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CLINICAL FEATURES OF MEASLES IN VACCINATED AND UNVACCINATED CHILDREN: DIFFERENTIAL DIAGNOSIS FROM COXSACKIE VIRUS INFECTION, RUBELLA, AND SCARLET FEVER, ALONG WITH INTERESTING LABORATORY FINDINGS

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Abstract

Measles, a highly contagious acute viral illness caused by the measles virus (a single-stranded RNA paramyxovirus), remains a significant global health concern despite the availability of an effective vaccine. It presents with a characteristic prodrome of the "three Cs" (cough, coryza, conjunctivitis) plus high fever, followed by pathognomonic Koplik spots and a centrifugal maculopapular rash. In unvaccinated children, the disease is typically severe, with complications such as pneumonia (1–6 per 100 cases), encephalitis, diarrhea, and otitis media occurring in up to 30% of cases; global estimates indicate approximately 10.3 million infections and 95,000 deaths in recent years, predominantly among unvaccinated children under 5 years. In vaccinated children (one or two doses of MMR), breakthrough infections are milder or "modified," with reduced fever intensity, absent or atypical Koplik spots, less pronounced rash, and markedly lower hospitalization and complication rates (e.g., vaccinated cases show statistically fewer severe symptoms and complications compared with unvaccinated, $p<0.05$ in multiple pediatric cohorts).

Interesting laboratory features include leukopenia (often <4,000/μL) with lymphopenia, mild thrombocytopenia, and occasional elevation of liver enzymes, while serological confirmation relies on measles-specific IgM (appearing 3+ days after rash onset) and RT-PCR for viral RNA. These markers, alongside clinical patterns, facilitate differential diagnosis from mimics such as Coxsackie virus (hand-foot-mouth disease with vesicular lesions on palms/soles/mouth), rubella (milder rash with postauricular lymphadenopathy, no Koplik spots), and scarlet fever (sandpaper-like rash, strawberry tongue, pharyngitis due to group A Streptococcus). In endemic or outbreak settings (e.g., resurgence in 2025 with thousands of U.S. cases, mostly unvaccinated), these tools enable rapid identification, isolation, and supportive management, including vitamin A supplementation (two doses 24 hours apart).

This review synthesizes etiopathogenetic mechanisms, comparative clinical features by vaccination status, differential diagnostic patterns, laboratory insights, and management considerations to optimize outcomes and underscore the critical role of vaccination in preventing morbidity.

Keywords: Measles; Vaccinated vs unvaccinated children; Clinical features; Koplik spots; Differential diagnosis; Coxsackie virus; Rubella; Scarlet fever; Laboratory findings (leukopenia, IgM serology); Vitamin A therapy; Global outbreaks

Introduction

Measles continues to pose a major public health challenge worldwide, with periodic resurgences driven by vaccine hesitancy, disrupted immunization programs, and international travel. Global incidence remains high, with an estimated 10.3 million cases in recent pre-2025 data and ongoing outbreaks in 2025 (e.g., over 1,100 confirmed U.S. cases by early 2026, 92–96% unvaccinated or unknown status; thousands in Europe and the Americas). In children, the disease is most severe in the unvaccinated, where the classic syndrome predominates, while vaccinated individuals experience attenuated "modified measles." Early clinical recognition, supported by laboratory markers, is essential for differential diagnosis from other childhood exanthems and for timely intervention to reduce complications and transmission (R0 12–18).

This review examines the inflammatory and immune basis of measles, contrasts clinical presentations by vaccination status, details differential diagnosis from Coxsackie virus, rubella, and scarlet fever, highlights interesting laboratory features, and discusses treatment/monitoring strategies, particularly relevant in resource-variable settings.

Etiopathogenesis of Measles

The measles virus enters via the respiratory tract, initially replicating in tracheal and bronchial epithelial cells before spreading to regional lymph nodes via infected macrophages. A primary viremia disseminates the virus systemically, followed by a secondary viremia that seeds skin, conjunctiva, and other organs. The characteristic rash results from cell-mediated immune response (T-cell infiltration) against virus-infected endothelial cells, while Koplik spots represent focal viral replication and immune reaction in oral mucosa. Profound transient immunosuppression occurs post-infection due to lymphopenia, impaired delayed-type hypersensitivity, and reduced IL-12 production, lasting weeks to months and increasing susceptibility to secondary bacterial infections. In vaccinated children with partial immunity, viral replication is limited, leading to milder systemic involvement and lower viral loads. Incubation is typically 10–14 days, with contagiousness from 4 days before to 4 days after rash onset.

