Current Infectious Disease Reports (2019) 21: 18
https://doi.org/10.1007/s11908-019-0671-z

SKIN, SOFT TISSUE, BONE AND JOINT INFECTIOUS DISEASE (N SAFDAR AND A POP-VICAS, SECTION EDITORS)

Mucocutaneous Features of Zika—a Review

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Published online: 30 April 2019

Abstract

Purpose of Review We review the range of dermatological signs seen in Zika infection and the possible relationship between the rash and viremia. We also hoped to explore the utility of mucocutaneous manifestations in narrowing the differential diagnosis from other similar flaviviruses.

Recent Findings Clinical manifestations of Zika infection share many similarities with other mosquito-borne viruses such as dengue. These include non-specific symptoms such as a fever, rash, arthralgia, myalgia, and conjunctivitis. The morphology of the rash in Zika infection is not very specific and commonly described as maculopapular and centrifugal that usually extends to become diffuse.

Summary We reviewed 123 publications, encompassing a total of 368 Zika cases. One hundred seven cases with rash had sufficient data for detailed analysis. 8.4% of cases with rash had hemorrhagic manifestations such as palatal petechiae and bleeding ulcers. Only 20 reported cases were tested for viremia during presence of rash, and 70.6% of these cases were positive. While mucocutaneous complications are common in Zika infection, more research is necessary to determine the impact of rash on diagnosis, prognosis, and transmissibility in Zika infection.

Keywords Zika · Exanthem · Conjunctivitis · Flavivirus · Arbovirus · Rash

Introduction and Background

The Zika virus is a mosquito-borne virus that was discovered in Africa in 1947 [1] with the first human infection in 1952 [2]. It has only come to global attention in the last decade for its neurologic and teratogenic complications. The virus is a *Flavivirus*, in the same family as dengue virus, West Nile virus, yellow fever virus, Japanese encephalitis virus, and tick-borne encephalitis virus. Interestingly, the flaviviruses tend to have certain clinical characteristics: dengue and yellow fever viruses result in more hemorrhagic manifestations, while West Nile virus and Japanese encephalitis virus cause more neurologic damage. The Zika virus falls more closely on the phylogenetic tree to dengue virus, with Zika and dengue sharing many clinical features [3]. It is also difficult to differentiate clinically and serologically from dengue.

The defining surveillance criteria for a suspect Zika case includes the presence of rash, fever, and conjunctivitis in an epidemiologically appropriate population. For example, in 2016, the Singapore Ministry of Health defined a possible Zika case as any person who had fever and rash, with at least another symptom of either headache, myalgia, arthralgia, or conjunctivitis, and a history of living, working, or studying in an outbreak area. These symptoms and signs are not specific to Zika infection, and are frequently present in other flavivirus infections. This review article aims to explore the following

This article is part of the Topical Collection on *Skin, Soft Tissue, Bone and Joint Infectious Diseases*

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clinical questions: what are the mucocutaneous signs and symptoms present in Zika infection, whether these signs correlate with viremia, and whether the timeframe in which these occur assist the clinician in managing Zika infection especially in patients at risk of other flaviviruses.

Two Different Lineages of Zika

The Zika virus is subdivided into two major lineages—African, and Asian. Although the Asian lineage is responsible for most of the recent outbreaks across the world in particular in the Americas (2012 to 2016), a phylogenetic study suggests that the divergence of the Asian lineage from the African lineage occurred approximately 180 years ago [4].

There is a paucity of data on the clinical features of infection by African lineage of Zika virus. There are, however, in vitro studies that suggest differences in virulence and pathogenicity between the two strains [5•]. The pattern of innate immune responses triggered by African and Asian Zika strains in the human dermal fibroblasts and epidermal keratinocytes is reportedly different [6•]. Whether these in vitro differences manifest as clinical differences between the Asian and African strains is currently unknown and difficult to explore given the very few published clinical reports of individuals infected by the African lineage of Zika virus.

Overview of Clinical Features of Zika

Zika virus infection can be asymptomatic in many and possibly the majority of cases. Reported clinical manifestations include fever, arthralgia, rash, pruritus, myalgia, conjunctivitis, diarrhea, retro-orbital pain, and headache. Rash is the commonest cutaneous sign, described as maculopapular starting from the trunk and spreading to the limbs and face. A review of 66 cases published up to December 2016 found that 59% of rashes were described as maculopapular, with 44% being pruritic. Bleeding manifestations such as purpura, gingival bleeding, and oral hemorrhagic blisters were also present [7••].

Conversely, cutaneous features are rare in the congenital Zika syndrome. The major features of congenital Zika syndrome include brain malformations and neurological signs such as hyper- or hypotonia. Jaundice, hepatosplenomegaly and ocular complications are also important signs [8].

Literature Review

A literature search on the United States National Library of Medicine's Pubmed database using "Zika" and limited to "Case reports," "Clinical study," "Meta-analysis," "Multicenter study," "Observational study," and "Randomized Controlled Trial" yielded a total of 267 publications between February 1976 and September 2018.

All English language case reports, case series, and cohort studies which provided accessible information on clinical features of Zika infection or congenital Zika syndrome, together with confirmation of Zika infection via either detection of Zika RNA or serology, were included. Publications that were not written in English were excluded from this review. Publications that could not be accessed or for which the abstracts did not provide sufficient information were also excluded. Thirdly, cases where the diagnosis was in doubt, or where there was more than one infection that could have contributed to the clinical signs as determined by one of the authors (XQK), were also excluded from this analysis.

For cases with a rash or conjunctivitis, available details about onset, duration, morphology, distribution, and associated itch were entered into the data collection sheet. The results for Zika polymerase chain reaction (PCR) tests and serology, where available, were also tabulated.

Results of Literature Review

Of the initial 267 publications, 123 publications fulfilled our inclusion criteria as stated above. The remaining 144 publications were excluded from this analysis as they were either unable to be accessed, written in a language other than English, not certain about the diagnosis of Zika, had confounding factors casting doubt on the cause of their clinical signs, had insufficient details regarding laboratory or clinical findings, or were irrelevant to this review.

Out of the 123 included publications, 10 publications were case series or cohort studies that reported the frequency of rash or conjunctivitis in their respective study populations, without further detail on individual cases. Seventeen publications reported neonatal cases where Zika infection was acquired prenatally or perinatally. The remaining 96 publications reported a total of 128 individual adult cases of Zika infection.

Cutaneous Features of Zika

For the 10 publications of case series or cohort studies which did not provide sufficient details for analysis of individual cases, a total of 216 out of 240 cases (90%) had rash. Comparably, 107 out of the 128 individual adult Zika case reports (83.6%) had a rash. 42.1% of these 107 individual cases described the rash as maculopapular, while another 12.2% of the 107 cases were described as erythematous macules or patches. 3/107 cases described the rash as an exanthem. Commonly affected distributions included the trunk, upper limbs, lower limbs, neck, and face. 6.5% of the 107 individual case rashes involved the palms and/or soles. 9/107 cases (8.4%) had hemorrhagic manifestations such as

petechiae, bleeding ulcers, ecchymoses, bleeding gums, and even spontaneous hematomas [9]. A middle-aged woman demonstrated a positive Rumpel-Leede sign, where linear petechiae were seen on her upper arm after a sphygmomanometer cuff had been inflated over it. The Rumpel-Leede sign has been observed in other flavivirus infections such as dengue and Chikungunya and is thought to be due to capillary fragility [10•].

The onset of rash was specified in 39 out of 107 individual adult Zika cases (Fig. 1). The earliest documented rash occurred on day 0 of symptoms, and the latest onset was on day 7. The median onset was on day 1, while the mean onset was day 2. The duration of rash was documented in 52 out of 107 individual adult Zika cases (Fig. 2). The shortest duration was 12 h [11], while the longest lasted up to 9 days [12]. The median duration was 5 days, and the average duration was 4.6 days. Not all cases which documented onset of rash gave the duration of rash, and vice versa.

The relationship between rash and viremia or viruria was not very clear. Of the reported 107/128 individual adult Zika cases who had a rash, only 20/107 cases were confirmed to have had Zika PCR of either whole blood, serum, urine, or saliva performed during the period of active rash. Cases without the onset or duration of rash documented could not be analyzed for this or if they were tested with Zika PCR outside the period of rash. 12/17 (70.59%) samples from serum or whole blood in patients with rash showed the presence of viremia. Thirteen of 20 cases were tested for urine Zika PCR during the rash; all were positive (100%). There were 2 cases that had negative serum but positive urine Zika PCR. Conversely, there were no cases with rash that had positive serum PCR but negative urine PCR. Although the numbers are small, this is consistent with other observations that urine PCR is more sensitive than serum PCR. Quantitative PCR titers were not reported.

Conjunctivitis in Zika

Compared to other flavivirus infections, conjunctivitis appears to be a more prominent feature of Zika virus infection. The presence of conjunctivitis was documented in 9 out of the 10 case series or cohort studies that did not have individual patient information. These yielded a total of 121 cases, of which 45 (37.19%) had conjunctivitis. This percentage is comparable to the frequency of conjunctivitis in the 128 individual adult Zika case reports where 47 patients (36.72%) had conjunctivitis. One patient had punctate keratitis and bilateral keratic precipitates requiring topical ciprofloxacin-dextromethorphan [13]. Ten of 47 cases specified the day of onset of conjunctivitis (Fig. 3); half demonstrated conjunctivitis on day 1. Nine out of the 10 cases had simultaneous onset of conjunctivitis with rash. The last case started to have conjunctivitis on day 2 and rash on day 3 of symptoms [14]. One case demonstrated conjunctivitis as late as day 10 of symptoms [15]. The median onset of conjunctivitis was day 1.5, and the mean was day 2.6. The duration of conjunctivitis was specified in 11 cases (Fig. 4): the shortest duration was 3 days, and the longest up to 11 days. The median duration was 5 days and the average duration 5.6 days.

