Title: Early Measles Vaccination in Infants Less than 12 Months: Global Practices, Immunity Outcomes, and Implications for Disease Prevention

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Background:

The current recommendation from the World Health Organisation is a two-dose measles vaccination series. This comprises a first dose of measles-containing vaccine (MCV1) at 12 months in low transmission areas or 9 months in areas with ongoing measles transmission, followed by a second dose (MCV2) at 15-18 months of age. However, many infants under 12 months become susceptible to measles infection before receiving MCV1 and are vulnerable to potentially severe complications of measles. Early vaccination through a supplementary dose (MCV0), which can be given as early as 6 months in high-risk settings, could bridge this gap but there is ongoing uncertainty about efficacy and sustained immunity with this approach.

Main Findings:

There are two key issues with early measles vaccination. Firstly, residual maternal antibodies may neutralise measles vaccine antigen. This can impede effective immune responses in younger infants and is most salient in mothers with previous natural infection, rather than vaccine-induced immunity. Secondly, younger infants have immature immune systems with altered T-cell and B-cell activation. Studies have noted lower mean titres of measles antibodies for infants who received MCV0 at 6 months, with only a minority reaching protective antibody titre levels. More durable and robust responses have been observed with vaccination after 9 months.

Fortunately, revaccination at 15 months appears to equalise these differences. There is a reassuring safety profile for MCV0, with <10% of infants under 12 months experiencing adverse effects within 8 weeks of receiving it, and comparable rates of AEs such as fever and skin reactions compared to placebo in infants aged 5-7 months.

Take home message:
While MCV0 can be valuable in high-risk and outbreak settings, it should not replace timely MCV1 at 9-12 months, as well as high MCV2 coverage, needed to sustain individual and population level immunity. Research into optimising measles vaccination is ever more important in an era of increasing vaccine hesitancy.

Quiz Club Questions:

1) In areas of high measles transmission, at what age is the first dose of MCV1 recommended?
    a. 6 months
    b. 9 months
    c. 12 months

d. 15 months
e. 18 months

Answer: b) 9 months
The World Health Organisation recommends that infants in areas of ongoing measles transmission receive the first dose of measles-containing vaccine at 9 months of age.

A supplementary dose (MCV0) can be given as early as 6 months in high-risk situations but does not count towards the recommended two-dose series. In areas where measles is eliminated or near elimination, the first dose is recommended at around 12 months of age. 15-18 months is the recommended age for receiving the second dose of measles-containing vaccine.

2) What is a known disadvantage of administering the supplementary measles vaccine (MCV0) before 9 months of age?
    a. Increased incidence of adverse effects, especially fever ≥39^{o}C
    b. Transient immune system suppression
    c. Higher rates of vaccine-associated measles
    d. Reduced vaccine immunogenicity and seroconversion rates
    e. Higher prevalence of vaccine hesitancy in caregivers

Answer: d) Lower vaccine immunogenicity and seroconversion rates
Early measles vaccination has been associated with lower vaccine immunogenicity and seroconversion rates, which can be attributed to residual maternal antibodies blunting the immune response and/or immature immune systems in younger infants. However, some studies have demonstrated that these differences can be equalised after another dose at 15 months.

Studies have not demonstrated a significant difference between adverse effects or vaccine-associated measles compared to placebo vaccination or older infants. Transient immune system suppression can be associated with natural measles infection, rather than vaccination, through elimination of memory immune cells.

3) Which statement is true regarding MCV2?
    a. It should be given at 12 months of age if a child has previously received a supplementary dose at 6 months of age.
    b. MCV2 is only recommended during measles outbreaks.
    c. It is given to provide more sustained immunity and contribute to herd immunity.
    d. MCV2 is not required if there is evidence of maternal antibodies.
    e. It is not recommended if IgG antibodies against measles are detected after the first vaccine dose.

Answer: c) It is given to provide more sustained immunity and contribute to herd immunity.
MCV2 is considered an essential component of routine two-dose measles vaccination series to ensure robust and durable immunity. MCV2 is generally recommended at 15-18 months

or older according to the World Health Organisation. This is not affected by previous MCV0, presence or absence of measles outbreaks, or IgG antibodies. The presence of maternal antibodies would support revaccination as these may neutralise measles antigen and lead to suboptimal T-cell and B-cell activation.

