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# Assessing population immunity for measles elimination – The promise and peril of serosurveys

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## 1. Introduction

All World Health Organization (WHO) Regions have goals to interrupt endemic measles circulation on or before 2020. This is a worthy, feasible (already achieved in the Region of the Americas) but formidable challenge, given the unique contagiousness of the measles virus, which demands homogeneous population immunity over 92% in most settings. High population immunity is necessary to ensure that the effective reproduction number is driven below 1, a pre-requisite for achieving and sustaining elimination.

To provide guidance for verifying measles elimination, the WHO has published a framework that details evidence across five domains required to substantiate an individual country's or Region's claim to have interrupted endemic measles virus transmission. These evidence domains are: (1) a careful description of measles epidemiology over an extended period; (2) indicators of the quality of epidemiological and laboratory surveillance; (3) laboratory evidence of the absence of an endemic or, following importation, a sustained transmission measles genotype; (4) confirmation of immunisation program sustainability; and (5) measures of robust population immunity by birth cohort [1]. The accurate determination of population immunity is constrained by the inadequate quality of routinely available administrative data in many settings i.e., recording of vaccine doses administered either during the routine immunisation programme or by supplementary immunisation activities (SIAs) as the numerator, while the denominator is estimated from census data after considering births, deaths, and migration. Although vaccine coverage data appears an efficient means for estimating immunity, the quality of coverage data and routinely reported measles case data is extraordinarily variable globally and this seriously compromises the

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construction of credible immunity profiles across all age groups, at different spatial scales, and in population sub-groups. Disproportionate delivery of vaccine often occurs during non-selective SIAs with individuals who are already immune from prior vaccination being more readily accessible to the health system. They are thus more commonly revaccinated than persons never previously vaccinated, and this further complicates coverage determination and, by extrapolation, immunity estimation. Use of incomplete or inaccurate surveillance data is a major hurdle to calculating population immunity derived from wild virus infection [2].

Well-designed vaccination coverage surveys provide snap-shot estimates of coverage during a defined time period. However, they may not accurately reflect immunity, because they do not account for vaccination failure. Such failures may be caused by compromised vaccine potency due to cold chain breaches, vaccinator error, interference by maternal antibodies when infants are only vaccinated during the first year of life and, for many failures, unknown reasons (e.g., optimal vaccination in the second year of life is associated with failure rates of around 5%). Most failures are considered primary vaccine failure (i.e., failure to ever make a protective immune response to the vaccine) although secondary vaccine failure (loss of immunity with increasing time since vaccination) has been documented. The magnitude of secondary failure is currently not well understood but available epidemiological evidence suggests that this is not currently a major issue.

One approach to determining population immunity that is gaining increasing support is conducting cross-sectional serological surveys (serosurveys). Such surveys are either conducted using serum samples available in public health laboratories collected for other purposes, usually diagnostic, or through community surveys that include blood or oral fluid collection. They can determine the prevalence, by birth cohort, of measles-specific IgG antibodies against pre-determined cut-off levels thought to correlate with immunity. In addition to providing a population immunity estimate at a specific point in time, their utility has been touted for identifying immunity gaps, providing information to guide immunisation activities, and shoring up the case for having achieved elimination [3]. Well designed and well conducted (quality assured field and laboratory practices) representative serosurveys potentially overcome the limitations of indirect estimates extrapolated from historically imperfect coverage and incidence data.

There are a number of examples, e.g., Australia, Japan and Republic of Korea, where national measles serosurveys have identified immunity gaps in specific age cohorts, assisted in refining the routine immunisation schedule or designing targeted SIAs, and then been used to evaluate and confirm the success of the specific strategies adopted to reduce the immunity gaps [4-6]. Macao Special Administrative Region, China, has conducted an annual serosurvey of 500 randomly selected laboratory samples across eight age-bands since 2002 and this has provided supportive evidence of robust population immunity against measles necessary to sustain measles elimination [7].

It is noteworthy that the four examples for nationwide application of serosurveys provided above are wealthy countries with sophisticated health systems able to deliver well-functioning immunisation programmes and sensitive disease surveillance. There are

a limited number of less developed countries that have secured the resources necessary to design, deliver, interpret and adequately respond to serosurveys [8]. In Cambodia, a nationwide serosurvey in 2012 identified a large measles immunity gap in children younger than 15 years of age prompting a nationwide SIA for children 9 months to 14 years, while in Nepal a nationwide serosurvey following their 2012 SIA confirmed achievement of high coverage. In Thailand, a serosurvey of military recruits found that >20% were measles IgG negative, resulting in a recommendation to offer a supplementary measles vaccine dose to young adult males.