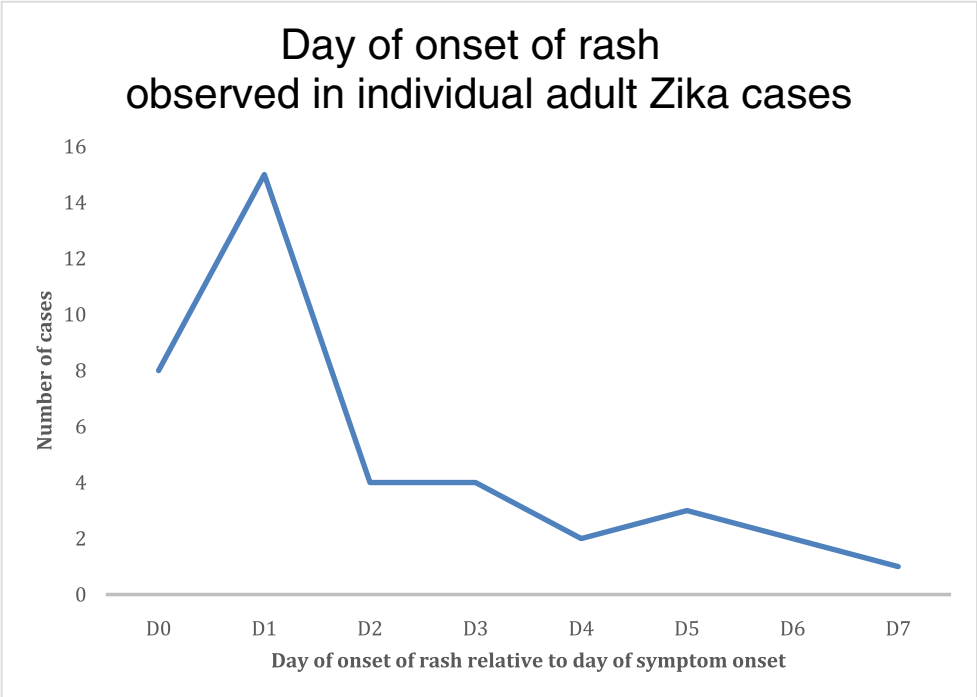

Fig. 1 The number of cases of rash observed in the individual adult Zika cases against the day of onset of rash relative to day of illness

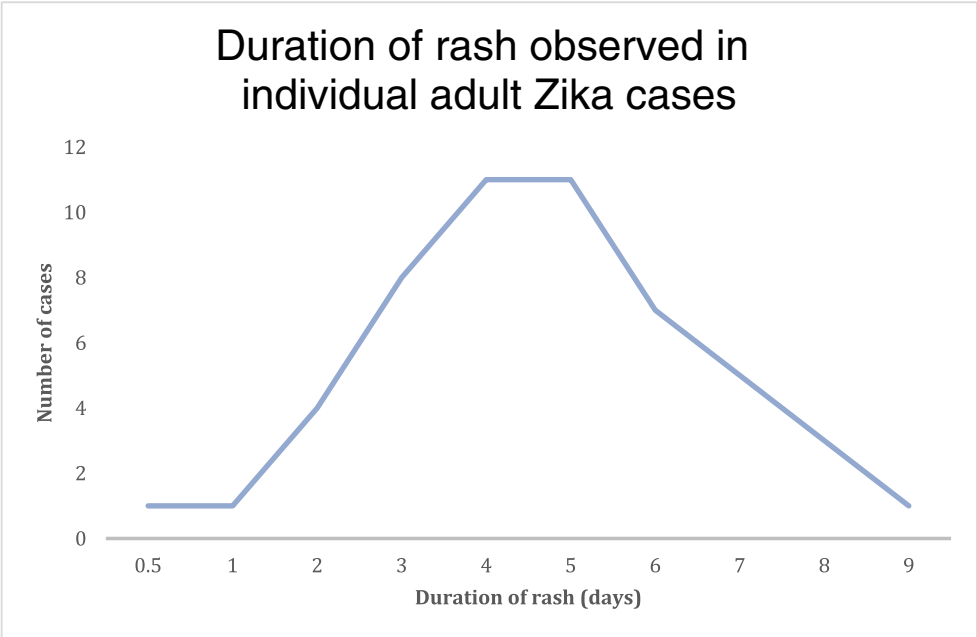

Fig. 2 The number of cases of rash observed in the individual adult Zika cases against the duration of rash in days

Zika PCR was performed in 5 cases while symptomatic with conjunctivitis. All 5 cases had positive urine Zika PCR (100%). four out of 5 cases were tested for viremia, with 1 out of 3 serum Zika PCR being positive, and 1 out of 1 whole-blood Zika PCR positive again reinforcing the better sensitivity of urine PCR for individuals with Zika virus infection.

Mucocutaneous Features in Neonates Born to Mothers Who Had Gestational or Perinatal Zika Infection

There were 17 publications on clinical neonatal Zika infections, whether acquired prenatally or perinatal. two of these publications were larger case series without individual case data about mucocutaneous features. Meneses et al. reported 87 cases of congenital Zika syndrome in which 71% of these cases were born with microcephaly, but did not report on the absence or presence of redundant scalp skin [16]. Van der Linden et al. reported 13 cases of congenital Zika syndrome in which 11/13 (84.61%) were diagnosed with postnatal microcephaly. 6/13 infants had craniofacial disproportion, and 3 of these infants had redundant scalp skin at birth. None of these 6 infants had microcephaly at birth, but it is not specified if they developed postnatal microcephaly later [17•].

In the remainder 15 publications, there were 20 individual neonatal cases of Zika acquired prenatally or perinatal. Sixteen of 20 individual case reports did not document the presence of any mucocutaneous features. Three of 20 had congenital Zika

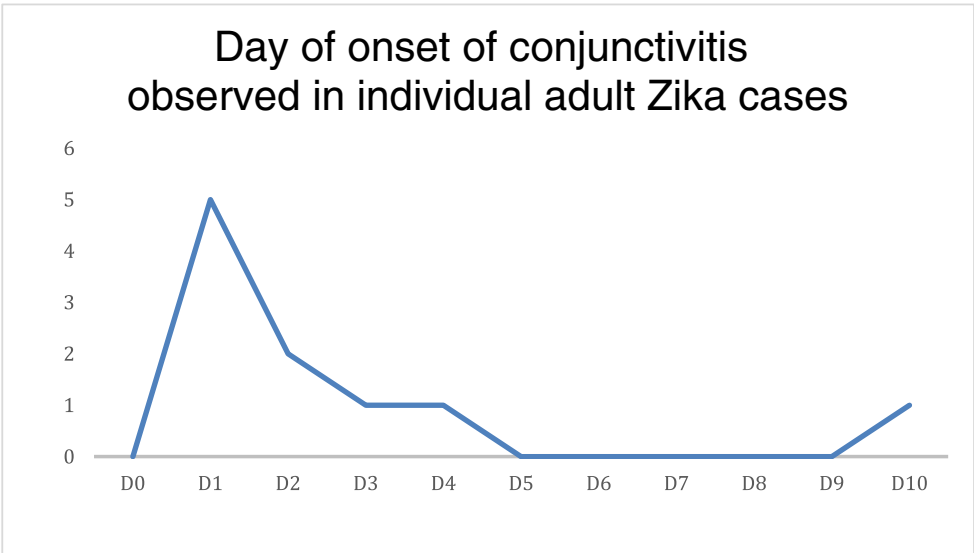

Fig. 3 The number of cases of conjunctivitis observed in the individual adult Zika cases against the day of onset of conjunctivitis relative to the day of symptom onset

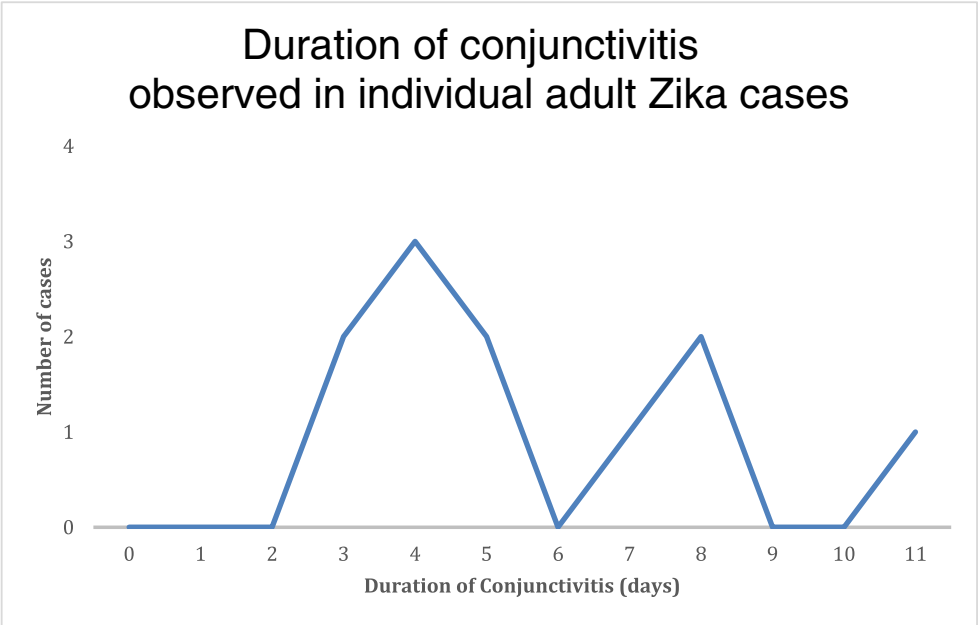

Fig. 4 The number of cases of conjunctivitis observed in the individual adult Zika cases against the duration of conjunctivitis in days

syndrome with severe microcephaly and redundant scalp skin at birth. One infant of the 20 presented with isolated diffuse rash on day 4 of life, likely having acquired Zika by breastfeeding. The neonate's mother had positive Zika PCR in her breastmilk, and neonatal serum Zika PCR was initially negative on day 3 of life, only becoming positive on day 4 at the onset of rash [18]. There were no neonates reported with conjunctivitis or other mucosal involvement.

Relationship Between Zika Viremia or Viruria and Rash

To determine the duration of viremia or viruria specifically in patients with rash, we evaluated information on serum, whole blood, and urine PCR results from the 107 individual adult Zika case reports; case series or cohort studies without raw data did not lend themselves to statistical analysis.

Out of 107 cases with rash, 77 cases had documented serum Zika PCR results. 49/77 cases had positive serum Zika PCR but 6 of these cases did not specify when the test was taken. 28/77 had negative first serum Zika PCR on first sampling. Table 1 demonstrates that most of the cases had their first positive serum Zika PCR taken in the first week of symptoms.

In contrast to this, Table 2 tabulates the first day of negative serum Zika PCR relative to day of illness. Forty-four of the 107 cases with rash had specified the day of first negative serum Zika PCR. The median time to a negative PCR was day 10.4 of illness, and mean is day 7.

We also compared serum to urine Zika PCR results. 46/107 cases had both serum and urine Zika PCR done. 17/46 cases had first positive sampling for both serum and urine PCR on the same day. 8/46 cases documented different first positive sampling dates for both serum and urine PCR—in 7 of these 8 cases, the first positive urine sample was taken at a later time compared to the first positive serum sample. One of the 8 cases had a positive serum Zika PCR with a negative concurrent urine Zika PCR [38]. 15/46 cases documented the dates when serum and urine Zika PCR became negative. In 10/15 cases, serum Zika PCR became negative before urine Zika PCR. In 5/15 cases, serum and urine Zika PCR were documented negative on the same day consistent with the observation that urine remained positive for Zika PCR longer than serum.

Whole-blood Zika PCR testing and saliva PCR were reported in a small number of cases of Zika with rash and thus are difficult to interpret in drawing conclusions about rash and viremia or salivary excretion of the virus.

