GUIDELINE

INFANT FEEDING IN AREAS OF ZIKA VIRUS TRANSMISSION

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WHO GUIDELINE[1]: INFANT FEEDING IN AREAS OF ZIKA VIRUS TRANSMISSION

EXECUTIVE SUMMARY

Purpose of the guideline

The purpose of this guideline is to provide a recommendation to guide governments, ministries of health, policy-makers and health-care workers in regions affected by transmission of Zika virus, in the development of local and national protocols and policies on infant feeding, including breastfeeding practices in areas of Zika virus transmission, and their implementation. It may also be used to inform communication to the general public.

Zika virus is a mosquito-borne virus transmitted by *Aedes* mosquitoes; the same mosquito also transmits other vector-borne diseases – dengue, chikungunya and yellow fever. Currently, there is no treatment or vaccine to protect specifically against Zika virus infection *(1)*.

This guideline is part of a body of work that explores available evidence for possible acceptable medical reasons for temporary or long-term cessation of breastfeeding *(2)*. It updates the interim guidance on breastfeeding in the context of the Zika virus published by WHO on 25 February 2016 *(3)*.

Guideline development methodology

This guideline was produced in response to a Public Health Emergency of International Concern *(4)* and followed a rapid advice framework in order to produce timely guidance. The process followed all the basic steps for guideline development, as outlined in the *WHO handbook for guideline development (5),* but with time modifications to meet the urgent need for advice.

The steps in developing the present evidence-informed recommendation included: (i) identification of priority questions and outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of the recommendation, including research priorities; and planning for (v) dissemination; (vi) implementation, equity and ethical considerations; and (vii) impact evaluation and updating of the guideline. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was followed *(6)*, to prepare evidence profiles related to preselected topics, based on up-to-date systematic reviews.

A guideline development group meeting on the Zika virus outbreak was held on 17–19 March, 2016 in Geneva, Switzerland. The guideline development group – Zika virus and infant feeding was established with experts in the areas of infant feeding, nutrition surveillance, nutrition in emergencies, paediatrics and infectious diseases (virology and risk assessment). During the meeting, the group discussed the balance of consequences of breastfeeding or consuming breast milk from a mother infected with Zika virus, and finalized the recommendation. Five experts served as technical peer-reviewers of the draft guideline.

[1] This publication is a World Health Organization (WHO) guideline. A WHO guideline is any document, whatever its title, containing WHO recommendations about health interventions, whether they be clinical, public health or policy interventions. A recommendation provides information about what policy-makers, health-care providers or patients should do. It implies a choice between different interventions that have an impact on health and that have ramifications for the use of resources. This WHO guideline has been approved by the WHO Guidelines Review Committee.

Available evidence

A systematic review following the procedures of the *Cochrane handbook for systematic reviews of interventions (7)* was commissioned to determine the risk of transmission of Zika virus through breast milk or other breastfeeding-related bodily fluids (i.e. blood, sweat and saliva), and to assess the presence of Zika virus and Zika-specific antibodies in breast milk and other breastfeeding-related bodily fluids. The search strategy included electronic databases as well as the Pan American Health Organization (PAHO)/WHO Zika research projects list *(8)* and the WHO-hosted International Clinical Trials Registry Platform *(9)*.

The review identified two case-reports describing three mother–infant pairs. The three breastfeeding mothers had confirmed Zika virus infection and were symptomatic within 3 days of delivery. Two of the three infants born of these mothers had confirmed Zika virus infection. The Zika virus was detected in the breast milk of all three mothers, and shown to be replicative in cell culture in samples from one mother. However, the current data are not sufficient to conclude transmission via breastfeeding. The systematic review also identified three surveys that confirmed the presence of the Zika virus in serum and saliva of adult women and men. No studies have investigated the presence of Zika virus in sweat.

The overall quality of evidence for suspected, probable or confirmed Zika virus infection among infants or young children breastfeeding from mothers with Zika virus infection, and the presence (detected by positive reverse transcription polymerase chain reaction [RT-PCR]) or culture of Zika virus in breast milk of mothers who are acutely ill with confirmed Zika virus infection was very low.

Recommendation

Infants born to mothers with suspected, probable or confirmed Zika virus infection, or who reside in or have travelled to areas of ongoing Zika virus transmission, should be fed according to normal infant feeding guidelines. They should start breastfeeding within one hour of birth, be exclusively breastfed for six months and have timely introduction of adequate, safe and properly fed complementary foods, while continuing breastfeeding up to two years of age or beyond.[1]

Remarks

The remarks in this section are intended to give some considerations for implementation of the recommendation, based on the discussion of the guideline development group.

- The recommendation is consistent with the *Global strategy for infant and young child feeding (10)*, as endorsed by the Fifty-fifth World Health Assembly, in resolution WHA54.2 in 2002, to promote optimal feeding for all infants and young children.
- Mothers who decide to breastfeed should receive skilled support from health-care workers to initiate and sustain breastfeeding, whether they or their infants have suspected, probable or confirmed Zika virus infection.
- Mothers and families of infants born with congenital anomalies (e.g. microcephaly), or those presenting with feeding difficulties, should be supported to breastfeed their infants. Skilled feeding support from health professionals, including breastfeeding support, should be provided *(11)*.

[1] This is a *strong* recommendation, that is, one for which the guideline development group is confident that the desirable effects of breastfeeding in the context of Zika virus transmission outweigh the undesirable effects. Implications of the recommendation for mothers are that most mothers with suspected, probable or confirmed Zika virus infection, or who reside in or have travelled within 2 week to areas of ongoing Zika virus transmission, would opt to breastfeed, but some would not. With regard to policy-makers, the recommendation means that breastfeeding in the context of Zika virus transmission could be adapted as a policy in most situations.

- Families and communities are central in supporting optimal infant and young child feeding and improving infant health. Community cadres, when properly trained and supported, can serve as resources for counselling, practical support to mothers for breastfeeding and complementary feeding, solving problems, negotiating with caregivers and facilitating interactive peer sessions. Being aware of the complex set of values around breastfeeding better equips health workers to support pregnant and lactating women with their infant-feeding choices, even in the context of an outbreak.
- Multidisciplinary teams may be necessary for infants who need specialist support in infant feeding, especially for infants who have difficulty breastfeeding. This may be the case in particular for infants born with congenital anomalies, including microcephaly, and long-term management may be necessary.

