


REVIEW

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## Measles vaccination in an increasingly immunized and developed world

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### ABSTRACT

Increased measles immunization has led to a significant decline in measles incidence and mortality. During 2016 it is estimated that fewer than 100,000 died from measles for the first time in recorded history. In highly immunized countries measles epidemiology has changed. Threats to national elimination goals and public health include aging cohorts of naïve people that exist from imperfect vaccination rates during the early years of immunization programs. This may be complemented by some loss of immunity in vaccinated populations. While childhood immunization must remain a focus for control efforts, due to higher mortality in the very young, these naïve adolescents and adults also accumulate as they age and add to the pool of susceptible people, perhaps beyond the view of those that are focused on childhood immunization. Here, features of measles epidemiology and control in highly immunized populations are reviewed, providing global data where necessary, to highlight why countries with high immunization coverage are still threatened by measles outbreaks and how changing dynamics may alter disease control.

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### Introduction

The measles virus is one of the most infectious pathogens known to man. In the pre-vaccination era measles infected more than 90% of children before they reached 15 years old, causing more than two million deaths.<sup>1</sup> In 2016 measles was estimated to infect fewer than 7 million people globally and kill less than 90,000 people, mostly children.<sup>2</sup> These deaths are entirely preventable through immunization. Immunization has caused the decline in measles in 2000 from 145 to 19 cases per million people in 2016. During the same period the estimated deaths declined correspondingly from 550,100 to 89,780, dropping below 100,000 deaths per annum for the first time since records began.<sup>2</sup> Measles immunization is estimated to have prevented 20.4 million deaths in this 16-year period.

Due to changing human demographics, increasing immunization and declining incidence, measles epidemiology is changing.<sup>2,3</sup> Globally, indicators of human development are increasing.<sup>4</sup> As human development index (HDI) scores increase, so is a country's likelihood of increasing the childhood single dose measles-containing vaccine (MCV1) coverage (Figure 1). This transition, however, is yet to fully manifest itself in concomitant declines in measles cases and incidences (Figure 1). The rest of this review looks at aspects of why that may be, using most recent or complete data from a range of sources.

### Measles virus and its clinical disease

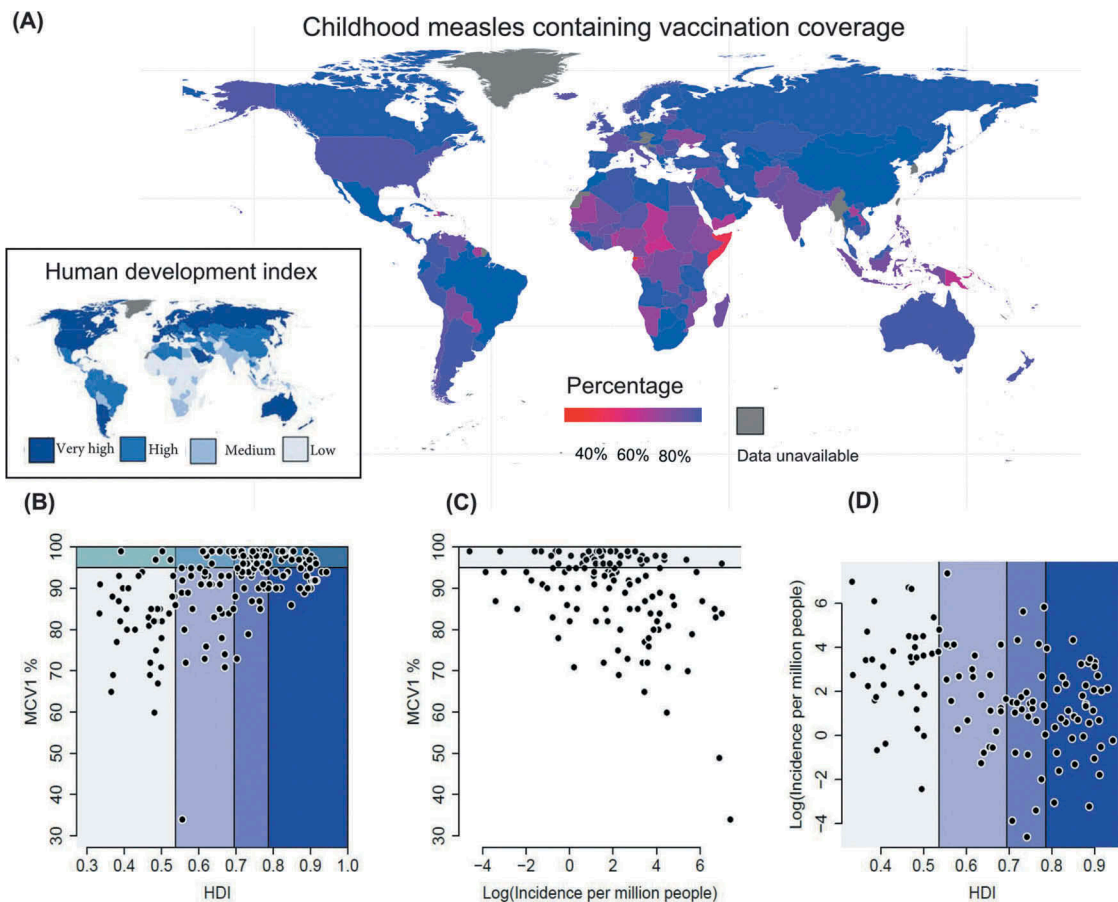
Measles virus is a single-stranded, negative-sense, enveloped RNA *Morbillivirus* in the family *Paramyxoviridae*