Discussion

Zika is an emerging infectious disease with a newly recognized syndrome—the congenital zika syndrome with a significant impact on public health. Mucocutaneous manifestations are a prominent feature of Zika virus infections in both individual case reports and large published case series. While it is possible that the high frequency of rash occurring in acute Zika infection is a function of clinical case definitions adopted by the various public health agencies (WHO and CDC), our literature review suggests that rash is very common in Zika virus infection. The percentage of individual adult Zika cases from case reports who developed rash (83.6%) was similar to that of the pooled cases from the 10 publications of case series

Table 1 Patients with either rash, conjunctivitis, or both symptoms

Patient	Presence of Rash	Onset of rash (day of illness)	Duration of rash (days)	Rash descriptor	Pruritus	Presence of conjunctivitis	Onset of conjunctivitis (day of illness)
1	Present	0	7	Erythematous rash, distribution unspecified	Yes, mild	Absent	Absent
2	Present	Unspecified	Unspecified	Unspecified	Unspecified	Absent	Absent
3	Present	Unspecified	Unspecified	Unspecified	Unspecified	Present	Unspecified
4	Present	1	4	Maculopapular rash over face, trunk, limbs. Palmoplantar involvement. Tactile allodynia	Yes	Present	1
5	Present	0	Unspecified	Maculopapular rash, distribution unspecified.	No	Absent	Absent
6	Present	Unspecified	Unspecified	Unspecified	Unspecified	Absent	Absent
7	Present	Unspecified	Unspecified	Unspecified, full text unavailable.	Unspecified, full text unavailable.	Present	Unspecified
8	Absent	Absent	Absent	Absent	No	Present	Unspecified
9	Present	Unspecified	Unspecified	Unspecified	Unspecified	Absent	Absent
10	Present	Unspecified	Unspecified	Unspecified	Unspecified	Absent	Absent
11	Present	Unspecified	Unspecified	Unspecified	Unspecified	Absent	Absent
12	Present	Unspecified	Unspecified	Unspecified	Unspecified	Absent	Absent
13	Present	Unspecified	Unspecified	Unspecified	Unspecified	Absent	Absent
14	Present	Unspecified	Unspecified	Unspecified	Unspecified	Present	Unspecified
15	Present	Unspecified	4	Maculopapular rash over trunk and extremities	No	Present	Unspecified
16	Present	Unspecified	7	Maculopapular rash over face, trunk, limbs	No	Present	Unspecified
17	Present	Unspecified	2	Generalized rash	Unspecified	Absent	Absent
18	Present	Unspecified	2	Generalized rash	Unspecified	Absent	Absent
19	Present	Unspecified	Unspecified	Maculopapular rash over face, abdomen	No	Absent	Absent
20	Present	1	3	Maculopapular rash over trunk, limbs	Yes	Absent	Absent
21	Present	1	6	Rash over face, upper limbs	No	Present	1
22	Present	1	5	Maculopapular rash over face, trunk, limbs	No	Present	1
23	Present	2	5	Maculopapular rash over face, trunk, limbs	No	Absent	Absent
24	Present	3	4	Maculopapular rash over face, trunk, upper limbs	Yes	Present	2
25	Present	Unspecified	Unspecified	Maculopapular rash over trunk, limbs. Palatal petechiae. Rumpel-Leede sign positive.	No	Absent	Absent
26	Present	1	6	Erythematous follicular macules and papules over trunk, upper limbs. Tender palmar pink papules. Palatal petechiae.	No	Absent	Absent
27	Present	2	Unspecified	Unspecified	Unspecified	Absent	Absent
28	Present	2	5	Erythematous edematous rash over malar region	No	Present	2
29	Present	Unspecified	3	Maculopapular rash over trunk, limbs	No	Absent	Absent
30	Present	Unspecified	3	Exanthem	Yes	Absent	Absent
31	Present	Unspecified	4	Exanthem	Yes	Absent	Absent
32	Present	Unspecified	5	Exanthem	Yes	Absent	Absent
33	Present	Unspecified	5	Yes, generalized	No	Absent	Absent
34	Present	Unspecified	3	Yes, over trunk, limbs	No	Absent	Absent
35	Present	Unspecified	6	Yes, distribution unspecified.	No	Absent	Absent
36	Present	Unspecified	Unspecified	Yes, over trunk, upper limbs	No	Absent	Absent
37	Present	Unspecified	Unspecified	Hemorrhagic gums, epistaxis, vaginal bleeding, hematuria, ecchymoses	No	Absent	Absent
38	Present	Unspecified	Unspecified	Oral hemorrhages	No	Absent	Absent
39	Present	1	8		No	Present	Unspecified

Table 1 (continued)

Patient	Presence of Rash	Onset of rash (day of illness)	Duration of rash (days)	Rash descriptor	Pruritus	Presence of conjunctivitis	Onset of conjunctivitis (day of illness)
				Diffuse "sandpaper rash" over face, trunk, limbs.			
40	Present	Unspecified	1	Maculopapular rash, diffuse	Yes	Absent	Absent
41	Present	Unspecified	5	Maculopapular rash, diffuse	No	Absent	Absent
42	Present	Unspecified	Unspecified	Morbilliform rash with dysesthesia over trunk, upper limbs, thighs	Yes	Absent	Absent
43	Present	Unspecified	Unspecified	Leg swelling with erythematous lesions and pustules	No	Absent	Absent
44	Present	Unspecified	Unspecified	Maculopapular rash, distribution unspecified.	Yes	Absent	Absent
45	Present	0	6	Erythematous mottled rash over trunk, limbs that became papular on day 3. Oral mucosal vesicles developed on day 3. Rash resolved day 5. Palmoplantar desquamation developed day 15.	Yes	Absent	Absent
46	Present	3	Unspecified	Erythematous rash over face, trunk	No	Absent	Absent
47	Present	Unspecified	Unspecified	Erythematous rash, generalized	No	Absent	Absent
48	Present	Unspecified	Unspecified	Maculopapular rash, generalized	No	Present	Unspecified
49	Present	Unspecified	Unspecified	Palatal petechiae	No	Present	Unspecified
50	Present	1	8	Erythematous rash, distribution unspecified	Yes	Present	Unspecified
51	Present	1	9	Unspecified	Unspecified	Absent	Absent
52	Present	Unspecified	Unspecified	Unspecified	Unspecified	Present	Unspecified
53	Present	Unspecified	Unspecified	Generalized rash over face, trunk, upper limbs	Yes	Present	Unspecified
54	Present	Unspecified	Unspecified	Maculopapular rash, distribution unspecified.	Yes	Absent	Absent
55	Present	Unspecified	3	Maculopapular rash over trunk, upper limbs	Yes	Absent	Absent
56	Present	Unspecified	Unspecified	Unspecified	Unspecified	Absent	Absent
57	Present	5	5	Erythematous rash over neck, trunk, limbs	Yes	Present	Unspecified
58	Present	Unspecified	Unspecified	Unspecified	Unspecified	Absent	Absent
59	Present	Unspecified	Unspecified	Unspecified	Unspecified	Absent	Absent
60	Present	Unspecified	Unspecified	Unspecified	Unspecified	Absent	Absent
61	Present	Unspecified	Unspecified	Maculopapular rash, distribution unspecified.	No	Absent	Absent
62	Present	Unspecified	Unspecified	Maculopapular rash, distribution unspecified.	No	Present	Unspecified
63	Present	Unspecified	Unspecified	Maculopapular rash, distribution unspecified.	No	Present	Unspecified
64	Present	0	5	Erythematous rash, generalized for first 5 days. Onset of generalized petechiae and bloody ulcers over tongue, buccal mucosa on D6	No	Absent	Absent
65	Present	1	Unspecified	Petechiae over lips, palate, extremities. Oral mucosal bleeding.	No	Absent	Absent
66	Present	4	5	Maculopapular rash over trunk, limbs, palms	No	Present	4
67	Present	Unspecified	2	Generalized skin rash	Unspecified	Absent	Absent
68	Present	Unspecified	3	Unspecified	Unspecified	Present	Unspecified
69	Present	3	4	Erythematous rash, generalized	No	Present	3
70	Present	3	6	Faint rash	Yes	Absent	Absent
71	Present	5	4	Generalized rash. Erythematous rash over cheeks	No	Absent	Absent
72	Present	Unspecified	Unspecified	Malar erythema with edema, generalized erythema over trunk with micropapules and follicular accentuation, ocular pruritus	Yes	Present	Unspecified
73	Present	1	5		No	Present	Unspecified

Table 1 (continued)

Patient	Presence of Rash	Onset of rash (day of illness)	Duration of rash (days)	Rash descriptor	Pruritus	Presence of conjunctivitis	Onset of conjunctivitis (day of illness)
				Maculopapular rash over trunk, limbs. Erythema over face			
74	Present	1	8	Erythematous non-blanching papular rash over trunk, upper limbs, head, neck, palms. Palatal petechiae.	No	Present	1
75	Absent	Absent	Absent	Absent	No	Present	Unspecified
76	Present	6	7	Erythematous rash over face, trunk, limbs. edema of hands and feet, enanthema over palate.	No	Present	Unspecified
77	Present	Unspecified	Unspecified	Erythematous rash	No	Absent	Absent
78	Absent	Absent	Absent	Absent	No	Present	Unspecified
79	Present	Unspecified	3	Pruritic rash over upper body	Yes	Present	Unspecified
80	Present	Unspecified	7	Pruritic rash over trunk, upper limbs	Yes	Present	Unspecified
81	Present	1	7	Maculopapular rash over abdomen, limbs	Yes	Absent	Absent
82	Present	1	4	Unspecified	Unspecified	Absent	Absent
83	Present	Unspecified	Unspecified	Rash on back and face	No	Present	Unspecified
84	Present	Unspecified	0.5	Rash over face, trunk	No	Absent	Absent
85	Present	Unspecified	Unspecified	Maculopapular rash over trunk, limbs	No	Absent	Absent
86	Present	Unspecified	Unspecified	Unspecified	Unspecified	Absent	Absent
87	Present	Unspecified	Unspecified	Maculopapular rash, generalized	No	Absent	Absent
88	Present	0	3	Erythematous rash over abdomen, upper limbs	No	Present	Unspecified
89	Present	Unspecified	2	Unspecified	Unspecified	Absent	Absent
90	Present	0	6	Yes, over face, trunk, limbs	No	Present	Unspecified
91	Present	Unspecified	Unspecified	Yes, over trunk, limbs	No	Absent	Absent
92	Present	7	5	Small red rash	No	Present	10
93	Present	1	Unspecified	Initially had pruritic maculopapular rash that started on day 1 of symptoms. On day 10, patient developed spontaneous subcutaneous hematomas in her arms and legs, without petechial bleeding.	Yes	Absent	Absent
94	Present	1	Unspecified	Maculopapular rash over trunk, extremities	No	Present	Unspecified
95	Present	Unspecified	Unspecified	Maculopapular rash over face, trunk, upper limbs	No	Present	Unspecified
96	Present	6	6	Rubelliform exanthema over upper chest	No	Absent	Absent
97	Present	Unspecified	Unspecified	Rash over face, trunk	No	Absent	Absent
98	Present	Unspecified	Unspecified	Maculopapular rash over face, trunk, limbs, palms, soles	No	Present	Unspecified
99	Present	Unspecified	4	Erythematous rash over face, trunk, limbs	Yes	Absent	Absent
100	Present	Unspecified	Unspecified	Maculopapular rash over trunk, limbs	No	Present	Unspecified
101	Present	2	4	Maculopapular rash over trunk, limbs	No	Present	Unspecified
102	Absent	Absent	Absent	Absent	No	Present	Unspecified
103	Present	5	4	Papular rash over extremities and involving palms	No	Present	Unspecified
104	Present	Unspecified	Unspecified	Maculopapular rash over face, trunk, extremities	No	Present	Unspecified
105	Present	Unspecified	Unspecified	Unspecified	Unspecified	Present	Unspecified
106	Present	Unspecified	Unspecified	Maculopapular rash over face, trunk, extremities	No	Absent	Absent
107	Present	Unspecified	Unspecified	Maculopapular rash over face, trunk, extremities	No	Present	Unspecified
108	Present	Unspecified	Unspecified	Maculopapular rash over trunk, limbs	No	Present	Unspecified
109	Present	0	3	Maculopapular rash over trunk. Aphthous ulcer onset day 3	No	Absent	Absent
110	Present	0	4		No	Absent	Absent