Research priorities

The guideline development group – Zika virus and infant feeding highlighted the limited evidence available on the risk of transmissibility of the Zika virus through breastfeeding. Further research findings may impact on the guidance being given on infant feeding in areas of Zika virus transmission. A number of specific clinical and programmatic research questions were identified as part of the discussions, and merit a strong call for further research in the following areas:

- the frequency and possible persistence of Zika virus in breast milk after symptomatic and asymptomatic infection in lactating women;
- the effects of pasteurization on providing safe donor milk;
- biological, behavioural and contextual factors that influence Zika virus transmissibility through breastfeeding (Zika viral load and the presence of viable Zika virus);
- the incidence of symptomatic and asymptomatic Zika virus infection in neonates from infected mothers;
- the clinical presentation of Zika virus infection in breastfed and non-breastfed infants and young children, including potential short- and long-term effects on neurocognitive development;
- the clinical presentation of Zika virus infection among lactating women and whether this affects their ability to breastfeed;
- management of feeding difficulties among children with Zika virus-related congenital anomalies, e.g. microcephaly;
- factors in the breast milk of women with a history of previous Zika virus infection that may have a protective effect against virus transmission, and how this affects clinical disease progression;
- factors that influence infant-feeding practices in the context of Zika virus outbreaks, including the values and preferences of the mother and others involved in the care of the infant, as well as the prevailing social values and practices in settings suffering from a Zika outbreak.

Plans for updating the guideline

The WHO steering group – Zika virus and infant feeding will continue to follow the research development in the area of infant feeding, especially in the context of the Zika virus outbreak. The steering group will meet at or before 6 months from publication of this guideline, to review any new data and determine whether an update might be indicated. If the guideline merits an update, or if there are concerns about the validity of the guideline, the Department of Nutrition for Health and Development will coordinate the guideline update, following the formal procedures of the *WHO handbook for guideline development (5)*.

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SCOPE AND PURPOSE

The purpose of this guideline is to provide a recommendation to guide the development of local and national protocols and policies on breastfeeding practices in the context of Zika virus, and their implementation. It is part of a body of work that explores available evidence for possible acceptable medical reasons for a mother to stop breastfeeding temporarily or permanently *(2)*.

This guideline will link with other emergency guidelines being developed in parallel that will provide recommendations on the care of pregnant women in the context of Zika virus infection, assessment and management of microcephaly in the context of Zika virus infection, and identification and management of Guillain–Barré syndrome in the context of Zika virus infection. The primary audiences are governments, ministries of health, policy-makers and health-care workers in regions affected by transmission of Zika virus. It may also be used to inform communication to the general public.

BACKGROUND

Zika virus is an arbovirus belonging to the *Flavivirus* genus. The symptoms of Zika virus infection are usually mild and include fever, skin rashes, conjunctivitis, muscle and joint pain, malaise and headache that last for 2–7 days *(12, 13)*. The virus was first identified from sentinel Rhesus monkeys in the Zika forest of Uganda in 1948 and subsequently isolated from *Aedes africanus* mosquitoes from the same forest *(14, 15)*. Zika virus infections have since been identified in several African countries, including Central African Republic, Côte d'Ivoire, Gabon, Nigeria, Sierra Leone and Uganda, *(16–22)*. It has also been identified in infections in Asia and the Pacific, such as in Cambodia, Indonesia, Malaysia, Pakistan and Yap Island, Federated States of Micronesia *(23–28)*.

The outbreak in Yap Island in 2007, the first epidemic reported until that time, had 49 confirmed cases *(24, 26)*. Outbreaks have since been documented from French Polynesia in 2013 *(29)* and from the Americas (Brazil and Colombia) *(30–32)* and Africa (Cabo Verde) in 2015 *(33)*.

A clustering of cases of fever and rash was detected in Brazil starting in February 2015 and these were confirmed to be caused by Zika virus on May 2015. In October 2015, both Cabo Verde and Colombia reported outbreaks of Zika virus disease. By December 2015, over 50 000 suspected cases of Zika virus disease were identified in 29 states in Brazil. In March 2016, the number of suspected Zika infections in Brazil was estimated to be between 500 000 and 1 500 000, with almost 60 000 in Colombia and almost 8 000 In Cabo Verde. As of May 2016, 60 countries and territories report continuing mosquito-borne transmission of Zika virus, of which, 46 countries are experiencing a first outbreak since 2015 with no previous evidence of circulation *(34)*. On 1 February 2016, the World Health Organization (WHO) declared the Zika virus outbreak and the associated clustering of microcephaly and Guillain–Barré syndrome a Public Health Emergency of International Concern *(4)*.

Zika virus is transmitted to humans through the bite of infected *Aedes* mosquitoes. Person-to-person transmission has also been reported from sexual contact *(35, 36),* blood transfusion *(37)* and perinatal transmission *(38)*. Although the main mode of Zika virus transmission is through infected *Aedes* mosquitoes, current widespread transmission of the virus has raised questions as to whether transmission can also occur during breastfeeding, a practice that is essential to the survival and development of infants and young children.

[1] This publication is a World Health Organization (WHO) guideline. A WHO guideline is any document, whatever its title, containing WHO recommendations about health interventions, whether they be clinical, public health or policy interventions. A recommendation provides information about what policy-makers, health-care providers or patients should do. It implies a choice between different interventions that have an impact on health and that have ramifications for the use of resources. This WHO guideline containing recommendations has been approved by the WHO Guidelines Review Committee.

Interim guidance on breastfeeding in the context of the Zika virus was published by WHO *(3)*. The recommendations contained in the interim guideline were agreed on through discussion and unanimous consensus by an expert group, which met via teleconference on 19 February 2016. During the discussion with experts, various areas were identified where limited evidence is available and recommendations for further research were made, as well as identifying the need for a systematic review of evidence.

OBJECTIVES

This guideline replaces the interim guidance on breastfeeding in the context of the Zika virus published by WHO on 25 February 2016 *(3)*. It will also contribute towards the update of evidence behind possible acceptable medical reasons for temporary or long-term use of breast-milk substitutes, which is made available both as an independent tool for health professionals working with mothers and newborn infants, and as part of the baby-friendly hospital initiative package *(2)*.

