Tropical Medicine and International Health doi:10.1111/tmi.13216

VOLUME 24 NO 5 PP 523–529 MAY 2019

Systematic Review

Zika transmission patterns: a meta-review

S. Runge-Ranzinger[1], A. C. Morrison[2], P. Manrique-Saide[3] and O. Horstick[1]

1 *Heidelberg Institute of Global Health, University of Heidelberg, Germany*
2 *Department of Entomology and Nematology, University of California, Davis, USA*
3 *Universidad Autonoma de Yucatan, Merida, Mexico*

Summary

OBJECTIVE To assesses what is known and identify knowledge gaps for Zika virus (ZIKV) transmission patterns.

METHODS Meta-review searching the databases BioSys; Cochrane Infectious Diseases Group Specialised Register and Cochrane Central Register of Controlled Trials; EMBASE; Google Scholar; LILACS; MEDLINE (PubMed); Web of Science; and WHOLIS with the term 'ZIKA'. Systematic reviews and reviews specifying the search methods and describing potential modes of transmission were eligible for analysis.

RESULTS Of 5,401 hits for 'Zika', 44 studies were assessed and 11 included after applying in- and exclusion criteria: six systematic reviews and five reviews with specified methods, covering all ways of possible transmission. Results can be grouped into transmission routes with good evidence and agreement between the studies (evidence on vector, mother-to-child and sexual transmission) and transmission routes with limited evidence. Transmission by breastfeeding, intrapartum, by animal bites or laboratory-based remains inconclusive, as these routes are suggested by single studies only. The risk of transfusion transmission is described and public health measures for safe transfusion should be taken as available.

CONCLUSION Our results imply the need for public health measures to limit transmission via vectors, mother-to-child, sexual transmission and blood transfusion. Also needed are long-term prospective cohort studies covering periods of active Zika virus transmission and measuring epidemiological parameters to establish evidence on other routes of transmission; seroprevalence studies; transmission dynamics modelling and modelling health impacts by different modes of transmission.

keywords Zika, transmission, meta-review

Introduction

Over 2 billion people are estimated to live in areas with potential Zika transmission [1]. Furthermore, in the Americas alone, over 5.4 million births occurred in 2015 within such areas, with the established risk of neurological deficits.

According to a WHO situation report in March 2017 [2] there were 84 countries, territories or subnational areas with evidence of vector-borne ZIKV transmission; 64 countries, territories or subnational areas where the competent vector is established but with no documented past or current ZIKV transmission. 13 countries have reported evidence of person-to-person transmission of ZIKV (of those five in the Americas, seven in Europe and one in the Western Pacific). 31 countries or territories have reported microcephaly and other central nervous system (CNS) malformations potentially associated with ZIKV infection, or suggestive of congenital infection. 23 countries or territories have reported an increased incidence of Guillain- Barré syndrome (GBS) and/or laboratory confirmation of a ZIKV infection among GBS cases.

For evidence-informed decision-making it is important that public health policies are backed up with research evidence. In order to tailor public health measures most effectively, we summarise the existing evidence on different Zika transmission routes. From the existing data in the mentioned WHO report, it is not only necessary to know where person-to-person transmission occurs, but which transmission route is responsible for virus transmission. In a recent scoping review [3], two key epidemiological questions on the natural history of the ZIKV

with sylvatic mosquito vectors and potential host species (animals) were answered based on literature until March 2016. However, numerous papers have addressed different ZIKV transmission patterns, warranting an analysis of this evidence.

The objectives of this meta-review are to systematically review, stratify and analyse all reported modes of transmission of Zika virus, including mosquito-borne and human-to-human transmission, published in systematic reviews or reviews with specified methods. It aims to address the research questions exploratively 'mapping key concepts, types of evidence and gaps in research, by systematically searching, selecting, and synthesising existing knowledge' [4]. Public health recommendations based on the results are described.

Methods

This meta-review followed the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [5].

