GUIDELINE

INFANT FEEDING IN AREAS OF ZIKA VIRUS TRANSMISSION

Second edition

World Health Organization

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Guideline: infant feeding in areas of Zika virus transmission, second edition

ISBN 978-92-4-002918-7 (electronic version)
ISBN 978-92-4-002919-4 (print version)

Photo credit (front cover): WHO/Jim Holmes

Cover design: Chris Yuen and Alberto March

Layout: Alberto March

CONTENTS

PUBLICATION HISTORY

This WHO guideline on infant feeding in areas of Zika virus transmission is an update of, and supersedes, previous WHO recommendations on infant feeding in areas of Zika virus transmission. WHO developed this guideline, first as interim advice on Breastfeeding in the context of Zika virus: interim guidance on 25 February 2016 and then as a rapid advice guideline WHO Infant feeding in areas of Zika virus transmission. This update expands the scope of the guideline to include an assessment of any potential risk of Zika virus infection through breastfeeding and feeding recommendations for infants presenting with congenital Zika virus syndrome or Guillain-Barré syndrome as well as support required by the mothers and caregivers of infants affected by these conditions. This guideline accompanies the WHO toolkit for the care and support of people affected by complications associated with Zika virus. To produce this guideline, the rigorous procedures for a standard guideline described in the WHO handbook for guideline development were followed. This document presents direct and indirect evidence as well as the evidence reviews that served to inform the recommendations herein.

ACKNOWLEDGEMENTS

WHO gratefully acknowledges the contributions of many individuals and organizations in preparing this guideline. Dr Maria Nieves Garcia-Casal, Dr Juan Pablo Peña-Rosas (responsible technical officer) and Dr Pura Rayco-Solon coordinated this normative work.

WHO extends its sincere thanks to Ms Mona Alsumaie, Dr Marianne Besnard, J.P. Dadhich, Dr Elsa Giugliani, Dr Laurent Kaiser, Ruowei Li, Dr Nishani Lucas, Dr Chessa Lutter, Ms Marie McGrath, Ms Monica Muti, Dr Celeste Naude, Professor Mical Paul, Dr Vanessa Aline Rouzier, Dr Mianne Silvestre, Professor Teck Chuan Voo and Ms Terrie Wefwafwa, who served as members of the Guideline Development Group.

WHO is grateful to the WHO Guidelines Review Committee Secretariat, in particular Ms Marion Blacker and Ms Rebekah Thomas, and members of the Guidelines Review Committee for their technical support throughout the process. Thanks are also due to Ms Alma Alic from the WHO Department of Compliance and Risk Management and Ethics for support in managing the conflicts-of-interest procedures.

WHO thanks Dr Natalia Aragón Velez, Dr Adriana Benavides, Dr Pierre Buekens, Dr Erica Ota, Ms Diana Valencia, and Dr Stanley Zlotkin for peer reviewing the final document before executive clearance by WHO and publication.

WHO gratefully acknowledges the contribution of the members of the WHO Guideline Steering Committee (in alphabetical order): Dr Ayoub Al Jawaldeh, Dr Mercedes Bonet Semenas, Dr Francesco Branca, Dr João Breda, Dr Shalini Desai, Dr Padmini Angela de Silva, Dr Tarun Dua, Dr Maria Nieves Garcia-Casal, Dr Fabio Gomes, Dr Laurence Grummer-Strawn, Dr Eve Lackritz, Dr Juan Pablo Peña-Rosas, Dr Pura Rayco-Solon, Dr Nigel Rollins, Dr Juliawati Untoro and Dr Maria Van Kerkhove, Ms Zita Weise Prinzo and Mr Gerardo Zamora Monge.

WHO is grateful for the technical contributions of Dr Cristina Palacios, Dr Hector Pardo-Hernandez and Dr Lisa Rogers to this work. Ms Rosa Seminario provided logistical support.

WHO thanks the systematic review teams that supported this work, especially Dr Joyce K. Andrade Velasquez, Dr Andrew Booth, Dr Fiona Campbell, Dr Chris Carroll, Ms Elizabeth Centeno, Dr Juan G. Chang Asinc, Dr Julia L. Finkelstein, Dr Maria Nieves Garcia-Casal, Dr Kate Ghezzi-Kopel, Heather S. Herman, Dr Melisa Medina-Rivera Dr Sabrina Martinez, Dr Saurabh Mehta, Dr Cristina Palacios, Dr Hector Pardo-Hernandez, Dr Juan Pablo Peña-Rosas, Dr Pura Rayco-Solon, Dr Clare Relton, Dr Lisa Rogers and Dr Mildred P. Zambrano Leal. Dr Cristina Palacios prepared the narrative summary of evidence in preparation for the final Guideline Development Group meeting.

Financial support

WHO acknowledges the financial support for this work received from the Bill & Melinda Gates Foundation and the United States Agency for International Development. WHO emphasizes that donors do not participate in any decision related to the guideline development process, including the composition of research questions, membership of the Guideline Development Groups, conducting and interpreting systematic reviews, or formulating the recommendations. The views of the funding bodies have not influenced the content of this guideline.

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

EXECUTIVE SUMMARY

In 2018, the World Health Assembly, through resolution WHA71.9 on infant and young child feeding, affirmed that "the protection, promotion and support of breastfeeding contributes substantially to the achievement of the Sustainable Development Goals on nutrition and health and is a core element of quality health care" and recognized that "appropriate, evidence-based and timely support of infant and young child feeding in emergencies saves lives, protects child nutrition, health and development and benefits mothers and families". The World Health Assembly requested WHO "to continue to update and generate evidence-based recommendations".

