	41 (5)
Curitiba	1300	66.2	7 (2)	11 (3)
Ananindeua	1050	194.3	10 (2)	16 (3)
Guarulhos	955	68	5.2 (1.5)	9 (2)
Manacapuru	946	949.7	23 (4)	23 (4)
Rio de Janeiro	766	11.3	3.8 (1.2)	6.9 (1.8)
Francisco Morato	635	354	8 (2)	5.9 (1.5)
Macapá	576	110.3	19 (4)	11 (3)

Regarding the spatial evolution of the outbreaks, the three separated peaks in cases in 2018, 2019, and 2020 can be associated with different geographical regions: North, Southeast, and Northeast. Initially, during 2018, cases were prevalent in the North region of the country, mainly in the states of Roraima, Amazonas, and Pará. An important outbreak took place in the neighbouring cities of Manacapuru and Manaus in the state of Amazonas, as is clear from Figure 3a.

After 2018, outbreaks continued in different parts of the country. In 2019, several measles outbreaks were detected in the Brazilian Southeast, mainly in the state of São Paulo. Outbreaks also arose in the Northeast region of the country in 2020 and, in 2021, cases were also reported in the North region. The spatial and temporal distribution of measles in different years and regions can be observed in Figure 3b, where we show the year of symptom onset for the first case in each municipality.

Estimation of age-stratified immune proportions

Using the screening method, we estimated the immune proportion, PPV(i), for each age group for the 10 municipalities with the highest numbers of cases during 2018–21. These municipalities, along with their total numbers of cases and incidence, are listed in Table 1. It is worth clarifying that we present results on the 10 municipalities with the most cases in the study period because of their considerable number of cases, which are distributed among different age groups. As the methodology proposed relies on case data to estimate immune proportions, administrative units with only a few cases could yield immune proportion estimates with large uncertainty. Thus, we chose to use the 10 municipalities with the most cases to exemplify the proposed methodology. Furthermore, because of the large number of cases, providing estimates for these municipalities becomes imperative. However, this does not mean that application of the methodology to other epidemiological contexts (e.g. to other Brazilian municipalities) is necessarily limited.

As the data included the possibility of a person ignoring their vaccination status, we calculated population immunity under the two scenarios described in section 'Uncertainty estimation'. We present the estimates of PPV(i) for age group and municipality in Figure 4.

It is possible to identify two scenarios by inspecting the results for different municipalities. First, there are municipalities for which the estimated immune proportion values are adequate for younger age groups but decrease for older ones (São Paulo, Francisco Morato, Guarulhos, Rio de Janeiro, and Curitiba). By contrast, the remaining cities (Manaus, Manacapuru, Belém, Ananindeua, and Macapá) show an immunity proportion below the 93% HIT across all age groups.

Additionally, we used the population per age group of each city, that is, the population pyramid, to calculate the proportion of susceptible individuals, S_0, which is the converse of the calculated immunities. Table 1 presents these numbers for both scenarios, 'Full' and 'Half', which were employed in the computation of estimates. On one hand, it can be observed that cities that showed significant differences between immunity proportions and the recommended HIT have a higher proportion S_0 for the two studied scenarios. For example, this is the case with Belém, which is calculated to have ∼36–41% of its population being susceptible. It is followed by the two cities with the highest incidence, Manacapuru and Manaus. For the other municipalities, as expected from the previous analysis, the departure from the HIT is considerably smaller.

Although the relationship between PCV and S_0 is straightforward, as one is used to calculate the other, it is interesting to observe the relationship between S_0 and incidence, as displayed in Figure 5. While higher incidences seem to be associated with higher S_0 values, there are some outliers, such as the case of Belém, which had the highest calculated S_0 but relatively low incidence. The lack of a strong association between S_0 and incidence is not inconsistent with our assumptions, as only the proportions of vaccinated among the cases are used for the calculation of immune proportions and, thus, of susceptible proportions.