Clinical Features of Measles in Unvaccinated and Vaccinated Children

In **unvaccinated children**, the classic presentation begins with a 2–4 day prodr ome of high fever (up to 40–41°C/104–105.8°F), malaise, and the three Cs: cough, coryza, and conjunctivitis (photophobia, watery eyes). Koplik spots—small white-blue papules on an erythematous buccal mucosa opposite the premolars—appear 1–2 days before the rash and are pathognomonic. The maculopapular rash erupts on day 3–5 (approximately 14 days post-exposure), starting at the hairline/face/ears, spreading centripetally to trunk and extremities, and fading with brownish desquamation over 5–7 days. Complications are frequent (up to 30%), including pneumonia, encephalitis (1/1,000), otitis media, diarrhea, and, rarely, subacute sclerosing panencephalitis (SSPE). Hospitalization rates reach 20–40% in young unvaccinated children, with higher mortality in malnourished populations.

In **vaccinated children**, breakthrough infections (primary or secondary vaccine failure) present as "modified measles": milder or absent prodrome, lower-grade or absent fever, infrequent or atypical Koplik spots, and a sparser, less confluent rash that may begin on extremities or resolve faster. Studies consistently show significantly fewer symptoms (e.g., reduced cough, rash prominence) and complications (hospitalization <10–15%, $p<0.05$ vs. unvaccinated cohorts in U.S., Iraqi, and Somali pediatric series). Two-dose recipients exhibit the mildest course, with transmission risk also reduced. Age influences severity, with extremes (infants, adolescents/adults) showing more complications regardless of status, but vaccination markedly attenuates overall disease burden.

Differential Diagnosis from Coxsackie Virus Infection, Rubella, Scarlet Fever and Drug Allergy with Rashes (Morbilliform Drug Eruption / Exanthematous Drug Reaction)

Measles must be differentiated from other febrile exanthems, particularly in partially vaccinated or outbreak settings:

- Coxsackie virus (enteroviral hand-foot-mouth disease or Boston exanthem): Summer/fall predominance; short or absent prodrome; fever with myalgias/sore throat; vesicular/ulcerative oral lesions and characteristic vesicles/papules on palms, soles, and buttocks (not generalized maculopapular). No Koplik spots; gastrointestinal symptoms prominent; rash does not spread cephalocaudally.

-Rubella (German measles): Milder prodrome (low-grade fever, malaise); discrete pink maculopapular rash starting on face but fading rapidly (1–3 days); prominent postauricular/suboccipital lymphadenopathy and arthralgia (adults); no Koplik spots or severe cough/conjunctivitis; generally benign course with rare complications.

- Scarlet fever (group A Streptococcus): Abrupt onset with sore throat/exudative pharyngitis; “sandpaper” punctate erythematous rash starting on neck/groin, intensifying in skin folds (Pastia lines), with circumoral pallor; strawberry tongue (white then red); no Koplik spots or respiratory prodrome; desquamation follows; responds to antibiotics.

Measles frequently presents with a morbilliform (maculopapular) rash that closely resembles many drug-induced exanthems, making differentiation challenging, especially in children on medications during febrile illnesses or in settings with recent drug exposure. Drug allergy rashes, particularly morbilliform drug eruptions (also called measles-like or exanthematous drug reactions), are among the most common cutaneous adverse drug reactions and account for the majority of maculopapular drug eruptions. These are typically type IV delayed hypersensitivity reactions triggered by drugs such as beta-lactam antibiotics (e.g., penicillins, cephalosporins), sulfonamides, anticonvulsants, allopurinol, NSAIDs, or others.

Drug Allergy with Rashes Symptoms Measles: Prominent 2–4 day prodrome with high fever (often >40°C), the classic “three Cs” (cough, coryza, conjunctivitis with photophobia and watery eyes), malaise, and sometimes diarrhea or vomiting. Systemic involvement is marked and precedes the rash. Drug eruption: Prodrome usually absent or minimal; fever, if present, is low-grade or part of a more severe hypersensitivity syndrome (e.g., DRESS). No prominent respiratory symptoms (cough, coryza, conjunctivitis) unless coincidental infection. Rash often appears without preceding severe systemic illness.