In order to refine the research question 'evidence of Zika transmission patterns' by identifying specific components the target population was set as 'global' and the outcomes of interest as studies on 'transmission'. Relevant sources of data (electronic databases, published and grey literature, relevant organisations websites, conferences, reports and consultation of stakeholders and experts) were identified while ensuring the comprehensiveness and the feasibility of the process. A search of the following databases was conducted: BioSys, Cochrane Infectious Diseases Group Specialised Register and Cochrane Central Register of Controlled Trials, EMBASE, Google Scholar, LILACS, MEDLINE (PubMed), Web of Science (WoS) and WHOLIS. The searches had no lower limit and concluded 15 June 2017. There were no language restrictions. Due to the relatively limited body of evidence by the time of search we decided to take a very broad strategy with the term 'Zika' only. Only on Google Scholar a combination of 'Zika and transmission' was used to limit the broad search in this database.

All hits for 'Zika' were screened by two researchers by title and by abstracts individually, and those with evidence for 'Zika Transmission' were categorised into different transmission routes. The two researchers involved in the initial screening process discussed in a second step all potential hits, to identify and categorise relevant studies and reach agreement in case of discrepancy. The full list of potentially relevant studies was shared with the other two researchers, disagreements were resolved by consensus. Bibliographies of all included papers were screened for further references and grey literature, duplicates were removed. Searches were fully documented and flow charts with results of the searches have been developed. After categorising all papers into relevant transmission categories inclusion and exclusion criteria were refined: Only systematic reviews and reviews specifying methods relevant to the topic/categories were included. Studies were excluded when not meeting these study designs. Potentially relevant hits were grouped into systematic reviews and reviews (i) with a specified methods section and (ii) transmission route described (Figure 1).

Two data extractors then independently searched and entered data into data extraction forms, such as author, title, journal, publication date and study design. Data extraction sheets were developed to evidence tables. An additional layer of analysis was added, comparing the subcategorised primary research studies with each individual systematic review/review with methods to better understand the amount and level of evidence behind a respective review. This strategy was considered most useful, since (i) possibilities for analysis of the strength of evidence for the different ways of transmission can be assessed from the reviews/systematic reviews and (ii) a quality assessment of the reviews/systematic review, compared to the extensive list of case studies also generated during the searches can be performed. Both analyses generated observations and conclusions for further studies for transmission.

Data extraction followed content analysis methods, using categories as these emerged during analysis of the results [6]. The included studies have been quality assessed with the PRISMA criteria, quality criteria were extracted and considered in the analysis.

Results

Descriptive analysis

Of 5401 hits on 'Zika', 44 studies were full assessed (Figure 1). The 44 studies were studies that fulfilled both inclusion and exclusion criteria, particularly with regards to study design (systematic review or review with specified methods), based on title and abstract. 11 were finally included after considering the full text: six systematic reviews and five reviews with specified methods, covering routes of possible transmission. Results can be grouped into (i) transmission routes with good evidence and agreement between the studies (evidence on vector, mother-to-child and sexual transmission) and (ii) transmission routes with limited evidence.

