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Can early measles vaccination control both measles and respiratory syncytial virus infections?

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Measles virus and respiratory syncytial virus (RSV) are two important global health pathogens causing substantial morbidity and mortality worldwide. The current measles vaccination schedule has the first dose given at 9–12 months of age and the second dose given at 15–18 months of age. Measles outbreaks have been associated with an increase in severe RSV infections in children younger than 6 months, probably as a result of measles-induced immunosuppression. A resurgence in measles cases was already occurring before the COVID-19 pandemic, which has affected global immunisation programmes, resulting in millions of children, mostly in low-income and middle-income countries (LMICs), missing out on their measles vaccine. This will leave many children living in the most vulnerable of circumstances highly susceptible to measles and RSV infections when current COVID-19 public health control measures are lifted. This Viewpoint discusses these issues and highlights the need for urgent action to address this looming crisis. The use of early measles vaccination at 4 months of age could be an effective strategy to prevent severe morbidity and death from both measles and RSV infections in many LMICs.

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Introduction

Measles virus and respiratory syncytial virus (RSV) represent two important global pathogens affecting paediatric populations over the last century.[1,2] The public health lockdown measures implemented during the COVID-19 pandemic have created an unusual situation whereby the circulation of viruses such as RSV and measles virus has been greatly reduced. Indeed, many countries have recently reported unusually high RSV seasons with steep increases in RSV cases after COVID-19 control measures were lifted.[3] At least 94 million children, many in low-income and middle-income countries (LMICs), have missed their scheduled measles vaccination due to disrupted global health-care systems during the COVID-19 pandemic.[1] It is likely that the transmission of measles will be high in many countries in the period after COVID-19 lockdowns. This current climate has reinforced the need to implement measles vaccine campaigns to protect unimmunised children and also to consider early measles vaccination at 4 months of age, which has recently been supported by safety, immunogenicity, and efficacy data.[4,5]

By 1982, live attenuated measles vaccine had been implemented in the national immunisation programmes of many countries, with global coverage increasing over subsequent years.[6] Since 2000, considerable reductions of measles virus infections and associated deaths have been reported. Interestingly, reductions in morbidity and mortality from other infectious diseases, including RSV, have also been documented. This observation is attributed to the non-specific effects of measles vaccine.[7–9] This is particularly relevant for RSV since there is no vaccine for this virus. Palivizumab, the only monoclonal antibody approved for RSV prevention, requires multiple injections during the RSV season and is very costly. In high-income countries, palivizumab is indicated only for a very restricted patient group (ie, extreme preterm infants or infants with congenital cardiovascular diseases). The effective use of palivizumab requires the ability to predict when the RSV season will occur, which is especially challenging during the COVID-19 era.

In this Viewpoint, we highlight the consequences of measles virus infections as well as the issues facing current measles vaccination programmes. We propose the consideration of early measles vaccination at 4 months of age to better control measles. For the reasons outlined in this Viewpoint, this approach could also reduce RSV infections in early life.

Immunosuppression following measles virus infections

It has long been recognised that measles virus infection induces substantial immunosuppression, leaving patients at increased risk of acquiring other viral and bacterial infections. Recent data in animal models and human studies showed significant changes in the B-cell repertoire following measles virus infection, characterised by a depletion of the pre-existing memory B-cell pool, as well as impairment of the genetic diversity and isotype composition of naive memory B cells. These changes increase susceptibility to other pathogens, such as RSV.[10–12] Children infected with measles virus have been found to have approximately 30% loss of antibody epitope binding across a range of pathogens, including RSV.[11] In fact, despite the successful generation of new naive B cells during recovery from measles virus infection, these cells expressed immature B-cell receptor repertoires and reduced B-cell diversity, limiting their ability to protect against secondary infections.[10]