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Early Measles Vaccination in Infants Less than 12 Months: Global Practices, Immunity Outcomes, and Implications for Disease Prevention

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Measles continues to be a global threat that can lead to serious complications, especially in young infants. The World Health Organization recommends a two-dose vaccine series at different timeframes depending on local measles transmission rates; starting at 9 months in areas with ongoing transmission and 12 months in areas with low transmission. This leaves the majority of infants under 12 months of age at risk of infection. Early vaccination has been proposed, however, the interplay between early vaccination, presence of maternal antibodies, and immaturity of the infant immune system may lead to a less robust immune response as suggested by some studies. Other studies suggest that infants vaccinated early have a similar response to older infants, especially after receiving the full vaccination series. The implications of early vaccination are discussed in both outbreak and non-outbreak settings, though further studies are needed to guide optimal timing of early vaccination.

Key words: measles; vaccination; infants.

INTRODUCTION

Measles virus (MV) is a paramyxovirus that causes an acute febrile illness characterized by cough, conjunctivitis, and coryza, followed by a morbiliform rash. It is highly contagious, with a reproduction number of 9-18, meaning a single case can infect 9 to 18 individuals in a susceptible population.[1–3] Although often considered self-limiting, measles can cause complications in 30% of cases, with higher rates among young infants and immunocompromised or malnourished individuals.[1,4,5] In children <5 years, common complications include pneumonia (6%), otitis media (7%), and diarrhea (8%).[5] Neurologic complications carry high mortality and include acute encephalitis (1-4 per 1000 cases), subacute sclerosing panencephalitis (SSPE) (4-11 per 100,000 cases),[5,6] and measles inclusion body encephalitis (1 per 1000 cases) in immunocompromised patients.[7]

Vaccination remains a safe and highly effective strategy to protect against measles and its complications. A single dose of a measles-containing vaccine (MCV) is 93% effective, while two doses increase effectiveness to 97%.[1,8,9] Several licensed MCVs are available, each including different attenuated MV strains. The most used strains include Moraten (used in the USA), Schwarz, Edmonston-Zagreb, and AIK-C, which are administered in various regions worldwide.[2,10,11] MCVs are available as monovalent or combination vaccines including measles-rubella, measles-mumps-rubella (MMR), and measles-mumps-rubella-varicella formulations. Regardless of the strain or valency, MCVs induce humoral and cellular immune responses comparable to natural MV infection, though of lower magnitude, aiming to elicit long-lasting immunity.[2,12]

GLOBAL IMPACT OF MEASLES VACCINATION

Since its global rollout in the 1960s, measles vaccination led to dramatic reductions in measles-associated morbidity, mortality, and healthcare costs. Between 1974 and 2024, measles vaccination is estimated to have saved 93.7 million lives worldwide.[13] An estimated 107,500 measles deaths occurred in 2022, predominantly among unvaccinated children under the age of five, a substantial reduction from 800,062 deaths in 2000.[8] Beyond mortality, vaccination has prevented innumerable cases of severe measles complications—including pneumonia, diarrhea, encephalitis, blindness, and SSPE, reducing long-term disability and morbidity.[9,14] Between 2000 and 2019, measles vaccination prevented an estimated 2580 million disability-adjusted life years (DALYs) across 112 low and

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Table 1. Variability of Timing of MCV1 and MCV2 Administration across WHO Regions

	AFR ($n=47$)	EMR ($n=22$)	EUR ($n=54$)	AMR ($n=47$)	SEAR ($n=11$)	WPR ($n=35$)	Total ($n=216$)
MCV1[17]							
6-8 months	1	0	0	0	0	1	2
9-11 months	45	11	4	1	11	9	81
12 months	1	11	37	41	0	25	115
13-15 months	0	0	11	5	0	0	16
18 months	0	0	2	0	0	0	2
MCV2[17]							
No MCV2	4	0	0	0	2	1	7
12 months	1	4	1	1	0	3	10
15-17 months	23	3	3	6	4	11	50
18 months	19	14	1	27	4	15	80
2-3 years	0	1	7	6	2	1	16
4-6 years	0	0	31	7	0	4	45
≥7 years	0	0	11	0	0	0	11

Abbreviations: AFR: African Region, EMR: Eastern Mediterranean Region, EUR: European Region, AMR: Region of the Americas, SEAR: South-East Asia Region, WPR: Western Pacific Region

middle-income countries. When projected to 2030, the total DALYs averted is estimated to reach 3110 million.[15] Measles outbreaks impose heavy economic burdens. In the U.S., the median cost per outbreak is US$1,523,08 (range, $9,862-$1,063,936).[16] In areas with ongoing transmission, measles vaccination offers high marginal returns; yielding an estimated US$76.5 for every dollar spent.[13] These gains underscore that measles vaccination is not only a lifesaving public health intervention but also one of the most cost-effective means to reduce hospitalization, long-term disability, and outbreak burden globally.