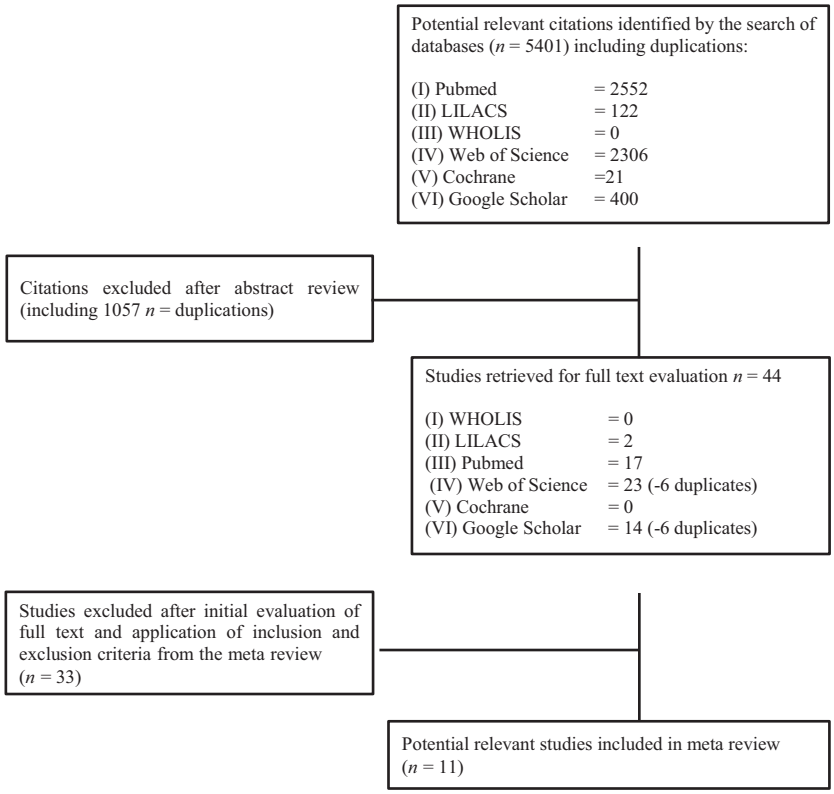

Figure 1 Study flow diagram.

Most of the articles retrieved in the overall search were case reports, however, some were summary articles – either reviews without methods, reviews with methods and systematic reviews – that assessed the evidence for transmission using the case reports. Of 44 articles retrieved for full text analysis, 11 such studies were considered further, six systematic reviews and five reviews specifying the methods of the searches (see supportive information, table 1 evidence table, and table 2 analysis table).

Modes of transmission

Eleven studies met our inclusion criteria. They principally described vector transmission, mother-to-child transmission (transplacentar, perinatal and breastfeeding), sexual transmission (male to female and male to male), and blood transfusion. Other routes of transmission discussed included monkey bites, needle stick injuries, transplants and haemodialysis. Of the included articles, six were systematic reviews [3, 7–11] and five were reviews, including a WHO guideline [12–16].

Most included studies were published in 2016, with the exception of Jimenez *et al.* [14] and Colt *et al.* [7].

Three of the included systematic reviews covered most potential modes of transmission [3, 8, 10], except for Grischott *et al.* [8] which focused soley on transmission, these reviews also included topics such as history and clinical manifestations. In contrast, the remaining systematic reviews focused on specific modes of transmission: breastfeeding [7], transplacental transmission [11] and sexual transmission [9].

Of the five non-systematic reviews, including a clear method section, as with the systematic reviews, other topics in addition to transmission were included [12, 13, 15], whereas the WHO guidelines [16] focused on sexual transmission, Salge *et al.* [11] on transplacental transmission and Jimenez *et al.* [14] on blood transfusion.

Despite the included systematic reviews citing the PRISMA statement [5], only Salge *et al.* [11] and Waddell and Greig [3] provided sufficient information in the methods section to meet most PRISMA criteria. All of the five non-systematic reviews included well detailed methods sections, however, searches and analysis were not systematic. The number of studies included in each of the included reviews (systematic and non-systematic) varied considerably, depending on the number of topics

covered, ranging from only four studies on a systematic review of transplacental transmission [11] to 233 studies in a comprehensive systematic review, also covering all known modes of transmission [3].

Stratifying by transmission mode, vector transmission is best described in the review by Waddell and Greig [3]. In an analysis of described vectors, it was highlighted that only mosquitoes act as vectors for ZIKV: '26 mosquito vector studies tested 45 different mosquito species for either a natural infection with ZIKV or evaluated the mosquito species for vector competence to transmit ZIKV. Eighteen species of mosquitoes were found to be positive for ZIKV during epidemiological sampling in Africa and Asia from 1956 to 2015 and eight were evaluated experimentally for vector competence. Studies on *Ae. aegypti* demonstrated that individual mosquitoes held under laboratory conditions transmitted ZIKV 33–100% of the time and transmission of the virus occurred irrespective of whether the mosquito was engorged with a blood meal'. Only three other reviews analysed vector transmission [12, 13, 15]. Plourde and Bloch [15] had to goal of identifying most competent vector: 'The *Ae. aegypti* mosquito appears to be the major vector in Asia and was the suspected primary vector for the French Polynesia outbreak, …. In Africa, the predominant *Aedes* species vector has not been definitively identified, although viral isolation studies suggest that *Ae.* albopticus was the likely vector in a 2007 Zika virus outbreak in Gabon'. Atif *et al.* [12] and Ibrahim [13] also investigated vector transmission, but not adding to or questioning these results.