It is important to recognise that the logistic, financial, human and laboratory resources required to conduct serosurveys are formidable, and exacting quality assurance of all aspects of such surveys underpin the validity and reliability of results. These impositions were explicitly recognised during the *Joint Symposium on Closing Immunity Gaps in Older Children and Adults Towards Measles and Rubella Elimination* held in 2016, which concluded that the "cost effectiveness of conducting new serosurveys to specifically detect age-related immunity gaps in large populations is questionable and the technical resource requirements may overstretch national capacity to deliver results that can be accurately interpreted" [9]. To reduce cost measles serosurveys could leverage nationally-representative surveys in which blood is collected, including Demographic Health Surveys, malaria indicator surveys, or nationally-representative HIV prevalence surveys. Serosurveys can be targeted to specific subpopulations where there are concerns that vaccine coverage and case surveillance data may not accurately reflect population immunity. The sample sizes required to precisely identify pockets of lower coverage by geography, age-group or specific risk factor, and confirm that all important population subsets have evidence of 95% seroprotection can be remarkably daunting.

The importance of standardised protocols to ensure the validity, reliability and comparability of serosurveys cannot be overstated. Currently only the European Region has published guidance on conducting standardised serosurveys, although global guidelines are under development. Standardisation is necessary to mitigate the weaknesses inherent in all surveys, particularly bias.

Selection bias results from a non-random sample with portions of the target population excluded from the sampling frame. This is particularly common when using banked sera. Although banked sera offer an efficient option, results should be interpreted with care. Greater access to laboratory services for population groups more likely to be immunised will affect the generalisability of results. However, prospective community serosurveys are also vulnerable to selection bias unless meticulous care is taken in constructing the sampling frame, ensuring representative sampling, and then rigorously conducting the fieldwork. Non-response due to refusal or non-availability to participate is a potential source of bias if non-participants differ systematically from participants.

Information bias is an equally perplexing potential pitfall when systematic non-random measurement errors affect data collection or laboratory methods. The validity of laboratory methods deserves specific attention. In serosurveys, an important potential source of information bias is the sensitivity and specificity of the laboratory assay used. The gold

standard for measuring measles IgG antibodies are virus neutralization assays [10]. The plaque reduction neutralization test (PRNT) detects functional neutralizing antibodies to measles, thought to be a reliable correlate of protection against infection. However, commercially produced enzyme immunoassays (EIA) are more commonly used for serosurveys. Their sensitivity, specificity and performance characteristics vary vastly and this can seriously impact the interpretation of results and comparisons over time or between areas.

Another controversial topic requiring global guidance is appropriate management of equivocal EIA results. In most cases they are likely to reflect existing immunological memory but currently variable reporting practices can markedly impact population immunity understanding [11].

An emerging issue is the interpretation of waning measles IgG antibody levels over time in post-elimination countries where there is no wild virus exposure to boost immunity [12]. Whether this really reflects compromised immunity is an unresolved question, and there might be a need to reconsider current guidance on protective antibody cut-off levels in elimination settings [13]. It is potentially dangerous to compute effective reproduction numbers from these results to infer the adequacy of population immunity, as was recently done in Australia (R = 1.7 in 2012 based on serosurvey results). Fortunately there was concurrent compelling epidemiological evidence of high levels of population-level protection in 2012, varying from $Re = 0.31$ (0.09–0.94 based on the distribution of generations of spread) to 0.89 (based on distribution of outbreak sizes [0.08–0.96] and proportion of imported cases [0.84–0.93]), and validated high immunisation coverage over many years [14].

Serosurveys are not without risk. When they are underpowered or poorly representative, their findings may lead to potentially ill-founded policy recommendations [15]. This problem may be further compounded by modellers using serosurvey results and extrapolating them well beyond their original purpose. A parallel risk is that an over reliance on serosurveys could perpetuate the current inadequate investment in strengthening routine surveillance in many countries [16]. For example, serosurveys covering large populations (e.g., national studies) may fail to detect specific subpopulations with high susceptibility, which could lead to sustained measles transmission if the virus is introduced.

In comparison to serosurveys, measles outbreaks are precision tools for diagnosing the magnitude and demographic characteristics of measles immunity gaps [17]. However, they depend on virus importations to test population immunity and detect these immunity gaps. It is of interest that the Americas achieved measles elimination with a focus on high immunisation coverage, scrupulous surveillance and diligent outbreak analysis, with only a small proportion of countries ever conducting serosurveys.

There is a role for serosurveys, if they are properly applied, to support measles elimination by providing a richer understanding of population immunity gaps. The future availability of point-of-contact antibody assessment and multiplex assays could simplify and enhance their application. However, their cross-sectional nature, sources of bias, quality and selection

of sampling and laboratory methods, and the considerable resource implications must be explicitly considered before embarking on this venture. It is also imperative that serosurvey results are not considered in isolation but in concert with other surveillance and coverage data. Improving routine data quality and conducting excellent case investigation and epidemiological analysis when outbreaks occur are pivotal to avoiding misinformed serosurvey assessment.

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