Dermatological manifestations during Dengue, Chikungunya, and Zika infections

Benedetta Sonego[a], *Antonio Schettini*[b], *Sinesio Talhari*[b], *Luiz Maciel*[b] *and Cesare Massone*[c]

Purpose of review
Arboviral infections caused by Dengue, Zika, and Chikungunya viruses continue to pose a significant global health threat, particularly in endemic regions. This review is timely because of the increasing prevalence of these infections, driven by factors such as urbanization and climate change. Dermatological manifestations of these viruses are crucial for early diagnosis, especially given the overlap in symptoms, which can complicate differential diagnosis.

Recent findings
Recent studies emphasize the importance of mucocutaneous symptoms in diagnosing arboviral infections. In Dengue, distinctive rashes like the 'islands of white in a sea of red' and hemorrhagic skin manifestations have been key diagnostic features. Zika is marked by a pruritic maculopapular rash and nonpurulent conjunctivitis, whereas Chikungunya often results in persistent rashes, desquamation, and hyperpigmentation, particularly on the face. Emerging research highlights the skin's role as both a primary infection site and an immune mediator in these viral diseases, offering new insights into their pathophysiology and potential therapeutic targets.

Summary
The unique dermatological profiles of Dengue, Zika, and Chikungunya are critical for guiding clinical diagnosis and treatment, especially in resource-limited settings. Understanding these cutaneous manifestations can improve early recognition, particularly in differentiating between these viruses in co-endemic areas. Future research may uncover novel therapeutic strategies by focusing on the interaction between these viruses and the skin's immune responses.

Keywords
arboviral infections, Chikungunya, Dengue, dermatological manifestations, Zika

INTRODUCTION

Arboviral infections, transmitted primarily by *Aedes aegypti* mosquitoes, represent a significant and growing global health concern [1,2]. Dengue virus (DENV), Zika virus (ZIKV), and Chikungunya virus (CHIKV) are the three most prevalent arboviruses worldwide, together accounting for millions of cases annually. Specifically, Dengue accounts for 400 million cases annually, Zika virus for 500 000 cases, and Chikungunya for 693 000 cases [1,2]. These viruses share common clinical and epidemiological features, yet each exhibit distinct dermatological manifestations that are critical for accurate diagnosis and management [3]. Over the last few decades, the incidence of these arboviral infections has surged dramatically due to changes in virus–vector–host interactions. Factors such as urbanization, globalization, deforestation, and increased international mobility have contributed to the widespread dissemination of the *Aedes* mosquito, along with the diseases it transmits [4,5]. The WHO is concerned about the pandemic potential of arboviruses like Dengue, Zika, and Chikungunya and through its Global Arbovirus Initiative, WHO is developing strategies to prepare for potential pandemics [6]. Similarly, the Pan American Health Organization

[a]Dermatology Clinic of Trieste, Maggiore Hospital, University of Trieste, Trieste, Italy, [b]Alfredo da Matta Hospital Foundation. Manaus-Amazonas, Brazil and [c]Dermatology Unit & Scientific Directorate, Galliera Hospital, Genoa, Italy

Correspondence to Benedetta Sonego, Maggiore Hospital, Piazza dell'Ospitale, 1 - 34125 Trieste, Italy. Tel: +39 403992056; e-mail: benedetta.sonego@gmail.com

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KEY POINTS

- Dermatological manifestations of Dengue, Zika, and Chikungunya are distinct and crucial for accurate differential diagnosis in endemic and nonendemic regions.
- Dengue is characterized by the 'islands of white in a sea of red' rash, hemorrhagic skin symptoms, and severe pruritus during recovery.
- Zika presents with a pruritic maculopapular rash, nonpurulent conjunctivitis, and peripheral edema, especially in pregnant women due to risks of congenital complications.
- Chikungunya often causes persistent rash, skin desquamation, and postinflammatory hyperpigmentation, with severe mucocutaneous eruptions observed in children.
- Recognizing the unique cutaneous features of each arbovirus aids in timely diagnosis and management, especially in resource-limited settings.

(PAHO) is addressing the challenge by providing tools for early diagnosis and management of these diseases in the Americas, where overlapping symptoms make diagnosis difficult.

Understanding the specific dermatological presentations of Dengue, Zika, and Chikungunya is essential for clinicians, particularly in endemic regions where co-infections and misdiagnoses are frequent and can lead to severe consequences.

This review aims to explore the dermatological features of these infections, emphasizing their role in differential diagnosis and guiding treatment decisions.