and is spread through a range of mechanisms, from airborne droplets to direct contact.<sup>5,6</sup> Symptoms typically start 10 to 12 days after exposure to the virus, however, crucially for disease transmission and control, people may be infectious up to four days before the start of the classical rash.<sup>6</sup> Initial clinical signs include fever, coughing, nasal discharge, and inflamed eyes. Small white spots form inside the mouth, followed by a rash on the face and body from two through to five days after the start of symptoms.<sup>1</sup> Overall symptoms typically last seven to ten days and following recovery most people are immune for life.<sup>6</sup> Complications, ranging from pneumonia, blindness, and meningitis, occur in approximately a third of cases. Measles can cause mental retardation as well as a fatal progressive neurologic disorder, subacute sclerosing panencephalitis. These complications are the reason measles kills and why mortality has declined with increased global measles immunization.<sup>1,6</sup>

### Global eradication efforts

The World Health Assembly (WHA) aimed to facilitate global measles *eradication* (zero cases worldwide) through achieving  $\geq 90\%$  national level and  $\geq 80\%$  district level MCV1 administration among children aged 1 year. This would effectively reduce global annual measles incidence to  $< 5$  cases per million and global mortality by 95% from the 2000 estimate. These targets were missed, with  $> 19$  cases per million estimated in 2016 and an 84% decline in mortality.<sup>2</sup>

Global eradication is facilitated through regional *elimination*. Measles elimination is defined as “the absence of



**Figure 1.** The relationship between human development index, vaccination and measles. A: a map of global single measles-containing vaccine (MCV1) coverage in children with the global human development index (HDI) shown (inset). The relationship between B: national childhood MCV1% and HDI, C: MCV1% and measles incidence, and D: measles incidence and HDI. Data are from WHO and UNDP for 195 countries in 2012 (most complete data). HDI colors (A, inset map) are the same in A-D.

endemic measles virus transmission in a region or other defined geographic area for  $\geq 12$  months, in the presence of a high quality surveillance system that meets targets of key performance indicators".<sup>2</sup> The Global Vaccine Action Plan aimed to eliminate measles in four of six World Health Organization (WHO) regions by 2015 and five by 2020, with all countries aiming for measles elimination by or before 2020. Dabbagh, et al.<sup>2</sup> and Orenstein, et al.<sup>7</sup> recently reviewed the progress towards these targets. Among the WHO regions, only the Region of the Americas (AMR) has eliminated measles. The AMR was verified free of endemic measles in September 2016.<sup>8</sup> This elimination was achieved through control programs established in the early 1990s, often coordinated through the Pan American Health Organization (PAHO), and comprised high routine vaccine coverage and mass campaigns along with case-based surveillance.<sup>9</sup> By 2017 countries verified endemic measles free comprised 24 in the European Region (EUR), six in the Western Pacific Region (WPR), and two in the South-East Asia Region (SEAR). However, with the exception of the Western Pacific Region (WPR) no region has sustained MCV1 coverage  $> 95\%$  since 2008.<sup>2</sup> For those countries in which endemic measles is eliminated, high population immunization coverage and surveillance are essential, because introductions can cause significant outbreaks.<sup>10-13</sup>

The reintroduction and establishment of endemic measles in Mongolia following elimination is evidence of the real risk to countries.<sup>14</sup>

### Immunization and population immunity

Two statistics are important for immunization and population immunity, when considering measles endemicity. The first is the proportion of a population that is immune, with a target of 95% set by WHO, because of measles' high infectivity.<sup>1</sup> The other is the absolute number of naïve people, as measles has a critical community size that allows population level persistence due to its immunizing infection.<sup>15</sup>