Table 1 (continued)

Patient	Presence of Rash	Onset of rash (day of illness)	Duration of rash (days)	Rash descriptor	Pruritus	Presence of conjunctivitis	Onset of conjunctivitis (day of illness)
111	Present	4	Unspecified	Maculopapular rash over trunk Maculopapular rash over trunk, thighs, neck	No	Present	Unspecified

Patient	Duration of conjunctivitis (days)	Result of whole-blood Zika PCR	Result of serum/plasma Zika PCR	Result of urine Zika PCR	Result of saliva Zika PCR	Publication
1	Absent	Not done	Not done	Positive on day 7	Not done	Regadas et al. (2018) [19]
2	Absent	Not done	Not done	Positive on day 3	Not done	Oliveira et al. (2018) [20]
3	Unspecified	Not done	Negative, unspecified when	Negative, unspecified when	Not done	Abdalla et al. (2018) [21]
4	4	Positive from days 1–4, negative on day 5	Positive from days 1–3, negative on day 4	Positive from days 1–7	Positive from days 2–3, negative on day 4	Tan et al. (2018) [22]
5	Absent	Not done	Positive from days 5–7, negative on day 15	Not done	Positive on day 5, negative on day 7	Ricciardi et al. (2017) [23]
6	Absent	Not done	Positive, unspecified when	Not done	Not done	Corrêa-Oliveira et al. (2017) [24]
7	Unspecified	Not done	Positive, unspecified when	Not done	Not done	Landais et al. (2017) [25]
8	Unspecified	Not done	Positive from days 1–115, negative on day 153	Positive from days 1–8, negative on day 29	Not done	Desclaux et al. (2018) [26]
9	Absent	Not done	Not done	Positive on day 9	Not done	Garcia-Bujalance et al. (2017) [27]
10	Absent	Not done	Not done	Positive on day 12	Not done	Garcia-Bujalance et al. (2017) [27]
11	Absent	Not done	Not done	Negative first sample taken on day 30	Not done	Garcia-Bujalance et al. (2017) [27]
12	Absent	Not done	Not done	Negative first sample taken on day 47	Not done	Garcia-Bujalance et al. (2017) [27]
13	Absent	Not done	Negative first sample taken on day 7	Positive on day 7	Not done	Pradhan et al. (2017) [28]
14	Unspecified	Not done	Positive on day 3	Positive on day 3	Positive on day 4	Percivalle et al. (2017) [29]
15	Unspecified	Negative first sample taken on day 3	Positive on day 6	Positive on day 3	Negative on day 3	Katanami et al. (2017) [30]
16	Unspecified	Positive on day 4	Negative, unspecified when	Positive on day 4	Positive on day 4	Hashimoto et al. (2017) [31]
17	Absent	Not done	Not done	Not done	Not done	Acosta-Reyes et al. (2017) [32]
18	Absent	Not done	Not done	Not done	Not done	Acosta-Reyes et al. (2017) [32]
19	Absent	Not done	Positive on day 2, negative on day 5	Positive on day 5, negative on day 24	Not done	Sotelo et al. (2017) [33]
20	Absent	Not done	Positive on day 3, negative on day 17	Positive on day 10, negative on day 17	Not done	Cavalcanti et al. (2017) [14]
21	5	Not done	Negative first sample taken on day 5	Positive on day 5	Not done	Cavalcanti et al. (2017) [14]
22	3	Not done	Positive on day 7, negative on day 9	Positive on day 9	Not done	Cavalcanti et al. (2017) [14]
23	Absent	Not done	Positive from days 5–7, negative on day 30	Positive on day 30, negative 8 months later	Not done	Cavalcanti et al. (2017) [14]
24	Unspecified	Not done	Positive on day 3	Positive on day 3	Not done	Penot et al. (2017) [34]
25	Absent	Not done	Not done	Not done	Not done	Kulkami et al. (2017) [10]
26	Absent	Not done	Positive from days 3–45	Positive from days 3–17, negative on day 18	Not done	Chen et al. (2017) [35•]
27	Absent	Positive from days 9–101, negative on day 112.	Not done	Positive from days 6–14, negative on day 21	Positive from days 9–21, negative on day 28	Froeschi et al. (2017) [36]
28	5	Not done	Positive, unspecified when	Not done	Not done	He et al. (2017) [37••]
29	Absent	Not done	Positive from days 18–107	Negative, unspecified when	Not done	Suy et al. (2016) [38]
30	Absent	Not done	Not done	Not done	Not done	Vomjaes et al. (2017) [39]
31	Absent	Not done	Not done	Not done	Not done	Vomjaes et al. (2017) [39]
32	Absent	Not done	Not done	Not done	Not done	Vomjaes et al. (2017) [39]
33	Absent	Not done	Positive on day 2, negative on day 3	Positive on day 2	Not done	Xu et al. (2016) [40]
34	Absent	Not done	Negative first sample taken on day 7	Negative first sample taken on day 7	Not done	Nicastri et al. (2016) [41]
35	Absent	Not done	Positive on day 2	Positive on day 2	Not done	Nicastri et al. (2016) [41]
36	Absent	Not done	Positive on day 3	Positive on day 3	Not done	Nicastri et al. (2016) [41]
37	Absent	Not done	Positive on day 7	Not done	Not done	Azevedo et al. (2016) [42]
38	Absent	Not done	Not done	Not done	Not done	Azevedo et al. (2016) [42]
39	Unspecified	Not done	Positive on day 9	Positive on day 15	Not done	Fabrizius et al. (2016) [43]
40	Absent	Not done	Negative first sample taken on day 23	Not done	Not done	do Rosário et al. (2016) [44]

Table 1 (continued)

Patient	Duration of conjunctivitis (days)	Result of whole-blood Zika PCR	Result of serum/plasma Zika PCR	Result of urine Zika PCR	Result of saliva Zika PCR	Publication
41	Absent	Not done	Negative first sample taken on day 8	Not done	Not done	do Rosário et al. (2016) [44]
42	Absent	Positive on day 2, negative on day 11	Not done	Positive from days 2–17, negative on day 37	Not done	Visseaux et al. (2016) [45]
43	Absent	Not done	Positive on day 3, negative on day 13	Not done	Not done	Siu et al. (2016) [46]
44	Absent	Not done	Not done	Positive on day 3	Not done	Gaskell et al. (2017) [47]
45	Absent	Positive from days 0–81.	Positive from days 0–8, negative on day 14	Positive from days 0–14, negative on day 21	Positive from days 0–14, negative on day 21	Murray et al. (2017) [48]
46	Absent	Not done	Not done	Not done	Not done	Cleto et al. (2016) [49]
47	Absent	Not done	Negative first sample taken on day 7	Positive on day 7	Not done	Zea-Vera and Parra et al. (2017) [50]
48	Unspecified	Not done	Positive, unspecified when	Not done	Not done	Swaminathan et al. (2016) [51]
49	Unspecified	Not done	Negative first sample taken on day 7	Positive on day 7	Not done	Swaminathan et al. (2016) [51]
50	Unspecified	Done, result not reported	Not done	Not done	Not done	Arsuaga et al. (2016) [12]
51	8	Done, result not reported	Not done	Positive on day 24	Not done	Arsuaga et al. (2016) [12]
52	Unspecified	Not done	Not done	Positive on day 7	Not done	Brent et al. (2016) [52]
53	Unspecified	Not done	Positive on day 6, negative on day 7	Positive from days 6–28	Positive on day 7, negative on day 17	Nicastri et al. (2016) [53]
54	Absent	Not done	Negative first sample taken day 3	Positive on day 3	Not done	Brooks et al. (2016) [54]
55	Absent	Not done	Positive from days 3–9	Positive on day 3, negative on day 14	Positive from days 5–47	Barzon et al. (2016) [55]
56	Absent	Not done	Negative first sample taken on day 17	Positive on day 91, negative on day 134	Positive from days 17–91, negative on day 134	Nicastri et al. (2016) [56]
57	Unspecified	Not done	Positive on day 10	Not done	Not done	Zhong et al. (2016) [57]
58	Absent	Negative first sample taken on day 93	Not done	Negative first sample taken on day 93	Not done	Mansuy et al. (2016) [58]
59	Absent	Not done	Negative first sample taken on day 19	Negative first sample taken on day 21	Not done	Harrower et al. (2016) [59]
60	Absent	Not done	Positive on day 4, negative on day 9	Positive on day 9	Not done	Harrower et al. (2016) [59]
61	Absent	Not done	Positive on day 3	Positive on day 3	Not done	Davidson et al. (2016) [60]
62	Unspecified	Not done	Negative first sample taken on day 3	Positive on day 3	Not done	Davidson et al. (2016) [60]
63	Unspecified	Positive from days 1–4, negative on day 11	Not done	Negative first sample taken on day 1	Not done	Prisant et al. (2016) [61]
64	Absent	Not done	Positive on day 3	Not done	Not done	Sharp et al. (2016) [62]
65	Absent	Not done	Negative first sample taken on day 5	Negative first sample taken on day 46	Negative first sample taken on day 46	Sharp et al. (2016) [62]
66	11	Positive from days 6–7, negative on day 14	Not done	Positive from days 7–14, negative on day 21	Positive from days 7–14, negative on day 21	Jang et al. (2016) [63]
67	Absent	Not done	Positive on 2nd month (day 56)	Not done	Not done	Perez et al. (2016) [64]
68	Unspecified	Not done	Positive, unspecified when	Not done	Not done	Furtado et al. (2016) [13]
69	4	Not done	Positive on day 2, negative on day 10	Positive from days 2–19	Positive on day 6, negative on day 10	Reusken et al. (2016) [65]
70	Absent	Not done	Negative first sample taken on day 8	Negative first sample taken on day 48	Negative first sample taken on day 134	Frank et al. (2016) [66]
71	Absent	Not done	Positive from days 5–7, negative on day 38	Positive on day 5, negative on day 38	Negative first sample taken on day 5	Frank et al. (2016) [66]
72	Unspecified	Not done	Positive on day 3	Positive on day 3	Not done	Burillo-Martinez et al. (2016) [67•]
73	Unspecified	Not done	Positive on day 2, negative on day 3	Positive from days 2–12, negative on day 14	Not done	Zhang et al. (2016) [68]
74	8	Not done	Negative first sample taken on day 4	Positive on day 4	Not done	Derrington et al. (2016) [69•]
75	Unspecified	Not done	Positive, unspecified when	Positive, unspecified when	Not done	Rozé et al. (2016) [70]
76	Unspecified	Not done	Positive on day 5	Positive on day 11	Positive on day 10	Brasil et al. (2016) [71]
77	Absent	Not done	Positive on day 3, negative on day 27	Negative first sample taken on day 27	Not done	Atkinson et al. (2016) [72]
78	Unspecified	Not done	Not done	Not done	Not done	Díaz-Quiñonez et al. (2016) [73]
79	3	Not done	Negative first sample taken on day 14	Negative first sample taken on day 24	Negative first sample taken on day 24	Deckard et al. (2016) [74]
80	7	Not done	Negative first sample taken on day 4	Negative first sample taken on day 17	Negative first sample taken on day 17	Deckard et al. (2016) [74]
81	Absent	Not done	Not done	Positive on day 3	Positive on day 3	D'Ortenzio et al. (2016) [75]
82	Absent	Not done	Negative first sample taken on day 16	Positive on day 16	Negative first sample taken on day 10	D'Ortenzio et al. (2016) [75]