WHO recommends exclusive breastfeeding for infants 0–6 months of age and continued breastfeeding to 2 years and beyond. WHO interim guidance published during the Zika virus outbreak was based on a limited volume of evidence under an emergency process during a Public Health Emergency of International Concern. Subsequent rapid advice and a WHO toolkit for supporting people affected by complications associated with Zika virus recommended that mothers with possible or confirmed Zika virus infection or exposure continue to breastfeed, since the benefits of breastfeeding outweigh any potential risk of Zika virus infection through breast-milk. Concerns about possible Zika virus transmission during breastfeeding remain, since the virus has been detected in breast-milk samples. It is not clear whether breast-milk from women with Zika virus has enough viral load or infectivity to lead to infection among infants. Also, during breastfeeding, other bodily fluids could be exchanged, such as sweat and blood, in addition to breast-milk.

There are also concerns related to the transmission of Zika virus infection from the mother to the fetus during pregnancy. Zika virus infection during pregnancy can result in microcephaly and other congenital anomalies among affected infants, known as congenital Zika syndrome. Zika virus infection is also associated with other complications, including preterm birth and miscarriage. An increased risk of nervous system complications is associated with Zika virus infection among children, including Guillain-Barré syndrome, neuropathy and myelitis.

Infants with congenital Zika syndrome may have a decline in nutritional status owing to hypotonia, abnormal metabolic demands because of spasticity and difficulties feeding. Among the latter, infants with congenital Zika syndrome are especially affected by dysphagia, difficulty feeding, gastroesophageal reflux and delayed gastric emptying. There are certain modifications to feeding depending on the spectrum of manifestations and their severity, which may include postural correction, adjustment of the environment and thickening feeds, among others, as age appropriate.

Support for the caregivers of infants with congenital Zika syndrome may aid the infants in achieving improved growth and nutritional status, attaining developmental milestones and enhancing the quality of life. WHO published guidelines for screening, assessment and management of neonates and infants with complications associated with Zika virus exposure in utero in 2016.

Although there is no longer an outbreak, Zika virus transmission continues in some areas. As of July 2019, 87 countries and territories across four of the six WHO regions (African Region, Region of the Americas, South-East Asia Region and Western Pacific Region) had evidence of autochthonous mosquito-borne Zika virus transmission. It is important to have a standard guideline as part of efforts to manage infant feeding in areas where there is transmission as the data about long-term outcomes associated with Zika virus infection among infants are becoming available.

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[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. All publications containing WHO recommendations are approved by the WHO Guidelines Review Committee.

Purpose of the guideline

The objective of this guideline is to provide global, science-informed recommendations on infant feeding in areas of Zika virus transmission.[1] The primary audience of this guideline is health professionals responsible for developing national and local health protocols, especially those related to infant feeding in infancy and early childhood. The primary audience also includes those directly providing care to infants, such as nurses, general medical practitioners, paediatricians, managers of maternal, newborn and child health programmes and relevant personnel in health ministries, in all settings. Lastly, this guideline is also of interest to pregnant or breastfeeding women living or travelling to areas where Zika virus transmission continues.

This guideline aims to help WHO Member States and their partners to make science-informed decisions on the appropriate actions in their efforts to achieve the Sustainable Development Goals, the resolutions of the World Health Assembly on infant and young child feeding and the global targets put forward in the comprehensive implementation plan on maternal, infant and young child nutrition, the global strategy for infant and young child feeding and the Zika Strategic Response Plan.

Guideline development method

WHO developed the present science-informed recommendations using the procedures outlined in the *WHO handbook for guideline development*. The steps in this process included: (1) identifying priority questions and outcomes; (2) retrieving the evidence; (3) assessing and synthesizing the evidence; (4) formulating recommendations, including research priorities; and planning for (5) dissemination; (6) implementation, equity and ethical considerations; and (7) impact evaluation and updating the guideline. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) method was followed for preparing evidence profiles related to preselected topics, based on up-to-date systematic reviews. The Confidence in the Evidence from Reviews of Qualitative Research (CERQual) method was used in assessing the findings from systematic reviews of qualitative evidence. The Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice based on Evidence (DECIDE) framework, an evidence-to-decision tool that includes intervention effects, the certainty (or quality) of the evidence, values and preferences, resources, equity, acceptability and feasibility criteria, was used to guide the formulation of the recommendations by the Guideline Development Group.

WHO convened two Guideline Development Group meetings, one on 11 April 2019 and another on 9 and 10 December 2019. The meetings were held virtually. At the first online meeting, the Guideline Development Group provided input into the scope of the guideline, assisted the WHO Guideline Steering Committee in developing the key questions in PICO format and set priorities for outcomes to guide the evidence reviews and focus the recommendations. On 24 July 2019, the WHO Guideline Steering Committee met to discuss expanding this guideline to include infant feeding recommendations for infants presenting with congenital Zika syndrome or Guillain-Barré syndrome and the support mothers and caregivers of these infants require to feed these infants.