Mother-to-child transmission can be distinguished into transplacentar, perinatal and breastfeeding transmission. For transplacentar transmission Grischott *et al.* [8] performed a systematic review and identified 12 articles with laboratory confirmed transmission and 10 with suspected transmission. The systematic analysis 'yielded a total of 133 of foetuses and newborns of mothers with laboratory-confirmed ZIKV infection in addition to more than 850 suspected ZIKV related cases in pregnancy. Among those 133 confirmed cases, 118 were reported from mothers living in or returning from Brazil. Among the more than 850 suspected cases, only 25 come from French Polynesia [17, 18] while all other cases were reported from Brazil. 11 mothers live in countries without autochthonous ZIKV transmission but had travelled to countries with ongoing ZIKV transmission' [19–21]. Some additional evidence was reported by Paixao *et al.* [10], Salge *et al.* [11], Atif *et al.* [12], Ibrahim [13], Jimenez *et al.* [14], Plourde and Bloch [15] and Waddell and Greig [3], partly with the same sources partly with additional, but not adding substantially to the conclusion that transmission from mother-to-child is established.

Perinatal transmission was assessed by Grischott *et al.* [8], Paixao *et al.* [10], Atif *et al.* [12] and Plourde and Bloch [15]. Most studies are citing one study only [22] that confirmed perinatal transmission.

As for breastfeeding, Colt *et al.* [7] focus on this possible route of transmission, concluding that 'to date, only two articles have been published on the potential risk of ZIKV transmission through breast milk. They describe two mothers with their newborns living in French Polynesia [22] and one healthy baby in New Caledonia' [23]. Waddell and Greig [3], Atif *et al.* [12], Ibrahim [13] and Plourde and Bloch [15] are not adding substantially to this quote.

Sexual transmission is confirmed by Moreira *et al.* [9] conducting a systematic review on sexual transmission and describing 18 studies reporting sexually acquired Zika Infection; 15 studies with male to female transmission, one study female to male and one study male to male, most of the infections are by partners who travelled to Zika affected regions. The authors reported that 'Modes of sexual transmission were unprotected vaginal intercourse in 96.2% (26/27), oral intercourse in 18.5% (5/27) and anal intercourse in 7.4% (2/27). Time of sexual intercourse concerning index case symptom onset was reported in 13/27 (48%) couples. Sexual intercourse occurred before, during and after the index's symptom onset in five (38.4%), seven (53.8%) and one (7.6%), respectively.' The WHO guideline [16], based on a review with a methods section, includes partly other case reports, but concludes the same. Some additional evidence was reported by Grischott *et al.* [8], some repetitive sources and a few additional studies were reported by Paixao *et al.* [10], Atif *et al.* [12], Ibrahim [13], Jimenez *et al.* [14], Plourde and Bloch [15] and Wadell and Greig [3].

On transfusion-transmitted Zika infection, Jimenez *et al.* [14] states specifically: 'In areas where ZIKV is circulating, the virus has been detected in blood donations, …. there have been four possible cases of transfusion-transmitted ZIKV'. Almost the same case reports are cited by Wadell and Greig [3], Paixao *et al.* [10] and Grischott *et al.* [8], for the systematic reviews. Musso [24] is also quoted by the reviews with methods, analysing this way of transmission [13, 15].

Two references were cited by Grischott *et al.* [8] and Atif *et al.* [12] confirming laboratory transmission and only one reference [25] suggested infection by a monkey bite, however, a mosquito bite could not be excluded. This was also reported by Jimenez *et al.* [14], Grischott *et al.* [8], Paixao *et al.* [10], Atif *et al.* [12] and Plourde and Bloch [15].