The duration of immunosuppression is unclear. Data from a monkey model suggest this lasts at least 5 months,[11] while epidemiological data suggest that it could be up to 1 year.[7] One epidemiological study showed that an increase in measles cases was followed by increased rates of non-measles, all-cause infectious disease mortality over the subsequent 2-year period.[13] Between April, 2015, and December, 2016, Mongolia suffered its largest measles virus outbreak in the last

23 years despite a reported measles vaccination coverage rate of 96%. We observed a strong association between measles deaths in infants younger than 12 months and the peak of RSV infection during the measles virus epidemic.[14] There was also a marked increase in severe pneumonia cases associated with RSV and all pneumonia admissions in the year following the measles epidemic.[14] It is possible that this spike in severe RSV cases was due to measles-virus-induced immunosuppression.

These data highlight the importance of measles vaccination, not only to prevent measles but also to prevent the consequences of measles—ie, the susceptibility to other infections, such as RSV.

Current issues with measles vaccine programmes

The live attenuated measles vaccine is used globally as a two-dose measles-containing vaccine (MCV) schedule, with the first dose (MCV1) given at 9–12 months of age and the second dose (MCV2) given at 15–18 months. It was predicted that if the measles vaccination coverage reached at least 95% in five WHO regions, the eradication of measles virus could be achieved by 2020.[15] However, a combination of recent conflict and weak immunisation systems in many LMICs have led to many children being unvaccinated or undervaccinated and the eradication of measles virus has yet to be achieved.[16] In many countries, vaccine hesitancy has become more prominent in the last 5 years, leading to reduced MCV coverage that might have contributed to measles outbreaks observed in almost every region of the world.[17] During 2018–19, the number of worldwide cases of measles virus infections had increased by nearly 300%.[11]

Measles vaccine coverage of 95% has not been achieved in many LMICs, including Bangladesh, India, Indonesia, Myanmar, Nepal, Papua New Guinea, Thailand, and a number of countries in Africa.[16,18] This suboptimal measles vaccination can lead to low-level population immunity during pregnancy, leaving infants susceptible to measles virus infections in the first few months of life due to lower maternal measles antibodies.[19] Additionally, maternal measles antibodies in vaccinated mothers also wane faster compared with natural infection.[19] By 3 months of age, only 29% of infants from vaccinated mothers are measles seropositive, compared with 60% of infants from naturally immune mothers.[19] This predisposes young infants (younger than 6 months) to measles infections before the first scheduled dose of measles vaccine (MCV1); this age group also has the highest mortality rate as a result of severe measles infections.[14]

The COVID-19 pandemic has severely disrupted global measles vaccination, threatening the progress already made towards the global measles eradication goal and posing a substantial risk of a high incidence of measles during the period after COVID-19 lockdowns. This risk could vary across regions, depending on how the measles vaccination programme of each country has been affected by the COVID-19 pandemic. Of note, before the pandemic, the incidence of measles cases in infants younger than 6 months varied across the WHO regions.[20] The highest proportions of measles cases in infants younger than 6 months were reported in countries of the African region and Western Pacific region, which were 37% and 32% of the total measles cases in each region, respectively.[20]

Urgent actions including early measles vaccination and catch-up vaccination are needed to protect children who have missed their measles vaccine, particularly infants younger than 6 months, who have the highest risk of mortality.

The need for alternative RSV prevention

RSV is a leading pathogen responsible for a great deal of morbidity and mortality in paediatric populations worldwide.[2] Children younger than 6 months exhibit a three-fold increase in mortality following RSV infection compared with children 12–59 months of age.[21] 80–99% of these deaths occur in LMICs.[2,21]