This guideline aimed to address the following questions:

1. For infants not infected with Zika virus, does breastfeeding (any or exclusive) or feeding of breast-milk from a lactating woman infected with Zika virus, compared with not breastfeeding, increase the risk of Zika virus transmission to the infant? Does a lactating woman vaccinated against Zika virus, compared with not breastfeeding, increase the risk of transmitting Zika virus to the infant or young child?
2. For infants (0–12 months old) affected by complications associated with Zika virus, what modifications in infant feeding practices compared with no modification or standard of care can improve infant outcomes?

[2] These areas are classified according to country, territory or subnational area into 1) Countries and territories with current or previous Zika virus transmission and 2) Countries and territories with established Aedes aegypti mosquito vectors, but no known cases of Zika virus transmission. The most recent classification is available in the latest Zika virus epidemiological update 2019.

3. Should the primary caregivers of infants (0–12 months old) affected by complications associated with Zika virus receive additional support to improving infant feeding compared with no additional support or standard of care to improve infant outcomes?

During the second online meeting, the Guideline Development Group members reviewed, deliberated and achieved consensus on the strength and direction of the recommendations presented herein. Through a structured process, the Guideline Development Group reviewed the balance between the desirable and undesirable effects and the overall certainty of supporting evidence, values and preferences of stakeholders, resource requirements and cost–effectiveness, acceptability, feasibility, human rights and equity.

Available evidence

To inform this guideline development process on managing infant feeding in the areas of Zika virus transmission, WHO commissioned three systematic reviews addressing: (1) evidence related to the presence in and transmission of Zika virus through breast-milk; (2) modifications in infant feeding practices and additional primary caregiver support to improve infant outcomes among infants affected by congenital Zika syndrome; and (3) the values and preferences of pregnant women, mothers, family members, health-care practitioners, policy-makers and health-care providers (midwives) concerning feeding when there is a risk of mother-to-child transmission of an infectious disease or when an infant or toddler is affected by congenital Zika syndrome. A literature update was also conducted on Zika vaccines and their current development status. The evidence available as of January 2021 is summarized below. Once the final vaccine products come to market, this section will need to be revised.

Risk of transmission through breast-milk, breastfeeding or expressed breast-milk in areas of Zika virus transmission

The updated systematic review aimed to assess the available evidence of the possible transmission of Zika virus through breast-milk intake or breastfeeding. This review was an update (data of search 18 June 2020) of a previous systematic review. The search strategy identified 2881 records, of which 1626 titles and abstracts were screened. There were 300 full-text articles assessed for eligibility, of which 14 remained for inclusion. These studies were reports from Brazil, Colombia, France, French Polynesia, New Caledonia, Thailand and the Bolivarian Republic of Venezuela. Collectively, they reported a total of 17 breast-milk samples from 17 women that were positive for Zika virus RNA by reverse transcription–polymerase chain reaction (RT-PCR) detection. Ten of these cases were described in case reports and seven in longitudinal studies. There were 10 cases where a breast-milk sample tested positive for viral RNA, but the infant had no infection. Among these, one newborn who was exclusively breastfed was tested at birth and followed up for seven months, while six other newborns were weaned when breast-milk tested positive. For another 10-month-old infant, breastfeeding was interrupted seven days after the onset of maternal symptoms and restarted four days after symptoms resolved. Of the seven infants who tested positive, five neonates and one five-month-old infant had confirmed Zika virus infection by RT-PCR test and one neonate had undetermined RT-PCR results. Among those with confirmed Zika virus infection by RT-PCR, there was one three-day-old neonate who had been breastfed since birth and a four-day-old-neonate fed both breast-milk and infant formula. One newborn was formula fed and one five-month-old infant was breastfed during the maternal symptomatic phase. Infant feeding practices were not reported in two newborn cases. All in all, evidence indicated Zika virus presence in breast-milk, and although three infants had virus present, no clear evidence of disease or clinical complications among infants could be associated with Zika virus in breast-milk or breastfeeding. The certainty of the evidence obtained in this systematic review was assessed as being very low.

Zika virus vaccine development for women who are breastfeeding

WHO has called for the development of a Zika virus vaccine that adheres to specific characteristics described in a target product profile. More than one vaccine may be required, depending on the needs of various population groups. Inactivated vaccines may be more adequate for women 15–49 years old and those who are pregnant, whereas live attenuated vaccines could be used among children, men and older adults. To date, 16 clinical trials have been registered to evaluate the safety and efficacy of candidate Zika virus vaccines, most of which are Phase 1 trials. The low number of new Zika virus infection cases recorded challenges the feasibility of Phase 3 field trials.

Feeding infants affected by complications associated with Zika virus

No eligible studies assessing modified infant feeding versus no modified infant feeding practices were identified. However, data from eight observational studies conducted in Brazil were examined, since they included important information related to the nutritional status of infants with congenital Zika syndrome or of infants whose mothers live in areas with active transmission of Zika virus, infant feeding practices and the outcomes of infants exposed to Zika virus or diagnosed with congenital Zika syndrome. These studies highlight the need for early nutrition interventions and caregiver support among infants affected by Zika virus or diagnosed with congenital Zika syndrome. They also underscore the importance of early nutrition interventions to reduce the risk of diminished nutritional status over time.