SUMMARY OF AVAILABLE EVIDENCE

A systematic review that followed the procedures of the *Cochrane handbook for systematic reviews of interventions (7)* was registered in PROSPERO, the international prospective register of systematic reviews of the University of York and the National Institute for Health Research, under the number CRD42016036667. The review was done to determine the risk of transmission of Zika virus through breast milk or other breastfeeding-related bodily fluids (i.e. blood, sweat and saliva) *(39)*. It also aimed to assess the presence of Zika virus and Zika-specific antibodies in breast milk and other breastfeeding-related bodily fluids. Annex 1 shows the question that was used as the basis of the review, in population, intervention, control, outcomes (PICO) format.

The search strategy aimed to identify included studies with any lactating women with suspected, probable or confirmed Zika virus infection (see Annex 2) *(40),* or infants and young children receiving breast milk from women infected with Zika virus. Critical outcomes included the incidence of suspected, probable or confirmed Zika virus infection in infants or young children who were currently consuming breast milk. Important outcomes included the presence and viability of the Zika virus in breast milk, serum, sweat or saliva of lactating women.

The search was conducted on 14 March 2016 on the following electronic databases: Cumulative Index to Nursing and Allied Health Literature (CINAHL), Index Medicus for the South-East Asian Region (IMSEAR), Latin American and Caribbean Health Literature (LILACS), Medline, Population Information Online (POPLINE), PubMed, Web of Science, Western Pacific Region Index Medicus (WPRIM) and WHO Library Database (WHOLIS). Ongoing and unpublished studies or case-reports were searched for in the WHO-hosted International Clinical Trials Registry Platform *(9)* and the Pan American Health Organization (PAHO) Zika research projects list (11 March 2016) *(8)*. The United States Centers for Disease Control and Prevention and the WHO and PAHO Zika outbreak teams were also contacted for recent or unpublished findings (11 March 2016). The review included observational studies, case-studies and surveillance reports.

A total of 472 records were identified though database searching after duplicates were excluded. Forty-two articles were assessed for elegibility. A total of 40 articles were excluded; the main reasons for exclusion were that the studies reported on non-Zika virus infections or ineligible populations. Although the search included studies with any women who were breastfeeding (either directly from the breast or expressing breast milk) regardless of the timing of the maternal infection (during pregnancy, at the time of delivery or postnatally), only three mother–infant pairs were found, all of them with suspected or confirmed infection during the perinatal period *(39)*.

Two studies were case-reports of three mother–infant pairs – two pairs from French Polynesia *(38)* and one pair from New Caledonia *(41)*. In the case-report from French Polynesia, two women delivered at 38 weeks' gestation with pruritic rash within 2–3 days of delivery. Both mothers and both neonates had Zika virus infection confirmed by positive reverse transcription polymerase chain reaction (RT-PCR) result on at least one serum sample. In one of the mothers (symptomatic with rash and mild fever on the third day after delivery), repeated serum RT-PCRs were done and showed positive results for the first and fifth days after delivery, and negative results on the eighth, eleventh and thirteenth days after delivery. Her viraemia was thus documented by RT-PCR to span at least 2 days before the onset of symptom and up to 4 days after the onset of symptoms. Samples of breast milk gave positive RT-PCR results but no replicative Zika virus particles were detected in cell culture. The authors hypothesized that the infants were probably infected in utero or intrapartum because the infants' sera were positive for the presence of Zika virus within 1 day of starting breastfeeding *(38)*. No long-term complications were reported for either of the two infants at 2 years of age (personal communication, M Besnard, Centre Hospitalier de la Polynésie Française).

In the mother–infant pair from New Caledonia, a febrile mother delivered a healthy infant after 37 weeks' gestation. Replicative Zika viral particles from breast milk were successfully inoculated into Vero cell culture. The infant's serum was negative for Zika virus on RT-PCR *(41)*. No long-term complications were reported for the child at 8 months of age (personal communication, M Dupont-Rouyezrol, Institut Pasteur de Nouvelle-Calédonie).

None of the breast milk samples from the three mothers had repeat RT-PCR tests. The duration or persistence of Zika virus RNA in the breast milk of these mothers was therefore not known. The systematic review thus found three breastfeeding mothers with confirmed Zika virus infection who were symptomatic within 3 days of delivery. Two of the three infants had confirmed Zika virus infection. The Zika virus was detected in the breast milk of all three mothers, and shown to be replicative in cell culture in samples from one mother. However, the data are not sufficient to conclude transmission via breastfeeding. The overall quality of evidence for suspected, probable or confirmed Zika virus infection among infants or young children breastfeeding from mothers with Zika virus infection, and the presence (detected by RT-PCR) or culture of Zika virus in breast milk of mothers who are acutely ill with confirmed Zika virus infection was very low (see Annex 4).

Three surveys from Yap Island, Federated States of Micronesia *(24),* Nigeria *(42)* and French Polynesia *(43)* were able to confirm the presence of the Zika virus in serum *(24, 42, 43)* and saliva *(43)* in both men and women studied in the surveys. None of these studies *(24, 42, 43)* had lactating women among the sample population. No studies have investigated the presence of Zika virus in sweat.

The ongoing WHO surveillance of the Zika virus outbreak has reported no adverse neurologic outcomes or severe diseases from infants and young children (0–23 months of age) with postnatally acquired, vector-borne Zika infection *(34)*.

RECOMMENDATION

Infants born to mothers with suspected, probable or confirmed Zika virus infection, or who reside in or have travelled to areas of ongoing Zika virus transmission, should be fed according to normal infant feeding guidelines. They should start breastfeeding within one hour of birth, be exclusively breastfed for six months and have timely introduction of adequate, safe and properly fed complementary foods, while continuing breastfeeding up to two years of age or beyond.[1]

[1] This is a *strong* recommendation, that is, one for which the guideline development group is confident that the desirable effects of breastfeeding in the context of Zika virus transmission outweigh the undesirable effects. Implications of the recommendation for mothers are that most mothers with suspected, probable or confirmed Zika virus infection or who reside in or travelled within two week to areas of ongoing Zika virus transmission would opt to breastfeed, but some would not. With regard to policy makers, the recommendation means that breastfeeding in the context of Zika virus transmission could be adapted as a policy in most situations.