DERMATOLOGICAL FEATURES OF DENGUE

Dengue fever is characterized by a biphasic illness, with an initial febrile phase that lasts 2–7 days, followed by a defervescence period. Dermatological manifestations can occur during both the febrile and recovery phases of the disease. A maculopapular rash typically appears early in the febrile stage, affecting areas like the face, chest, and limbs, and is often described as 'islands of white in a sea of red', a distinguishing characteristic of Dengue [7▪]. This description refers to areas of unaffected skin interspersed within the surrounding erythema, offering a unique diagnostic clue that sets Dengue apart from other viral rashes.

As the disease progresses, particularly in more severe forms such as Dengue Hemorrhagic Fever (DHF) or Dengue Shock Syndrome (DSS), cutaneous signs may include petechiae, ecchymoses, and purpura (Figs. 1 and 2). These hemorrhagic manifestations result from increased capillary fragility and leakage, which can lead to life-threatening complications if untreated [7▪,8▪]. Skin desquamation, particularly on the palms and soles, is a common feature during the recovery phase of the illness, often accompanied by intense pruritus, which may persist for several weeks even after the fever resolves [8▪].

The clinical dermatological manifestations of Dengue, as described in the article of Salazar Flórez *et al.* [9▪], highlight the differences between children and adults in the hyperendemic state of Colombia. Dengue in children under 12 years old is commonly characterized by a rash, pruritus, and hypotension, with fever being a universal symptom. Dermatological signs such as itching and rash are more prevalent

FIGURE 1. Dengue: (a) purpuric rash on the trunk; (b) the purpuric rash that does not fade when vitro-pression. Courtesy of Sinesio Talhari, MD.

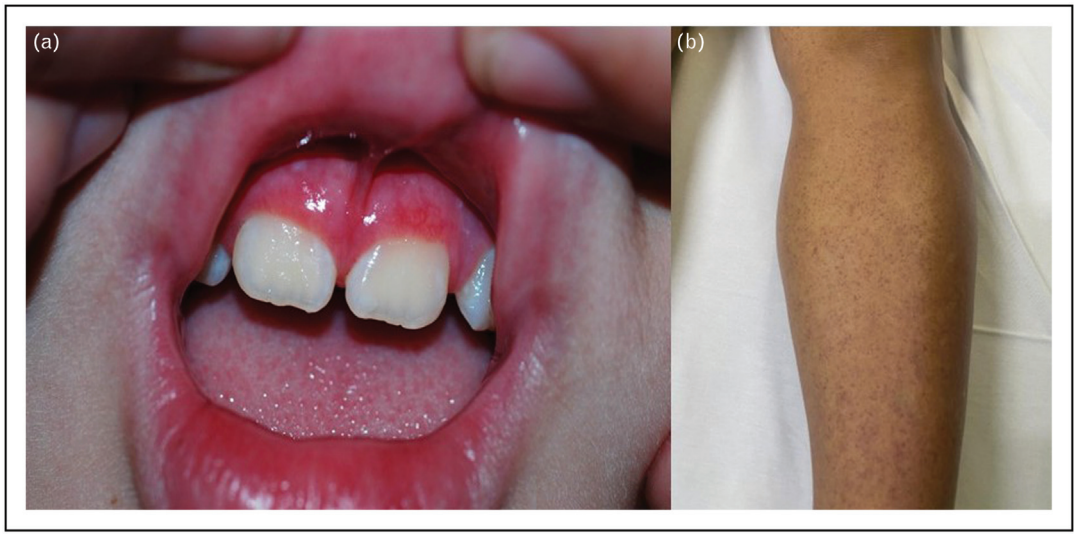

FIGURE 2. Dengue: (a) oral involvement with gingival and lip reddish and swelling; (b) purpuric and maculo papular rash on the left arm. Courtesy of Sinesio Talhari, MD.

in children, whereas older individuals typically experience general symptoms like headache, retro-orbital pain, back pain, dizziness, and chills. Severe Dengue, which includes more dangerous symptoms like hemorrhagic manifestations and vascular leakage, is more commonly observed in children, particularly in cases with pronounced hypotension. In adults, symptoms like hematuria and tachypnea are more prevalent. Elevated lymphocyte and platelet counts are typical in children, whereas older individuals show higher levels of hematocrit, hemoglobin, and basophils. These findings are crucial for healthcare providers to differentiate Dengue from other febrile illnesses and manage the disease effectively, particularly in younger populations where severe cases are more common [9▪].