Table 1 (continued)

Patient	Duration of conjunctivitis (days)	Result of whole-blood Zika PCR	Result of serum/plasma Zika PCR	Result of urine Zika PCR	Result of saliva Zika PCR	Publication
83	Unspecified	Not done	Positive on day 9	Positive from days 10–12	Not done	Li et al. (2016) [76]
84	Absent	Not done	Positive on day 15	Not done	Not done	Bocanegra et al. (2016) [11]
85	Absent	Not done	Not done	Not done	Not done	Bocanegra et al. (2016) [11]
86	Absent	Not done	Positive on 4th week (day 28)	Not done	Not done	Driggers et al. (2016) [77]
87	Absent	Not done	Positive on day 4	Not done	Not done	Cardona-Cardona and Rodríguez Morales (2016) [78]
88	Unspecified	Not done	Positive from days 4–29	Positive on day 4	Positive on day 4	Barzon et al. (2016) [79]
89	Absent	Not done	Negative first sample taken on day 1	Negative first sample taken on day 1	Not done	Carteaux et al. (2016) [80]
90	Unspecified	Not done	Positive from days 38–109	Not done	Not done	Venturi et al. (2016) [81]
91	Absent	Not done	Positive from days 39–93	Not done	Not done	Venturi et al. (2016) [81]
92	4	Not done	Not done	Not done	Not done	Deng et al. (2016) [15]
93	Absent	Negative first sample taken on day 17	Not done	Positive on day 17	Not done	Karimi et al. (2016) [9]
94	Unspecified	Not done	Positive, unspecified when	Not done	Not done	Weitzel and Cortes (2016) [82]
95	Unspecified	Not done	Not done	Not done	Not done	Chen (2016) [83]
96	Absent	Not done	Negative first sample taken on day 6	Not done	Not done	Gyurech et al. (2016) [84]
97	Absent	Not done	Positive on day 6	Positive on day 7	Not done	Korhonen et al. (2016) [85]
98	Unspecified	Not done	Not done	Not done	Not done	Shinohara et al. (2016) [86]
99	Absent	Not done	Negative first sample taken on day 4	Not done	Not done	Zammarchi et al. (2015) [87]
100	Unspecified	Not done	Not done	Not done	Not done	Summers et al. (2015) [88]
101	Unspecified	Not done	Negative first sample taken on day 3	Not done	Not done	Tappe et al. (2015) [89]
102	Unspecified	Not done	Positive on day 3	Not done	Not done	Alera et al. (2015) [90]
103	Unspecified	Not done	Positive on day 6, negative on day 10	Positive on day 6	Not done	Fonseca et al. (2014) [91]
104	Unspecified	Not done	Positive on day 5, negative on day 36	Not done	Not done	Wæhre et al. (2014) [92]
105	Unspecified	Not done	Negative first sample taken on day 8	Not done	Not done	Oehler et al. (2014) [93]
106	Absent	Not done	Positive on day 5	Not done	Not done	Kutsuna et al. (2014) [94]
107	Unspecified	Not done	Negative first sample taken on day 6	Positive on day 6	Not done	Kutsuna et al. (2014) [94]
108	Unspecified	Not done	Positive on day 5	Not done	Not done	Kwong et al. (2013) [95]
109	Absent	Not done	Negative first sample taken on day 4	Not done	Not done	Foy et al. (2011) [96]
110	Absent	Not done	Negative first sample taken on day 5	Not done	Not done	Foy et al. (2011) [96]
111	Unspecified	Not done	Negative first sample taken on day 5	Not done	Not done	Foy et al. (2011) [96]

or cohort studies (90%). The rash often developed within the first 2 days of illness and was unlikely to occur after the first week of symptoms. It lasted an average of 4.6 days. The rash most commonly manifested as maculopapular (42.1%), but could also include hemorrhagic signs (8.4%) (Fig. 5).

Possibly because of the inclusion of rash but not conjunctivitis in the case definition, there were fewer patients who had reported conjunctivitis compared to rash (37% versus 83.6–90%) in the published case reports. Patients tended to develop conjunctivitis early in the course of the disease (median of day 1.5), and this often coincided with the onset of rash. The duration of conjunctivitis was on average slightly longer than that of rash (4.6 versus 5.6 days). Due to the limitations of serial testing for Zika virus infection, it is not possible to determine the relationship between the duration of fever and/or conjunctivitis and infectivity. There are reports of persistence of Zika virus in conjunctival fluids for up to a month after the onset of infection raising the possibility that tears like other body fluids may be an important mode of transmission [106].

The diagnosis of Zika versus other flaviviruses is a challenging one. Chikungunya and dengue viruses are both flavivurses that are also transmitted by the *Aedes* spp. mosquito, and thus often endemic in the same geographic locations as Zika. Hanley et al. compared the common clinical and laboratory features of Zika with that of dengue infections in 2 prospective cohorts of patients in Singapore. In this study, there were 130 cases of Zika and 175 cases of dengue. It was found that the presence of both a rash and conjunctivitis within the first 5 days of symptom onset in a suspected case increased the probability of Zika infection by 35 to 44%, but had no effect on the post-test probability of dengue infection. Conversely, the absence of rash in the first 5 days of symptomatic illness decreased the

Table 2 Studies in which rash or conjunctivitis was measured as an outcome

Study	Purpose of study	Primary outcomes of study	Related outcomes to our study	Number of patients	Frequency of rash	Frequency of conjunctivitis
García-Bujalance et al. (2017) [27]	To investigate the persistence and infectivity of Zika virus in semen	Semen Zika PCR was detected from days 14–96 since onset of illness.	4 out of 5 infected men had rash. 3 out of 4 men with rash had a positive semen viral culture for Zika. 2 out of 4 men with rash had positive urine Zika PCR. All men, including the asymptomatic man, had positive semen Zika PCR.	5	0.80	0.00
Passos et al. (2017) [97]	To investigate whether co-circulation of Zika with dengue could have occurred before the reported cases in 2015	Frozen semen samples collected during an outbreak in 2013, which tested negative for dengue, were tested for Zika PCR and there were positive results. This suggests that Zika virus was already circulating in Brazil in 2013.	3 out of 210 samples collected during dengue outbreak were both negative for dengue and positive for Zika. A retrospective review of their symptoms revealed that none of them had exanthema, and only 1 of the 3 cases had eye redness.	3	0	0.33
Joguet et al. (2017) [98•]	To investigate the effects of Zika infection on semen and how long Zika virus persists in semen and body fluids	There was an increase in abnormal sperm and decrease in total sperm count at day 30 post symptom onset. Recovery was observed between days 90–120. Whole-blood Zika PCR remained positive up to day 120 for 3 patients in this study.	Serum and urine Zika PCR were positive in all patients by day 7 post symptom onset. Serum Zika PCR remained positive up to day 30 for 26.7% of patients as compared to 13.3% for urine Zika PCR. Authors also concluded that whole-blood Zika PCR was more sensitive than serum or urine Zika PCR as whole-blood Zika PCR had the highest positivity rate of 62 out of 92 samples and was detected at up to day 120 for 3 patients.	15	0.93	0.80
da Silva et al. (2017) [99]	To investigate the percentage of acute zika infection in a cohort of patients admitted for Guillain-Barré syndrome, meningoencephalitis, or transverse myelitis.	35 of 40 patients enrolled in this study had serologic or molecular evidence for recent Zika infection.	This study reported a high incidence of rash (83%) in the patients with Zika infection.	35	0.83	0.29
Duijster et al. (2016) [100]	To investigate the epidemiological, virological, and clinical characteristics of imported Zika infection	There were 18 cases in this study, of which 17 had rash, 16 had fever, 13 had arthralgia, 8 had conjunctivitis. 13 cases had checked for dengue, and 3 of these were weakly positive for dengue IgM.	11 out of 17 patients with rash experienced pruritus. Rash could be localized or generalized.	18	0.94	0.44
Brasil et al. (2016) [101•]	To characterize the clinical, epidemiological, and virological features of Zika disease in the outbreak in Rio de Janeiro in 2015.	Zika was present in Rio de Janeiro in Jan 2015 and the number of infections peaked in May/June 2015. Common symptoms in this cohort included headache, myalgia,	97% of cases had rash, 79% had pruritus, 56% had conjunctivitis, 21% had enanthema/petechiae/bleeding, 20%	119	0.97	0.56

Table 2 (continued)

Study	Purpose of study	Primary outcomes of study	Related outcomes to our study	Number of patients	Frequency of rash	Frequency of conjunctivitis
		arthralgia, conjunctivitis, lower back pain, and itching. Study authors concluded that pruritus should be included in the case definition by Pan American Health Organization as it was the second most frequent symptom in the study.	had nasal congestion, 15% had coryza.			
Meaney-Delman et al. (2016) [102]	To highlight the range of outcomes when pregnant women become infected with zika.	This study included 9 cases, of which there were 2 early losses, 2 elective terminations, 3 live births, and 2 further continuing pregnancies at that time.	The report provided more details for 4 of the 9 cases. In all 4 cases, the pregnant women had experienced rash.	4	1.00	0.00
Hills et al. (2016) [103]	To highlight that sexual transmission of Zika is more common than previously reported.	Study described 3 cases in which female partners who had not traveled developed confirmed Zika infections. They had had sexual intercourse with male partners who had traveled and were symptomatic at the time of intercourse.	This report also shows that rash and conjunctivitis are common symptoms in Zika, being present in 83% and 67% of the cases featured here respectively.	6	0.83	0.67
Thomas et al. (2016) [104]	This report characterized the features of zika disease that occurred during the outbreak from Nov 23, 2015 to Jan 28, 2016 in Puerto Rico	The study found that 93% of patients lived in eastern Puerto Rico or the San Juan metropolitan area. 77% of patients had rash, 77% had myalgias, 73% had arthralgia, and 73% had fever.	77% of patients had rash and 27% had conjunctivitis.	30	0.77	0.27
Buathong et al. (2015) [105]	Study reported cases spread throughout Thailand to show that Zika was endemic.	Study reported cases spread throughout Thailand to show that Zika was endemic.	All 5 cases in this report had fever and maculopapular rash, while only 2 of 5 had conjunctivitis.	5	1.00	0.40

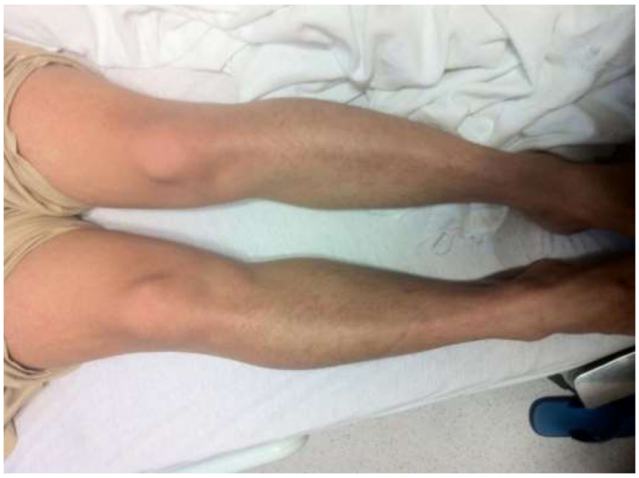

Fig. 5 Maculopapular rash in a patient with Zika virus infection

probability of Zika infection by approximately 35 to 44% [107••]. In line with the case reports reviewed above, another analysis of the same two cohorts showed conjunctivitis to be more important than rash in distinguishing zika virus infection from dengue fever. This was recently shown in a validated model [108].