Rationale

The guideline development group – Zika virus and infant feeding took into consideration the following factors during the deliberations:

- Breastfeeding has significant benefits for mothers and children, in low-, middle-, and high-income countries. Children who are breastfed for longer periods have lower infectious morbidity and mortality, fewer dental malocclusions and higher intelligence than do those who are breastfed for shorter periods, or not breastfed. Breastfeeding also benefits mothers. It can prevent breast cancer and improve birth spacing, and might reduce a woman's risk of diabetes and ovarian cancer. Scaling-up breastfeeding can prevent an estimated 823 000 child deaths and 20 000 deaths from breast cancer every year *(44, 45)*.
- Zika virus RNA has been detected in breast milk from three mothers with confirmed Zika virus infection *(38, 43),* and replicative virus was identified in cell culture *(43)*. The breast milk samples where Zika virus RNA was found were collected at a time when the mothers were RT-PCR positive for Zika virus in serum samples and had clinical disease.
- Based on the documented presence of Zika virus RNA (detected by RT-PCR) and replicative Zika virus (detected in cell culture) in breast milk samples, breast milk may be considered as potentially infectious. However, there are currently no documented reports of Zika virus being transmitted to infants through breastfeeding.
- The frequency of virus detection, virus kinetics and size of viral load of Zika virus in breast milk is unknown. Though the Zika virus is known to circulate in the blood before the person infected is symptomatic and the virus is detected, these parameters are not known in relation to the virus kinetics in breast milk.
- No long-term complications have been documented for either of the two reported cases of newborn infants with confirmed Zika virus infection *(38)*. However, in countries with ongoing transmission of Zika virus, there is scientific consensus that infection with Zika virus is a cause of Guillaine–Barré syndrome, including among children who are less than 15 years of age *(34)*. No adverse neurologic outcomes or severe diseases have been reported to date from infants and young children (0–23 months of age) with postnatally acquired Zika infection *(34)*. Any change to this situation should be carefully monitored.
- Overall, the guideline development group felt that there was minor variability in values and preferences around breastfeeding in the context of Zika. Mothers and caregivers, when reassured about breastfeeding in the context of Zika virus, support and place a high value on breastfeeding in most communities.
- In light of the evidence available, the benefits of breastfeeding for the infant and mother outweigh any potential risk of Zika virus transmission through breast milk.

Remarks

The remarks in this section are intended to give some considerations for implementation of the recommendation, based on the discussion of the guideline development group – Zika virus and infant feeding.

- The recommendation is consistent with the *Global strategy for infant and young child feeding (10)*, as endorsed by the Fifty-fifth World Health Assembly in resolution WHA54.2 in 2002, to promote optimal feeding for all infants and young children.
- Mothers who decide to breastfeed should receive skilled support from health-care workers to initiate and sustain breastfeeding, whether they or their infants have suspected, probable or confirmed Zika virus infection.

- Mothers and families of infants born with congenital anomalies (e.g. microcephaly), or those presenting with feeding difficulties, should be supported to breastfeed their infants. Skilled feeding support from health professionals, including breastfeeding support, should be provided *(11)*.
- Families and communities are central in supporting optimal infant and young child feeding and improving infant health. Community cadres, when properly trained and supported, can serve as resources for counselling, practical support to mothers for breastfeeding and complementary feeding, solving problems, negotiating with caregivers and facilitating interactive peer sessions. Being aware of the complex set of values around breastfeeding better equips health workers to support pregnant and lactating women with their infant-feeding choices, even in the context of an outbreak.
- Multidisciplinary teams may be necessary for infants who need specialist support in infant feeding, especially for infants who have difficulty breastfeeding. This may be the case in particular for infants born with congenital anomalies, including microcephaly, and long-term management may be necessary.

Research priorities

The guideline development group – Zika virus and infant feeding highlighted the limited evidence available on the risk of transmissibility of the Zika virus through breastfeeding. Further research findings may impact on the guidance being given on infant feeding in areas of Zika virus transmission. A number of specific clinical and programmatic research questions were identified as part of the discussions, and merit a strong call for further research in the following areas:

- the frequency and possible persistence of Zika virus in breast milk after symptomatic and asymptomatic infection in lactating women;
- the effects of pasteurization on providing safe donor milk;
- biological, behavioural and contextual factors that influence Zika virus transmissibility through breastfeeding (Zika viral load and the presence of viable Zika virus);
- the incidence of symptomatic and asymptomatic Zika virus infection in neonates from infected mothers;
- the clinical presentation of Zika virus infection in breastfed and non-breastfed infants and young children, including potential short- and long-term effects on neurocognitive development;
- the clinical presentation of Zika virus infection among lactating women and whether this affects their ability to breastfeed;
- management of feeding difficulties among children with Zika virus-related congenital anomalies, e.g. microcephaly;
- factors in the breast milk of women with history of previous Zika virus infection that have a protective effect against virus transmission, and how this affects clinical disease progression;
- factors that influence infant-feeding practices in the context of Zika virus outbreaks, including the values and preferences of the mother and others involved in the care of the infant, as well as the prevailing social values and practices in settings suffering from a Zika outbreak.

DISSEMINATION, IMPLEMENTATION AND EQUITY CONSIDERATIONS

Dissemination

The current guideline will be posted on the WHO website, including the sites for the Zika virus health topic *(46),* the nutrition website *(47)*, the WHO e-Library of Evidence for Nutrition Actions (eLENA) *(48)* and social media. In addition, it will be disseminated through a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centres, universities, other United Nations agencies and nongovernmental organizations. Communications around the guideline will be managed by the Department of Communications, with support from the WHO steering group – Zika virus and infant feeding.

Implementation

As this is a global guideline, Member States are expected to adapt the recommendation according to their setting and feasibility. Public health nutrition and child health programmes that include optimal feeding strategies for infants and young children require supportive policies, social norms, employment conditions and health-care services that enable women to breastfeed. WHO regional and country offices assist with these processes.

