Review

Acute Therapies for Measles During Vaccine Coverage Decline

Amandeep Kaur , Ugo Alaribe , Joseph Varon , Sidra Hassaan , Matthew Halma *

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Review

Acute Therapies for Measles During Vaccine Coverage Decline

Amandeep Kaur [1], Ugo Alaribe [1], Joseph Varon [1,2], Sidra Hassaan [3] and Matthew Halma [2,4,*]

[1] Dorrington Medical Associates, 2219 Dorrington Street, Houston, Texas, 77030, USA
[2] Independent Medical Alliance, 2001 L St. NW Suite 500, Washington, DC 20036, USA
[3] Department of Pharmacy at Jinnah University for Women, 5-C, Nazimabad, Karachi-74600, Pakistan
[4] Open Source Medicine Foundation, Open Source Medicine OÜ, Pärnu mnt. 139c, Tallinn, 11317, Estonia
* Correspondence: mhalma@imahealth.org

Abstract

Measles represents one of the most contagious viral infections, and its reappearance in the context of diminishing vaccination rates has sparked a fresh interest in treatment and preventative measures. Current and new acute therapies were analyzed in this systematic review, along with their relationship to measles virology and clinical outcomes. Despite only being used off-label, ribavirin and interferon-α have been shown in small clinical studies to reduce the severity of the disease and its associated complications.Vitamin A supplementation is the only commonly recommended treatment that has strong evidence of lowering morbidity and mortality, especially in young children who are vitamin A-deficient. Traditional Chinese medications like Tanreqing and Xiyanping have demonstrated symptomatic improvements in clinical trials but need mechanistic validation, while investigational potential treatments like the polymerase inhibitor ERDRP-0519 and monoclonal antibodies against the fusion protein exhibit strong preclinical efficacy. While vaccination is essential as a preventive measure, adjunctive therapies, particularly vitamin A and innovative antiviral techniques, provide valuable tools to enhance outcomes and mitigate complications in under-vaccinated individuals.

Keywords: measles; acute therapies; ribavirin; interferon-α; vitamin A supplementation; antiviral drug development

1. Introduction

Measles is one of the world's most contagious viral diseases, with an estimated basic reproduction number (R_0) of 12–18, the highest among human pathogens (1). Despite the availability of a safe and effective vaccine for decades (2), measles cases have surged in recent years (3). In 2023 alone, over 10.3 million cases and 107,000 deaths were reported worldwide, representing a 21% increase over the previous year and reversing years of progress toward measles elimination (4,5).

Multiple factors are contributing to this resurgence, including vaccine hesitancy, healthcare system disruptions caused by the COVID-19 pandemic, and disparities in vaccine access across regions (6). The World Health Organization and UNICEF reported that 22 million children missed their first measles-containing vaccine dose in 2022, the highest number since 2008, leaving millions susceptible to outbreaks (6). In the United States, the CDC recorded 285 confirmed cases in the first half of 2024, nearly five times the 58 cases reported in all of 2023, with 40% requiring hospitalization, often in unvaccinated children under five years of age (7).

These trends underscore the urgency of strengthening immunization programs and improving vaccine equity. They also highlight the need for additional strategies, including research into acute therapeutics, to protect under-vaccinated populations during outbreaks and reduce measles-related complications and deaths.

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2. Epidemiology of Measles

Measles, once an endemic disease in the USA, was considered eliminated in 2000, owing to wide vaccination coverage [8]. The decade prior to the introduction of the measles vaccine in 1963 was marked by approximately 500 deaths by measles per year, mostly in children [9]. Prior to the introduction of the measles vaccine, measles infections were ubiquitous, affecting 95% of the population under 15 years of age [9]. Following the introduction of the measles vaccine, measles infection rates dropped precipitously, with less than 10% of counties in the USA reporting any cases of measles.

Despite the success of measles vaccination, vaccination coverage has declined significantly. In Canada, the rate of Measles, Mumps, and Rubella (MMR) vaccine coverage has declined from 89.5% in 2019 to 82.5% in 2023 [10]. Trust in medical authorities has declined since the COVID-19 pandemic [11], which has affected childhood vaccination rates. Additionally, we may be observing transference of distrust into other fields, as climate change skepticism is highly correlated with being unvaccinated for COVID-19 [12], and climate change skepticism appears to have risen since the pandemic [13].