Support for primary caregivers of infants (0–12 months old) affected by complications associated with Zika virus

No eligible studies assessing support for caregivers of infants affected by complications associated with Zika virus were retrieved. Instead, the same eight observational studies mentioned above were examined. In general, family and community values and preferences and economic considerations play a role in the decision-making of pregnant women and mothers on infant feeding. Mothers and the family members of infants affected by congenital Zika syndrome reported frustration, fear, stress, anxiety and additional burden regarding the needs of their infants and the potential complications, such as choking or reflux. In addition, the caregivers of infants exposed to Zika virus or diagnosed with congenital Zika syndrome will most likely require continuing support in various areas of care and well-being.

Recommendations

To ensure that the recommendations are correctly understood and applied in practice, guideline users may want to refer to the remarks and the evidence summary, including the considerations on implementation.

Breastfeeding or expressed breast-milk in areas of Zika virus transmission

- 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 *(strong recommendation, very-low certainty of evidence)*.
- Infants fed with expressed breast-milk from 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 *(strong recommendation, very-low certainty of evidence)*.
- There is insufficient evidence to make a recommendation on breastfeeding or expressed milk from a lactating woman vaccinated against Zika virus, since no vaccine is available yet.

Infant feeding among infants affected by complications associated with Zika virus

- Among infants (0–12 months) affected by complications associated with Zika virus infection, infant feeding practices should be modified (such as adjusting the environment, postural correction or thickening feeds) to achieve and maintain optimal possible infant growth and development *(strong recommendation, very-low certainty of evidence)*.

Support for primary caregivers of infants (0–12 months old) affected by complications associated with Zika virus

- Mothers and caregivers of infants affected by complications associated with Zika virus (such as feeding difficulties) should receive skilled support from health-care workers to initiate and sustain optimal infant feeding practices (*strong recommendation, very-low certainty of evidence*).

Remarks

1. All the recommendations in this guideline were considered strong, although the certainty of the evidence was low or very low for the priority critical outcomes. In most of the studies included, the certainty of the indirect or direct evidence was low or very low because of experimental details, especially the type of study, imprecision, publication bias or indirect evidence with viruses similar to Zika virus. Despite the shortcomings of the available evidence, the Guideline Development Group opted to issue recommendations. To achieve this, GRADE guidance on developing science-informed recommendations when there is limited or non-existing published direct evidence is to incorporate indirect evidence and the collective expert evidence approach in the form of a structured and systematic approach to elicit the collective experience of the guideline group members. For this guideline, the Guideline Development Group was presented with the evidence-to-decision frameworks that considered the balance of desirable and undesirable anticipated effects, values and preferences of people affected by the recommendations, among other aspects. This approach is in agreement with the WHO guideline development procedures, specifically with guidance on developing recommendations integrating evidence across multiple domains.
2. Although Zika virus has been detected in human breast-milk, there is no clear evidence about the origin and a still undefined risk of transmission to the infant. Since Zika virus infection is mild for infants, the balance between desirable and undesirable effects favours breastfeeding versus not breastfeeding.
3. The modifications to infant feeding would be similar to that of infants with similar symptoms regardless of whether these symptoms are associated with Zika virus or not.
4. The recommendation on skilled support from health-care workers is consistent with previous WHO recommendations on protecting, promoting and supporting breastfeeding in facilities providing maternity and newborn services and on counselling women to improve breastfeeding practices.

Research gaps

The Guideline Development Group identified important knowledge gaps that need to be addressed through primary research, which may affect these recommendations. More research is needed related to the resources, feasibility, acceptability and equity of modifying feeding among infants affected by complications associated with Zika virus and on the type of additional support to provide to caregivers of these infants, since no direct evidence was found. The following questions were identified as those that demand urgent priority:

- determining the viral load needed to transmit Zika virus through breast-milk;
- understanding the views of pregnant women, mothers, family members, health-care practitioners, policy-makers and health-care providers (midwives) concerning infant feeding when there is a risk of potentially transmissible Zika virus;
- how breastfeeding or feeding breast-milk to infants from a lactating woman infected with Zika virus affects health equity;
- evaluating the acceptability or feasibility of breastfeeding or feeding breast-milk to infants from a lactating woman infected with Zika virus;
- how infant feeding modifications affects important infant outcomes among those affected by complications associated with Zika virus and evaluating the resources, feasibility, acceptability and equity of these modifications; and
- how providing additional support and follow-up to caregivers for improving infant feeding affects those affected by complications associated with Zika virus and evaluating the resources, feasibility, acceptability, continuity and equity of this support.

Plans for updating the guideline

WHO will continue to follow research developments in infant feeding in areas of Zika virus transmission, including the availability of a Zika virus vaccine in the market. WHO will follow the dynamic system of giving priority to technical products on norms and standards data and research for country impact and will maintain literature surveillance to respond rapidly to any changes in the epidemiology of Zika virus transmission along with any emerging evidence relevant to ensure that accurate, relevant and up-to-date guidance is available to countries and their partners globally.

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

1. INTRODUCTION

Zika virus is an arbovirus belonging to the *Flavivirus* genus *(1)*. 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 *(2,3)*. Rare sporadic cases of Zika virus infection were recorded between the 1960s and 1980s in Africa and Asia until 2007, when the first outbreak of Zika virus disease was recorded in the Micronesian island of Yap *(4)*. The next large outbreak was in French Polynesia and in other countries and territories in the Pacific in 2013 and then in Brazil in 2015 and in other countries in the Americas *(5)*. Since the end of 2016, Zika virus transmission has markedly declined in the Americas. As of July 2019, 87 countries and territories in the subtropical and tropical areas have reported evidence of mosquito-transmitted Zika virus infection *(6)*. In addition, in October 2019, the first case of locally acquired Zika virus was confirmed in France *(7)*. The spatial heterogeneity in Zika virus infection rates created pockets of susceptible populations that can sustain transmission in the future *(6)*.