Every woman has the right to the highest attainable standard of health, free from violence or discrimination. In the context of Zika virus transmission, a mother who decides to breastfeed her infant may be subject to stigmatization, disrespect or abuse. Member States must take action to prevent and eliminate this discrimination. For instance, governments should give greater support for research and action on disrespect and abuse; initiate, support and sustain programmes designed to improve the quality of maternal care in general, and infant-feeding support in particular; emphasize the rights of women to dignified and respectful health care; generate data on respectful care practices and systems of accountability; and involve all stakeholders, including women, in efforts to improve the quality of care *(49)*.

Ethical and equity considerations

Breastfeeding encompasses a complex set of behaviours, values, beliefs and social roles that interplay with the implementation of actions to protect, promote and support breastfeeding. A recommendation for breastfeeding, as in the case of this guideline, represents a challenge, since relevant epidemiological studies concerning the transmissibility of the Zika virus from the mother to the child and the mobidity risks of a Zika infection to the child are not yet fully available to make a comprehensive benefit versus harm assessment. Further contextualization is useful in addressing this public health challenge *(50, 51),* with the considerations listed next.

- **Political feasibility and community acceptance:** the recommendation of breastfeeding in a context of potential transmission of viral disease to the infant should be based on evidence and understanding the context of its application. Alternatives should not be ruled out based on the assumption of damage to the public image of breastfeeding by potential cases of Zika infection related to breastfeeding. Particular attention must be given to avoiding and tackling the potential stigmatization of women infected with the Zika virus who breastfeed.
- **Population-level utility:** an accurate understanding of the values of members of the community is important in assessing the usefulness of a recommendation to breastfeed during a Zika outbreak. Individuals should agree, or be comfortable with, the recommendation. Raising awareness of the complex set of values around breastfeeding better equips health workers to support pregnant and lactating women with their infant-feeding choices, even in the context of an outbreak.

- **Fairness and equity in implementation and monitoring:** in order to assess whether the expected benefits are likely to be distributed equitably in the community, continuous screening of the breastfeeding infant and lactating mother should be carried out, in order to monitor any unwanted harm or adverse effect due to transmission of the virus. It is important to include data disaggregated by socioeconomic variables in monitoring, in order to understand which populations groups are more affected or vulnerable to the outbreak or may need more support for breastfeeding.
- **Expected efficiencies and costs associated with the proposed action:** if the burden associated with the recommendation is evaluated, breastfeeding falls into what could be considered one of the least expensive alternatives in infant feeding during a Zika outbreak, while remembering that the long-term effects of the infant's exposure to an infected mother are yet to be fully clarified.

Monitoring and evaluation of guideline implementation

Monitoring and evaluation should be built into the implementation process, in order to provide important lessons for uptake and further implementation. For evaluation at the global level, the WHO Department of Nutrition for Health and Development has developed a centralized platform for sharing information on nutrition actions in public health practice implemented around the world. By sharing programmatic details, specific country adaptations and lessons learnt, this platform will provide examples of how guidelines are being translated into actions. The *Global database on the Implementation of Nutrition Action (GINA) (52)* provides valuable information on the implementation of numerous nutrition policies and interventions.

GUIDELINE DEVELOPMENT PROCESS

This guideline was produced in response to a Public Health Emergency of International Concern *(4)* and followed a rapid advice framework in order to produce timely guidance. The process followed all the basic steps for guideline development, as outlined in the *WHO handbook for guideline development (5)*, but with time modifications to meet the urgent need for advice. For instance, the formal planning proposal was submitted through the WHO emergency operations incident management system rather than to the WHO Guidelines Review Committee for prioritization and review.

Advisory groups

A WHO steering group on Zika virus and infant feeding, led by the Department of Nutrition for Health and Development, was established with representatives of the Departments of Maternal, Newborn, Child and Adolescent Health; Reproductive Health and Research; and Pandemic and Epidemic Diseases at WHO headquarters and the WHO Regional Office for the Americas (see Annex 5). The steering group met regularly and guided the overall supervision of the guideline development process, as well as the retrieval, assessment and summary of the evidence. The steering group – Zika virus and infant feeding provided administrative support for guideline development; drafted the scope of the guideline and key questions in population, intervention, control, outcomes (PICO) format; identified the systematic review team and guideline methodologist; developed and finalized the planning proposal; helped with the selection of the guideline development group – Zika virus and infant feeding and the external review group; oversaw the evidence retrieval, assessment and synthesis; collected and assessed disclosures of interest; and managed conflicts in consultation with the Office of Compliance, Risk Management and Ethics. Dr Pura Rayco-Solon and Ms Zita Weise Prinzo drafted the recommendation, based on the decisions of the guideline development group and drafted the final guideline, as well as managing the peer-review process.

A guideline development group for Zika virus and infant feeding was established with seven members, to advise WHO in the areas of infant feeding, nutrition surveillance, nutrition in emergencies, paediatrics and

infectious diseases (virology and risk assessment). They were selected from the WHO advisory panels, a call for experts and suggestions from WHO departments. The list of names of the guideline development group – Zika virus and infant feeding and their areas of expertise appears in Annex 6. Efforts were made to balance this guideline development group in terms of geography and sex and with diverse perspectives. If important perspectives and stakeholders were missing from the guideline development group, these were represented in the peer-reviewers (see Annex 7) and external review group (see Annex 8).

Scope of the guideline, evidence appraisal and decision-making

An initial set of questions to be addressed in the guidelines was the starting point for formulating the recommendation. The questions were drafted by technical staff at the Evidence and Programme Guidance Unit, Department of Nutrition for Health and Development, based on the interim guidance on infant feeding and Zika virus. The PICO format was used (see Annex 1). The questions were discussed and reviewed by the WHO steering group – Zika virus and infant feeding.

A systematic review *(38)* based on the PICO question was used to summarize and appraise the evidence. The review was done by the systematic review team (see Annex 9). Evidence profiles were prepared according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, to assess the overall quality of the evidence (see Annex 4) *(53, 54)*.

A guideline development group meeting on the Zika virus outbreak was held on 17–19 March, 2016 in Geneva, Switzerland. Four subgroups met on the above dates to discuss the emergency guidelines on (i) the assessment and management of microcephaly; (ii) identification and management of Guillain–Barré syndrome; (iii) care of pregnant women; and (iv) infant-feeding practices in the context of Zika virus. This meeting was jointly organized by the WHO headquarters Departments of Maternal, Newborn, Child and Adolescent Health; Mental Health and Substance Abuse; Nutrition for Health and Development; and Reproductive Health and Research.