CURRENT MEASLES VACCINE RECOMMENDATIONS

The World Health Organization (WHO) recommends a two-dose measles vaccination series, with timing guided by local transmission rates, age-specific incidence, and the health system's capacity to reach children at different ages. In areas with ongoing transmission, the first dose of MCV (MCV1) is recommended at 9 months of age, followed by the second dose (MCV2) at 15-18 months of age. In areas with low measles transmission (ie, elimination or near elimination settings), MCV1 is recommended at 12 months of age, and MCV2 is recommended at 15-18 months of age, or at school entry if school enrollment is high and MCV1 coverage is >90%.[2] As a result, measles vaccination schedules vary widely across WHO regions (Table 1).

The minimum interval between MCV1 and MCV2 is 4 weeks regardless of transmission rates. China and South Africa are exceptions to the standard measles vaccination schedule, as both initiate measles vaccination earlier than the WHO-recommended age of 9 months. In China, MCV1 is administered at 8 months and MCV2 at 18 months, while in South Africa, MCV1 is given at 6 months and MCV2 at 12 months.[2]

A supplementary dose (MCV0) that does not count towards the two-dose series is licensed to be given as early as 6-months of age in high-risk situations. These include infants in areas with high measles incidence among those aged <9 months; in outbreak settings; exposed to or at risk of contact with confirmed measles cases; traveling to outbreak areas; with HIV or born to HIV-positive mothers; awaiting solid organ transplant (anticipated ≥28 days post-vaccination); or living as refugees, internally displaced, or in conflict zones (Table 2).[2,12,18] According to the WHO, MCV given before 9 months of age should be considered MCV0. However, classifications vary, with some countries treating doses before 12 months as MCV0, while others count doses given before 9 months as MCV1.

MEASLES VACCINATION DECLINES AFTER THE CORONAVIRUS DISEASE 2019 (COVID-19) PANDEMIC

Measles is resurging globally, driven by declining vaccination rates and compounded by the COVID-19 pandemic, rising vaccine hesitancy, and persistent health inequities. In 2020 alone, an estimated 20 million children missed MCV1 due to the COVID-19 pandemic.[19] As of 2024, no WHO region regained its pre-COVID-19 MCV1 coverage levels.[8] In 2024, global coverage was only 84% for MCV1 and 76% for MCV2, which is far below the 95% threshold needed for herd immunity.[2,12] In the U.S., MMR vaccination among kindergartners dropped from 95.2% in the 2019-2020 school year to 92.7% in the 2023-2024 school year.[20] This immunization gap contributed to a global measles surge, rising from 869,770 confirmed cases in 2019 to 10.3 million in 2023.[21] In 2024, Europe recorded its highest number

Table 2. Role of Early Measles Vaccination (MCV0) Compared With Routine MCV

	Early MCV (MCV0)	Routine MCV1/MCV2
Primary purpose	Targeted risk reduction during periods of highest infant vulnerability	Establish durable individual and population-level immunity
Timing	≥ 6 months of age in specific high-risk circumstances	MCV1 at 9–15 months; MCV2 at ≥15–18 months (or school entry in some settings)
Programmatic role	Supplementary dose	Primary vaccination series
Indications	Outbreaks, humanitarian emergencies, high-transmission settings, special populations	Routine childhood immunization programs
Contribution to long-term immunity	Limited when given alone; requires subsequent doses	2-dose series essential for durable immune memory
Relationship between strategies	Complements but does not replace routine doses	2-dose series required regardless of receipt of MCV0

of measles cases since 1997.[22] The decline in measles vaccination rates is multifactorial. The COVID-19 pandemic not only disrupted routine vaccination, but also reallocated resources to other healthcare needs, and worsened vaccine hesitancy due to distrust in the health system.[2,23] Additionally, most children who did not receive any MCV doses are refugees or live in conflict zones, highlighting their vulnerability and persistent inequities in vaccine access.[21,24,25]

MATERNAL ANTIBODIES AND MEASLES PROTECTION

Infants under 12 months of age are especially vulnerable to severe measles and its complications due to their immature immune systems and waning maternal antibodies. In the post-vaccine era, most women of childbearing age globally have received MCV.[11] Interestingly, mothers who are vaccinated against measles confer fewer antibodies with lower avidity and longevity to their infants compared to mothers who had natural infection.[26–31] However, any residual antibodies can blunt the immune response to MCV, reducing its effectiveness.[30,32] Recent studies show that maternal antibodies fell below protective levels as early as 3 months of age in infants born to vaccinated mothers, highlighting that those infants are susceptible to measles at a younger age and can represent a break in herd immunity, thus acting as a possible source for measles introduction and spread.[25,33,34]