Measles is transmitted through airborne respiratory droplets and can remain infectious on surfaces or in the air for up to two hours, allowing rapid spread among susceptible individuals. Transmission begins several days before the onset of the characteristic rash and continues for several days afterward, contributing to explosive outbreaks in populations with low vaccine coverage [14]. The extremely high R_0 of 12–18 explains why at least 95% coverage with two doses of a measles-containing vaccine is required to maintain herd immunity and prevent outbreaks [1].

Global surveillance shows significant setbacks: in 2023, only one-third of countries achieved recommended measles surveillance targets, and global MMR vaccine coverage declined from 86% in 2019 to 83% in 2023 [4,5]. These declining trends have led to rising outbreaks even in countries with previously strong immunization programs, often affecting communities with persistent gaps in coverage [7].

High-risk populations include infants too young for vaccination, malnourished or immunocompromised children, pregnant women, and displaced or marginalized groups. While case fatality rates average 0.1–0.3% in high-income settings, they can reach 3–6% or higher in low-resource environments, underscoring the stark inequities in measles outcomes [15]. Addressing these challenges requires both sustained vaccination efforts and the development of adjunctive therapies that could help reduce severe disease and mortality during outbreaks.

3. Virology & Pathology

Measles virus (MeV) is an enveloped, negative-sense, single-stranded RNA virus in the genus Morbillivirus of the family Paramyxoviridae [16]. The virus encodes six structural proteins, including the hemagglutinin (H) and fusion (F) glycoproteins, which mediate attachment to host cells and membrane fusion, respectively. MeV primarily infects immune and respiratory epithelial cells by binding to CD150/SLAM receptors on lymphocytes and nectin-4 on epithelial cells, initiating replication in the respiratory tract before systemic dissemination [17].

The systemic spread of MeV leads to viremia, infecting multiple organs and causing a range of clinical manifestations. One hallmark of measles infection is profound immune suppression, characterized by the depletion of preexisting B and T cell memory, a process known as “immune amnesia,” which results in increased susceptibility to secondary infections for months or even years after recovery [18]. Recent studies have demonstrated that incomplete regeneration of B cell populations after measles infection contributes to this prolonged vulnerability, further increasing risks of severe illness [19].

The characteristic descending maculopapular rash of measles results from a cell-mediated immune response targeting virus-infected endothelial cells in the skin (20). Severe complications, including pneumonia, diarrhea, encephalitis, and otitis media, remain leading causes of measles-associated deaths, particularly in malnourished children in low-resource settings [16]. A rare but fatal

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complication, subacute sclerosing panencephalitis (SSPE), can develop years after initial infection, resulting in progressive neurological deterioration due to persistent MeV infection in the central nervous system. Understanding the detailed virology and immunopathogenesis of measles is critical to guiding vaccine strategies and informing research on potential antiviral therapies.

To strengthen the utility and clinical relevance of this systematic review, we have expanded the discussion to more directly relate the identified therapies to their mechanistic actions and to the pathophysiology of measles. For instance, therapies such as interferon α-2a and ribavirin have been contextualized with respect to their antiviral properties and roles in modulating the innate immune response [21,22], while vitamin A's immunomodulatory and epithelial reparative functions are now emphasized as central to its observed benefits in reducing morbidity [23,24]. Chinese herbal formulations, such as Tanreqing and Xiyanping, have been discussed in light of their potential anti-inflammatory and antiviral mechanisms, although more mechanistic data are needed [25].

Furthermore, the recent resurgence of measles cases in the United States, especially in the first half of 2024, with 285 confirmed cases and a 40% hospitalization rate (primarily among unvaccinated children), underscores the urgency of actionable therapeutics. This outbreak has been driven, in part, by declining vaccine coverage and increasing vaccine hesitancy, trends exacerbated by the COVID-19 pandemic and misinformation. According to the Centers for Disease Control and Prevention [26], formerly well-controlled regions are now experiencing community transmission, emphasizing the need not only for preventative strategies but also for acute care options to reduce complications in vulnerable populations.

