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Measles, immune suppression and vaccination: direct and indirect nonspecific vaccine benefits

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Summary The measles virus is among the most transmissible viruses known to infect humans. Prior to measles vaccination programs, measles infected over 95% of all children and was responsible for over 4 million deaths each year. Measles vaccination programs have been among the greatest public health achievements reducing, eliminating endemic measles in the whole of the Americas and across much of the globe. Where measles vaccines are introduced, unexpectedly large reductions in all-cause childhood mortality have been observed. These gains appear to derive in part from direct heterologous benefits of measles vaccines that enhance innate and adaptive immune responses. Additionally, by preventing measles infections, vaccination prevents measles-associated short- and long-term immunomodulating effects. Before vaccination, these invisible hallmarks of measles infections increased vulnerability to non-measles infections in nearly all children for weeks, months, or years following acute infections. By depleting measles incidence, vaccination has had important indirect benefits to reduce non-measles mortality. Delineating the relative importance of these two modes of survival benefits following measles vaccine introduction is of critical public health importance. While both support continued unwavering global commitments to measles vaccination programs until measles eradication is complete, direct heterologous benefits of measles vaccination further support continued commitment to measles vaccination programs indefinitely. We discuss what is known about direct and indirect nonspecific measles vaccine benefits, and their implications for continued measles vaccination programs.

Introduction

The measles virus is one of the most transmissible pathogens known to infect humans and, as the etiologic agent responsible for measles infections, among the worst offenders of childhood mortality.[1] The virus, a negative stranded *Morbillivirus*, in the family *Paramyxoviridae*, is transmitted within aerosolized droplets via the respiratory route, allowing for efficient transmission.[1–3] The basic reproductive number (R_0) for the virus (i.e. the number of

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secondary infections expected from an index case within a susceptible population) is estimated between 14–18, but this number can increase substantially under appropriate conditions.[4] Its high transmissibility results in explosive epidemics that deplete the susceptible population, and thus persistence of the virus requires large populations sizes, generally over 200,000 to maintain person-to-person transmission.[5,6] Prior to measles vaccination programs (MVP), infection with the measles virus was a near certainty, infecting 95–98% of children, with millions of deaths globally each year.[7,8] Vaccine programs have dramatically reduced the burden of measles across the globe, slashing measles incidence and associated mortality to mere fractions of their historical baselines. Additionally, where MVPs have been implemented, striking reductions in all-cause childhood mortality have been noted. These benefits exceed, often by large margins, what would be expected by reductions in measles associated mortality alone.[9–13] As global measles elimination edges closer, the biology underlying these extra dividends has come under intense scrutiny[14] as it will impact design of future global MVPs in a post-measles world.

Measles vaccination

Vaccination against the measles virus is one of the great public health accomplishments of the past half-century. Since 1980, when global measles vaccination (MV) efforts began to take hold, measles-associated mortality has decreased 95%, from an estimated 2.6 million deaths annually, to an estimated 134,000 in 2015.[1,15] 50 years after the introduction of the first measles vaccine in 1963, endemic measles was declared eliminated in North America and by 2016, elimination of endemic measles was declared for the whole of the Americas region, the first WHO region to achieve this monumental task. Region-wide elimination crowned a 22-year effort of intense vaccination programs that began with a commitment by member states in 1994 to eliminate measles by 2000. Elimination was largely achieved by 2002, but imported cases continued and the secular trend of measles remained stable with an average of only 153 imported cases annually for the region between 2003–2010.[16] Since then, larger outbreaks across Brazil, Canada, Ecuador and the United States have led to 8–10 fold increases in the annual number of cases, threatening the gains of the previous decades.[16] These outbreaks in regions with high vaccination coverage, which are not limited to the Americas region, are multifactorial, but likely result from increased travel to and from measles endemic regions, gaps in surveillance, and increasing numbers of voluntarily unvaccinated individuals.[17] Nevertheless, the highest regional rate of infection in the Americas has remained below the WHO upper threshold of 5 cases per 1 million required to declare regional elimination,[18] making measles the fifth infectious disease to be eliminated from the Americas, following rubella and congenital rubella syndrome (2015), polio (1994) and smallpox, which was declared eradicated in 1980.

In England and Wales, where measles vaccination programs were initiated in 1968, notified cases have been reduced from over 400,000 annually in 1940 to fewer than 2300 in 2010, with mortality falling from over 1000 deaths annually, to zero deaths from acute infections over the same duration.[19] Similar to the Americas, measles notifications have increased in recent years, with 6000 notifications in 2013, the highest in nearly two decades and a 3-fold increase from the 2005 low of 2,089 notifications.[19]

Globally, it is estimated that 4.25 million measles deaths have been averted between 2012 and 2014 alone because of MVPs.[18] By 2016, 79% of WHO member states had incorporated two dose measles containing vaccines into their national vaccination schedules and, in Europe, 21 of 53 member states had verified elimination. However, global elimination remains only on the horizon. Aside from the Americas, no WHO region has achieved the 2015 elimination goals set out in the WHO Global Measles and Rubella Strategic Plan, 2012–2020, and progress since 2015 has showed signs of slowing down. The strategic plan no longer suggests that a timeframe for elimination be set, but rather continued and persistent efforts towards that end be maintained, with review no later than 2020 to determine if specific timeframes for elimination should be set.[18]

While progress towards elimination continues, measles remains among the most urgent public health priorities. Despite the gains made, measles remains responsible for >100,000 deaths annually, mostly of young children.[1,20] Additionally, owing to high transmissibility, classic presenting symptoms, and high vaccine effectiveness, measles serves as a 'canary in the coalmine' for the state of vaccination programs – when programs breakdown, measles is often the first vaccine preventable disease to rise up.[7]

Measles vaccination and reduced all-cause mortality

Where measles vaccines have been introduced, large reductions in all-cause childhood mortality have been observed. The extra benefits have been broadly termed "nonspecific", "off-target", or "heterologous" vaccine effects[10–13,21–25] and range from mild effects on non-measles mortality, to mortality reductions of 40–90%, with the greatest benefits often observed to scale with disease incidence.[10,26–29]

Interest in broad heterologous effects of measles containing vaccines, and other live vaccines, notably bacille Calmette-Guérin (BCG), polio, and whole cell pertussis containing vaccines has grown substantially over the past four decades. However, until recently, no clear consensus on whether the observed effects are real (versus, for example, artifacts of study design) had been reached, and still no consensus exists on the biological mechanisms. Given the magnitude of the effects and potential to inform national vaccine schedules, in 2013 the WHO commissioned a Strategic Advisory Group of Experts (SAGE) to thoroughly review the literature on the subject. The group was charged, in part, with determining if sufficient clinical or laboratory evidence exists to consider incorporating these observations, beneficial or detrimental, into recommendations for vaccination programs.[14] After two thorough systematic reviews, one on the epidemiology of the observed effects[22] and the other on the potential immunological underpinnings,[23] The SAGE group concluded that evidence exists to support observations of reduced mortality following measles and BCG vaccine programs. However, the group determined there exists too little