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COMMENTARY

Measles vaccine immune escape: Should we be concerned?

Luojun Yang[1] · Bryan T. Grenfell[1,2] · Michael J. Mina[3,4]

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Introductions of measles containing vaccines, initially in the United States in 1963, the United Kingdom in 1968, and globally thereafter have caused measles cases to plunge worldwide over the past half-century [1]. By any metric, the measles vaccine is among the most successful public health interventions of modern times and is directly responsible for the near elimination of the virus in much of the world—an incredible achievement for a pathogen that only 50 years ago infected almost every child born. It is estimated that since the year 2000, the measles vaccine has prevented over 21 million deaths from acute measles virus infections globally [2]. Furthermore, new ecological and immunological evidence suggests that this number could be far greater—by preventing measles-associated long-term "immunological-amnesia" [3, 4]. However, despite the magnificent successes of the global measles vaccine program, including a declaration of measles elimination in the Americas that persisted through much of the 2000s [5, 6], millions of measles cases continue to occur each year, primarily in Africa, but increasingly in Europe, Asia, and the Americas. In the past year, four nations (UK, Brazil, Greece, and Venezuela) lost World Health Organization (WHO) measles elimination status and the United States is teetering on the brink of losing this status [7]. So far in 2019, worldwide reported measles cases have nearly tripled compared to the same point in 2018 and overall are the highest they have been since 2006. In the US, the number of cases is the highest it has been in over 25 years [7].

Measles has a basic reproductive number (R0) between 12 and 19, making it one of the most transmissible pathogens known to infect humans [1]. This extraordinary transmissibility means that the presence of measles outbreaks can serve, to a certain extent, as a 'canary in the coal mine' for the health of a nation's vaccine program. Once population immunity against measles dips below the herd immunity threshold of ~ 94% (1 − 1/R0), outbreaks of measles begin to present themselves [8]. Although there are multiple circulating strains of measles, the virus is considered to be serologically monotypic. Thus, when measles vaccines, which are comprised of a measles genotype A virus, are administered in the full two dose regimen, they are considered to provide life-long immunity to all circulating strains of the virus and, therefore, measles outbreaks are assumed to primarily reflect problems with vaccine coverage. In this issue of the European Journal of Epidemiology, Javelle and colleagues [9] review the existing literature underlying this assumption and argue that it may be time to re-evaluate whether the assumptions of a single serotype indeed remain valid. In discussing the rise of measles cases, particularly in regions with reportedly high vaccine coverage, the authors present a compelling case suggesting that the measles virus may be escaping immunity—a notion that, if confirmed, would have potentially far-reaching and important consequences for measles control and elimination efforts. The arguments put forth by the authors are provoking and while they lack a 'smoking-gun' may nevertheless warrant further consideration and perhaps at some point, as their title states, a need for a 'paradigm shift' in thinking regarding measles vaccine efforts.

A core assumption underlying much of measles vaccinology and epidemiology is that despite multiple circulating measles strains, the measles virus remains serologically monotypic and thus vaccination against a single strain represented in the vaccine is sufficient to protect against all strains. Thus, unlike influenza, for example, escape from vaccine derived immunity (vaccine escape) is not considered

✉ Michael J. Mina
mmina@hsph.harvard.edu

1 Department of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ, USA

2 Fogarty International Center, National Institutes of Health, Bethesda, MD, USA

3 Center for Communicable Disease Dynamics, Department of Epidemiology, Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, MA, USA

4 Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

to have a role in recent upticks in measles infections. However, Javelle et al. cite an accumulating number of measles cases occurring among individuals with recorded two-dose measles vaccination (secondary vaccine failures) and question whether measles truly remains serologically monotypic. Shorter half-life of vaccine-induced immunity compared with immunity acquired from natural infection, especially in the absence of natural boosting, is often accused of leading to these secondary vaccine failures. However, pointing at cases where pre-exposure neutralizing antibody titers to the vaccine strain were measured above the protective-threshold, the authors argue that genetic and antigenic drift away from the vaccine strain may also be at fault—causing decreased vaccine efficacy or even vaccine escape by certain strains [9].

Among the evidence supporting vaccine escape, the global rise of measles genotype B3 could indicate an increasing threat [9]. At least one report that evaluated neutralizing antibody titers among vaccinated individuals against 3 circulating measles strains, plus the vaccine strain, observed diminished neutralizing capacity for genotype B3 compared to circulating strains, D4 and H1, as well as the vaccine strain [10]. Although B3 is the dominant endemic strain on the African continent, elsewhere in the world B3 was relatively rare just 10 years ago. In recent years however, B3 has spread to all six WHO regions and continues to be associated with outbreaks in highly vaccinated populations [1]. In Europe, B3 is now a major genotype causing large epidemics and smaller outbreaks throughout the whole of the continent [11–14]. In the United States, B3 has caused numerous recent outbreaks, including the famous Disneyland outbreak in California in 2015 [15]. Similar patterns have been noted globally [16]. In California, in 2014–2015, among 30 measles cases where vaccination status was known, 10 cases occurred among fully vaccinated or serologically confirmed to be protected individuals [17]. It should of course be noted that the denominators differ dramatically—the vast majority of the population is vaccinated and thus 10 cases among the whole population still is a relatively small incidence. However, looking just at healthcare workers, where the denominator is much smaller than the general population, at least 9 healthcare personnel, 6 with known appropriate vaccination status or protective measles antibody levels, and 3 with unknown status, were symptomatically infected [17]. Six of these individuals had face-to-face contact with symptomatic individuals, but three did not know their exposure. Although the large fraction of unvaccinated individuals was surely the major driver of the epidemic, that there were considerable numbers of fully vaccinated and serologically considered to be protected individuals who became symptomatic is troubling.