A recent study investigating the natural decay of maternal measles antibodies in unvaccinated infants from 11 countries of different measles incidence and vaccination rates showed that infants in Guatemala, where maternal vaccination rates are high and measles incidence is low, had antibody levels below the protective threshold by 2.5 months, using the WHO endorsed threshold of 120 mIU/mL via Plaque Reduction Neutralization Test (PRNT).[2,35] However, in Pakistan, where maternal vaccination rates are low and measles incidence is high, infants' measles antibodies fell below the protective threshold by 6.2 months. In all eleven countries included in the study, less than 50% of infants had protective measles antibodies by 6 months of age, except in Pakistan. Regardless of country of birth or measles transmission rates, most infants were susceptible to measles before the recommended age for MCV1.[35] Similarly, a Canadian study found that by the first month of life, 20% of infants did not have protective measles antibodies. By 3 months of age, 92% of infants did not have measles protective antibodies, and none had any maternal antibodies by 6 months of age. The odds ratio (OR) of measles susceptibility increased with increasing infant age (adjusted OR: 2.13; 95% CI: 1.52-2.97).[33] Of note, the protective threshold used in the study was 192 mIU/mL via PRNT, which is higher than the WHO endorsed threshold of 120 mIU/mL.[2,33]

This was also found by a Chinese study where the number of infants with protective measles antibodies decreased with age; from 98% by 1 month to 53.2% by 8 months. Infants tended to have a more robust protective antibody titer if they lived in a rural setting (OR: 24.62, 95% CI: 8.43-71.94, $P<.001$), which could be due to natural immune boosting from circulating measles, or if their mother had measles antibody titers equal to or greater than 1:3200 (OR: 7.13, 95% CI: 3.67-13.82, $P<.001$), suggestive of natural infection. Moreover, infants born to mothers with presumed natural infection based on their birth year were more likely to be protected compared to those born to younger mothers (OR: 1.27, 95% CI: 0.64-2.54, $P=.49$). Notably, the study utilized Enzyme-linked Immunosorbent Assay (ELISA) tests with a protective threshold of IgG antibody titer of 1:200 or greater.[28] Although widely available, ELISA tests are less sensitive for detecting low protective antibody levels, and PRNT remains the gold standard for assessing seroprotection.[34] A prospective randomized study evaluating seroconversion 24 months after MCV1 via ELISA showed age-dependent immune responses, with rates of 87%, 95%, and 98% for infants vaccinated at 9, 12, and 15 months, respectively.[26] The study also highlighted that mothers with natural measles infection conferred higher antibody titers to their infants, leading to greater interference with vaccine-induced immunity. Among 9-month-old infants, seroconversion was seen in only 76.3% of

those whose mothers had natural infection, compared to 95.6% in those whose mothers were vaccinated, demonstrating the impact of maternal antibody type and level.[26]

Maternal antibody dynamics are critical to interpreting early infant measles susceptibility, particularly in elimination settings where maternal immunity is largely vaccine derived.

MCV BETWEEN 6-11 MONTHS OF AGE

The current WHO recommendations are to administer MCV1 at 12 months in elimination settings, at 9 months in high transmission regions, and MCV0 as early as 6 months in high-risk outbreak settings.[2] However, this leaves most infants under 12 months susceptible to infection. While early vaccination has been proposed to address this gap, its long-term effectiveness remains under debate due to concerns about suboptimal immune responses during preschool and early school years. We present a synthesis of current evidence (Table 3).

Evidence from Outbreak Settings

MCVs are effective at preventing measles in outbreak settings.[11] During an outbreak in Quebec, Canada, MCV0 was administered to infants aged 6-11 months and the overall effectiveness of early vaccination was 73% (95% CI: 32-89%) immediately upon receipt of the vaccine, increasing to 96% (95% CI: 72-99%) one week post-vaccination, reflecting the time needed to mount an immune response.[38] Of the 79 infants included, 15 (19%) developed measles—9 of 23 unvaccinated (39%) and 6 of 56 vaccinated (11%), corresponding to a relative risk of 3.6 (95% CI: 1.5-9.1). Notably, younger infants aged 6-8 months had a higher attack rate than those aged 9-11 months regardless of their vaccine status.[38] Similarly, a randomized control trial conducted during an outbreak in Guinea-Bissau where early MCV was given at 4.5 months showed a vaccine efficacy of 91% (62%-98%) for clinically diagnosed measles infection and 94% (74%-98%) for serologically diagnosed measles infection when evaluated from enrollment to 21 days after receiving MCV1 at 9 months.[11]