The draft recommendation on infant feeding and Zika virus was prepared by the WHO steering group – Zika virus and infant feeding (see Annex 5). This was presented at the guideline meeting. The chairperson of the guideline development group, Dr Danielsson, was nominated at the opening of the consultation and the nomination was approved by all members of the guideline development group.

The guideline development group was asked to consider the draft recommendation in the light of the evidence presented. A decision-making framework was used to lead discussion and decision-making. This included considerations such as (i) the balance between desirable and undesirable effects of the recommendation; (ii) the quality of the available evidence; (iii) values and preferences related to the recommended interventions in different settings; and (iv) the feasibility and resource implications for programme managers in different settings. A summary of these discussions is presented in Annex 3.

The guideline development group used a simple consensus-building process to finalize the recommendation. Consensus was defined as agreement by all the members of the guideline development group. The chair and WHO Secretariat (see Annex 10) summarized the discussions of the guideline development group. The draft rapid response guidance was sent for peer-review before being sent for clearance to the incident manager of the Zika response and the guidelines review committee.

Peer-reviewers (see Annex 7) reviewed the draft guideline, in order to ensure there were no important omissions, contradictions or inconsistencies with scientific evidence or programmatic feasibility; and assist with clarifying the language, especially in relation to implementation and how policy-makers and programme staff might read and interpret it.

The WHO steering group – Zika virus and infant feeding reviewed all comments and revised the document, in order to ensure clarity of the recommendation while maintaining consistency with the original meaning.

MANAGEMENT OF COMPETING INTERESTS

Declarations of interest were requested of all members of the evidence-synthesis teams, all members of the guideline development group, and all external persons invited to review the recommendation following the guideline development process. This process was managed by the WHO steering group for this guideline development process, in compliance with the WHO conflict-of-interest policy. At the guideline meeting, each member verbally disclosed any interests and presented any action previously communicated after the conflicts-of-interest analysis. None of the members of the guideline group had any conflicts of interest to declare.

PLANS FOR UPDATING THE GUIDELINE

This guideline was produced in response to a public health emergency and followed a rapid-advice framework. The WHO steering group will continue to follow the research development in the area of infant feeding, especially in the context of the Zika virus outbreak. The steering group will meet at or before 6 months from publication of this guideline, to review any new data and determine whether an update might be indicated. If the guideline merits an update, or if there are concerns about the validity of the guideline, the Department of Nutrition for Health and Development will coordinate the guideline update, following the formal procedures of the *WHO handbook for guideline development (5)*.

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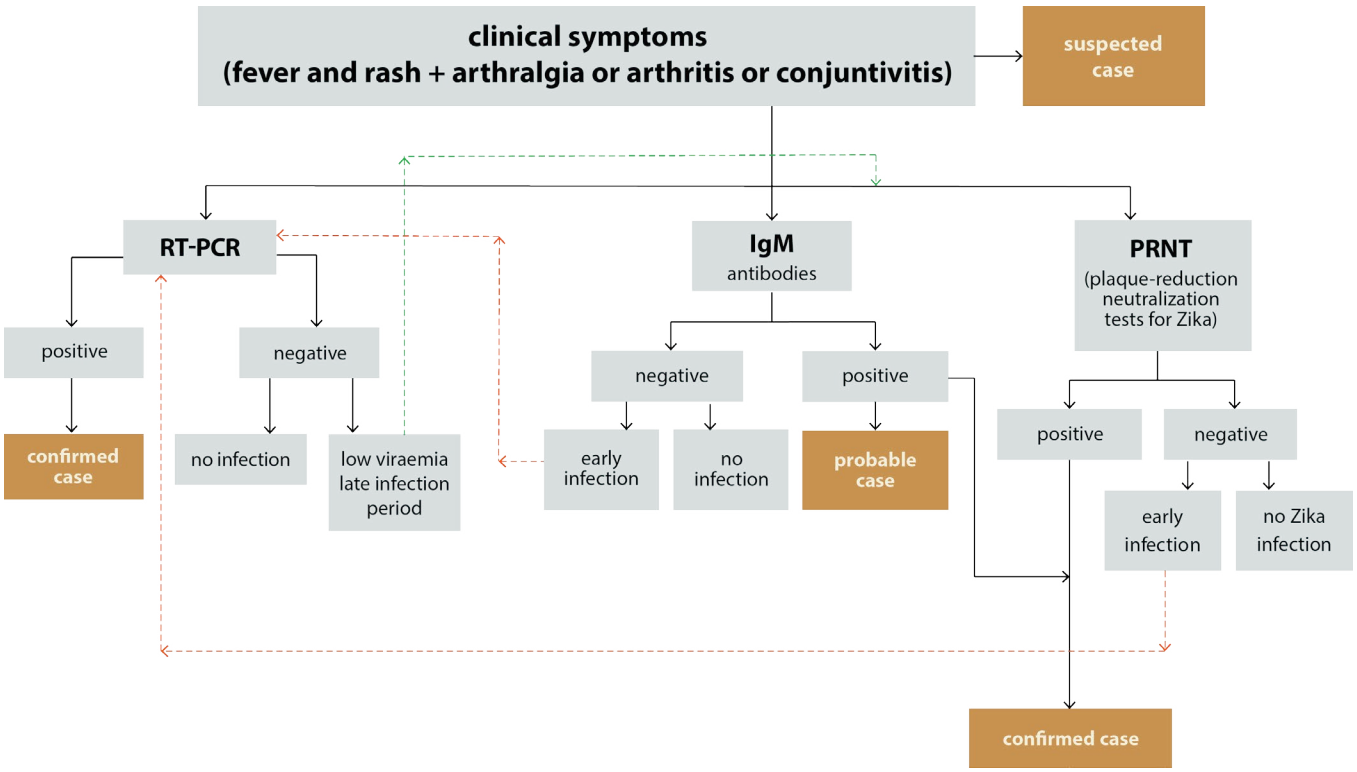
ANNEX 1. QUESTION IN POPULATION, INTERVENTION, CONTROL, OUTCOMES (PICO) FORMAT

In infants or young children not infected with Zika virus, does breastfeeding (any or exclusive) from a lactating woman infected with Zika virus, compared to not breastfeeding, result in Zika virus transmission to the infant or young child?