Some authors discussed infections by needle stick injury, transplant – especially kidney transplant – or haemodialysis, however, no sources of evidence were reported.

Evidence level of included studies

When comparing the primary research studies included by the different systematic and non-systematic reviews with methods, there is very little consistent use of evidence to underline a particular mode of transmission.

For vector transmission Waddell and Greig [3] use vector species and competence articles, a concept that is also followed by Plourde and Bloch [15], however, with fewer sources, and also different sources. The reviews dealing with this topic use almost no sources.

The same is observed for mother-to-child transmission, whereas Grischott *et al.* [8] reports on cases and suspected cases with key references, Paixao *et al.* [10], Salge *et al.* [11], Atif *et al.* [12], Ibrahim [13], Jimenez *et al.* [14], Plourde and Bloch [15] and Waddell and Greig [3] use only very few references. When analysing perinatal transmission, the studies looking into this mode of transmission are relying mostly on only one study (Besnard [22]). The same applies to breastfeeding, addressed by Colt *et al.* [7], all other articles use the same references, or refer to Colt *et al.* [7].

When analysing the sources used by the included studies to establish sexual transmission as an important mode of transmission, the more recent systematic review of Moreira *et al.* [9] used case reports and studies analysing the existence of ZIKV in body fluids. This approach is shared, but with fewer sources by the WHO guidelines [16] and Grischott *et al.* [8]. The other studies analysing sexual transmission are using only very few references.

Transfusion transmission relies also on very few documented cases, for laboratory transmission there is historic evidence reported. Also, some ways of transmission are discussed, without having any evidence available, e.g. transplant, and haemodialysis.

Discussion

Discussion on transmission

When considering the presented evidence from systematic reviews and reviews with a method, several ways of transmission have been described, which can be grouped into ways of transmission with good evidence and agreement between the studies and ways of transmission with limited evidence.

Good evidence and agreement in the studies

- Vector borne transmission: Mosquitoes, particularly *Aedes*, have been identified as susceptible and competent vectors of ZIKV. In the analysed literature, there is large agreement on this way of transmission. There is however a discussion about the vector competence of other mosquitoes but *Aedes*.
- Mother-to-child transmission has been documented in case studies, and there is agreement on this way of transmission in the present studies.
- Sexual transmission is established, particularly male to female, and there is clear agreement in the studies discussing this way of transmission.

Limited evidence

- Breastfeeding may be a possible way of transmission, but there is very little evidence and the key specific systematic review underlines that 'the data are not sufficient to conclude ZIKV transmission via breastfeeding. More evidence is needed to distinguish breastfeeding transmission from other perinatal transmission routes'. This is in line with the conclusion of a recent systematic review by Mann *et al.* [26].
- Also, there is very limited evidence for perinatal transmission, which has been further investigated in a recent systematic review by Soriano-Arandes [27].
- Transmission via blood products is a potential way of transmission, but the evidence is scarce. Most studies dealing with this way of transmission recommend testing for ZIKV in affected areas.

Among the evidence to analyse the transmission of ZIKV, there is a good balance of high- level evidence focusing on a broad scope (scoping reviews), but also reviews of specific questions (systematic reviews), underlining the usefulness of this methodology to establish known facts, and to identify the unknown. Perhaps this shows also the usefulness of this method particularly in outbreak situations, to rapidly assess the body of evidence and to establish practical public health interventions.

However, the use of evidence in the analysed systematic reviews and reviews with methods is very variable: Whereas there are comprehensive searches available in at least one study for each topic (vector borne transmission, mother-to-child transmission and sexual transmission), the use of primary resarch for this topic is highly variable. Quality of the data search is also an issue and limit also the quality of data on transmission. Perhaps this underlines the necessity for additional discussion in

expert consensus, not relying only on high-level summaries for public health decision-making.