Even though MCV0 is effective in preventing measles in outbreak settings, concerns remain about its long-term effects of diminishing the immune response to subsequent MCV doses.[44] Studies from the Netherlands investigating the long-term immune response to early vaccination (6-12 months of age) after an outbreak found that those who received MCV0 between 6-8.5 months of age had MV-specific antibody levels below the protective threshold (120 mIU/mL via PRNT) at 6 years of age, despite receiving MCV1 at 14 months. In contrast, those who received MCV0 after 8.5 months of age showed a more durable immune response.[43,45] At the time of these studies, the vaccine schedule in the Netherlands recommended MCV1 at 14 months and MCV2 at 9 years of age. As of January 2025, the Netherlands updated their recommendations to administer MCV1 at 14 months and MCV2 at 3 years, shortening the inter-dose interval and potentially mitigating concerns about immune durability.[46] These findings are most relevant to countries administering MCV2 at 6 years or later, especially where most infants receive MCV1 before 9 months, creating a longer interval between doses, and warranting reassessment of vaccination schedules. Nonetheless, the results support that MCV1 timing, and potentially the MCV1-MCV2 interval, significantly influences MV-specific neutralizing levels, with vaccination at 9-12 months linked to more sustained immunity.

Evidence in Non-Outbreak Settings

In non-outbreak settings, the data is even more inconsistent. A 1980-1981 prospective U.S. cohort study using cytopathic effect neutralization tests, hemagglutination inhibition, and ELISA showed that MCV before 10 months of age induced protective antibody levels, though at lower rates compared to older infants, even after revaccination at 15 months when assessed 8 months after.[36] Maternal antibody titers and immunity source were not reported, limiting assessment of their contribution to the higher immune responses observed among older infants. Other studies comparing MCV administered at 6, 9, and 12 months of age showed that, at three months post-vaccination, infants vaccinated at 6 months had a lower geometric mean titer (GMT) of measles antibodies and low PRNT seroconversion rates, while those vaccinated at 9 and 12 months had similar and more robust responses.[27,47]

This contrasts other data showing that infants vaccinated between 6-9 months of age had a less robust immune response via PRNT, but revaccination at 12-15 months effectively boosted immunogenicity.[32,48] In a Canadian study, infants who received MCV at 6 months of age followed by MMR at 15 months of age showed 98.9% seropositivity 8 weeks after MMR, with 70% demonstrating measles-specific cellular immunity.[40] At 27 months of age, 98.4% of infants maintained protective antibody levels; further supporting that early vaccination does not impact long-term immunity when followed by a second MCV.[40] The study utilized ELISA for blood samples obtained before 27 months, and PRNT for samples obtained at 27 months.[40] A similar U.S. study using PRNT and ELISA found that 74% of infants vaccinated at 6 months developed protective antibodies, though their GMTs were significantly lower than those who only received MMR at 15 months. Revaccination with MMR at 15 months eliminated those differences.[37] Moreover, a randomized trial of 647 infants aged 5-7 months showed higher MCV0 immunogenicity in those $\geq$6 months than in those <6 months by PRNT and ELISA; differences resolved after MCV1 at 15 months, with all demonstrating adequate immune responses.[30]

Additional Factors Influencing the Immune Response to Early MCV Administration. Infant immune immaturity limits