Discussion

In this work, we proposed an adaptation of the screening method, which is a tool to compute VE, to estimate age-stratified immune proportions of a population. The methodology proposed uses

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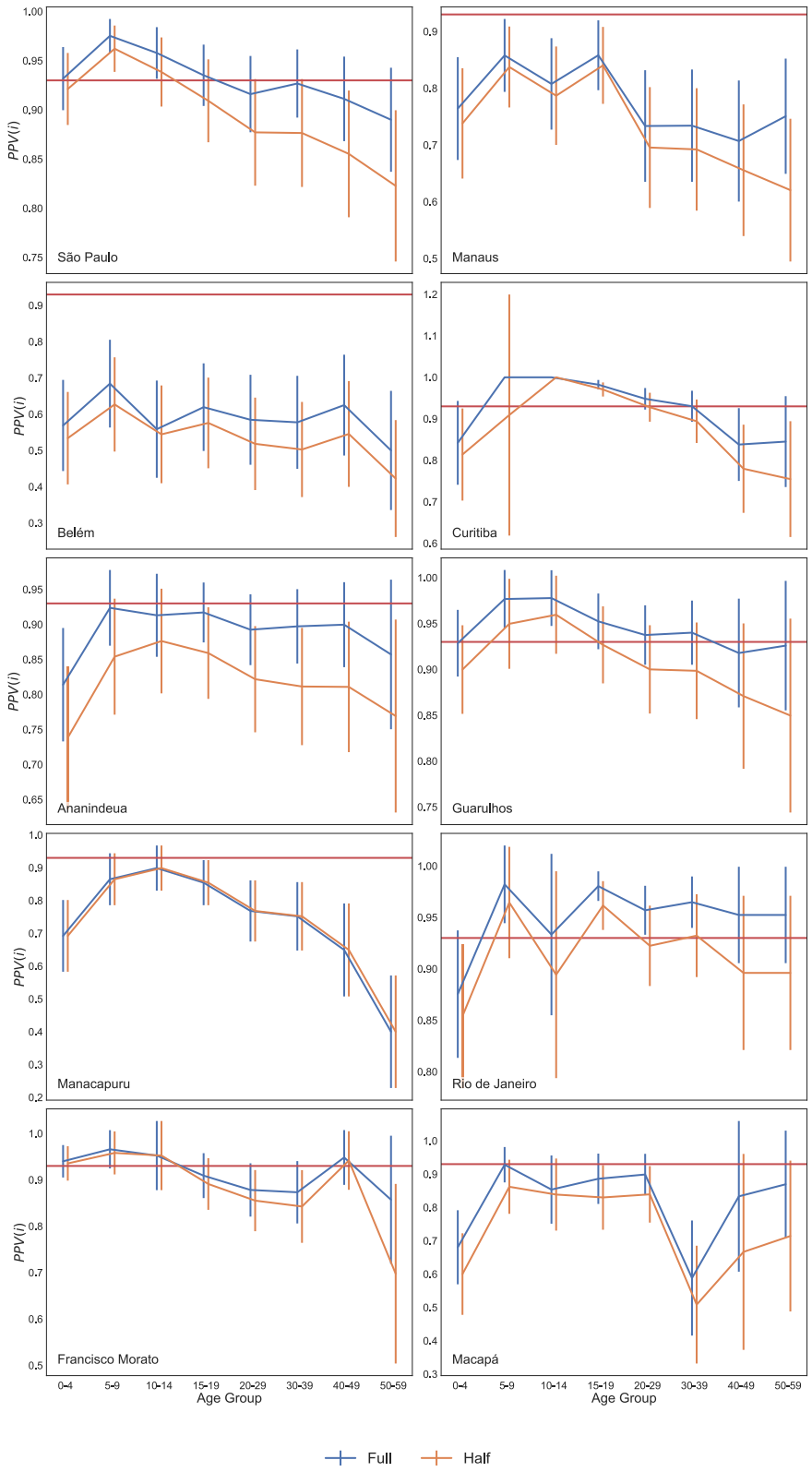

Figure 4 Estimated immunity proportion per age group for the 10 cities with the most cases in Brazil in the period 2018–2021. These values are calculated assuming all people who ignore their vaccination status are vaccinated ('Full') and also assuming half of these cases are vaccinated ('Half'). The horizontal red line represents the herd immunity threshold.

