



Review

Measles – The epidemiology of elimination

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ABSTRACT

Tremendous progress has been made globally to reduce the contribution of measles to the burden of childhood deaths and measles cases have dramatically decreased with increased two dose measles-containing vaccine coverage. As a result the Global Vaccine Action Plan, endorsed by the World Health Assembly, has targeted measles elimination in at least five of the six World Health Organisation Regions by 2020. This is an ambitious goal, since measles control requires the highest immunisation coverage of any vaccine preventable disease, which means that the health system must be able to reach every community. Further, while measles remains endemic in any country, importations will result in local transmission and outbreaks in countries and Regions that have interrupted local endemic measles circulation.

One of the lines of evidence that countries and Regions must address to confirm measles elimination is a detailed description of measles epidemiology over an extended period. This information is incredibly valuable as predictable epidemiological patterns emerge as measles elimination is approached and achieved. These critical features, including the source, size and duration of outbreaks, the seasonality and age-distribution of cases, genotyping pointers and effective reproduction rate estimates, are discussed with illustrative examples from the Region of the Americas, which eliminated measles in 2002, and the Western Pacific Region, which has established a Regional Verification Commission to review progress towards elimination in all member countries.

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1. Background

Global measles control has been very successful. Estimated deaths fell by 74% from 535,300 in 2000 to 139,300 in 2010 [1]. Indeed reductions in measles mortality accounted for 23% of the estimated decline in all-cause child mortality in children under 5 years of age from 1990 to 2008 [2].

The initial strategy of a measles immunisation program is measles control; once this is achieved the focus shifts to outbreak prevention, elimination and finally eradication. In 2010, an expert advisory committee was convened by the World Health Organization (WHO) to assess the feasibility of measles eradication. The panel determined that eradication was indeed biologically, technically and operationally feasible; and concluded that measles can

and should be eradicated using activities to strengthen routine immunisation services [3–5].

2. The goal of measles elimination

The WHO Global Vaccine Action Plan for 2012–2020 has established the target of measles and rubella elimination in at least five WHO Regions by 2020 and Member States in all six Regions have established goals to eliminate measles by 2020 or before [6]. Elimination is defined as “the absence of endemic measles transmission in a defined geographical area, in this case all countries in a WHO Region, for ≥ 12 months in the presence of a well-performing surveillance system” [7]. To verify that elimination has been achieved three essential criteria must be met: the interruption of endemic measles virus transmission for a period of at least 36 months from the last known endemic case; in the presence of a high-quality surveillance system that is sensitive and specific enough to detect imported and import-related cases; and genotyping evidence should support interruption. Detailed evidence across five

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domains must be presented to substantiate an individual country or Region's claim of having interrupted endemic measles transmission: a detailed description of measles epidemiology over an extended period; indicators of the quality of epidemiological and laboratory surveillance; measures of population immunity by birth cohort; laboratory evidence of absence of an endemic genotype; and confirmation of immunisation programme sustainability.

The elimination of endemic measles transmission was achieved in the Region of the Americas in 2002 and sustained for more than a decade despite ongoing incursions of virus from other parts of the world [8]. This remarkable achievement has led to many lessons learnt and given impetus to achieving elimination in other Regions. The Region of the Americas was the first region to eliminate polio, and is now leading the way with measles. The experience has also highlighted the ongoing challenges involved in sustaining elimination – measles anywhere is a problem everywhere. By May 2014 the USA had experienced more cases of measles than in any whole year since elimination was achieved, linked to importations and subsequent outbreaks [9]. Brazil and Canada have also experienced large outbreaks this year [10].