In the Philippines, despite increasing vaccine coverage, large outbreaks of measles have increased substantially since 2014 [18]. Unlike in previous years where outbreaks have generally tracked with decreasing vaccine coverage, recent epidemics in the Philippines occurred in the presence of increasing vaccine coverage and this has also coincided with the introduction of B3 [18], raising the question of whether these two features might be related and whether immune escape could be a component.

Paralleling the rise of B3, another strain, D8, has also emerged globally and in 2018 the two strains together accounted for 95% of all of the sequenced measles strains reported globally [16]. A recent review of the Measles Nucleotide Surveillance (MeaNS) database [19] shows that between August 2018 and July 2019, the dominant strain across nearly all WHO regions with the exception of the Africa region was D8, with B3 the next most abundant. Thus, outside of Africa (as well as much of the Middle East, where B3 is now also dominant), D8 accomplished a near global sweep in the past year. Whether D8 will continue as the globally dominant strain remains unknown.

To our knowledge, no published literature has explored whether D8, like B3, might show reduced neutralizing titers following vaccination. In addition, the study that detected reduced neutralizing titers against B3 was in only a small subset of individuals [10]. The dearth of data is, at least in part because assessment of neutralizing antibody titers is not a formal component of measles surveillance. Indeed, it is rarely a component of any pathogen surveillance program, which is usually based on clinical or syndromic data, direct pathogen detection and sequencing, or serological surveys using assays that do not directly assess neutralization (i.e. ELISA and HAI).

Though B3 and D8 have emerged as the most abundant strains across the globe, the vast majority of cases remain among unvaccinated individuals. It remains unknown whether their emergence may attributed at all to immune escape or if it simply reflects global travel patterns in the context of increasingly insufficient vaccine coverage [20]. However, an analysis of 400 measles cases in California from 2000 to 2015, revealed that genotype B3 may have a significantly higher effective reproductive number than other genotypes that have caused recent outbreaks in the United States, including in vaccinated individuals [21], suggesting a difference at the virus level may be partially to blame. Whether immune protection has any role however remains an open question.

Current data is inconclusive about whether measles virus is escaping vaccine-induced immunity. One useful metric to evaluate would be to collect and report measles cases by both vaccination status and genotype. Trends in incidence of measles of a particular genotype among vaccinated individuals versus unvaccinated individuals would suggest genotype specific vaccine escape. Another essential epidemiological measure is the transmissibility of secondary infections in

previously immune individuals. In the worst-case scenario, if the effective reproductive number of an escaping virus is greater than one among a fully-vaccinated community, vaccine coverage data would become unreliable in predicting outbreak risk. Thus far, current evidence shows that secondary measles infections, when in vaccinated individuals, are usually more mild and cause few or no secondary cases [21, 22]. However, when interacting with pockets of unvaccinated individuals, even minimal vaccine escape could spark large outbreaks. In addition, depending on the mechanism, evolutionary theory predicts that vaccination may favor the emergence of more virulent strains, leading to more severe infections once spread to the under-vaccinated communities [23]. To combat future measles outbreaks, continuing molecular and serological surveillance of measles genetic evolution and population immunity at finer spatial resolutions is unarguably a necessity.

Although Javelle et al. suggest several strategic changes to address the emerging problem of measles vaccine failures, cost-effective evaluations of alternative policy rely on first untangling various drivers behind the problem. Whether waning immunity or vaccine escape is the major cause of rising vaccine failures determines whether incorporation of more booster doses into the vaccine schedule or development of a new vaccine, for example containing mixed strains, would be most effective. A convenient check on waning immunity is to look at vaccine effectiveness data grouped by time elapsed from vaccination, as has been used to trace recent mumps resurgence in the U.S. [24]. Contrary to what has been observed for mumps, our own unpublished analyses do not thus far support a decreasing trend in measles vaccine effectiveness following vaccination. A major technical gap in measuring measles immunity, however, is that the results of traditional immunological assays (i.e. ELISA and HI) do not necessarily translate well into actual protection, particularly strain specific protection [25]. New, higher resolution antibody detection systems that can detect antibodies to highly specific epitopes are becoming increasingly available [26] and present exciting potential to address this gap by quantifying with increased resolution strain-specific immunity and heterogeneity in vaccine responses.

Despite the apparent rise in secondary vaccine failures, vaccination remains the central component of any measles control and elimination program. Enhanced evaluations of the protective thresholds, both population-based and immunologic, will be instrumental in maintaining trajectories towards elimination. To date there remains no smoking gun that pins vaccine failures on immune escape. However, given that vaccine failures do occur, remaining vigilant and open to potentially new paradigms will be critical. If vaccine escape is at some point detected, especially given the immense ecological pressure that the virus currently faces, the knowledge that has been accrued over decades surrounding measles biology and transmission will undoubtedly place us in an efficient position to, if needed, develop new vaccines and approaches that continue crucial efforts towards global measles elimination.

Author contributions All authors contributing equally to this work.

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