Singapore is one of the few high-income countries that have experienced Zika outbreaks. The actual specific diagnosis of Zika virus infection is complicated by the high degree of cross-reactivity between the different flaviviruses. While there are commercially available serodiagnostics available for Zika virus infection, they lack specificity. PCR is much more specific but availability is limited in the predominantly resource-limited countries where Zika virus infection has occurred. The World Health Organization (WHO) and United States Centers for Diseases Control and Prevention (US CDC) case definitions of Zika virus infection both incorporate rash as one of the clinical criteria for diagnosis of Zika virus infection. As such, it is possible that rash is over-represented as a clinical manifestation in published reports or case series of Zika virus infection as cases would not be tested or diagnosed with Zika virus infection in the absence of rash in settings with relatively limited resources.

The timing of rash appearance may also help distinguish Zika versus dengue infection. Meltzer et al. retrospectively analyzed 49 cases of travelers with Zika infection and suggested that the onset of rash in Zika is usually in the first 2 days of symptoms, compared with dengue infection, where rash onset is usually at defervescence, around the fifth day of symptoms. This is consistent with our finding that the median onset of rash in individual adult patients with acute Zika infection is day 1, and mean onset is day 2 [109•].

For neonates with congenital Zika syndrome, the presence or absence of redundant scalp skin is not often highlighted in the literature. In Van der Linden et al.'s study, 3 infants with craniofacial disproportion who were normocephalic at birth had redundant scalp skin, but later progressed to develop postnatal microcephaly [17•]. Three other cases in the literature had redundant scalp skin associated with severe microcephaly. Further prospective studies are required to evaluate whether redundant scalp skin at birth in a normocephalic infant with congenital Zika syndrome can predict the development of postnatal microcephaly. There were no mucosal features reported in congenital Zika syndrome or in the single infant who had acute Zika infection via transmission through breastfeeding.

Conclusion

Zika has emerged as a major cause of morbidity particularly from the point of view of neurological complications and the congenital zika syndrome. While mucocutaneous complications are common, they are often non-specific. It is important for every clinician working in a climate where the *Aedes* spp. mosquito is prevalent to recognize the spectrum of these signs, especially as the presence of rash with conjunctivitis may guide diagnostic testing to improve the management of patients with acute febrile illnesses in particular pregnant women.

Compliance with Ethical Standards

Conflict of Interest Xuan Qi Koh, Nisha S. Chandran, Paul A. Tambyah declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Dick GWA, Kitchen SF, Haddow AJ. Zika virus. I. Isolations and serological specificity. Trans R Soc Trop Med Hyg. 1952;46(5):509–20.
2. Smithburn KC. Neutralizing antibodies against certain recently isolated viruses in the sera of human beings residing in East Africa. J Immunol. 1952;69(2):223–34.
3. Barzon L, Trevisan M, Sinigaglia A, Lavezzo E, Palù G. Zika virus: from pathogenesis to disease control. FEMS Microbiol Lett [Internet]. 2016;363(18). https://doi.org/10.1093/femsle/fnw202.
4. Gong Z, Xu X, Han G-Z. The diversification of Zika virus: are there two distinct lineages? Genome Biol Evol. 2017;9(11):2940–5.
5.• Anfasa F, Siegers JY, van der Kroeg M, Mumtaz N, Stalin Raj V, de Vrij FMS, et al. Phenotypic differences between Asian and African lineage Zika viruses in human neural progenitor cells.

mSphere [Internet]. 2017;2(4). https://doi.org/10.1128/mSphere.00292-17 **This paper demonstrated in vitro differences between the pathogenicity of Asian and African strains of Zika virus on central nervous progenitor cells. The authors postulated that such differences contributed to the masking of the association of Zika with congenital microcephaly due to earlier circulating African strains being more pathogenic such that fetuses did not survive to term. More research is required to investigate whether there are phenotypic differences in skin cells as well, since there are no published reports of African Zika virus infection for comparison of clinical mucocutaneous features with Asian Zika infection.**

6.• Kim J-A, Seong R-K, Son SW, Shin OS. Insights into ZIKV-mediated innate immune responses in human dermal fibroblasts and epidermal keratinocytes. J Invest Dermatol [Internet]. 2018. https://doi.org/10.1016/j.jid.2018.07.038 **This is a recently published paper that explained the cellullar mechanisms induced by Zika infection in the skin at the point of entry when infected via mosquito bite.**

7.•• Dobson JS, Levell NJ. Spotting Zika spots: descriptive features of the rash used in 66 published cases. Clin Exp Dermatol [Internet]. 2018. https://doi.org/10.1111/ced.13733 **This publication analysed the descriptors used to describe the dermatological features in 66 cases of Zika that were published before December 2016. The report showed that the rash associated with Zika infection could have a wide spectrum of morphologies**.

8. Pomar L, Vouga M, Lambert V, Pomar C, Hcini N, Jolivet A, et al. Maternal-fetal transmission and adverse perinatal outcomes in pregnant women infected with Zika virus: prospective cohort study in French Guiana. BMJ. 2018;363:k4431.

9. Karimi O, Goorhuis A, Schinkel J, Codrington J, Vreden SGS, Vermaat JS, et al. Thrombocytopenia and subcutaneous bleedings in a patient with Zika virus infection. Lancet. 2016;387(10022):939–40.

10.• Kulkarni SA, Strobelt E, Sargsyan Z. Capillary Fragility in Zika Virus Infection. Am J Med. 2017;130(2):e59 **This is a case report of positive Rumpel-Leede sign in a woman with confirmed Zika infection. She also had palatal petechiae. The authors noted that other flaviviruses such as dengue and Chikungunya have been associated with Rumpel-Leede sign, which in these situations was attributed to an immunologic process causing increased capillary fragility. They hypothesize that this could be a similar underlying mechanism causing petechiae in Zika infection.**

11. Bocanegra C, Sulleiro E, Soriano-Arandes A, Pou D, Suy A, Llurba E, et al. Zika virus infection in pregnant women in Barcelona, Spain. Clin Microbiol Infect. 2016;22(7):648–50.

12. Arsuaga M, Bujalance SG, Díaz-Menéndez M, Vázquez A, Arribas JR. Probable sexual transmission of Zika virus from a vasectomised man. Lancet Infect Dis. 2016;16(10):1107.

13. Furtado JM, Espósito DL, Klein TM, Teixeira-Pinto T, da Fonseca BA. Uveitis associated with Zika virus infection. N Engl J Med. 2016;375(4):394–6.

14. Cavalcanti MG, Cabral-Castro MJ, Gonçalves JLS, Santana LS, Pimenta ES, Peralta JM. Zika virus shedding in human milk during lactation: an unlikely source of infection? Int J Infect Dis. 2017;57:70–2.

15. Deng Y, Zeng L, Bao W, Xu P, Zhong G. Experience of integrated traditional Chinese and Western medicine in first case of imported Zika virus disease in China. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue. 2016;28(2):106–9.

16. do Meneses JA, Ishigami AC, de Mello LM, de Albuquerque LL, de Brito CAA, Cordeiro MT, et al. Lessons learned at the epicenter of Brazil's congenital Zika epidemic: evidence from 87 confirmed cases. Clin Infect Dis. 2017;64(10):1302–8.

17.• van der Linden V, Pessoa A, Dobyns W, Barkovich AJ, van der Júnior HL, Filho ELR, et al. Description of 13 infants born during October 2015-January 2016 with congenital Zika virus infection without microcephaly at birth - Brazil. MMWR Morb Mortal Wkly Rep. 2016;65(47):1343–8 **This case series reported the presence of redundant scalp skin in 3 out of 13 cases of congenital Zika syndrome. No other mucoctaneous features have been reported in association with congenital Zika syndrome to date.**

18. Besnard M, Dub T, Gérardin P. Outcomes for 2 children after peripartum acquisition of Zika virus infection, French Polynesia, 2013-2014. Emerg Infect Dis. 2017;23(8):1421–3.

19. Regadas VC, de Silva MCE, Abud LG, Labadessa LMPL, de Oliveira RGG, Miyake CH, et al. Microcephaly caused by congenital Zika virus infection and viral detection in maternal urine during pregnancy. Rev Assoc Med Bras. 2018;64(1):11–4.

20. de Oliveira MI, Namiyama GM, Cabral GB, Ferreira JL, Taniwaki N, Afonso AMS, et al. Isolation of infectious Zika virus from a urine sample cultured in SIRC cells from a patient suspected of having rubella virus. Rev Inst Med Trop Sao Paulo. 2018;60:e15.

21. Abdalla LF, Santos JHA, Barreto RTJ, Souza EME, D'Assunção FF, Borges MA, et al. Atrial fibrillation in a patient with Zika virus infection. Virol J. 2018;15(1):23.

22. Tan CH, Tan LK, Hapuarachchi HC, Lai YL, Wong PSJ, Yap G, et al. Viral and antibody kinetics, and mosquito infectivity of an imported case of Zika fever due to Asian genotype (American Strain) in Singapore. Viruses [Internet]. 2018;10(1). https://doi.org/10.3390/v10010044.

23. Ricciardi MJ, Magnani DM, Grifoni A, Kwon Y-C, Gutman MJ, Grubaugh ND, et al. Ontogeny of the B- and T-cell response in a primary Zika virus infection of a dengue-naïve individual during the 2016 outbreak in Miami, FL. PLoS Negl Trop Dis. 2017;11(12):e0006000.

24. Corrêa-Oliveira GE, do Amaral JL, da Fonseca BAL, Del-Ben CM. Zika virus infection followed by a first episode of psychosis: another flavivirus leading to pure psychiatric symptomatology. Braz J Psychiatr. 2017;39(4):381–2.

25. Landais A, Césaire A, Fernandez M, Breurec S, Herrmann C, Delion F, et al. ZIKA vasculitis: a new cause of stroke in children? J Neurol Sci. 2017;383:211–3.

26. Desclaux A, de Lamballerie X, Leparc-Goffart I, Vilain-Parcé A, Coatleven F, Fleury H, et al. Probable sexually transmitted Zika virus infection in a pregnant woman. N Engl J Med. 2018;378(15):1458–60.