An independent International Expert Committee (IEC) was established by the Pan American Health Organization in 2010 with the purpose of documenting the elimination of measles, rubella and congenital rubella syndrome in the Region of the Americas, and has not yet reported its conclusions. During the period of the IEC deliberations, several measles outbreaks occurred that were brought under control. In 2011 Canada experienced the largest outbreak of measles the Region had seen since elimination. This was linked to multiple importations into Quebec from a large outbreak in France but brought under control within 12 months, so that endemic transmission was not re-established [11]. The experience of this and several other outbreaks have underlined the importance of not only having elimination-level coverage of greater than 95% to ensure population immunity levels reach 95%, but also of ensuring the quality of coverage data at every administrative level. Outbreaks in marginalised communities, including Aboriginal peoples, have demonstrated the necessity of reaching every community [12,13]. The Caribbean has successfully protected its population from measles and sustained elimination despite receiving large numbers of tourists, many coming from other Regions where measles is not controlled. Haiti, for example, demonstrates how determination and political will enabled elimination to be achieved in the face of multiple major challenges including recurrent natural disasters [14].

In the Western Pacific region, encouraging progress was made in recent years with coverage of one dose of measles-containing vaccine increasing from 85% in 2000 to 97% within a decade and reported second routine dose coverage reaching 91% [15]. The largest supplementary immunisation activity in history was conducted in China in 2010, with over 103 million children vaccinated. The results of these activities were reflected in a 91% reduction in reported measles cases between 2000 and 2011, and an estimated 84% reduction in deaths between 2000 and 2012 [16]. However, the Western Pacific is experiencing an increase in measles incidence which started in 2013 and has continued through mid-2014 with ongoing outbreaks in China, The Philippines, Vietnam and Papua New Guinea [17].

As the Americas and Western Pacific have achieved and sustained or made progress towards measles elimination, distinctive common epidemiological patterns have emerged across remarkably diverse populations confirming theoretical predictions. These shared features, which appear synonymous with elimination, provide a template that individual countries striving towards elimination can apply to judge their own progress.

3. Incidence rates may be misleading

Although the absence of locally acquired measles cases within a country with sensitive surveillance is a wonderful aspiration, this is generally only achieved by countries that are isolated or remote and having few international travel movements to and from measles-endemic countries. Mongolia and many remote island countries in the Western Pacific have enjoyed this experience for a number of years [18]. However, while measles is endemic anywhere in the world and the current scale of international travel is maintained, the integrity of most countries' population immunity will be regularly tested by importation of measles virus in non-immune residents returning from endemic areas or infectious visitors from endemic areas. An indicative incidence rate was nominated by the WHO as a milestone towards achieving elimination. This was set at less than one laboratory or epidemiologically confirmed measles case per million population annually; excluding imported cases [19]. However, once a country succeeds in eliminating measles, this indicator is no longer helpful. For countries with relatively large numbers of visitors and local international travellers compared to their population denominator, for example Australia and countries of the Caribbean, despite interrupting endemic measles transmission this indicator may still be regularly exceeded because of multiple short chains of local transmission following importations [20]. In that situation, the classification of cases as imported or import-related (for onward transmission) is the key to documenting that elimination is being sustained. If chains of transmission extend beyond 12 months, then measles is by definition no longer eliminated.

4. Sleuthing the source of infection

Of much greater value than incidence is the early detection and careful categorisation of all measles cases by their source of infection; "imported", "import-related", "endemic" or "unknown" [19,21]. Ideally 80% or more of all confirmed measles cases should be "imported" or "import-related". In the Western Pacific, this was achieved by the three countries with measles activity that were recently verified as having interrupted endemic measles transmission; Australia, Macao (Special Administrative Region of China), and the Republic of Korea. The fourth country Mongolia had experienced no measles cases for a four year period and had consistently detected and investigated an adequate number of rash and fever cases to exclude measles. This vouched for the sensitivity of their surveillance.

The ability to categorise measles source for the majority of cases reflects the thoroughness and timeliness of epidemiological investigation, including the submission of appropriate specimens to permit laboratory confirmation of cases, while simultaneously revealing the integrity of herd immunity. Where a large proportion of cases are of "unknown" origin it is challenging to confirm that ongoing local transmission is not occurring. All "unknown" source cases need to be carefully analysed temporally and spatially at local level in an attempt to rule out ongoing chains of transmission [22]. This cluster mapping should assess possible overlapping infectious and incubation periods of subsequent detected cases. In these instances genotyping of unknown source cases can assist in distinguishing the likely origin/s of virus.