Population:	Any women who are breastfeeding, directly from the breast or expressing breast milk, with suspected, probable or confirmed Zika virus infection. This includes lactating participants who are currently breastfeeding or not, as well as those who were breastfeeding prior to a presumptive diagnosis of Zika virus infection. • Subgroup by timing of maternal infection: o Any time during pregnancy (but not acutely ill at the time of delivery) o Acutely ill at the time of delivery (within 2 weeks prior to or after onset of labour) o Infected postnatally (2 weeks after birth or beyond) • Subgroup by infant classification: o low birth weight (<2500 g) o preterm (<37 completed weeks of gestation) o presence of congenital anomaly
Intervention:	Breastfeeding or consumption of breast milk
Control:	No exposure to breast milk and not breastfeeding
Outcomes:	Suspected, probable or confirmed case of Zika virus infection among infants Presence of Zika virus in breast milk, serum, sweat or saliva

ANNEX 2. CASE DEFINITIONS AND MAIN DIAGNOSTIC TEST INTERPRETATIONS FOR ZIKA VIRUS



IgM: immunoglobulin M; RT-RCR: reverse transcription polymerase chain reaction.

ANNEX 3. SUMMARY OF THE CONSIDERATIONS OF THE GUIDELINE DEVELOPMENT GROUP – ZIKA VIRUS AND INFANT FEEDING FOR DETERMINING THE STRENGTH OF THE RECOMMENDATION

Quality of evidence:	Based on the two case-reports of three mother–infant pairs in which the lactating mother had confirmed Zika virus infection during the time of delivery, there was no unequivocal evidence of transmission through breastfeeding. However, the limited number of cases makes the quality of the evidence very low. New evidence may affect the validity of the conclusions of this guideline.
Values and preferences:	Literature on the values and preferences on breastfeeding of mothers living with HIV, a virus known to be transmissible through breastfeeding, were presented to the guideline development group *(55, 56)*. The studies showed that that mothers living with HIV balance complex influences in deciding their preferred infant-feeding strategies and express a range of feelings, weighing feelings of loss and self-blame with the view of responsibility and "good mothering". Women revealed that their infant-feeding choices were influenced by variations in social and cultural norms and messaging and guidelines regarding breastfeeding. Influences on infant-feeding choices include advice from clinic staff, previous infant-feeding experiences, desires to protect their infant from HIV and involvement of other care providers. The members of the guideline development group considered that the values and preferences of mothers for breastfeeding when infected with Zika virus (a mostly mild and transient infection) will be different from those when infected with HIV (a lifelong largely incurable infection), and that mothers know the difference between these two infections. Clear messaging can further reassure mothers and caregivers that although the Zika virus can be found in breast milk, it is not known whether its presence in breast milk will lead to transmission via this route. Furthermore, even if there were to be transmission through breast milk and breastfeeding, it is not known whether there will be serious consequences for the infant. Anecdotal evidence from Brazil shows that the WHO interim recommendations to support breastfeeding in the context of Zika virus have been well accepted in countries affected by the outbreak. Overall, the guideline development group – Zika virus and infant feeding felt that there was minor variability in the values and preferences around breastfeeding in the context of Zika virus.

Balance between benefits and harms:	There is clear evidence for the benefits of breastfeeding. Additional potential benefit from antibodies in the breast milk has been shown with other infectious diseases and may be plausible with the Zika virus. On the other hand, there is no documented evidence that transmission through breastfeeding has occurred. The severity of the clinical presentation, or the risk of complications for a postnatally infected infant (through vector-borne transmission or otherwise), is not known. In countries with ongoing transmission of Zika virus, there is scientific consensus that infection with Zika virus is a cause of Guillain–Barré syndrome, including among children who are less than 15 years of age. To date, no adverse neurologic outcomes or severe diseases have been reported among infants and young children (0–23 months of age) with postnatally acquired Zika infection. With the evidence that is currently available, there are manifest benefits from breastfeeding and little evidence of harm, even in the context of Zika virus.
Cost and feasibility:	There will be resource implications associated with disseminating and implementing the recommendation for breastfeeding, as well as a need for resources to maintain confidence and support for breastfeeding in areas affected by the outbreak. This cost will increase in areas where the practice of breastfeeding (whether infected with the Zika virus or not) is less accepted and is not the norm. This cost can further affect the feasibility of implementing recommendations for breastfeeding in areas of Zika virus transmission. However, the guideline development group felt that the costs associated with not breastfeeding will be higher and more resource intensive. In addition, the costs will be inequitably higher among the more vulnerable and poor populations.

ANNEX 4. GRADE SUMMARY OF FINDINGS TABLE

Breastfeeding (any or exclusive) from a lactating woman with suspected, probable or confirmed Zika virus infection compared to not breastfeeding in infants and young children

Patient or population: infants and young children

Setting: areas of Zika virus transmission

Intervention: breastfeeding from mothers with suspected, probable or confirmed Zika virus infection

Comparison: not breastfeeding from mothers with suspected, probable or confirmed Zika virus infection