The symptoms caused by Zika virus in the general population are mild, consisting of flu-like febrile illness for a few days *(8)*. However, the most alarming feature of Zika virus infection is during pregnancy, with its ability to cause microcephaly, congenital malformations and fetal demise *(8)*.

The diagnosis of Zika virus infection usually involves serological tests for Zika virus antibodies (immunoglobulin M (IgM) or IgG) or nucleic acid amplification test for Zika virus viral RNA. These approaches have limitations *(6,9–12)*; both false-positive and false-negative results can occur with nucleic acid amplification testing, which is only useful during a short window when Zika virus viraemia is present (beginning 3–5 days after illness onset and persisting for about one week). Serological testing is limited because cross-reactivity to other flaviviruses can lead to false-positive results and, as the incidence of Zika virus declines, the rate of false-positives increases. Also, limited information is available on the persistence of IgM antibodies, which creates challenges for diagnosing acute infection. Because of these limitations, serological testing is used to classify "probable infection" and RNA testing for confirmed infection.

Zika virus is primarily transmitted to humans through the bite of infected *Aedes* mosquitoes, mainly *Aedes aegypti*. It can also be transmitted less virulently by sexual contact *(13–15)*, blood transfusion *(16–18)*, blood products *(19)* or organ transplantation *(16,20)*. Zika virus has also been detected in urine, saliva, amniotic fluid, female genital tract secretions, semen, cerebrospinal fluid, aqueous humour, conjunctival fluid and nasopharyngeal swabs. It has been shown to be vertically transmitted through transplacental maternofetal passage or during birth *(15–17,21)*. The incubation period for Zika virus is not clear. It is thought to be similar to that of other mosquito-borne flaviviruses: probably less than one week *(22)*.

There are concerns for possible transmission of Zika virus during breastfeeding since it has been detected in breast-milk samples *(21,23–28)*. WHO recommends exclusive breastfeeding the first six months of life and continued to two years and beyond. It is unclear whether breast-milk carries enough viral load or infectivity to lead to infection among infants *(27–30)* or whether breast-milk possesses antiviral activity. An in vitro study with 39 samples of human milk investigated the antiviral activity of human milk against two flaviviruses, Zika virus and Usutu virus. Human milk showed antiviral activity against Zika virus and Usutu virus at all stages of lactation, with no significant differences in the activity of colostrum, transitional or mature milk. The mechanism of action studies demonstrated that colostrum does not inactivate viral particles but hampers the binding of both flaviviruses to cells *(31)*. In addition, during breastfeeding there could be exchange of other bodily fluids, such as sweat and blood, in addition to breast-milk.

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WHO released an interim guideline on breastfeeding in the context of Zika virus in 2016 during the outbreak *(32)*, with a rapid advice guideline following later that year *(1)*. WHO published a toolkit for the care and support of people affected by complications associated with Zika virus in 2017 *(33)*. In these documents, WHO recommended that mothers with possible or confirmed Zika virus infection or exposure continue to breastfeed, since the benefits of breastfeeding for the infant and mother outweigh any potential risk of Zika virus infection through breast-milk.

Transmission of Zika virus infection from mother to fetus during pregnancy may result in microcephaly (smaller than normal head size) and other major congenital anomalies among infants, collectively referred to as congenital Zika syndrome. Depending on its severity, microcephaly may lead to seizures, hearing and vision deficits, intellectual disability and impaired development and be life threatening. Zika virus infection may also lead to Guillain-Barré syndrome, including acute inflammatory demyelinating polyneuropathy, acute motor axonal neuropathy, ophthalmoplegia, ataxia and areflexia *(6)*. Congenital Zika virus infection abnormalities in neurodevelopment, hearing and vision could appear postnatally, mainly during the first year of life. An in vitro study on the effects of Zika virus infection in the established mature myelinated central nervous system shows that Zika virus infection affects central nervous system cells even after myelination, a process critical for saltatory conduction and neuronal function, has taken place *(34)*.

Proper nutritional status is a great concern for infants with congenital Zika syndrome. Poor nutritional status may occur due to decreased muscle tone leading to minimal activity, reduced feeding, dysphagia, difficulty feeding, gastroesophageal reflux, delayed gastric emptying and abnormal metabolic demands because of spasticity *(35)*. Support for the caregivers of infants with congenital Zika syndrome may be a protective factor for optimizing long-term nutritional status, attaining developmental milestones and enhancing the quality of life.

In 2016, WHO published recommendations for screening, assessing and managing neonates and infants with complications associated with Zika virus exposure in utero *(36)*. In this publication and in the 2017 toolkit for the care and support of people affected by complications associated with Zika virus *(33)*, WHO recommended assessment for signs of neurodevelopmental abnormalities, including feeding difficulties, for infants born to mothers with suspected, probable or confirmed Zika virus infection during pregnancy, even without microcephaly. Follow-up visits should occur at three, nine and 24 months of age at a minimum. In addition, comprehensive neurodevelopmental assessment and supportive therapy should be in place for irritability, seizures and swallowing difficulties for infants with congenital Zika syndrome. Developmental and neurological assessment should be performed with the full engagement of caregivers to identify developmental delays and other nervous system abnormalities such as epilepsy and disorders of movement, posture and swallowing. Further, supplementation may be appropriate for children with poor weight gain through additional feeding and complementary foods. Fortification with micronutrients may also be needed if nutritional deficiencies are present *(33)*.