5. Epidemic curves – barometers of progress towards elimination at every level

Epidemic curves are most commonly used to understand the evolution and magnitude of a particular outbreak, while

monitoring the success of any control measures implemented. They have an additional important utility. Applying this epidemiological tool at various resolutions (sub-national, national and Regional) over multiple years following the introduction of measles containing vaccine provides useful complementary evidence of progress towards elimination [23]. In highly endemic situations large measles epidemics occur in cycles with a 1–4 year periodicity and with a defined seasonal pattern even in inter-epidemic years. As higher uniform population immunity is achieved the scale of epidemics, both their duration and absolute number of cases, progressively decreases. Epidemic frequency simultaneously decreases with increasing time intervals between epidemics. Another uniform feature as elimination is approached is the loss of epidemic seasonality.

6. The canary in the coalmine

As will be seen in the discussion of reproduction numbers below, measles is incredibly infectious. This transmissibility of measles allows immunity gaps to be revealed; measles serving as the sensitive “canary in the coalmine” detecting deficiencies in vaccination coverage, pockets of susceptible individuals, vaccine refusers or marginalised groups, and causing multiple generations of infection where coverage is inadequate.

Measles outbreaks are our instructor; if they are carefully analysed by the demographic characteristics of those affected, including their location, age group, social, cultural, religious and ethnic features, they reveal population pockets or age cohorts vulnerable to measles because of inadequate immunity. Outbreaks can pinpoint communities with geographical or shared socio-cultural features that are consistently missing out on the benefits of measles vaccine. This may be the result of health service failure to provide equitable access to child health programmes or resistance against immunisation by defined groups. Both Canada and Australia have seen examples of religious groups with inadequate vaccination coverage serving as the launch pad for international measles transmission [9,24–26].

Where measles epidemiology points to broader community immunity gaps by age cohort or locality, this knowledge may be supplemented or confirmed by conducting serological surveys of measles immunity and then applied to creatively fill diagnosed immunity gap/s. A good example comes from the recent experience of Japan. After a large outbreak in 2007 and 2008 particularly affecting teenagers, a catch-up measles vaccination program was introduced in two school years, the first year of junior high school (12–13 years) and the third year of high school (17–18 years) from 2008 to 2012 [27]. This effectively plugged the immunity gap revealed by the outbreak and confirmed serologically.

The nature of outbreaks can also highlight health service deficiencies permitting the spread of measles amongst vulnerable non-immune groups. This was a particular feature of recent outbreaks in a number of countries that have interrupted endemic measles transmission, including the Republic of Korea, Australia and the USA [28–30]. A common feature of these outbreaks was measles predominantly occurring in young children, most too young to be immunised or only having received a single measles vaccine dose, with nosocomial spread due to deficiencies in infection control. In all cases measures were taken to strengthen triage and isolation practices, and promote the vaccination of health care staff. Compared with polio, elimination of measles relies more heavily on strong routine services both because of the requirement to reach all communities with such high coverage, and because the vaccine is delivered by injection.

7. Estimating R_0 and R_e

A valuable epidemiological measure of an infectious agent's transmissibility is its basic reproduction number (R_0) – the average number of secondary cases generated by a primary case in a completely susceptible population. Measles is the most infectious communicable disease known with a R_0 of 12–18 [31,32]. This infectiousness poses a massive challenge to elimination as in most settings 95% or more of the population will need to be immune to ensure adequate herd immunity to prevent or contain outbreaks following introduction of virus, and allowing for vaccine effectiveness of 90%, coverage needs to be even higher. Herd immunity can be thought of as a threshold level of immunity in the population above which measles no longer spreads, mathematically calculated from R_0 .

