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Non-vector-borne transmission of Zika virus: A systematic review

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Zika virus;
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Summary *Background:* Increasing numbers of confirmed cases of Zika virus (ZIKV) infection resulting from non-mosquito-borne transmission have been reported.
Methods: We performed a systematic literature review (PRISMA guidelines) on intrauterine, intrapartum, sexual and animal bite ZIKV transmission. The presence of the virus in breast milk, urine, saliva and blood transfusions was also reviewed.
Results: The search resulted in 285 papers of possible relevance, of which we included 53 in the systematic review. Mother-to-child transmission was most frequently described with adverse infant outcomes including microcephaly, intracranial calcification and fetal death. Zika virus RNA has been detected in amniotic fluid, breast milk, seminal fluid, saliva, urine and blood. Semen and blood products have proved to be infectious. Male-to-female and male-to-male ZIKV transmission is documented. There are contradictory results concerning the infectiousness of breast milk and urine and data on saliva, animal bites, transplantation, needlestick injury and laboratory work are inconclusive.
Conclusions: Our systematic analysis shows that non-vector-borne ZIKV transmission plays a role in the spread of ZIKV and has great societal impact. It has important public health implications for the prevention and control of ZIKV globally and will be a basis for policy and further research.

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1. Introduction

Over the past months, the number of reported cases of Zika virus (ZIKV) infections and reported cases of microcephaly and fetal brain malformations have dramatically increased in Latin America. On February 1st 2016, WHO Director-General, Dr Margaret Chan, declared that the clusters of microcephaly cases and other neurological disorders, in areas affected by Zika virus, constituted a PHEIC ("public health emergency of international concern") [1]. A total of 5079 cases of microcephaly were registered with the Brazilian government by February 6th, 2016. This number increased to 7015 cases by April 9th [2]. On April 13th, CDC officially concluded that Zika "is a cause of microcephaly and other severe fetal brain defects" [3]. Based on a report summarizing evidence that supports causality of ZIKV for severe fetal brain anomalies [4], ZIKV is now considered a cause of thousands of cases of microcephaly and other severe fetal brain defects.

ZIKV is transmitted by the bite of several mosquito species, notably the daytime active *Aedes aegypti* and the less anthropophilic *Aedes albopictus*. The latter prefers sylvatic environments [5] and is also found in the USA as far north as southern Minnesota and Maine [6] and in parts of southern Europe [7]. Long lists of mosquito species, from which Zika virus strains were isolated, have already been published [8,9]. The actual vectorial capacity, however, still remains unclear and geographic variability in vector competence of the same *Aedes* subspecies is likely [10,11]. The increasing threat of non-vector-borne transmission, including intrauterine mother-to-child transmission, has not yet been evaluated. These modes of transmission include human-to-human transmission via all body fluids and also animal-to-human transmission, transmission via placenta or breast milk, sexual transmission, transmission via saliva or droplets, urine, conjunctival/lacrimal fluid, transfusion or needlestick. Some of these modes of transmission have never been documented with any other arbovirus. The aim of this systematic review is, therefore, to unite and evaluate all research findings about non-arthropod-borne routes of ZIKV transmission, to provide an evidence base for the critical appraisal of the current state of knowledge on which health care guidelines and prevention efforts rely.

2. Methods

2.1. Literature extraction

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [12]. A systematic review of the literature of cases with non-vector-borne transmission of ZIKV was performed using the electronic databases PubMed, Embase, CINAHL and Scopus. The cut-off date for searches was March 31st 2016. The discussion, however, contains some newer, relevant articles that were published while writing this paper. Official reports from Ministries of Health and other surveillance reports were also screened.

The literature search strategy included "Zika" and one of the following search items:

pregnan*, women, malformation, congenital, sex*, microcephaly, fetal, foetal, fetus, foetus, birth, perinatal, sperm, semen, saliva, kiss*, transfusion, urine, breast milk, nursing, transplantation, vertical transmission, monkey bite, animal bite, needle stick.

An asterisk was used for abridged terms. Articles in English, Spanish, Portuguese, French and German were reviewed (for search methods see Appendix 1). We also searched for reports of cases of non-vector-borne transmission from Ministries of Health and public health community platforms.

2.2. Screening, inclusion and exclusion criteria

Eligibility criteria were original articles or case reports of non-arthropod-borne Zika virus infection as well as studies on body fluids where Zika virus or RNA was detected. Because detection of Zika virus infection after the viraemic phase is difficult, laboratory-confirmed proof of infection is missing in many cases of presumptive mother-to-child transmission. For this reason, we included both research reports on laboratory-confirmed Zika infection as well as epidemiological studies on suspected Zika-induced cases of microcephaly. Most articles in the first group were either case reports or case series, but *in vitro* and *in vivo* studies were also eligible. In addition to the records extracted from databases, we added 9 records identified through other sources, as shown in Fig. 1. After excluding all duplicates and papers that did not meet the inclusion criteria, the remaining articles were screened by two authors (FG, PS). Guidelines for clinical practice were discarded assuming that they were based on primary research literature and case descriptions already identified through our search strategy. We also discarded articles that were written in other languages than indicated above, 12 that were not available and 3 articles referring to the same patient groups without providing additional data. The remaining records were read in detail by one author (FG) who hand-searched reference lists to verify that no relevant articles were missing from this systematic review. Two authors (FG and PS) made an independent selection among the full-text articles assessed for eligibility, discussed their choices and consequently agreed upon a final selection. Full-text analysis was performed for all the included articles. Exclusion criteria included papers where a vector-borne transmission could not be ruled out with high probability or descriptions of cases published elsewhere which did not publish additional findings. Finally, a total number of 53 articles were included in the findings table (see Fig. 1).

2.3. Data extraction

Of a total of 53 original articles that were included in the final selection, 8 articles provided information on more than one possible mode of non-vector transmission. This explains why one and the same article is included in several tables. We used a uniform tool to extract data from eligible papers and recorded data on the journal, title, lead author, date of publication, location, type of paper, patients, symptoms of Zika in the patients, and key findings