Global MCV1 coverage reached 85% in 2009, but has remained around this proportion. In 2016 the African Region (AFR, 72%) and Eastern Mediterranean Region (EMR, 77%) regions had the lowest coverage, followed by the SEAR (87%), AMR (92%), EUR (93%) and WPR ( $> 95\%$ ).<sup>2</sup> In the EUR MCV1 coverage was greater in 2012 (95%) than 2016 and district-level declines have occurred in highly immunized ( $> 90\%$  MCV1) countries.<sup>2,12</sup>

Globally, coverage with a second measles containing vaccine (MCV2) reached 64% in 2016, substantially up from 15% in 2000.<sup>2</sup> MCV2 may be crucial to induce and maintain

immunity, as a range of factors can affect vaccine efficacy and people receiving both MCV doses are less often reported as cases.<sup>11</sup> In China a third MCV dose is given, with eight-month, 18 month and 6 year-old children the target age classes for vaccination. A similar strategy was used in Japan from 2008 for five years, with high school children receiving a third MCV.<sup>13</sup>

Measles immunization strategies that vaccinate only the very young (< 1 year-old) are not efficient.<sup>11,16,17</sup> Mathematical models have suggested vaccination coverage as low as 85% of children aged 1 to 7 years at five-yearly intervals is sufficient in Israel, but the majority of studies in Europe suggest a minimum of 87% coverage is essential to prevent endemic measles circulation and most estimates are higher than 90%.<sup>18–21</sup> In New Zealand it was estimated that approximately 92% immunity was required.<sup>22</sup> In Japan immunity levels have been measured up to 92%, but age-structure estimates have suggested herd immunity may be above 80% but lower than the 90 to 95% required to prevent ongoing transmission.<sup>23,24</sup>

Even within regions with high immunization coverage naïve populations may exceed the critical community size for measles, estimated at 250,000 to 500,000, allowing the virus to persist at the population level.<sup>15,25–27</sup> Dabbagh, et al.<sup>2</sup> estimated globally 20.8 million infants did not receive MCV1 in 2016.<sup>2</sup> The majority of those (53%) are in countries with lower than 95% MCV1 immunization rates and large birth cohorts. In addition, evidence of some vaccine ‘failure’, waning immunity and pockets of susceptible populations suggest that relying on minimum percentages to be vaccinated alone may leave areas, cohorts, or communities susceptible to outbreaks in countries with highly immunized populations.<sup>11,28,29</sup> Here, spatial and contact structure will play key roles in determining measles epidemiology (see below).<sup>30–31</sup>

Trentini and colleagues estimated residual susceptibility to measles ranges from 3% in the UK to more than 10% in Kenya and Ethiopia.<sup>32</sup> They estimated that in high-income, well immunized countries (> 90% MCV1), such as Italy, Singapore, and South Korea, only approximately 20% of susceptible individuals are < 5 years old.<sup>5</sup> This change is partly due to reduced fertility and the authors estimated that that change alone “contributed to almost half of the reduction in measles incidence” in those countries through a reduction in naïve young populations. This is similar to recent estimates from New Zealand,<sup>11,22</sup> Europe,<sup>33</sup> and China, where the age distribution of measles cases has changed in response to both demographic and vaccination processes.<sup>3</sup>

A major cause of many susceptible people in an immunized population is due to the transition period. When most countries establish immunization programs, there is a transition period from the introduction of MCV to high childhood immunization levels. This transition period leads to cohorts of youths and young adults with lower immunity than their parents, who gained immunity through natural infection when young, and the very young children in which high MCV1 immunization rates have been reached. These cohorts with lower immunity track through time to increase the proportion of susceptible adults. Reduced population immunity due to waning vaccine immunity may further increase the

numbers of older people with lower immunity (see below). Interestingly, the transition period is often longer in countries with longer histories of MCV usage, such as New Zealand.<sup>11</sup> This should be less important in countries that have rapidly transitioned from low to high immunization, because the transition from natural infection to vaccine induced immunity does not allow for such cohorts to exist.