To strengthen the utility and clinical relevance of this systematic review, we have expanded the discussion to more explicitly connect the identified therapies to their mechanisms of action and to the pathophysiology of measles. Interferon alpha-2a and ribavirin, for example, are discussed in the context of their direct antiviral activity against the measles virus and their roles in modulating innate immune pathways to limit viral replication [21,22]. Vitamin A is examined for its immunomodulatory effects and ability to restore epithelial integrity, which is critical in preventing secondary infections [23,24]. Traditional Chinese formulations such as Tanreqing and Xiyanping are considered for their possible antiviral and anti-inflammatory effects, though further mechanistic studies are warranted [25].

In parallel, we address the growing concern of measles resurgence in the United States. In the first half of 2024, 285 confirmed cases were reported, with a 40% hospitalization rate—most among unvaccinated children [26]. This resurgence is closely linked to declining vaccination rates and increasing vaccine hesitancy, trends accelerated by the COVID-19 pandemic and misinformation. These epidemiologic shifts have allowed community transmission to re-emerge in regions previously free of measles. Against this backdrop, the mechanistic understanding of available therapeutics becomes increasingly important, as effective antiviral and supportive interventions could mitigate severe outcomes in unvaccinated or high-risk populations.

This updated analysis integrates therapeutic mechanisms with current outbreak dynamics, making the review directly relevant to both clinical decision-making and public health policy in the U.S. and beyond.

4. Acute Treatment of Measles

While prevention remains the most effective strategy against measles, cases do occur in unvaccinated individuals or through breakthrough infections. In such scenarios, acute treatment strategies are essential not only for managing the infection itself but also for mitigating potential long-term sequelae of measles, such as immune amnesia and increased susceptibility to secondary infections [18,19]. Currently, no antivirals are approved specifically for measles virus infection; management remains largely supportive. However, several pharmacologic, immunomodulatory, and experimental approaches have emerged, each supported by varying degrees of clinical and preclinical evidence.

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4.1. Antiviral Therapies (Ribavirin and Interferon-α)

Ribavirin, a broad-spectrum nucleoside analog, has been used compassionately in severe or immunocompromised measles cases, with reports of reduced illness duration and fewer complications [18,27]. A double-blind, randomized, placebo-controlled trial further demonstrated that ribavirin-treated children experienced milder disease and fewer complications compared to controls [28].

Similarly, interferon-α (IFN-α-n1) has been evaluated in pediatric measles. In a randomized study, orally administered IFN-α significantly reduced the duration of fever, malaise, and rash, while demonstrating a favorable safety profile without major hematologic, renal, or hepatic toxicity [29]. Despite these promising results, both ribavirin and interferon remain off-label for measles and are generally reserved for severe or life-threatening cases, particularly in immunocompromised patients [18].

4.2. Vitamin A Supplementation

The World Health Organization recommends supplemental vitamin A in all children with severe measles infection, but this recommendation is often ignored in high-resource settings, including the USA [30]. Vitamin A's effect may be less in older children [31], as well as in children in high-resource settings who are not likely to be vitamin-A deficient [32].

Vitamin A supplementation is the most consistently validated adjunct therapy in measles management. Randomized controlled trials and meta-analyses have demonstrated that high-dose vitamin A (200,000 IU for children and 100,000 IU for infants, administered on two consecutive days) significantly reduces measles-related mortality, particularly in children under two years of age [33–35]. WHO guidelines endorse vitamin A supplementation during acute measles episodes, especially in vitamin A–A-deficient populations [35]. Measles does not currently have a specific antiviral treatment recommended by any major health organization [14].

4.3. Investigational Antivirals

Novel small-molecule inhibitors targeting the measles virus RNA-dependent RNA polymerase (RdRp) have demonstrated substantial preclinical promise. ERDRP-0519, for example, showed potent antiviral activity by locking the polymerase in an inactive conformation, thereby halting viral RNA synthesis [36,37]. In non-human primates, both prophylactic and therapeutic administration of ERDRP-0519 prevented clinical disease, reduced viral shedding, and improved survival [28]. Additional structural studies confirmed the molecular mechanism, showing that ERDRP-0519 inhibits all RNA synthesis through direct interaction with the L protein of the viral polymerase [37].