27. García-Bujalance S, Gutiérrez-Arroyo A, De la Calle F, Díaz-Menéndez M, Arribas JR, García-Rodríguez J, et al. Persistence and infectivity of Zika virus in semen after returning from endemic areas: report of 5 cases. J Clin Virol. 2017;96:110–5.

28. Pradhan F, Burns JD, Agameya A, Patel A, Alfaqih M, Small JE, et al. Case report: Zika virus meningoencephalitis and myelitis and associated magnetic resonance imaging findings. Am J Trop Med Hyg. 2017;97(2):340–3.

29. Percivalle E, Zavattoni M, Fausto F, Rovida F. Zika virus isolation from semen. New Microbiol. 2017;40(3):197–8.

30. Katanami Y, Kutsuna S, Taniguchi S, Tajima S, Takaya S, Yamamoto K, et al. J Travel Med [Internet]. 2017;24(5). https://doi.org/10.1093/jtm/tax031.

31. Hashimoto T, Kutsuna S, Tajima S, Nakayama E, Maeki T, Taniguchi S, et al. Importation of Zika virus from Vietnam to Japan, November 2016. Emerg Infect Dis. 2017;23(7):1223–5.

32. Acosta-Reyes J, Navarro E, Herrera MJ, Goenaga E, Ospina ML, Parra E, et al. Severe neurologic disorders in 2 fetuses with Zika virus infection, Colombia. Emerg Infect Dis. 2017;23(6):982–4.

33. Sotelo JR, Sotelo AB, Sotelo FJB, Doi AM, Pinho JRR, de Oliveira RC, et al. Persistence of Zika virus in breast milk after

infection in late stage of pregnancy. Emerg Infect Dis. 2017\;23(5):856–7.
34. Penot P, Brichler S, Guilleminot J, Lascoux-Combe C, Taulera O, Gordien E, et al. Infectious Zika virus in vaginal secretions from an HIV-infected woman, France, August 2016. Euro Surveill [Internet]. 2017;22(3). https://doi.org/10.2807/1560-7917.ES.2017.22.3.30444.
35.• Chen L, Hafeez F, Curry CL, Elgart G. Cutaneous eruption in a U.S. woman with locally acquired Zika virus infection. N Engl J Med. 2017;376(4):400–1 **This is 1 of 3 case reports in which a skin biopsy was performed and histology reported. All 3 histologies reported superficial perivascular lymphocytic infiltrate.**
36. Froeschl G, Huber K, von Sonnenburg F, Nothdurft H-D, Bretzel G, Hoelscher M, et al. Long-term kinetics of Zika virus RNA and antibodies in body fluids of a vasectomized traveller returning from Martinique: a case report. BMC Infect Dis. 2017;17(1):55.
37.•• He A, Brasil P, Siqueira AM, Calvet GA, Kwatra SG. The emerging Zika virus threat: a guide for dermatologists. Am J Clin Dermatol. 2017;18(2):231–6 **This paper compares the clinical characteristics of Zika with that of Chikungunya, dengue and West Nile virus.**
38. Suy A, Sulleiro E, Rodó C, Vázquez É, Bocanegra C, Molina I, et al. Prolonged Zika virus viremia during pregnancy. N Engl J Med. 2016;375(26):2611–3.
39. Vinhaes ES, Santos LA, Dias L, Andrade NA, Bezerra VH, de Carvalho AT, et al. Transient hearing loss in adults associated with Zika virus infection. Clin Infect Dis. 2017;64(5):675–7.
40. Xu BY, Low SG, Tan RTH, Vasanwala FF. A case series of atypical presentation of Zika virus infection in Singapore. BMC Infect Dis. 2016;16(1):681.
41. Nicastri E, Pisapia R, Corpolongo A, Fusco FM, Cicalini S, Scognamiglio P, et al. Three cases of Zika virus imported in Italy: need for a clinical awareness and evidence-based knowledge. BMC Infect Dis. 2016;16(1):669.
42. Azevedo RSS, Araujo MT, Martins Filho AJ, Oliveira CS, Nunes BTD, Cruz ACR, et al. Zika virus epidemic in Brazil. I. Fatal disease in adults: clinical and laboratorial aspects. J Clin Virol. 2016;85:56–64.
43. Fabrizius RG, Hendel-Paterson B, Anderson K, Walker PF, Maalim S, Kaiser RM. Guillain–Barré syndrome associated with Zika virus infection in a traveler returning from Guyana. Am J Trop Med Hyg. 2016;95(5):1161–5.
44. do Rosário MS, de Jesus PAP, Vasilakis N, Farias DS, Novaes MAC, Rodrigues SG, et al. Guillain-Barré syndrome after Zika virus infection in Brazil. Am J Trop Med Hyg. 2016;95(5):1157–60.
45. Visseaux B, Mortier E, Houhou-Fidouh N, Brichler S, Collin G, Larrouy L, et al. Zika virus in the female genital tract. Lancet Infect Dis. 2016;16(11):1220.
46. Siu R, Bukhari W, Todd A, Gunn W, Huang QS, Timmings P. Acute Zika infection with concurrent onset of Guillain-Barré Syndrome. Neurology. 2016;87(15):1623–4.
47. Gaskell KM, Houlihan C, Nastouli E, Checkley AM. Persistent Zika virus detection in semen in a traveler returning to the United Kingdom from Brazil, 2016. Emerg Infect Dis. 2017;23(1):137–9.
48. Murray KO, Gorchakov R, Carlson AR, Berry R, Lai L, Natrajan M, et al. Prolonged detection of Zika virus in vaginal secretions and whole blood. Emerg Infect Dis. 2017;23(1):99–101.
49. Cleto TL, de Araújo LF, Capuano KG, Rego Ramos A, Prata-Barbosa A. Peripheral neuropathy associated with Zika virus infection. Pediatr Neurol. 2016;65:e1–2.
50. Zea-Vera AF, Parra B. Zika virus (ZIKV) infection related with immune thrombocytopenic purpura (ITP) exacerbation and antinuclear antibody positivity. Lupus. 2017;26(8):890–2.
51. Swaminathan S, Schlaberg R, Lewis J, Hanson KE, Couturier MR. Fatal Zika virus infection with secondary nonsexual transmission. N Engl J Med. 2016;375(19):1907–9.
52. Brent C, Dunn A, Savage H, Faraji A, Rubin M, Risk I, et al. Preliminary findings from an investigation of Zika virus infection in a patient with no known risk factors - Utah, 2016. MMWR Morb Mortal Wkly Rep. 2016;65(36):981–2.
53. Nicastri E, Castilletti C, Balestra P, Galgani S, Ippolito G. Zika virus infection in the central nervous system and female genital tract. Emerg Infect Dis. 2016;22(12):2228–30.
54. Brooks RB, Carlos MP, Myers RA, White MG, Bobo-Lenoci T, Aplan D, et al. Likely sexual transmission of Zika virus from a man with no symptoms of infection - Maryland, 2016. MMWR Morb Mortal Wkly Rep. 2016;65(34):915–6.
55. Barzon L, Pacenti M, Franchin E, Lavezzo E, Trevisan M, Sgarabotto D, et al. Infection dynamics in a traveller with persistent shedding of Zika virus RNA in semen for six months after returning from Haiti to Italy, January 2016. Euro Surveill [Internet]. 2016;21(32). https://doi.org/10.2807/1560-7917.ES.2016.21.32.30316.
56. Nicastri E, Castilletti C, Liuzzi G, Iannetta M, Capobianchi MR, Ippolito G. Persistent detection of Zika virus RNA in semen for six months after symptom onset in a traveller returning from Haiti to Italy, February 2016. Euro Surveill [Internet]. 2016;21(32). https://doi.org/10.2807/1560-7917.ES.2016.21.32.30314.
57. Zhong Y-B, Liu X-Q, Deng Y-C, Xu P-H, Zhong G-R, Zhang W. First case of laboratory-confirmed Zika virus infection imported into China. Chin Med J. 2016;129(16):2013–4.
58. Mansuy JM, Pasquier C, Daudin M, Chapuy-Regaud S, Moinard N, Chevreau C, et al. Zika virus in semen of a patient returning from a non-epidemic area. Lancet Infect Dis. 2016;16(8):894–5.
59. Harrower J, Kiedrzynski T, Baker S, Upton A, Rahnama F, Sherwood J, et al. Sexual transmission of Zika virus and persistence in semen, New Zealand, 2016. Emerg Infect Dis. 2016;22(10):1855–7.
60. Davidson A, Slavinski S, Komoto K, Rakeman J, Weiss D. Suspected female-to-male sexual transmission of Zika virus - New York City, 2016. MMWR Morb Mortal Wkly Rep. 2016;65(28):716–7.
61. Prisant N, Bujan L, Benichou H, Hayot P-H, Pavili L, Lurel S, et al. Zika virus in the female genital tract. Lancet Infect Dis. 2016;16(9):1000–1.
62. Sharp TM, Muñoz-Jordán J, Perez-Padilla J, Bello-Pagán MI, Rivera A, Pastula DM, et al. Zika virus infection associated with severe thrombocytopenia. Clin Infect Dis. 2016;63(9):1198–201.
63. Jang H-C, Park WB, Kim UJ, Chun JY, Choi S-J, Choe PG, et al. First imported case of Zika virus infection into Korea. J Korean Med Sci. 2016;31(7):1173–7.
64. Perez S, Tato R, Cabrera JJ, Lopez A, Robles O, Paz E, et al. Confirmed case of Zika virus congenital infection, Spain, March 2016. Euro Surveill [Internet]. 2016;21(24). https://doi.org/10.2807/1560-7917.ES.2016.21.24.30261.
65. Reusken C, Pas S, GeurtsvanKessel C, Mögling R, van Kampen J, Langerak T, et al. Longitudinal follow-up of Zika virus RNA in semen of a traveller returning from Barbados to the Netherlands with Zika virus disease, March 2016. Euro Surveill [Internet]. 2016;21(23). https://doi.org/10.2807/1560-7917.ES.2016.21.23.30251.
66. Frank C, Cadar D, Schlaphof A, Neddersen N, Günther S, Schmidt-Chanasit J, et al. Sexual transmission of Zika virus in Germany, April 2016. Euro Surveill [Internet]. 2016;21(23). https://doi.org/10.2807/1560-7917.ES.2016.21.23.30252.
67.• Burillo-Martínez S, Fernández-Ruiz M, Pérez-Rivilla A, Zarco-Olivo C. Zika virus infection: an emerging disease the dermatologist must know about. Actas Dermosifiliogr. 2016;107(8):687–9 **This is 1 of 3 case reports in which a skin biopsy was**

performed and histology reported. All 3 histologies reported superficial perivascular lymphocytic infiltrate.