## Disease incidence and transmission in highly immunized populations

In 2016 the reported measles cases numbered 132,137, which corresponds to an estimated reduction to 19 cases per million people globally. In the AMR the estimated measles incidence was less than five cases per million. In highly immunized countries where endemic measles is eliminated, outbreaks are initiated by measles importations.<sup>13,34–36</sup> In the USA from 2009 to 2014, 275 importations from 58 countries caused 66 outbreaks totaling > 1264 cases. These were larger figures than the previous 7 years,<sup>34</sup> and a similar pattern is observed in other countries, such as New Zealand,<sup>11</sup> Japan,<sup>13,35,36</sup> and China.<sup>25</sup> In 2017, the European Union (EU) experienced a resurgence of measles with several outbreaks and 37 fatalities.<sup>33</sup> Twenty-eight EU countries reported 14,600 measles cases, equivalent to 28.3 cases per million people, with Romania (5,608), Italy (5,098), Greece (967) and Germany (929) reporting the greatest numbers.

Gastañaduy and colleagues estimated the reproduction number, the average number of secondary cases per infection,  $R$ , to assess the transmissibility of measles in the USA from 2001 to 2014.<sup>37</sup> Measles elimination requires  $R$  at < 1. The authors used four approaches, each suggested  $R$  was well below 1 (range 0.72 to 0.45, with no 95% confidence interval (CI) > 1). However, they noted year-to-year variability in the values of  $R$  and an increase in transmissibility in recent years. These reflect recent estimates from other highly immunized countries. In New Zealand, after years of very low incidence, analyses suggest that measles  $R$  often includes or exceeds one (0.18 to 3.92) despite high levels of population immunity. Similarly,  $R$  has been estimated as high as 9 (2 to 151 95% CI) in Japan from outbreaks and 1.5 to 3 from serological analyses.<sup>24,35</sup>

The age distribution of New Zealand measles cases reflected the age distribution of naïve individuals, with increased case age in more recent years.<sup>11</sup> A similar increase in case age may be seen in other countries such as China,<sup>3,25,38,39</sup> and may be occurring in an ongoing outbreak in Japan.<sup>40</sup> In Japan there has been a pronounced shift in ages affected, with the majority of cases (range 50 to 100%) in each of five years experiencing measles outbreaks since 2011 being in > 20 year-old people.<sup>36</sup> In EU countries children under five comprised 37% of all 14,600 cases in 2017 and had the highest incidences (366 and 164 cases per million population in < 1 year and 1–4 year-olds respectively).<sup>33</sup> However, adults  $\geq$  20 years old were 38% of cases in 2017. The majority of cases were unvaccinated, ranging from 72% in 25–29 year-olds, to 96% in < 1 year-old children too young to receive the vaccination.<sup>33</sup>

Australia has an established measles serosurveillance program.<sup>41</sup> The measles-specific IgG seroprevalence and R were estimated for 2012 to 2013, and compared with previous serosurveys (1996 to 1999, 2002 and 2007). Seronegative and equivocal sero-status individuals in age groups increased through time for all ages groups, from 2 to 39 years old.<sup>41</sup> Like the New Zealand situation, in Australia R has increased from 0.57 in 1999 to 1.7 in 2012 to 2013.<sup>41</sup> Increases in R in highly immunized populations may reflect a series of issues, including spatial heterogeneity in population immunity,<sup>29</sup> but studies also suggest vaccine induced measles-specific IgG antibodies decline with time since vaccination and maternally-derived immunity may wane faster if vaccine derived.<sup>41-44</sup> Vaccinated people may be susceptible to measles for a range of reasons, including maternally-derived antibody interference, infection before an immune response has been developed, and poor vaccine storage and handling affecting vaccine efficacy,<sup>45-47</sup> but waning immunity may increasingly play a role.<sup>41</sup> This poses numerous questions and requires further study, and yet supports the case for sustaining a highly immunized population.<sup>42</sup>

### Disease and mortality in highly immunized populations

Measles deaths declined globally from 550,100 (95% CI = 374,000 to 896,500) in 2000 to 89,780 (95% CI = 45,700 to 269,600) in 2016.<sup>2</sup> Vaccination is estimated to have prevented approximately 20.4 million deaths from 2000 to 2016.<sup>2</sup> Deaths in developed countries are less common than in developing countries. In 2017, 37 measles deaths were reported by eight European countries, comprising 26 in Romania, four in Italy, two in Greece, and one each in Bulgaria, France, Germany, Portugal and Spain.<sup>33</sup> Recent examples of deaths include a fatal case in Italy, during a measles outbreak that started in early January 2017 causing 2,851 cases, of which 73% were greater than 15 years old. Most of the cases (89%) were unvaccinated and 6% received just one dose. Complications were reported in 35% of patients and one 9 year-old patient died.<sup>10</sup> In Romania, a large outbreak is ongoing, with 55 deaths reported from over 13,700 since the epidemic began in 2016,<sup>48</sup> despite previous efforts to improve vaccination rates, which have led to high (e.g. 94% in 2014) childhood immunization levels.<sup>49,50</sup>