The enhanced RSV disease caused by a formalin-inactivated RSV vaccine (FIRSV) in trials in the USA in 1966 impeded RSV vaccine development for decades.[22] Only after better understanding of the enhancement mechanism of FIRSV and the discovery of the conformational structure of RSV fusion protein, particularly the relationship between its conformational states and neutralising antibody responses, has RSV vaccine development progressed over the last few years.[22] RSV F protein is a viral surface envelope protein that is conserved between the two RSV subgroups A and B, and is chosen as the antigenic target for more than 50% of vaccine and monoclonal antibody candidates.[23] Apart from palivizumab, which has been available since 2003, there are now 42 products in preclinical and clinical stages, including ResVax (Novavax) and nirsevimab (AstraZeneca), which have already completed phase 3 and phase 2b clinical trials, respectively.[23] ResVax is an adult RSV vaccine, evaluated as a maternal vaccine, whereas nirsevimab is a long-acting monoclonal antibody (mAb) to be administered to infants at the beginning of the RSV season. Despite the encouraging results from clinical trials, both products have their limitations.[23] For nirsevimab, with its 70% efficacy, emerging resistant RSV strains represent a potential obstacle to widespread use. Under strong immune pressure generated by mAbs, RSV escape mutants can be generated, particularly in young infants in whom the virus has been frequently reported to have a significantly higher replication.[24] For ResVax, the vaccine failed to meet its primary endpoint, with only 39% reduction in medically significant RSV infections and 42% reduction in lower respiratory tract infections (LRTIs) associated with RSV,[25] although a reduction in all-cause LRTIs throughout the first year of life presented the first evidence that prevention of RSV in early infancy might prevent subsequent respiratory disease. Unfortunately, a safe and effective RSV vaccine

that can protect infants younger than 6 months is unlikely to be available in the near future, while the highest incidence of severe RSV infections continues to occur in this age group.[2]

Severe RSV infections in early life can require hospitalisation and be life-threatening. Furthermore, early RSV bronchiolitis could be associated with development of recurrent wheezing or asthma later in life.[2] Therefore, other prevention options need to be considered to reduce the burden of early RSV infection globally.

Could early measles vaccination protect against measles virus infection and severe RSV disease?

The use of early measles vaccination (ie, MCV0) given before MCV1 is already a recognised strategy to protect infants at high risk of measles virus infections. In high-risk settings where optimal measles vaccine coverage has not been achieved, WHO has recommended MCV0 to be given at 6 months of age as an emergency solution to prevent measles outbreaks.[26] In the current COVID-19 pandemic climate, this strategy is more relevant than ever. However, this recommendation still leaves infants younger than 6 months highly susceptible to severe measles virus infections, as many of them would no longer have immunity provided by maternal measles antibodies by 4 months of age.[19] These same children are also at the highest risk of getting severe RSV infections.[2] We believe that early measles vaccination with MCV0 given at 4 months of age (in either a three-dose schedule [MCV0, MCV1, and MCV2] or a two-dose schedule [MCV0 and MCV1]) represents a feasible approach to reduce the burden of both measles virus and RSV infections in children in the first few months of life.[10–13] This is particularly relevant for LMICs during the current COVID-19 crisis, as these countries have historically high burdens of measles virus infection. COVID-19 has exacerbated their already strained immunisation services, leading to a serious risk of surging measles cases.

So far, the safety, immunogenicity, and efficacy of early measles vaccination is available only for the two-dose schedule (ie, MCV0 and MCV1). Clinical trials of early measles vaccination have provided some encouraging results, showing that early measles vaccination in a two-dose schedule (MCV0 given at 4 months or 4·5 months or 6 months and MCV1 given at 9 months) was immunogenic, safe, and effective.[5,9,27–29] A pooled analysis showed high seropositivity (98%) and vaccine efficacy (95%) in children given this early two-dose MCV schedule. These results are comparable to a conventional two-dose MCV schedule starting at 9 months of age or later (ie, MCV1 and MCV2).[4] No evidence of reduced measles-virus-specific cellular immune responses in children who received an early dose of MCV was found.[30]