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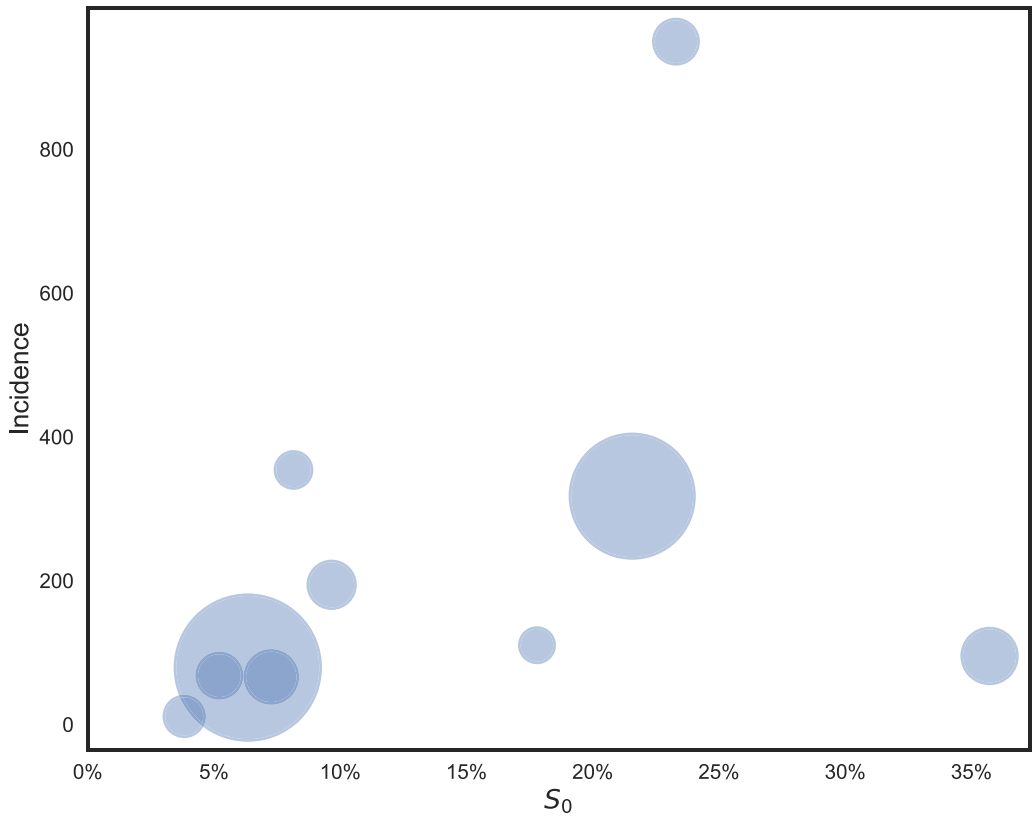

Figure 5 Incidence per 100.000 inhabitants as a function of the calculated S0 in the 'Full' scenario, where the area of points is proportional to the absolute number of cases.

only basic surveillance data, such as the age group and vaccination status of notified cases. In particular, we exemplified its application using data from the 10 cities with the most measles cases in Brazil during the 2018–21 epidemics, and we were able to estimate their immune proportions as well as their total susceptible populations. The results obtained provide important insights for the design of surveillance and immunization measures of measles in the country.

On one hand, some of the affected cities display susceptibilities below the HIT for several age groups, such as Manaus and Belém. This indicates a systematic failure in vaccine coverage over the years up to the period studied in these regions. In particular, it is consistent with recent reports[27] that signal issues with vaccine coverage in the North region of the country. Moreover, the susceptible proportions calculated for the municipalities of Belém and Ananindeua are consistent with serological studies conducted in these municipalities for certain age groups, which also indicate the presence of large susceptible cohorts.[28,29] This spatial pattern—municipalities in the North region having lower immune proportions—could possibly be related to socioeconomic factors that influence access to healthcare. Although MMR coverage values in deprived regions such as the North region were traditionally higher, as shown by,[30] so is vaccination heterogeneity among municipalities, which can lead to the formation of susceptible clusters. Furthermore, recent decreases in MMR coverage have been shown to be more pronounced in deprived regions such as the North, which also indicates healthcare access issues. This is consistent with another recent study,[31] which showed that COVID-19 vaccination coverage values in Brazil were profoundly affected by regional inequality.