Pathognomonic Mucosal Findings Measles: Koplik spots (small white-blue-gray papules on an erythematous base, typically opposite the premolars on buccal mucosa) are highly specific, appearing 1–2 days before the rash and lasting 1–3 days. Enanthem is common. Drug eruption: No Koplik spots or characteristic enanthem. Oral involvement, if any, is nonspecific (e.g., mild erythema or erosions in severe cases).

Rash Characteristics and Progression Measles: Maculopapular rash starts on the face (hairline, behind ears), spreads centripetally (cephalocaudal) to trunk and extremities over 3–5 days, becomes confluent on upper body, blanches early, then fades with brownish discoloration and fine desquamation. Drug eruption: Rash often begins on trunk or proximal extremities, spreads outward (centrifugal tendency in some cases), may be symmetric, pruritic (itching is prominent, unlike measles where itch is mild or absent), and less likely to show strict cephalocaudal progression. Confluence and desquamation can occur but are variable.

Timing and Exposure History Measles: Incubation 10–14 days post-exposure; rash ~day 14 from exposure. History of contact with measles case or low vaccination coverage. Drug eruption: Typically appears 4–14 days (most often 7–10 days) after starting the offending drug; resolves with drug discontinuation (though may persist briefly). Recent drug history (especially antibiotics during presumed viral illness) is key.

Associated Features Measles: Profound immunosuppression post-infection; complications like pneumonia or encephalitis possible. Drug eruption: May include pruritus, facial edema (in some), or evolve to more severe forms (e.g., DRESS with lymphadenopathy, eosinophilia, organ involvement). Itch is a strong clue favoring drug reaction.

Clinical clues (Koplik spots, centrifugal rash progression, three Cs) plus exposure history and vaccination status guide suspicion; laboratory confirmation is essential in ambiguous cases.

Interesting Laboratory Features

Routine complete blood count (CBC) often reveals leukopenia (<4,000/μL) with lymphopenia (supportive of viral etiology; statistically lower WBC/lymphocyte counts vs. controls, $p<0.005$ in multiple studies) and occasional mild thrombocytopenia or relative lymphocytosis during recovery. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) may be altered, reflecting immune dynamics. Mildly elevated liver enzymes (transaminitis) and C-reactive protein (CRP) are common but less pronounced than in bacterial infections. Serological testing shows measles-specific IgM positivity (gold standard for acute infection, detectable 3–10 days post-rash; sensitivity increases with repeat testing if early negative). IgG indicates immunity or past infection (high-avidity IgG in secondary vaccine failure). RT-PCR on nasopharyngeal swab, throat swab, or urine detects viral RNA (highest yield 0–5 days post-rash) and distinguishes wild-type from vaccine strain. These accessible markers aid early diagnosis, severity assessment, and differentiation from bacterial mimics (e.g., higher leukocytosis/CRP in scarlet fever). In vaccinated cases, viral load is lower and IgM response may be blunted or delayed.

Treatment Considerations and Role of Laboratory Markers in Monitoring

No specific antiviral exists; management is supportive (hydration, antipyretics, eye care). Vitamin A supplementation is recommended by WHO/CDC for all children with measles (two doses 24 h apart: 50,000 IU <6 months, 100,000 IU 6–11 months, 200,000 IU ≥12 months) to reduce mortality and ocular complications, especially in hospitalized or malnourished cases. Antibiotics target secondary bacterial infections (e.g., pneumonia). Isolation (airborne precautions) and post-exposure prophylaxis (MMR within 72 h or immunoglobulin) are critical. Laboratory markers (normalization of leukopenia/lymphopenia, declining CRP, negative follow-up PCR) monitor resolution and detect complications/relapse risk. In outbreaks, serology/PCR confirms cases and guides public health response. Vaccination (two MMR doses, 93–97% effective) remains the cornerstone of prevention.

Conclusion

Measles clinical features differ markedly by vaccination status, with unvaccinated children experiencing severe classic disease and vaccinated children showing attenuated modified forms. Characteristic patterns (Koplik spots, rash progression) combined with targeted differential diagnosis from Coxsackie, rubella, and scarlet fever, and supported by interesting laboratory findings (leukopenia/lymphopenia, IgM serology, RT-PCR), enable prompt recognition and management. These tools are vital amid 2025 global resurgences, reducing morbidity when integrated with supportive care (including vitamin A) and high vaccination coverage. Future efforts should focus on sustaining >95% two-dose coverage to prevent outbreaks and protect vulnerable pediatric populations.

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