Health issues among infants with congenital Zika syndrome may persist into adulthood, increasing the risk of poor health and additional requirements for health-care services *(35)*. In Brazil, a case series ascertained 30 children with Zika-related microcephaly who were born during the 2015 epidemic in the state of Pernambuco. Children were referred for endocrinological evaluation between February and August 2019. Of the 30 children, 97% had severe microcephaly. The average age at the endocrinological consultation was 41 months, and 53% were female. The most common endocrine dysfunctions were short stature, hypothyroidism and obesity *(37)*.

Improving the knowledge, skills and behaviour of the caregivers of infants affected by complications of Zika virus infection may be imperative to preserving health, maximizing development and promoting quality of life. In turn, this may reduce the need for additional health-care services in the future *(35)*. Although there is no longer an outbreak, Zika virus transmission continues in some areas of the world. It is important to have a standard guideline as part of efforts to manage infant feeding in areas with transmission. Other interim WHO guidance on Zika virus has been updated, including recommendations for preventing the sexual transmission of Zika virus *(38)*. Since data about long-term outcomes associated with Zika virus infection among infants are becoming available, the WHO guideline on infant feeding in areas of Zika virus transmission will be updated into a standard WHO guideline, following the WHO processes for guideline development.

Objectives

The WHO Guideline Steering Committee gave priority to updating the interim guidelines published in 2016 into a standard WHO guideline, since Zika virus transmission continues in some areas. The primary goal of this guideline is to provide recommendations on infant feeding in areas with Zika virus transmission.

Scope

The 2030 Agenda for Sustainable Development and the United Nations Decade of Action on Nutrition 2016–2025 have revitalized momentum for improving nutrition and have affirmed a clear leadership role for WHO. Nutrition contributes directly to achieving the 2030 Sustainable Development Goals, especially Sustainable Development Goal 2 (End hunger, achieve food security and improved nutrition and promote sustainable agriculture) and is a decisive enabler for Sustainable Development Goal 3 (Ensure healthy lives and promote well-being for all at all ages). United Nations General Assembly Resolution 70/259 proclaims 2016–2025 to be the United Nations Decade of Action on Nutrition and specifically called on WHO and the Food and Agriculture Organization of the United Nations to lead its implementation. In 2012, Member States endorsed six global targets for improving maternal, infant and young child nutrition. These targets, set for 2025, are vital for identifying priority areas for action and catalysing global change. In addition, the Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020 lays out diet-related targets for noncommunicable diseases.

The WHO Department of Nutrition and Food Safety works in collaboration with other WHO departments and programmes and with external partners to support countries and their partners in successfully designing and implementing effective strategies for achieving optimal nutrition in their population using science-informed policy options and best practices in both stable and emergency settings.

As part of this mandate to provide comprehensive programme guidance and support to WHO Member States and their partners to accelerate the successful implementation of effective and safe health action for country impact. All public health recommendations published by WHO strictly comply with the method described in the *WHO handbook for guideline development (39)*. This science-informed process is informed by systematic reviews of the evidence. Systematic reviews following the Cochrane methods are used to assess the evidence for outcomes that are critical for decision-making. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) method is used to assess the overall quality of evidence and establish the strength of the recommendations, considering the balance among risks and benefits, values, preferences and costs *(40)*. The Confidence in the Evidence from Reviews of Qualitative Research (CERQual) method uses a similar approach conceptually to the GRADE tools but is used in assessing findings from systematic reviews of qualitative evidence *(41)*.

Population of interest

The population affected by these recommendations includes infants in areas of Zika virus transmission and their mothers and caregivers. The recommendations in this guideline equally apply to parents who may not identify as "women" or "mothers", including transgender and non-binary parents.

Priority questions

Framed using the population (P), intervention (I), comparison (C) and outcome (O) (PICO) format, the questions for this recommendation were as follows.

1. Among infants not infected with Zika virus (P), does breastfeeding (any or exclusive) or feeding of breast-milk from a lactating woman infected with Zika virus (I), compared with not breastfeeding (C), increase the risk of Zika virus transmission to the infant (O)?
2. Among infants (0–12 months old) affected by complications associated with Zika virus (P), what modifications in infant feeding practices (I) compared with no modification or the standard care (C) can improve infant outcomes (O)?

3. Should primary caregivers of infants (0–12 months old) affected by complications associated with Zika virus (P) receive additional support for improving infant feeding (I) compared with no additional support or standard care (C) to improve infant outcomes (O)?

Annex 1 lists the key questions and outcomes guiding the evidence review and synthesis for the recommendations in this guideline.

Target audience

The primary audience includes professionals responsible for developing national and local health clinical procedures, especially those related to feeding in infancy and early childhood. The primary audience also includes people directly providing care to infants, including primary care practitioners, nurses, general medical practitioners, paediatricians, managers of maternal and child health programmes and relevant staff members in health ministries, in all settings.

This guideline may be of interest to professional societies involved in the care of infants, nongovernmental organizations concerned with promoting breastfeeding and equity in child health and implementers of maternal and child health and nutrition programmes. This guideline may also be of interest to pregnant or breastfeeding women living or travelling to areas where Zika virus transmission continues.