Recently, longitudinal datasets in different populations on the beneficial non-specific effects of measles vaccine on morbidity and mortality of other infectious diseases including RSV have been reported.[7–9] The underlying mechanism of this observation is still not clear. Of note, having measles vaccine as the most recent vaccination was reported to be associated with 30% reduction of RSV hospitalisation in a retrospective study in Denmark.[8]

Measles vaccine could prevent severe RSV infections by three potential biological mechanisms: (1) preventing measles-virus-induced immunosuppression; (2) potential heterologous protection between measles virus and RSV; and (3) non-specific effects or trained immunity induced by measles vaccine. By directly preventing measles virus infection and its associated immunosuppression through measles vaccination, the host susceptibility to infection by non-measles pathogens such as RSV might be reduced.[7–9] Mina and colleagues reported that measles virus infection in children resulted in a 33% (range 12–73%) reduction in their pre-existing pathogen-specific antibody repertoires, including RSV,[11] highlighting the broad immunological impact of measles virus infection. The potential heterologous protection between measles virus and RSV could be mediated through T-cell cross-protective responses. T-cell cross-protective responses between RSV and measles virus was reported in vitro and in vivo in mouse models,[31] but it is not clear which viral protein(s) are involved in this response. Our understanding of the precise mechanism of T-cell cross-reactive responses between measles virus and RSV is still poor and more research is needed. It is likely that the non-specific effects of the live attenuated measles vaccine might play a role in protection against other unrelated pathogens.[32] This is due to the trained immunity induced by measles vaccine. This effect is explained by innate immune memory, which has the capacity to respond to a secondary unrelated pathogen after the first challenge with a live attenuated vaccine, such as BCG.[32] However, trained immunity has not been directly examined in the context of measles virus and RSV infections. It is also important to understand whether the difference in specific vaccine responses and non-specific effect profiles of different measles vaccines is due to the vaccine per se or the genetic variation in different target populations, as was observed with BCG vaccines.[32]

Considerations for early measles vaccination

There are several considerations for early measles vaccination at 4 months of age to prevent severe measles as well as RSV infections. These include: (1) concerns regarding reduced protection or immunogenicity which might explain why until now this approach has not been recommended; (2) which schedule and which measles vaccine should be used; and (3) the impact of early measles vaccination on other co-administered vaccines.

Reduced protection or immunogenicity

The potential risk of early measles vaccination on a lower seroconversion rate due to the presence of maternal antibodies was raised in a WHO Position Paper in 2017.[33] Reduced antibody avidity and cellular responses have also been cited as potential concerns for early measles

vaccination.[33] Existing data on low seroconversion rates were based on observational studies and one clinical trial with serology data before 1990, at a time when population-based maternal antibody titres were high. A 2019 meta-analysis by Nic Lochlainn and colleagues used more recent seroepidemiological data. Although they still reported some reduced seroconversion in the early measles vaccination group, they also highlighted that the available evidence from randomised controlled studies was scarce and no evidence of reduced measles-virus-specific cellular immune responses was found in the early measles vaccination group.[4] The potential risk of an immunological trade-off associated with early measles vaccination requires further research. In this context, WHO still recommends MCV0 at 6 months of age only as a supplemental dose to the conventional two doses (MCV1 and MCV2) and not to replace any doses in the current schedule.[33]

Given the current strain on financial resources and health-care systems in LMICs, exacerbated by the COVID-19 pandemic, the three-dose schedule (ie, MCV0, MCV1, and MCV2) might not be feasible. An early two-dose measles vaccination starting at 4 months of age (ie, MCV0 and MCV1) might offer a balance between cost and urgency while providing protection against severe measles virus infections in the highest risk group. This approach would provide sufficient time for preparation of the MCV2 campaign if needed. Modelling analysis using measles epidemiological data from before the COVID-19 pandemic would be helpful to inform decision making for individual LMICs to choose which strategy is likely to be of most benefit.