Table 3. Summary of the Main Studies Evaluating Early Administration of MCV

Study	Design	Groups and timing of MCV (n)	Seroprotection threshold	Outbreak setting (Yes/No)	Outcomes
Stetler et al. (1986)[36]	Prospective cohort	Early MCV: MCV0 at <10 months and MCV1 at 15 months (254) Control: MCV1 at 15 months (129)	≥1:8 via HI ≥0.056 via ELISA ≥ 1:4 via CPEN	Yes	• MCV0 provided short term protection that waned by 15 months • Revaccination at 15 months restored antibody titers but did not achieve the same durability and level compared to the control group
Johnson et al. (1994)[37]	Prospective cohort	Early MCV: MCV0 at 6 months and MCV1 at 15 months (17) Control: MCV1 at 15 months (22)	NT 0.16 ≥ EIA 0.17 ≥ IgM EIA	No	• The seroconversion rate of infants vaccinated at 6 months of age was lower than the control group • Infants who seroconverted after MCV0 had a lower GMT compared to the control group • The GMT after receiving MCV1 was not different from the control group
De Serres et al. (1996)[38]	Prospective cohort	Early MCV: MCV0 between 6-11 months and MCV1 at 15 months (56) Control: MCV1 at 15 months (23)	≥ 120 mIU/mL via PRNT	Yes	• Early MCV was effective in preventing spread of measles in infants between 6-11 months, and all had protective antibody levels by 15 months of age after MCV1
Gans et al. (1998)[39]	Prospective cohort	Early MCV: MCV0 at 6 and MCV1 at 12 months (23) or MCV0 9 and MCV1 at 12 months (20) Control: MCV0 at 12 months (22)	≥ 120 mIU/mL via PRNT	No	• Measles protective antibodies were more robust in older infants with less maternal antibodies • T-cell proliferation and stimulation was similar across all age groups and did not correlate with the presence of protective measles antibodies • Vaccination induced a TH1 response with cytokine production that improved with age
Gans et al. (2001)[27]	Prospective cohort	Early MCV: MCV0 at 6 and MCV1 at 12 months (93) or MCV0 at 9 and MCV1 at 12 months (77) Control: MCV1 at 12 months (78)	≥ 120 mIU/mL via PRNT	No	• IFN-γ concentrations were equivalent regardless of passive antibody status at the time of vaccine administration • T-cell proliferation and stimulation was similar across all age groups • The seroconversion rate increased with increasing age • Infants vaccinated at 6 months of age had lower GMTs compared to older infants vaccinated at 9 even after MCV1, but all infants regardless of age had protective antibody levels after MCV1
Gans et al. (2004)[32]	Prospective cohort	Early MCV: MCV0 at 6 and MCV1 at 12 months (32) or MCV0 at 9 and MCV1 12 months (23) Control: MCV1 at 12 months (83)	≥ 120 mIU/mL via PRNT	No	• Half of 6-month-old infants had maternal antibodies, while none of 12-month-old infants had any maternal antibodies • Infants who had maternal antibodies at 6 and 9 months had lower GMTs compared to their counterparts that did not have maternal antibodies • Infants who received MCV0 at 6 and MCV1 at 12 months had a lower GMT than those who received MCV0 at 9 and MCV1 at 12 months and those received MCV1 at 12 months only
Redd et al. (2004)[26]	Randomized Prospective cohort	Group 1: MCV0 at 9 months (285) Group 2: MCV1 at 12 months (358) Group 3: MCV1 at 15 months (347)	Indirect EIA	No	• Infants born to mothers with history of measles had lower seroconversion rates across all age groups • Seroconversion rates increased with increasing age, but no difference was observed between those vaccinated at 12 months and 15 months

(continued)

Table 3. Continued.

Study	Design	Groups and timing of MCV (n)	Seroprotection threshold	Outbreak setting (Yes/No)	Outcomes
Carson et al. (2005)[40]	Prospective cohort	Infants born to mothers with natural infection: MCV0 at 6 months and MCV1 at 15 months (61) Infants born to vaccinated mothers: MCV0 at 6 months and MCV1 at 15 months (239)	≥ 0.200 via EIA, 120 mIU/mL via PRNT (used in sample obtained at 27 months only)	Yes	• All infants had measles neutralizing antibodies at 27 months after receiving MCV0 at 6 months and MCV1 at 15 months, though infants born to mothers with natural infection had a lower GMT
He et al. (2014)[41]	Prospective cohort	Early MCV: MCV0 at 8 months and MCV1 at 18 months (140) Control: MCV1 at 12 months and MCV2 at 22 months (140)	≥200 mIU/mL via ELISA	No	• All infants seroconverted after the first MCV • GMT were similar in both groups after receiving 2 doses of MCV
Vittrup et al. (2024)[30]	Randomized controlled trial (immunogenicity data)	Early MCV: MCV0 between 5-7 months and MCV1 at 15 months (290) Control: placebo between 5-7 months and MCV1 at 15 months (357)	120 mIU/mL via PRNT, ≥11 Nove Tec Units (NTU) via IgG ELISA	No	• Before the intervention, 88% of mothers and 15% of infants had protective antibodies • Maternal antibodies >40 mIU/mL led to lower seroprotection levels in infants receiving MCV0 • Premature infants (32-37 weeks' gestation) had a better response to MCV0 (GMR 13.4 [95% CI: 4.9–36.1]) compared to term infants (GMR 4.0 [95% CI: 3.2–4.9]) • Infants aged ≥6 months had a GMR of 4.6 (95% CI: 3.7–5.7) after MCV0, versus 2.5 (95% CI: 1.3–4.6) in those aged <6 months • After MCV1 at 15 months, MCV0 recipients had higher antibody levels than those who received placebo (GMT: 1804 vs. 1174).
Brinkman et al. (2019)[42] and Van der Staak et al. (2025)[43]	Prospective cohort	Early MCV: MCV0 between 6-12 months and MCV1 at 14 months (79) Control: MCV1 at 14 months (42)	≥ 120 mIU/mL via PRNT	Yes	• At 6-years post vaccination, infants who received MCV between 8.5-12 months had a similar response to those who received it at 14 months • Infants <8.5 months that had primary vaccine failure to early MCV developed a similar response to those who only received MCV at 14 months • Infants who received MCV before 8.5 months had a lower GMT and had accelerated antibody decay compared to those who received it after 8.5 months or at 14 months, despite receiving a second dose at 14 months