Also worrying is the fact that for breastfeeding and perinatal transmission, the studies refer to very few case reports. It is very difficult to base public health recommendations on so few studies. This picture is even worse for animal bites and laboratory transmission. The recommendations to screen blood products and organ transplants for ZIKV infection are probably enforcing this procedure anyway, even if the literature does not produce much evidence for the risk and/or quantifying the risk as also confirmed by the review of Levi [28].

This meta-review has several limitations. Quality of included systematic review and reviews with a methods section is an issue, but also the quality of the original studies included in the reviewed articles. This limits the information that can be derived from both individual reviews and this meta-review. A further concern is that not all routes of transmission have been described so far, particularly in outbreak situations, which further limits the information that can be derived from this meta-review.

Conclusions

Evidence on vector, mother-to-child and sexual transmission (often demonstrated by infection of partners from travellers), seems conclusive considering the available evidence and agreements between published high-level-evidence summaries and warrants appropriate measures for primary prevention. Transmission via breastfeeding, intrapartum, by animal bites or laboratory based is suggested by single studies, but remains inconclusive. Further studies need to establish this risk. The risk of transfusion transmission is described and public health measures for safe transfusion should be taken. So far there is no literature describing transmission by transplant or haemodialysis; this warrants further investigation.

This meta-review on ZIKV transmission, which is based on comparing high-level evidence, finds agreement among studies on the importance of vector borne transmission, mother-to-child transmission and sexual transmission. Modelling of the importance of each way of transmission in the overall transmission dynamics is however needed, also to establish evidence-informed public health policy recommendations. Further specific research questions arise with the aim to initiate more clinical research to assess ways of transmission where evidence is scarce, for example breastfeeding, perinatal transmission and transmission via transfusion, as highlighted by Gregory 2017 [29].

The conclusions have limitations due to the information available from the primary studies. This is even worse when considering the number of studies published in an outbreak situation as in the case of Zika. However, even with the limited evidence for transmission modelling of transmission dynamics should be attempted despite the resulting technical difficulty. This is particularly important since many assumptions are made for notoriously difficult *Aedes* control, mostly derived from dengue-related studies. Our analysis shows that there is also an urgent research need for:

- Long-term prospective cohort studies that cover periods of active Zika virus transmission and measure epidemiological parameters
- Mapping of human cases and epidemiological surveillance data
- Seroprevalence studies
- Transmission dynamics modelling
- Modelling health impacts by different modes of transmission.

Acknowledgements

This study received funding by the Special Programme for Research and Training in Tropical Diseases of the World Health Organization (WHO/TDR, contract number WCCPRD5295811 2017/700816).

References

1. Messina JP, Kraemer MU, Brady OJ *et al.* Mapping global environmental suitability for Zika virus. *Elife* 2016: **5**: 1–19.
2. WHO. *WHO Zika Virus, Situation Report (10/03/2017)*. WHO: Geneva, 2017.
3. Waddell LA, Greig JD. Scoping review of the Zika virus literature. *PLoS ONE* 2016: **11**: e0156376.
4. Colquhoun HL, Levac D, O'Brien KK *et al.* Scoping reviews: time for clarity in definition, methods, and reporting. *J Clin Epidemiol* 2014: **67**: 1291–1294.
5. Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009: **6**: e1000097.
6. Pope C, Ziebland S, Mays N. Qualitative research in health care. Analysing qualitative data. *BMJ* 2000: **320**: 114–116.
7. Colt S, Garcia-Casal MN, Pena-Rosas JP *et al.* Transmission of Zika virus through breast milk and other breastfeeding-related bodily-fluids: a systematic review. *PLoS Negl Trop Dis* 2017: **11**: e0005528.
8. Grischott F, Puhan M, Hatz C, Schlagenhauf P. Non-vector-borne transmission of Zika virus: a systematic review. *Travel Med Infect Dis* 2016: **14**: 313–330.