2. EVIDENCE AND RECOMMENDATIONS

The following section outlines the recommendations and the corresponding narrative summary of evidence for the questions given priority. The summary of the balance between the desirable and undesirable effects and the overall certainty of the supporting evidence, values and preferences of stakeholders, resource requirements, cost–effectiveness, acceptability, feasibility and equity that were considered in determining the strength and direction of the recommendations are also presented.

All the recommendations in this guideline were considered strong, although the certainty of the evidence was low or very low for the priority critical outcomes. In most studies included, the certainty of the evidence was low or very low because of experimental details, especially the type of study, imprecision, publication bias or indirect evidence with viruses similar to Zika virus. Despite the shortcomings of the available evidence, the Guideline Development Group opted to issue recommendations. To achieve this, GRADE guidance on developing evidence-informed recommendations when there is limited or non-existing published direct evidence is to incorporate indirect evidence and the collective expert evidence approach in the form of a structured and systematic approach to elicit the collective experience of the guideline group members. For this guideline, the GDG was presented with the evidence-to-decision frameworks that considered the balance of desirable and undesirable anticipated effects, values and preferences of people affected by the recommendations, among other aspects. This approach is in agreement with the WHO guideline development procedures, specifically with guidance on developing recommendations integrating evidence across multiple domains. Annexes 2 and 3 present the GRADE summary of findings tables and the GRADE CERQual evidence profiles informing this guideline.

2.1 Breastfeeding or expressed breast-milk in areas with Zika virus transmission: among infants not infected with Zika virus, does breastfeeding (any or exclusive) or feeding of breast-milk from a lactating woman infected with Zika virus, compared with not breastfeeding, increase the risk of transmitting Zika virus to the infant?

SUMMARY OF EVIDENCE

Evidence from four systematic reviews *(29,30,42,45)* was assessed to address this question. These reviews addressed the risk of transmitting Zika virus through breast-milk *(29,42,45)* and the presence of Zika virus in human milk *(30)*.

Two of these reviews *(29,30)* included case reports and case series in which Zika virus was detected in human milk. Two case reports were included in both reviews, describing three mother–infant pairs in which the mothers had confirmed Zika virus infection and were symptomatic within three days of delivery. Two of the three infants born to these mothers had confirmed Zika virus infection. 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 were 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 had investigated the presence of Zika virus in sweat.

The second review *(30)* also identified one additional case report and two case series in which Zika virus was detected in human milk. In one series of two cases, Zika virus was found in human milk samples collected five days after the onset of maternal symptoms of infection, but cell cultures were negative for infectious virus in both cases. In the remaining case reports or series, human milk samples collected 3–4 days after the onset of maternal symptoms of the infection were positive for Zika virus; cell cultures were also positive for infectious virus. Among three other women, Zika virus was not detected in breast-milk samples collected four or more days after onset of symptoms. Finally, the virus was found in colostrum samples 14 days after the onset of symptoms and in milk samples 23 and 32 days after onset. Cell culture also showed infectious Zika virus particles in the samples.

The third review *(42)* included nine studies with 10 cases identified. Five of the cases were infected with Zika virus during pregnancy (considered as the transplacental route of infection or at delivery), one case was infected

0–4 days after birth, two cases were infected between eight weeks and six months after birth and two cases were infected beyond six months after birth. The breast-milk of mothers from five cases confirmed the presence of Zika virus; two newborns were breastfed from birth, one case avoided breastfeeding and, for one case, whether the baby was breastfed was not specified. One case appeared to have been infected just before delivery, with positive Zika virus in the mother right after delivery and transient positive Zika virus in the baby with a mild rash, but follow-up at 32 months indicated that the baby had no complications and was breastfed for two months. Two other cases had positive Zika virus in urine but not in breast-milk, with one case fully breastfeeding for five months without symptoms in the baby. The two final cases had positive Zika virus in serum, with one case being positive with Zika virus in breast-milk and infectious particles in cell culture. In this case, breastfeeding was avoided (the infant was 11 months old) and resumed after the maternal rash disappeared. The baby was negative for Zika virus and asymptomatic at least by day 17. The other case also breastfed her infant (10–11 months old) during the symptomatic maternal period, and the infant was asymptomatic and negative for Zika virus. This review included the cases described in the 2018 review *(30)*.

The last review *(45)* included seven observational studies (one cohort and six case reports). This review found that three of seven children breastfeeding from women with suspected, probable or confirmed Zika virus infection had evidence of the infection themselves *(45)*. Among cohort studies, there was no confirmed Zika virus infection among infants and children breastfeeding from a woman with suspected, probable or confirmed Zika virus infection (0% risk, 0 of 6).

ADVERSE SYMPTOMS OR EVENTS (NOT TYPICALLY ASSOCIATED WITH THE INFECTION)

No adverse outcomes were reported.

LONG-TERM EFFECTS ON THE INFANTS

One of the study authors was contacted, who confirmed that no long-term complications were reported for either of the two infants in his study at two years of age.

Independently of the route of transmission, the consequences of Zika virus infection among infants are generally mild and transient.