On the other hand, other municipalities show a high susceptibility in the youngest age categories—especially from 0 to 15 years—that either decreases monotonously with age or has some age groups—mainly 20 to 40 years—with a coverage lower than the HIT. This is the case with municipalities such as São Paulo, signalling a failure of coverage in older age groups, a result that was expected because of the coverage estimates for people aged >20 years. The vaccine coverage was reportedly lower than the HIT[32] before the 2000s, so cohorts born before this time, that is, groups aged >20 years during the epidemic period, have vaccination coverage values below the recommended one. Thus, these groups could contribute to transmission, even although measles is usually considered to be a childhood disease. However, it is also remarkable that some municipalities have high susceptibility among the youngest, most vulnerable age groups, even municipalities where historical coverage tends to be high. This is consistent with reports about declining vaccine coverage for both the first and second doses of the MMR vaccine in recent years in Brazil.[28]

In the context of the re-emergence of several VPDs, this analysis shows the importance of acknowledging that both young and old age groups can contribute significantly to transmission because of failures in vaccine coverage, even for diseases traditionally known as childhood diseases, for which routine vaccination at a young age is recommended. While coverage for children could be recovered by vaccination campaigns as a result of mandatory vac-

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cination coverages, this is not the case for adults, for whom it is more difficult to design vaccination catch-up campaigns. Furthermore, in the case of measles, this is particularly worrying, because this indicates immune proportions below HIT of the MMR vaccine, which also protects against mumps and rubella.

The screening method has been used to estimate VE in previous literature, for cases in which the proportions of vaccinated individuals are well-known. By contrast, knowing VE, we have shown that this method can be used to estimate effective proportions of immunized individuals using the proportion of vaccinated people among the cases in a certain age group for different cities. This type of analysis could enable similar estimations for different groups, not only stratified by age and location, but also taking into account different social factors. In principle, given a good estimate for VE, it could be used to estimate immune proportions for other resurgent VPDs.

It is also worth highlighting that the proposed methodology, as used in the current study, assumes that the majority of the population should receive a single vaccine dose with a given VE. If VE were higher, either because another vaccine was used or because two doses are administered, the calculated immune proportions are likely to be underestimated.

When compared with serological surveys, which demand a great deal of field and financial effort, the proposed methodology arises as a cheaper alternative if case data are available for a given population and age group. Therefore, our methodology is severely limited by the lack of available case data for estimation, and a considerable number of cases is needed to produce reliable immunity proportion estimates. Moreover, while serosurveys can be conducted for different epidemiological contexts, our methodology is restricted to diseases for which vaccination is available.

Another plausible methodology to reconstruct immunity profiles is the use of historical vaccine records of routine and supplementary immunization actions. This method is limited by a lack of available immunization data, thus limiting the age groups for which these calculations are possible. For instance, official dose application data from the Brazilian Ministry of Health are available for years after 1994. Thus, an inference of immunity for older age groups would not be possible. Conversely, provided sufficient information on cases for a certain age group exists, using the proposed application of the screening method is feasible.

Author contributions

Denise Cammarota (Conceptualization [equal], Data curation [lead], Formal Analysis [lead], Methodology [equal], Visualization [lead], Writing—original draft [lead]), Renato Mendes Coutinho (Conceptualization [equal], Methodology [equal], Supervision [equal], Writing—review & editing [equal]), and Roberto Kraenkel (Conceptualization [equal], Methodology [equal], Supervision [equal], Writing—review & editing [equal]).

Conflicts of interest

None declared.

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Ethical approval

Not required.

Data and code availability

Data and code to reproduce the results of this work are available at https://github.com/denisecammarota/measles-vacc-coverage.

Declaration of Generative AI and AI-assisted technologies in manuscript preparation

None declared.

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