9. Moreira J, Peixoto TM, Siqueira AM, Lamas CC. Sexually acquired Zika virus: a systematic review. *Clin Microbiol Infect* 2017: **23**: 296–305.
10. Paixao ES, Barreto F, Teixeira Mda G, Costa Mda C, Rodrigues LC. History, epidemiology, and clinical manifestations of Zika: a systematic review. *Am J Public Health* 2016: **106**: 606–612.
11. Salge AKM, Castral TC, Sousa MC, Souza RRG, Minamisava R, Souza SMB. Zika virus infection during pregnancy and microcephaly in newborns: an integrative literature review. *Revista Eletronica de Enfermagem* 2016: **18**: 1–14.
12. Atif M, Azeem M, Sarwar MR, Bashir A. Zika virus disease: a current review of the literature. *Infection* 2016: **44**: 695–705.
13. Ibrahim NK. Zika virus: epidemiology, current phobia and preparedness for upcoming mass gatherings, with examples from World Olympics and Pilgrimage. *Pak J Med Sci* 2016: **32**: 1038–1043.
14. Jimenez A, Shaz BH, Bloch EM. Zika virus and the blood supply: what do we know? *Transfus Med Rev* 2017: **31**: 1–10.
15. Plourde AR, Bloch EM. A literature review of Zika virus. *Emerg Infect Dis* 2016: **22**: 1185–1192.
16. WHO. *Prevention of Sexual Transmission of Zika Virus. Interim Guidance Update*. 1-5. WHO: Geneva, 2016.
17. Cauchemez S, Besnard M, Bompard P *et al.* Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study. *Lancet* 2016: **387**: 2125–2132.
18. ECDC. *Rapid Risk Assessment: Zika Virus Disease Epidemic: Potential Association With Microcephaly and Guillain- Barré Syndrome. (Fourth update)*. ECDC: Stockholm, 2016.
19. Driggers RW, Ho CY, Korhonen EM *et al.* Zika virus infection with prolonged maternal viremia and fetal brain abnormalities. *N Engl J Med* 2016: **374**: 2142–2151.
20. Meaney-Delman D, Hills SL, Williams C *et al.* Zika virus infection among U.S. pregnant travelers – August 2015-February 2016. *MMWR Morb Mortal Wkly Rep* 2016: **65**: 211–214.
21. Mlakar J, Korva M, Tul N *et al.* Zika virus associated with microcephaly. *N Engl J Med* 2016: **374**: 951–958.
22. Besnard M, Lastere S, Teissier A, Cao-Lormeau V, Musso D. Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014. *Euro Surveill* 2014: **19**: pii: 20751.
23. Dupont-Rouzeyrol M, Biron A, O'Connor O, Huguon E, Descloux E. Infectious Zika viral particles in breastmilk. *Lancet* 2016: **387**: 1051.
24. Musso D, Nhan T, Robin E *et al.* Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014. *Euro Surveill* 2014: **19**: pii: 20761.
25. Leung GH, Baird RW, Druce J, Anstey NM. Zika virus infection in Australia following a monkey bite in Indonesia. *Southeast Asian J Trop Med Public Health* 2015: **46**: 460–464.
26. Mann TZ, Haddad LB, Williams TR *et al.* 2018. Breast milk transmission of flaviviruses in the context of Zika virus: a systematic review. *Paediatr Perinat Epidemiol*: **32**:358–368.
27. Soriano-Arandes A, Rivero-Calle I, Nastouli E *et al.* What we know and what we don't know about perinatal Zika virus infection: a systematic review. *Expert Rev Anti Infect Ther* 2018: **16**: 243–254.
28. Levi ME. Zika virus: a cause of concern in transplantation? *Curr Opin Infect Dis* 2017: **30**: 340–345.
29. Gregory CJ, Oduyebo T, Brault AC *et al.* Modes of transmission of Zika virus. *J Infect Dis* 2017: **216**: S875–S883.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Analysis table for transmission.

Table S2. Evidence table transmission.

Corresponding Author **Silvia Runge-Ranzinger**, Heidelberg Institute of Global Health, University of Heidelberg, Germany Im Neuenheimer Feld 365 69120 Heidelberg, Germany; E-mail: Olaf.Horstick@uni-heidelberg.de