In parallel, monoclonal antibodies against the measles virus fusion (F) protein have been developed. Cryo-electron microscopy revealed that mAb 77 stabilizes the prefusion state of the F protein, effectively blocking its transition to the postfusion state required for viral entry [38]. In vivo studies demonstrated that this antibody provided strong antiviral activity even at low doses. Together, ERDRP-0519 and fusion protein–targeting antibodies represent the most advanced candidates for future therapeutic development.

4.4. Supportive and Passive Immunotherapies

Although not antiviral, antibiotics such as co-trimoxazole play an important role in reducing secondary bacterial complications, particularly pneumonia, which remains a leading cause of measles-related deaths in resource-limited settings [39]. Intravenous immunoglobulin (IVIG) may be given post-exposure to high-risk individuals, providing temporary passive immunity and reducing the risk of developing severe measles. However, IVIG does not act directly against the virus itself. Table 1 outlines the summary of clinical trials on the treatment of measles.

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Table 1. Table Summary: Clinical Trials on Measles Treatments.

Study Title	Population	Intervention	Comparator	Key Outcomes	Study Design	ROB2 Risk
Vitamin A in Measles (Yao et al.)	98 children (6 mo–12 yrs)	Vitamin A (2.5M IU PO) + routine care	Routine care only	↓ fever, cough, photophobia, hospitalization; ↓ complications	RCT (randomized, unblinded, single-center)	Moderate
Acyclovir + Xiyanping (Zhao et al.)	76 patients (5–25 yrs)	Acyclovir + Xiyanping IV	Acyclovir only	↓ rash, fever, sore throat; ↑ QoL and total effective rate	RCT (randomized, unblinded)	Moderate
Tanreqing in Adults (Zhu et al.)	76 adults (18–27 yrs)	Tanreqing IV + standard care	Ribavirin + vitamins	↓ fever, rash, cough; ↓ complication rate	RCT (randomized, unblinded, single-center)	Moderate
Measles Enema + Western Med (Zhang et al.)	108 children (5 mo–6 yrs)	TCM enema + Western meds	Western meds only	↑ total efficacy; ↓ symptom resolution time	RCT (randomized, unblinded, single-center)	Moderate
Glycyrrhizin + Ribavirin (Jian et al.)	103 patients (5–38 yrs)	Ribavirin + Glycyrrhizin IV × 7–10 days	Ribavirin only	↑ total effective rate; ↓ rash, fever, hospital stay; ↓ complications	RCT (randomized, 2-center, unblinded)	Moderate
Interferon α-2a vs Ribavirin (Wang et al.)	81 patients (3–26 yrs)	Interferon α-2a IM × 3 days	Ribavirin IV × 5 days	↓ fever, rash appearance/resolutio	RCT (quasi-randomized by	Moderate–High

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		n; ↓ complications	admission date, unblinded, single-center)

5. Conclusion

While immunization remains the cornerstone of prevention, declining vaccine coverage and the resurgence of outbreaks highlight the urgent need for effective therapeutic strategies. Among currently available interventions, vitamin A supplementation remains the only consistently validated adjunctive therapy, with proven benefits in reducing morbidity and mortality. Ribavirin and interferon-α, although not yet part of routine care, provide proof-of-concept that targeted antiviral approaches are feasible. Promising advances include ERDRP-0519, which has shown efficacy in primate models, and monoclonal antibodies that target viral entry mechanisms.

Emerging therapeutics, including polymerase inhibitors and monoclonal antibodies, represent promising future options, but clinical validation is urgently needed. As vaccine uptake falters, sustainable measles control will require a dual approach: renewed investment in immunization programs, combined with research and implementation of adjunctive therapies to protect vulnerable populations during outbreaks. This integrated strategy ensures both immediate patient care and long-term disease control.

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Abbreviations

The following abbreviations are used in this manuscript:

R_0	Reproductive number
CDC	Centers for Disease Control and Prevention
MMR	Measles, Mumps, and Rubella
MeV	Measles virus
SSPE	Subacute Sclerosing Panencephalitis
IFN-α-n1	Interferon-α
IVIG	Intravenous immunoglobulin
RdRp	RNA-dependent RNA polymerase

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