A study conducted by Fera *et al.* [8▪] on Dengue patients in Reunion Island in 2019 found that mucocutaneous symptoms were present in over 80% of cases. The study involved 163 PCR-confirmed Dengue cases at the University Hospital of La Réunion, all examined by a dermatologist. The most common dermatological symptoms included itching, erythematous rashes, and oral involvement. While these cutaneous manifestations were not directly associated with severe Dengue, the presence of ecchymotic purpura was linked to more advanced disease presentations, underscoring the importance of dermatological examination in Dengue patients [8▪]. Pruritus and rash were notably associated with flu-like symptoms, such as myalgia and arthralgia, which are common in Dengue and further complicate the differential diagnosis with Chikungunya and Zika [8▪].

Interestingly, Dengue's interactions with the skin are not just limited to these visible manifestations. The skin plays a crucial role as both a primary site of infection and an immunological battleground [7▪]. The cutaneous manifestations during DENV infection are influenced by the dynamic interaction between the virus and the skin's innate immune system. Upon being bitten by an infected mosquito, the DENV infiltrates the skin's epidermal and dermal layers, targeting various cells such as keratinocytes, Langerhans cells, fibroblasts, macrophages, and mast cells. Once infected, these cells produce a cascade of pro-inflammatory signals that activate the body's antiviral immune responses [7▪]. However, this inflammatory environment and this immune response, can paradoxically facilitate viral spread. For instance, infected skin cells can recruit resident mononuclear cells to the site of infection, which subsequently become infected and spread the virus systemically [7▪].

This dynamic interaction between DENV and the cutaneous microenvironment remains an area of active research, particularly regarding how the skin's innate immune system, including antimicrobial peptides and cytokines, influences disease progression and severity. Understanding these processes could lead to novel therapeutic approaches aimed at mitigating the systemic spread of the virus by targeting these early interactions [7▪].

DERMATOLOGICAL FEATURES OF ZIKA

Zika virus presents with a different dermatological profile, despite sharing some features with Dengue

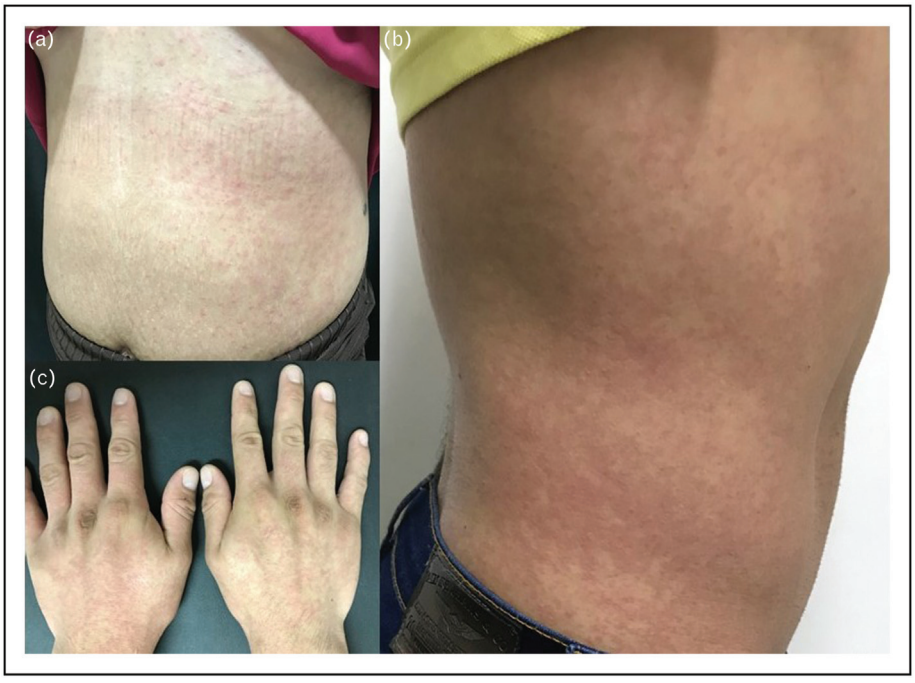

FIGURE 3. Zika: pruritic maculopapular rash on the trunk (panels a and b), and on the dorsum of the hands (panel c). Coutersy of professor Luiz Maciel, MD.

and Chikungunya. A pruritic maculopapular rash with a more pronounced papular component, is the hallmark cutaneous symptom of Zika virus infection, typically appearing early in the disease course, often within 1–4 days after the onset of fever and joint pain [10]. This rash usually begins on the face and rapidly spreads to the trunk, limbs, and occasionally, the palms and soles, which is relatively uncommon for most viral rashes. Although the Zika rash is pruritic, vesicular lesions are uncommon, and unlike Dengue, Zika is not typically associated with hemorrhagic manifestations (Fig. 3) [11].