### Measles cost estimates in highly immunized populations

In developing countries, the cost to society from measles (e.g. through disability-adjusted life years, DALYs) is largely due to premature deaths. However, in highly immunized and developed nations the economic impact of cases is still high. The containment of a single case of measles in Iowa, USA, was estimated to cost > US\$142,000 in 2004.<sup>51</sup> Sixteen outbreaks in the USA in 2011 involving a total of 107 people, lasting an average of 22 days, required between

42,600 and 83,100 personnel hours, at a cost of between US \$2.7 and US\$5.3 million.<sup>52</sup> Significant effort was spent on 8,900 to 17,500 contacts, each requiring 4.7 personnel hours at a cost of US\$298 per contact.<sup>52</sup> Recent analyses of the public health and economic consequences of reduced vaccination in the USA suggest a 5% decline in MCV coverage would lead to an estimated 3-fold increase in measles cases for children aged 2 to 11 years and an additional US\$2.1 million in costs per annum.<sup>53</sup>

In New Zealand the cost of 187 confirmed and probable measles cases in 2014 was estimated to be > US\$864,000 due to earnings lost, case management and hospitalization costs.<sup>22</sup> In China, a measles outbreak among office workers led to a total of 7,930 contacts being identified, with household costs estimated at US\$605 per case and control costs of US\$17,481 per case.<sup>38</sup> Mental retardation cases and deaths were not reported among the cases in New Zealand or China, but such tragic cases would significantly increase the direct and societal costs.

### Supplementary immunization activities

In lower income countries with typically high fertility, susceptible individuals are very young, for example, in Ethiopia ~ 60% susceptible were < 10 years old.<sup>32</sup> These can often be the target of supplementary immunization activities (SIAs) and Dabbagh, et al.<sup>2</sup> reported approximately 119 million people received supplementary MCV in 2016. These SIAs were undertaken during 33 mass immunization campaigns in 31 countries, including Ethiopia.<sup>2</sup> The coverage was high ( $\geq 95\%$  in 20 SIAs) and in these countries SIAs were responsible for more than 25% of immunized individuals, including ~ 45% in Ethiopia.<sup>32</sup>

The necessity of SIAs in highly immunized populations may be questioned (Figure 1). In Beijing, China, since 2006 migrant college students have been required to have MCV administered, presumably because of cohorts of poorly immunized young adults.<sup>3,25</sup> As discussed above, altered age structure of measles cases in high income/immunization coverage countries is now likely reflecting changing distributions of naïve people in the populations. This feature, and possible waning vaccine induced immunity, suggests SIAs may be required for older cohorts even when childhood immunization rates are high.<sup>3,6,11,12,22,30,32,35,54</sup> In Japan higher vaccination coverage is estimated to have decreased natural immunity boosting through declining incidence and reduced measles exposure, leading to higher case numbers in 20 to 29- and 30 to 39-year-old age groups and suggestions that immunization of “these age groups might be important for eliminating imported viruses”.<sup>44</sup>

The societal return on investment suggests measles vaccination programs are hugely beneficial financially.<sup>16,55,56</sup> In highly immunized countries SIAs can still be beneficial. Estimates from the Republic of Korea and New Zealand suggest SIAs are cost effective with benefit-cost ratio of between 1.03 and 1.27 in Korea,<sup>57</sup> and must cost more than US\$66 (and potentially up to US\$1877) per immunized person in New Zealand before the financial costs outweigh the benefits.<sup>22</sup>

## Discussion

Globally MCV1 coverage of children has plateaued, despite improvements in human development. Aging cohorts of naïve people often exist as imperfect immunization programs take time to implement.<sup>22,24</sup> These older naïve populations may have different disease outcomes to younger cases and may pose different case management issues than the very young. Complemented by some loss of vaccine-derived immunity, these older cohorts may increasingly contribute to the local, national and international transmission of measles, threatening regional elimination and global eradication efforts.<sup>11,25,58,59</sup> Cost-benefit analyses are required to determine the economic and societal benefits of SIAs among older cohorts. Future studies must continue to monitor changing seroprevalence of measles antibodies in aging and highly immunized populations,<sup>23,41</sup> and control efforts may need to be consider including older cohort SIAs,<sup>44</sup> in addition to maintaining high child immunization rates if global measles eradication is to be achieved.

## Disclosure of potential conflicts of interest

No potential conflict of interest was reported by the author.

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