Abbreviations: MCV: measles-containing vaccine, HI: hemoagglutination inhibition, ELISA: enzyme-linked immunosorbent assay, CPEN: cytopathic effect neutralization, NT: neutralization test, EIA: enzyme immunoassay, GMT: geometric mean titer, PRNT: plaque reduction neutralization test, TH1: T helper 1, GMR: geometric mean ratio

durable immune responses.[34] The immune response to measles involves a complex interaction between cell-mediated and humoral immunity, in which T-cell activation leads to B-cell activation and subsequent antibody production. The infant immune system expresses lower levels of co-stimulatory signals resulting in attenuated T-cell responses and diminished B-cell activation, which when coupled with a reduced plasma cell lifespan leads to short-lived antibody production.[49] A study assessing the immunogenicity of measles vaccination at 6, 9, and 12 months of age via PRNT showed that only 36% of 6-month-old infants without maternal antibodies achieved protective antibody titers, compared with 100% of 9- and 12-month-old infants,[27] emphasizing that maternal antibodies are only partially responsible for a decreased immune response to early administration of MCV. The intrinsic immune immaturity and reduced antibody production seem to improve by 9 months, as evidenced by infants vaccinated at that time mounting similar PRNT responses to those vaccinated at 12 months (Figure 1).[39]

It is important to highlight that measures of immunogenicity may not directly correspond to clinical protection. Thus, lower antibody levels do not necessarily indicate an increased risk of disease. Some studies suggest that even though early-vaccinated infants may have lower antibody levels, memory B-cells can be activated to produce protective antibodies upon measles exposure.[2,50] However, because these findings are primarily from regions with ongoing transmission, where frequent exposure to