One of the distinguishing features of Zika virus infection is the presence of nonpurulent conjunctivitis, which occurs in a significant proportion of cases. This conjunctivitis, along with the pruritic rash and mild systemic symptoms, helps to differentiate Zika from both Dengue and Chikungunya, particularly in early stages where the clinical overlap is considerable [11]. Zika is also characterized by peripheral edema, which further sets it apart from the other arboviruses. During the Zika outbreaks in Peru in 2016 and 2017, over 80% of symptomatic cases presented with a pruritic maculopapular rash [10]. This rash typically lasted for about 3–5 days, though itching could persist beyond the resolution of the rash, and antihistamines were often ineffective in alleviating the pruritus [10]. Other cutaneous findings, though less common, included petechiae on the hard palate and minor involvement of the palms and soles. Although Zika is generally considered a milder illness compared with Dengue and Chikungunya, the rash was often the primary reason patients sought medical attention during the outbreak, highlighting the diagnostic importance of this cutaneous manifestation [10]. In pregnant women, early recognition of Zika's rash and associated symptoms is particularly critical due to the risk of congenital Zika syndrome, which can result in severe birth defects, including microcephaly. Dermatological signs in affected newborns, such as scarring and hyperpigmentation, are linked to extensive neurological damage caused by the virus, and while these findings are not well documented, they represent an important area of ongoing research [11].

In nonendemic regions, the Zika rash could easily be mistaken for other viral or inflammatory conditions like urticaria. Recognizing the rash as an early indicator of Zika virus infection is crucial for timely diagnosis, particularly in pregnant women, who are at risk of severe congenital complications [10].

DERMATOLOGICAL FEATURES OF CHIKUNGUNYA

Diagnosis of these mucocutaneous manifestations of Chikungunya can be challenging as they often resemble other common dermatoses.

FIGURE 4. Chikungunya: maculopapular rash on the face (panels a and b); hyperpigmentation on the dorsum of the hands (panel c). Coutersy of professor Luiz Maciel, MD.

The early cutaneous manifestation of Chikungunya, occurring within the first month of fever, includes a maculopapular rash often accompanied by intense pruritus [12▪]. The rash typically appears between the third and fifth day of illness, usually affecting the trunk, limbs, and occasionally, the face. In about 40–50% of cases, the cause is thought to be due to immune complex deposition in the skin's capillaries, a type III hypersensitivity reaction (Fig. 4) [13].

Unlike Dengue, Chikungunya's rash tends to persist for a longer duration and is often associated with desquamation of the skin, particularly in the later stages of the disease [13].

Other early-onset dermatological manifestations include vesiculobullous eruptions, severe mucocutaneous eruptions resembling Stevens–Johnson syndrome and toxic epidermal necrolysis. Lesions with a flagellated appearance, dermatitis involving the genital areas and orogenital ulcers have also been described [12▪].

Some patients affected by CHIKV report exacerbations of preexisting skin conditions such as psoriasis or erythroderma [12▪,13,14]. Additionally, the virus has been implicated in triggering autoimmune skin disorders like vitiligo, though the mechanisms behind these associations are not yet fully understood [14,15].

Among the late-onset dermatological manifestations, hyperpigmentation and lichenoid eruptions have been observed. Additionally, diffuse alopecia and exacerbation of acne have also been described [12▪].

In children, Chikungunya can cause more severe dermatological manifestations, including bullous lesions and erythema around the joints. Vesiculobullous eruptions, skin peeling, xerosis, and conditions such as erythema nodosum and vasculitis-like lesions are more common in infants [14]. These skin manifestations are particularly concerning in pediatric patients, as they can be severe and may require specialized care. Nail abnormalities, such as periungual desquamation, melanonychia, and subungual hemorrhage, have been reported in some cases [13].