As has been discussed, individual outbreaks are enormously informative but the collective wisdom gained from an analysis of the distribution of outbreak sizes and their duration (or generations of infection resulting from each imported case) can provide a further measure of the robustness of elimination and the effective reproduction number, R_e , which is the actual average number of secondary cases that result from an infectious case in a particular population. R_e depends on the level of susceptibility in the population, in contrast to the basic reproduction number (R_0), which is the average number of secondary cases arising from one infectious case in a totally susceptible population [33]. Well established methods exist to estimate R_e from outbreak data and these have been applied in the United States, Canada and Australia [34–36]. During the elimination scenario, where the proportion of susceptibles is sufficiently low that sustained transmission is not possible, the vast majority of outbreaks are small in size (single digit number of secondary cases) and there are on average few generations of spread, with R_e sustained well below the epidemic threshold of 1.

These methods can be utilised over time to monitor trends and can also be applied to birth cohorts and at subnational level, with adequate confidence levels, to explore for heterogeneity of risk [35]. Sero-surveys may also provide useful data to provide estimates of R_e and signal the risk of impending outbreaks [37].

8. Elimination paradoxes

It is often disconcerting for public health programmes when the majority of measles cases occur in children too young to have received one or two doses of measles containing vaccine. It is important to note that this generally represents a relative increase in cases in this age-group and not an absolute increase. The immediate temptation is to shift the lower recommended age for vaccination to young infants. Although it may be necessary in specific situations, for example large outbreaks, to provide a supplementary dose of vaccine at 6 months of age this should not replace the dose provided from 8 to 12 months of age, as sero-conversion and protection is significantly lower during younger infancy due to maternal antibody interference with the child's immune response to the vaccine [38].

Similarly measles incidence may increase in older age groups in absolute or relative terms, typically amongst adults or teenagers who may have been part of the first birth cohorts to receive measles containing vaccine. Generally programme coverage builds over time and many programmes initiated measles vaccination with only a single dose. Thus it is not surprising that there is often an increased proportion of susceptibles in these age cohorts and a relatively higher burden of infection amongst these individuals during community outbreaks in areas approaching or having achieved measles elimination.

A further conundrum is worth brief mention. IgM serology remains as the backbone of measles laboratory confirmation in most countries. Although these tests, performed in WHO approved laboratories, are generally excellent for programme purposes, like any test they are not 100% specific. In low prevalence elimination environments IgM serology will have a low positive predictive value, i.e. a considerable proportion of tests will provide false positive results. Indeed, if no measles cases are occurring, then all positive test results are expected to be false positives. Other diagnostic tests particularly immunofluorescence, which may be used in the early phases of disease, is particularly prone to high false positivity. Guidelines have been developed to assist in the interpretation of results in these settings but it is particularly important not to view laboratory results in isolation from the clinical presentation, travel history and careful description of contact with possible cases [39].

9. Conclusions

Measles' transmission dynamics, particularly its infectiousness, and distinctive clinical picture result in predictable epidemiological patterns as elimination is approached. There is no single indicator of elimination. Careful analysis of the: source, size and duration of outbreaks; genotyping, temporality and geography of "unknown source" cases; seasonality and age-distribution of cases; and effective reproduction rate provide a good indication of progress or achievement of interruption of endemic transmission and the integrity of population immunity. High quality coverage data are essential, at sub-national, district and even community levels, to guide decision-making. Clearly the quality of epidemiological data is dependent on the quality of surveillance and specifically the early investigation and confirmation of suspected measles cases [40].

While the epidemiology may be elegant it is critical that the understandings extracted are applied for "action". This is particularly pertinent as measles is often not only a "canary in the coalmine" for measles immunity gaps but more broadly reflects on deficits in child health programme access or health service delivery.

The elimination of measles brings additional benefits through strengthening health systems and better delivery of other vaccines including rubella. Measles will tell us quickly if we are off track, direct our efforts towards elimination and confirm our arrival if we allow its epidemiology to be our teacher.

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