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with not breastfeeding from mothers infected with Zika Virus	Risk with breast-feeding from mothers infected with Zika virus				
Suspected Zika virus infection among infants or young children breastfeeding from mothers with Zika virus infection	—	1/3 (33.3%)		3 (2 observational studies)	⨁ ◯ ◯ ◯ VERY LOW[1]	Based on the WHO interim case definition to classify and report cases of Zika virus infection *(40)*, a **suspect case** is a person presenting with rash and/or fever and at least one of the following: arthralgia, arthritis or conjunctivitis. Given the difficulty of determining arthralgia, arthritis or conjunctivitis among infants, we considered presentation with fever or rash among infants born to mothers with suspected, probably or confirmed Zika virus infection as a suspect case. Mother 1 initiated breastfeeding to Newborn 1 on the day of delivery. She was a confirmed case of Zika virus infection detected by serum RT-PCR and saliva RT-PCR on day 2. Newborn 1 did not develop symptoms though had confirmed Zika virus infection by serum RT-PCR and saliva RT-PCR on day 3 *(38)*. Mother 2 was confirmed with Zika virus infection on days 1 and 5 post-delivery by serum RT-PCR and initiated breastfeeding on day 3. Newborn 2 had a rash on day 4 and was subsequently confirmed to have Zika virus infection on day 4 by serum RT-PCR and on day 8 by urine RT-PCR *(38)*. Newborn 2 was considered a suspect case (prior to confirmation by RT-PCR). Mother 3 initiated breastfeeding to Newborn 3 on the day of delivery. She was a confirmed case of Zika virus infection detected by serum RT-PCR on day 3. Newborn 3 did not develop fever or rash *(41)*.
Probable Zika virus infection among infants or young children breastfeeding from mothers with Zika virus infection	—	—				A **probable case** is a suspected case with presence of immunoglobulin M (IgM) antibody against the Zika virus and an epidemiological link. None of the three newborn infants were tested for IgM against the Zika virus by enzyme-linked immunosorbent assay *(38, 41)*.

Breastfeeding (any or exclusive) from a lactating woman with suspected, probable or confirmed Zika virus infection compared to not breastfeeding in infants and young children

Patient or population: infants and young children

Setting: areas of Zika virus transmission

Intervention: breastfeeding from mothers with suspected, probable or confirmed Zika virus infection

Comparison: not breastfeeding from mothers with suspected, probable or confirmed Zika virus infection

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with not breastfeeding from mothers infected with Zika Virus	Risk with breast-feeding from mothers infected with Zika virus				
Confirmed Zika virus infection among infants or young children breastfeeding from mothers with Zika virus infection	—	2/3 (66.7%)	—	3 (2 observational studies)	⨁ ◯ ◯ ◯ VERY LOW[1]	Mother 1 initiated breastfeeding to Newborn 1 on the day of delivery. On day 2 following delivery, Mother 1 had a confirmed case of Zika virus infection detected by serum RT-PCR and saliva RT-PCR. On day 3, Newborn 1 had confirmed Zika virus infection by serum RT-PCR and saliva RT-PCR *(38)*. Mother 2 was confirmed with Zika virus infection on days 1 and 5 post-delivery by serum RT-PCR and initiated breastfeeding on day 3. Newborn 2 tested negative for Zika virus on day 0 and day 3 by serum RT-PCR, but had confirmed Zika virus infection on days 4 and 7 by serum RT-PCR and on day 8 by urine RT-PCR *(38)*. Both mothers had clinical signs of rash within days of delivery, and the authors concluded that vertical Zika virus transmission probably occurred during vaginal delivery *(38)*. Mother 3 initiated breastfeeding on the day of delivery and developed fever and maculopapular rash in the following days. On day 3 post-delivery, Mother 3 tested positive for Zika virus infection by serum RT-PCR and test results for Newborn 3 were reported as ambiguous *(41)*. The data are not sufficient to conclude that the transmission of the virus from the two mothers to the two infected infants was through breastfeeding. Other considerations include transmission through perinatal routes (in utero or during delivery).

Breastfeeding (any or exclusive) from a lactating woman with suspected, probable or confirmed Zika virus infection compared to not breastfeeding in infants and young children

Patient or population: infants and young children

Setting: areas of Zika virus transmission

Intervention: breastfeeding from mothers with suspected, probable or confirmed Zika virus infection

Comparison: not breastfeeding from mothers with suspected, probable or confirmed Zika virus infection

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with not breastfeeding from mothers infected with Zika Virus	Risk with breast-feeding from mothers infected with Zika virus				
Presence of Zika virus in breast milk (RT-PCR) of mothers who are acutely ill with confirmed Zika virus infection	—	3/3 (100.0%)	—	3 (2 observation-al studies)	⨁ ◯ ◯ ◯ VERY LOW[1]	Mother 1 had a confirmed case of Zika infection detected by serum RT-PCR and saliva RT-PCR on day 2 after delivery. On day 3, the breast milk from Mother 1 was found, by RT-PCR, to contain Zika virus *(38)*. Mother 2 was confirmed with Zika infection on days 1 and 5 post-delivery by serum RT-PCR On day 8, the Zika virus RT-PCR results from Mother 2 were positive in the breast milk *(38)*. Mother 3 tested positive for Zika infection by RT-PCD on day 3 post-delivery. Breast milk from Mother 3 was positive for Zika virus by RT-PCR on day 4 *(41)*. Because of the documented presence of Zika virus RNA (detected through RT-PCR) in breast milk, breast milk may be considered as potentially infectious. However, there are currently no documented reports of Zika virus being transmitted to infants through breast milk or breastfeeding.

Breastfeeding (any or exclusive) from a lactating woman with suspected, probable or confirmed Zika virus infection compared to not breastfeeding in infants and young children

Patient or population: infants and young children

Setting: areas of Zika virus transmission

Intervention: breastfeeding from mothers with suspected, probable or confirmed Zika virus infection

Comparison: not breastfeeding from mothers with suspected, probable or confirmed Zika virus infection

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with not breastfeeding from mothers infected with Zika Virus	Risk with breast-feeding from mothers infected with Zika virus				
Culture of Zika virus from breast milk of mothers who are acutely ill with confirmed Zika virus infection	—	1/3 (33.3%)	—	3 (2 observational studies)	⨁◯◯◯ VERY LOW[1]	Cultures of breast milk from Mothers 1 and 2 were negative for Zika virus *(38)*. Breast milk culture was positive for Zika virus from the breast milk of Mother 3 on day 4 after delivery *(41)*. Because of the documented presence of replicative Zika virus (detected in cell culture) in breast milk, breast milk may be considered as potentially infectious. However, there are currently no documented reports of Zika virus being transmitted to infants through breast milk or breastfeeding.

CI: confidence interval; **RT-PCR:** reverse transcription polymerase chain reaction.

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

For details of studies included in the review, see references *(38, 39, 41)*.

[1]The evidence is based on three mother–infant pairs from two case-reports. A case report of two mother-infant pairs was from the Zika virus outbreak in French Polynesia from 2013 to 2014 (Mother 1 and Mother 2) *(38)*. The second case report was from the Zika virus outbreak in New Caledonia in 2015 (Mother 3) *(41)*.

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