Chikungunya can lead to long-term skin changes, particularly residual pigmentation. This often manifests as postinflammatory hyperpigmentation on the face, which is especially common in individuals with darker skin tones. The pigmentation may appear as freckle-like spots or larger patches and can persist for several months after the initial rash has resolved. This phenomenon, sometimes referred to as the 'Chik sign' or 'Brownie nose appearance' is distinctive to Chikungunya and is not typically observed in Dengue or Zika infections [16]. It manifests as brownish hyperpigmentation, typically on the nose. This distinctive nasal pigmentation often lingers during the postinfective phase and can be particularly useful for diagnosing Chikungunya, especially in resource-limited areas where serological testing is not readily available. Although the pigmentary changes are asymptomatic, they may persist for several months [17].

A brief case report from the *Indian Journal of Pediatrics* described a case of neonatal Chikungunya

with Chik sign. The report details a full-term male infant who presented with blackish discoloration of the face, starting on the 10th day of life, which eventually spread across the body. The infant's mother had a history of high-grade fever in the last month of pregnancy, and both mother and child tested positive for IgM antibodies for Chikungunya. Despite initial concerns, including ruling out congenital adrenal hyperplasia, the infant's condition improved, and the hyperpigmentation cleared up over time [16].

A notable feature of Chikungunya infection is its potential to cause severe joint pain and arthritis-like symptoms, which can last for months to years in some patients. This chronic arthralgia, combined with the long-lasting dermatological sequelae, makes Chikungunya a particularly debilitating disease for some individuals [13].

DIFFERENTIAL DIAGNOSIS AND CHALLENGES

The similarity in cutaneous symptoms of Dengue, Chikungunya, and Zika viruses poses a challenge in nonendemic regions, where arboviral infections may be mistaken for other viral or inflammatory conditions, such as urticaria or viral exanthems unrelated to arboviruses. This diagnostic difficulty is also observed in endemic regions, where the clinical presentations of the three arboviruses, particularly their shared dermatological features, make accurate diagnosis challenging for healthcare providers.

Although all three viruses share several overlapping symptoms (fever, rash, and joint pain) the subtle differences in their dermatological presentations are key to making an accurate diagnosis [18] (Table 1). Dengue's rash is notable for its 'white island' pattern and it is often associated with hemorrhagic manifestations and capillary fragility, leading to petechiae and purpura. In contrast, Chikungunya tends to cause a more persistent rash with significant pruritus, skin desquamation, and facial hyperpigmentation, whereas Zika is marked by its pruritic rash, nonpurulent conjunctivitis, and peripheral edema [15,19▪].

Given the clinical overlap, laboratory confirmation is essential for distinguishing between these infections. Diagnostic tools such as reverse transcription–PCR (RT-PCR) and serological assays are widely used to confirm infections, though cross-reactivity between dengue and Zika serological tests can complicate diagnosis [20,21▪]. In regions where these viruses co-circulate, co-infections are not uncommon, further challenging clinical diagnosis [21▪].

CONCLUSION

Understanding the dermatological manifestations of Dengue, Chikungunya, and Zika is crucial for prompt diagnosis and management, particularly in regions where these viruses co-exist. Although laboratory testing remains the gold standard for definitive diagnosis, recognizing the distinct cutaneous features of each disease can guide clinicians

Table 1. Comparison of Dengue, Zika and Chikungunya arbovirus infections, in particular dermatological manifestations

Virus	Geographic distribution	Initial symptoms	Timing from symptoms to skin manifestations	Skin manifestations
Dengue	Tropical and subtropical regions, especially in the Americas, Southeast Asia, and Africa	Sudden fever, headache, retro-orbital pain, myalgia, arthralgia, nausea, vomiting	3–5 days	Maculopapular rash with island of sparing, petechiae, purpura, desquamation of palms/soles during recovery with intense pruritus
Zika	Africa, Southeast Asia, the Pacific Islands, the Americas	Mild fever, rash, joint pain, nonpurulent conjunctivitis	Concomitant	Maculopapular cephalocaudal rash, peripheral edema, pruritus
Chikungunya	Africa, Asia, Europe, and the Americas	Fever, severe joint pain, headache, muscle pain	2–5 days	Persisting maculopapular rash on trunk and limbs, intense pruritus, desquamation in later stages, vesiculobullous eruptions, hyperpigmentation ('Chik sign'), exacerbations of preexisting skin conditions

toward the correct diagnosis. As research continues to uncover the mechanisms behind these viruses' interactions with the skin, new insights may lead to better diagnostic tools and treatment strategies aimed at mitigating both the immediate and long-term effects of these arboviral infections.

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Conflicts of interest

There are no conflicts of interest.

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