68. Zhang F-C, Li X-F, Deng Y-Q, Tong Y-G, Qin C-F. Excretion of infectious Zika virus in urine. Lancet Infect Dis. 2016;16(6):641–2.
69.• Derrington SM, Cellura AP, McDermott LE, Gubitosi T, Sonstegard AM, Chen S, et al. Mucocutaneous findings and course in an adult with Zika virus infection. JAMA Dermatol. 2016;152(6):691–3 **This is 1 of 3 case reports in which a skin biopsy was performed and histology reported. All 3 histologies reported superficial perivascular lymphocytic infiltrate.**
70. Rozé B, Najioullah F, Signate A, Apetse K, Brouste Y, Gourgoudou S, et al. Zika virus detection in cerebrospinal fluid from two patients with encephalopathy, Martinique, February 2016. Euro Surveill [Internet]. 2016;21(16). https://doi.org/10.2807/1560-7917.ES.2016.21.16.30205.
71. Brasil P, Sequeira PC, Freitas AD, Zogbi HE, Calvet GA, de Souza RV, et al. Guillain-Barré syndrome associated with Zika virus infection. Lancet. 2016;387(10026):1482.
72. Atkinson B, Hearn P, Afrough B, Lumley S, Carter D, Aarons EJ, et al. Detection of Zika virus in semen. Emerg Infect Dis. 2016;22(5):940.
73. Díaz-Quiñonez JA, Escobar-Escamilla N, Wong-Arámbula C, Vázquez-Pichardo M, Torres-Longoria B, López-Martínez I, et al. Asian genotype Zika virus detected in traveler returning to Mexico from Colombia, October 2015. Emerg Infect Dis. 2016;22(5):937–9.
74. Deckard DT, Chung WM, Brooks JT, Smith JC, Woldai S, Hennessey M, et al. Male-to-male sexual transmission of Zika virus–Texas, January 2016. MMWR Morb Mortal Wkly Rep. 2016;65(14):372–4.
75. D'Ortenzio E, Matheron S, Yazdanpanah Y, de Lamballerie X, Hubert B, Piorkowski G, et al. Evidence of sexual transmission of Zika virus. N Engl J Med. 2016;374(22):2195–8.
76. Li J, Xiong Y, Wu W, Liu X, Qu J, Zhao X, et al. Zika virus in a traveler returning to China from Caracas, Venezuela, February 2016. Emerg Infect Dis. 2016;22(6):1133–6.
77. Driggers RW, Ho C-Y, Korhonen EM, Kuivanen S, Jääskeläinen AJ, Smura T, et al. Zika virus infection with prolonged maternal viremia and fetal brain abnormalities. N Engl J Med. 2016;374(22):2142–51.
78. Cardona-Cardona AF, Rodríguez Morales AJ. Severe abdominal pain in a patient with Zika infection: a case in Risaralda, Colombia. J Infect Public Health. 2016;9(3):372–3.
79. Barzon L, Pacenti M, Berto A, Sinigaglia A, Franchin E, Lavezzo E, et al. Isolation of infectious Zika virus from saliva and prolonged viral RNA shedding in a traveller returning from the Dominican Republic to Italy, January 2016. Euro Surveill. 2016;21(10):30159.
80. Carteaux G, Maquart M, Bedet A, Contou D, Brugières P, Fourati S, et al. Zika virus associated with meningoencephalitis. N Engl J Med. 2016;374(16):1595–6.
81. Venturi G, Zammarchi L, Fortuna C, Remoli ME, Benedetti E, Fiorentini C, et al. An autochthonous case of Zika due to possible sexual transmission, Florence, Italy, 2014. Euro Surveill. 2016;21(8):30148.
82. Weitzel T, Cortes CP. Zika virus infection presenting with postauricular lymphadenopathy. Am J Trop Med Hyg. 2016;95(2):255–6.
83. Chen LH. Zika virus infection in a Massachusetts resident after travel to Costa Rica: a case report. Ann Intern Med. 2016;164(8):574–6.
84. Gyurech D, Schilling J, Schmidt-Chanasit J, Cassinotti P, Kaeppeli F, Dobec M. False positive dengue NS1 antigen test in a traveller with an acute Zika virus infection imported into Switzerland. Swiss Med Wkly. 2016;146:w14296.
85. Korhonen EM, Huhtamo E, Smura T, Kallio-Kokko H, Raassina M, Vapalahti O. Zika virus infection in a traveller returning from the Maldives, June 2015. Euro Surveill [Internet]. 2016;21(2). https://doi.org/10.2807/1560-7917.ES.2016.21.2.30107.
86. Shinohara K, Kutsuna S, Takasaki T, Moi ML, Ikeda M, Kotaki A, et al. Zika fever imported from Thailand to Japan, and diagnosed by PCR in the urines. J Travel Med [Internet]. 2016;23(1). https://doi.org/10.1093/jtm/tav011.
87. Zammarchi L, Tappe D, Fortuna C, Remoli M, Günther S, Venturi G, et al. Zika virus infection in a traveller returning to Europe from Brazil, March 2015. Eurosurveillance. 2015;20(23):21153.
88. Summers DJ, Acosta RW, Acosta AM. Zika virus in an American recreational traveler. J Travel Med. 2015;22(5):338–40.
89. Tappe D, Nachtigall S, Kapaun A, Schnitzler P, Günther S, Schmidt-Chanasit J. Acute Zika virus infection after travel to Malaysian Borneo, September 2014. Emerg Infect Dis. 2015;21(5):911–3.
90. Alera MT, Hermann L, Tac-An IA, Klungthong C, Rutvisuttinunt W, Manasatienkij W, et al. Zika virus infection, Philippines, 2012. Emerg Infect Dis. 2015;21(4):722–4.
91. Fonseca K, Meatherall B, Zarra D, Drebot M, MacDonald J, Pabbaraju K, et al. First case of Zika virus infection in a returning Canadian traveler. Am J Trop Med Hyg. 2014 Nov;91(5):1035–8.
92. Wæhre T, Maagard A, Tappe D, Cadar D, Schmidt-Chanasit J. Zika virus infection after travel to Tahiti, December 2013. Emerg Infect Dis. 2014;20(8):1412–4.
93. Oehler E, Watrin L, Larre P, Leparc-Goffart I, Lastere S, Valour F, et al. Zika virus infection complicated by Guillain-Barre syndrome–case report, French Polynesia, December 2013. Euro Surveill [Internet]. 2014;19(9) Available from: https://www.ncbi.nlm.nih.gov/pubmed/24626205.
94. Kutsuna S, Kato Y, Takasaki T, Moi M, Kotaki A, Uemura H, et al. Two cases of Zika fever imported from French Polynesia to Japan, December 2013 to January 2014 [corrected]. Euro Surveill [Internet]. 2014;19(4) Available from: https://www.ncbi.nlm.nih.gov/pubmed/24507466.
95. Kwong JC, Druce JD, Leder K. Zika virus infection acquired during brief travel to Indonesia. Am J Trop Med Hyg. 2013;89(3):516–7.
96. Foy BD, Kobylinski KC, Chilson Foy JL, Blitvich BJ, Travassos da Rosa A, Haddow AD, et al. Probable non-vector-borne transmission of Zika virus, Colorado, USA. Emerg Infect Dis. 2011;17(5):880–2.
97. Passos SRL, Borges Dos Santos MA, Cerbino-Neto J, Buonora SN, Souza TML, de Oliveira RVC, et al. Detection of Zika virus in April 2013 patient samples, Rio de Janeiro, Brazil. Emerg Infect Dis. 2017;23(12):2120–1.
98.• Joguet G, Mansuy J-M, Matusali G, Hamdi S, Walschaerts M, Pavili L, et al. Effect of acute Zika virus infection on sperm and virus clearance in body fluids: a prospective observational study. Lancet Infect Dis. 2017;17(11):1200–8 **This prospective cohort study of 15 male patients found not only that recovery of sperm abnormalities occurred between days 90–120 post-Zika infection, but also that whole-blood Zika PCR was more sensitive than serum or urine Zika PCR. This was based on whole-blood Zika PCR being detected for 3 patients at up to day 120 post-infection, and having the highest frequency of positivity in 62 out of 92 samples.**
99. da Silva IRF, Frontera JA, Bispo de Filippis AM, do Nascimento OJM, RIO-GBS-ZIKV Research Group. Neurologic complications associated with the Zika virus in Brazilian adults. JAMA Neurol. 2017;74(10):1190–8.
100. Duijster JW, Goorhuis A, van Genderen PJJ, Visser LG, Koopmans MP, Reimerink JH, et al. Zika virus infection in 18 travellers returning from Surinam and the Dominican Republic,

The Netherlands, November 2015-March 2016. Infection. 2016;44(6):797–802.

101.• Brasil P, Calvet GA, Siqueira AM, Wakimoto M, de Sequeira PC, Nobre A, et al. Zika virus outbreak in Rio de Janeiro, Brazil: clinical characterization, epidemiological and virological aspects. PLoS Negl Trop Dis. 2016;10(4):e0004636 **In this retrospective study of 119 patients during the 2015 Zika outbreak in Rio de Janeiro, the high incidence of pruritus (79%) prompted the authors to suggest the inclusion of itch in the Pan American case definition.**

102. Meaney-Delman D, Hills SL, Williams C, Galang RR, Iyengar P, Hennenfent AK, et al. Zika virus infection among U.S. pregnant travelers - August 2015-February 2016. MMWR Morb Mortal Wkly Rep. 2016;65(8):211–4.

103. Hills SL, Russell K, Hennessey M, Williams C, Oster AM, Fischer M, et al. Transmission of Zika virus through sexual contact with travelers to areas of ongoing transmission - continental United States, 2016. MMWR Morb Mortal Wkly Rep. 2016;65(8):215–6.

104. Thomas DL, Sharp TM, Torres J, Armstrong PA, Munoz-Jordan J, Ryff KR, et al. Local transmission of Zika virus–Puerto Rico, November 23, 2015-January 28, 2016. MMWR Morb Mortal Wkly Rep. 2016;65(6):154–8.

105. Buathong R, Hermann L, Thaisomboonsuk B, Rutvisuttinunt W, Klungthong C, Chinnawirotpisan P, et al. Detection of Zika virus infection in Thailand, 2012-2014. Am J Trop Med Hyg. 2015;93(2):380–3.

106. Tan JJL, Balne PK, Leo Y-S, Tong L, Ng LFP, Agrawal R. Persistence of Zika virus in conjunctival fluid of convalescence patients. Sci Rep. 2017;7(1):11194.

107.•• Ho HJ, Wong JGX, Mar Kyaw W, Lye DC, Leo YS, Chow A. Diagnostic accuracy of parameters for Zika and dengue virus infections, Singapore. Emerg Infect Dis. 2017;23(12):2085–8 **This is a prospective cohort study that demonstrated that the highest likelihood for laboratory-confirmed Zika was the presence of both rash and conjunctivitis at first presentation to clinical care.**

108. Yan G, Pang L, Cook AR, Ho HJ, Win MS, Khoo AL, et al. Distinguishing Zika and dengue viruses through simple clinical assessment, Singapore. Emerg Infect Dis. 2018;24(8):1565–8.

109.• Meltzer E, Leshem E, Lustig Y, Gottesman G, Schwartz E. The clinical spectrum of Zika virus in returning travelers. Am J Med. 2016;129(10):1126–30 **This retrospective analysis of clinical manifestations of Zika infections in returning travellers found that the occurence of rash in Zika was usually early in the course of illness as contrasted to dengue, when the onset of rash tended to coincide with defervescence around day 5 of illness. In addition, the absence of thrombocytopenia and lymphopenia in Zika was notable differences when compared to dengue, where cytopenias could be severe.**