Measles vaccines and schedules

There are eight different measles vaccine strains in use worldwide.[34,35] The Edmonston-Zagreb strain is the vaccine strain most widely used in the WHO Expanded Programme on Immunization.[34,35] This strain was also used in two recent trials of early measles vaccination, showing good immunogenicity and safety in preventing measles virus infections.[5,9,27–29] Of note, there are also two formulations of measles vaccine: single measles vaccine and combination vaccines such as the measles-mumps-rubella (MMR) vaccine. The MMR vaccine contains the Edmonston-Zagreb strain and live attenuated strains of mumps and rubella viruses. However, the MMR vaccine is not part of the national immunisation schedules of many LMICs and is usually only available in the private sector due to the higher cost. More studies are required to evaluate whether there is a difference in the effectiveness of different measles vaccine strains. For public health, the best vaccine is often the most affordable and accessible in the country.

Co-administration of measles vaccines with other vaccines

Another consideration is whether measles vaccine can be co-administered with other routine childhood vaccines, although this is not necessarily an issue just for early measles vaccination. At 4 months or 9 months of age, measles vaccine is likely to be administered at the same time as a number of other important vaccines. We have previously reported that measles vaccine given at the same time as ten-valent pneumococcal conjugate vaccine (PCV10) at 9 months of age did not affect measles antibody titres.[36] Further studies are needed to understand the interaction between measles vaccine and other co-administered vaccines.

Potential public health benefits from early measles vaccination

Between 2016 and 2019, there was a 50% increase in measles deaths worldwide that claimed 207 500 lives.[1] Around the same time, in 2015, there were at least 50 000 deaths among hospitalised patients with RSV LRTIs.[2] The majority of both measles and RSV deaths were in infants younger than 6 months.

There is currently no vaccine for RSV, whereas measles vaccine is effective and safe. Early measles vaccination at 4 months of age would provide a simple method of providing protection against both measles and severe RSV infections in the most vulnerable age group, particularly during the COVID-19 pandemic.

The potential public health impact of early measles vaccination on severe RSV infections has not been modelled or estimated. However, given the epidemiological data associating measles and RSV infections and deaths, it is reasonable to speculate that even partial protection offered by early measles vaccination is likely to save many lives, particularly those in LMICs.[11] This approach would be important particularly during this pandemic time, when measles vaccinations have been delayed or missed in many countries. A pronounced surge in measles outbreaks globally once restrictions are eased is likely to occur.[1] This has already been seen for RSV in several high-income countries and is likely to be much worse in LMICs.[3]

Despite these probable benefits of early measles vaccination, it should also be acknowledged that this approach will not prevent severe RSV in children younger than 4 months or in preterm infants, who are at a much higher risk of severe RSV disease. Protection of these groups would be through RSV maternal antibodies or maternal vaccination or through use of long-acting mAbs in the case of preterm infants. However, these long-acting mAbs are not currently available and are likely to be out of reach for many LMICs due to their high cost.

Conclusion

Early measles vaccination at 4 months of age is a feasible strategy now to protect against measles virus infections in early life as well as potentially providing indirect protection against severe RSV infections. This intervention is particularly relevant in the current COVID-19 climate, in

which measles virus infections are expected to surge due to the low measles vaccine coverage as a result of disruption in global measles vaccination programmes. This issue is relevant for LMICs and should be an urgent priority for global research and discussion as part of the public health response. This strategy has the potential to considerably reduce morbidity and mortality caused by two important pathogens affecting paediatric populations worldwide.

Contributors

LAHD conceptualised the Viewpoint, performed the literature search, and drafted the manuscript. ZQT and PVL critically reviewed the manuscript. EKM conceptualised the Viewpoint, contributed to the literature search, and critically reviewed the manuscript.

Declaration of interests

EKM participated on a data safety monitoring board for Novavax for a COVID-19 vaccine trial and in an advisory group for Merck on pneumococcal vaccines (no payment or support was received for either), outside of the submitted work. All other authors declare no competing interests.

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