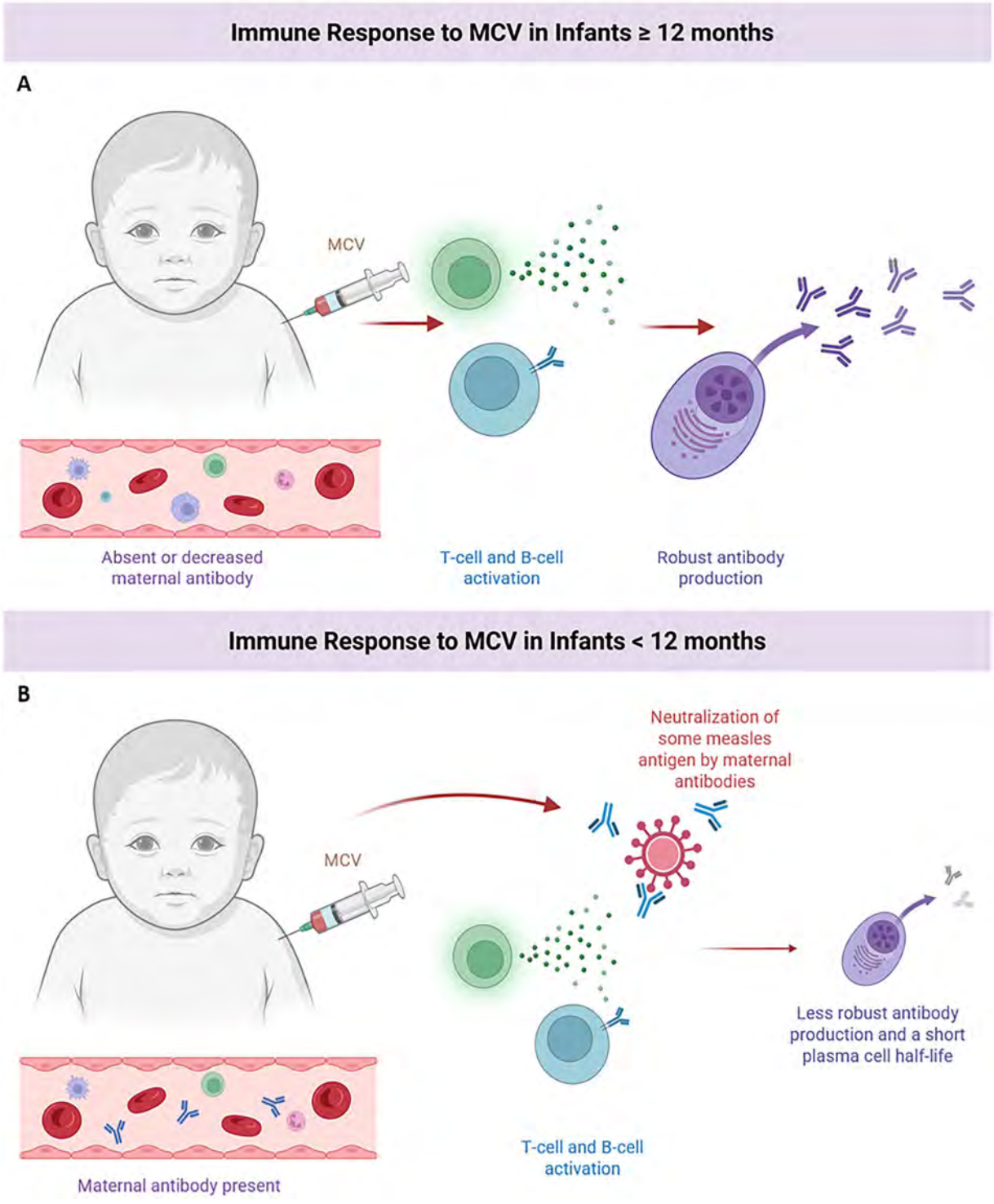

Figure 1. (A) In infants ≥12 months of age with absent or decreased measles-specific maternal antibodies, there is no interference between MCV and maternal antibodies, therefore, MCV antigens lead to T-cell and B-cell activation and a robust immune response. (B) In infants <12 months of age with measles-specific maternal antibodies, there is potential interference between MCV and maternal antibodies in addition to a less mature immune system which could lead to a less robust immune response. Created with BioRender.com.

the MV may naturally boost immunity, it remains uncertain if the same immune response would be observed in elimination or low-transmission settings.[28,50,51]

Safety Profile of Early MCV Administration. MCV has not shown a safety signal in younger infants, and has been given safely as early as 4.5 months of age.[11,47] Following

a large measles outbreak in Japan, only 6 of 8,062 infants vaccinated early (6-11 months) developed vaccine-associated measles (0.74 per 1000 doses), a rate comparable to infants vaccinated at 12 months of age.[52] Vaccine-associated measles is a rare manifestation caused by the attenuated vaccine strain, typically reported in immunocompromised hosts, and was identified in this study only through enhanced surveillance.

In a randomized trial of 6,539 infants aged 5-7 months, adverse events (AEs) within 6 weeks were similar between MCV0 and placebo; including fever ≥39°C (10% vs 9.3%) and skin reactions. Serious AEs (25 infants) were unrelated or unlikely related to vaccination.[30] A systematic review of 24 studies found that fewer than 10% of infants aged <12 months experienced any AE within 8 weeks of receiving MCV0. Reported events included injection site-reactions, fever, rash, respiratory and gastrointestinal symptoms, irritability and decreased appetite.[53]

Remaining Challenges. Effective MCV0 use requires accurate documentation and reliable follow-up to ensure it supplements, rather than replaces, routine MCV series. Poor record-keeping may overestimate MCV1 and MCV2 coverage. Robust systems are needed to support timely subsequent doses, particularly in mobile or resource-limited populations, with vaccination status reviewed at every healthcare encounter and at school entry.

Another important technical challenge in measles research is the lack of standardized methods for assessing measles immunity across studies. The PRNT remains the gold standard for measuring protective antibodies, but it is labor-intensive, and difficult to standardize across laboratories, limiting its feasibility for large-scale surveillance. ELISA, while more practical and widely used, risks underestimating immunity at a population level.[34,40,44] Additionally, the currently used seroprotection threshold and its correlation with clinical protection, is based on historical literature.[34] Furthermore, most contemporary studies investigating early measles vaccination between 6-11 months of age are restricted to single-dose studies, and the lack of standardized multi-dose studies hinders the ability of physicians and public health professionals to offer updated evidence-based recommendations and devise effective measles prevention strategies.

A bigger threat to measles prevention and elimination is vaccine hesitancy and the rise of vaccine-related misinformation. In response, the WHO published the Big Catch Up in 2023, which is a global vaccine recovery plan to catch up, restore, and strengthen the global intake of vaccines. It aims to reach zero-dose children, followed by restoring vaccine coverage to pre-COVID-19 levels, and then sustaining and strengthening progress through targeted strategies.[54]

CONCLUSION

Early MCV (MCV0) plays an important role in protecting young infants during their most vulnerable period, particularly in outbreak settings and high-transmission regions. However, MCV0 should not replace timely administration of MCV1 within the 9-12 month window, which elicits a more robust and sustained immune response. Optimal vaccination schedules and strategies must be adapted to local epidemiology to balance early protection with long-term effectiveness, which are influenced by maternal antibodies and infant immune maturity. Across all settings, high MCV2 coverage remains essential for sustained individual and population-level immunity.

The lack of standardized methods for assessing immunity, reliance on historical seroprotection thresholds, and limited multi-dose data in early infancy highlight the need for further research to guide current vaccination strategies.

Conflicts of interest

- Amna AlSaihati: No conflict
- Manu Chaudhary: No conflict
- Liset Olarte: No conflict

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