ADDITIONAL CONSIDERATIONS

The potential mechanism explaining why Zika virus is present in milk but appears to not infect the infant has been explored *(48)*. In a recent study, donated human breast-milk samples were infected with various strains of Zika virus (including the African and Asian strains). Infection of all strains was inhibited only if the human breast-milk had been frozen. Fresh milk does not inhibit Zika virus infection; however, when the milk was stored, the inhibition of the virus increased in some samples as quickly as in 30 minutes and the infection was completely lost after two days of storage. Cold storage of milk also inactivates the virus. The mechanism to explain the effect of stored breast-milk on the Zika virus is that the antiviral activity in milk, present in the fat-containing cream fraction of milk, quickly destroys the viral particle integrity. Storing or processing the milk may release lipases that could generate free fatty acids that destroy the Zika virus membrane. The variability observed in this activity may be explained by the fat composition of milk, which also varies among women.

Desirable effects

The desirable anticipated effects of breastfeeding or feeding of breast-milk (any or exclusive) from a lactating woman infected (suspected, probable or confirmed) with Zika virus are large compared with not breastfeeding among infants not infected with Zika virus.

Undesirable effects

The undesirable anticipated effects of breastfeeding or feeding of breast-milk (any or exclusive) from a lactating woman infected (suspected, probable or confirmed) with Zika virus are small compared with not breastfeeding among infants not infected with Zika virus.

Certainty of the evidence

The overall certainty of evidence for suspected, probable or confirmed Zika virus infection among infants breastfeeding or receiving milk from mothers with Zika virus infection and the presence of Zika virus in the breast-milk of mothers who are acutely ill with confirmed Zika virus infection was very low *(29,42)*. Grading was not performed for two of the identified systematic reviews *(30,41)*.

ZIKA VIRUS VACCINE

Although Zika virus infection is usually self-limiting, serious complications may occur, especially among pregnant women. Evidence indicates that even asymptomatic infection among pregnant women may result in congenital Zika syndrome. Whether sterilizing immunity or a robust T-cell response is needed to prevent transplacental transmission remains unknown *(49,50)*.

WHO has called for developing a Zika virus vaccine that adheres to specific characteristics described in a product profile that can be found online *(51)*. More than one vaccine may be required, depending on the needs of different population groups. Inactivated vaccines may be more adequate for women of childbearing age and those who are pregnant, whereas live attenuated vaccines could be used among children, men and older adults. Higher-potency vaccines could be appropriate for immunocompromised people, and DNA- or vector-based vaccines may result in longer-lasting immunity *(52)*.

As of January 2019, 16 clinical trials were registered to evaluate the safety and efficacy of candidate Zika virus vaccines. Most were Phase 1 trials (14, 87%), with nine completed (56%). The remaining trials are still open, either recruiting (4, 25%) or not recruiting (3, 19%). All trials specified that pregnancy or planning to get pregnant are exclusion criteria, some requiring a negative pregnancy test before enrolment. The main characteristics of these trials are available at the WHO vaccine pipeline tracker *(51)*.

The low number of new Zika virus infection cases recorded challenges the feasibility of Phase 3 field trials. At this time, no vaccine for Zika is commercially available.

SUMMARY OF THE CONSIDERATIONS FOR DETERMINING THE DIRECTION AND STRENGTH OF THE RECOMMENDATIONS

These recommendations were informed by the evidence presented above, with explicit consideration of the factors listed next.

Certainty of the evidence

The overall certainty of the evidence for whether breastfeeding or feeding of breast-milk (any or exclusive) from a lactating woman infected with Zika virus increases the risk of Zika virus transmission to the infant is very low. The overall certainty of the evidence for presence of Zika virus in breast-milk from women with suspected, probable or confirmed Zika virus infection is very low.

Balance of benefits and harms

Overwhelming evidence is available on how breastfeeding positively affects child survival, health and development and maternal health. The benefits of breastfeeding or of feeding breast-milk (any or exclusive) from a lactating woman infected with Zika virus (suspected, probable or confirmed) compared with not breastfeeding among infants and not infected with Zika virus far outweigh the potential harm.

Values and preferences

A qualitative systematic review *(44)* found very limited evidence on potentially transmissible Zika virus. The search was therefore expanded to include studies considering (1) the presence of a transmissible disease other than HIV; and (2) the presence of HIV *(53)*. For the former, eight studies were identified. The evidence base had a moderate risk of bias: most studies presented a clear question and qualitative design, used appropriate methods

and reported clear findings. New mothers report being sad and anxious that their circumstances mean they cannot breastfeed and that their bond with their child might be affected as a result. However, mothers appear to be willing to learn about these risks and to adapt their feeding practices accordingly, if advice is communicated in an appropriate and sensitive manner and trustworthy and affordable alternative feeding options are available. Health-care providers and decision-makers reported community attitudes that failure to breastfeed indicated contagion; while mothers reported experiencing guilt and stigma for the same reason and a need not to be seen not breastfeeding. Health-care providers and decision-makers also reported a lack of confidence among mothers in the alternatives to breastfeeding, and mothers and community members report that access to such alternatives and their cost are prohibitive.

A systematic scoping review on the processes and outcomes of antenatal care that are important to healthy pregnant women *(54)* could be applicable to mothers and mothers-to-be infected with Zika virus. This review included 21 articles with 1264 women. In general, the quality of the included studies was moderate. This review found that, overall, women value a positive pregnancy experience, which includes preventing threatening risks and illness and achieving competence and autonomy, especially on how to take care of the baby .

SUMMARY

Overall, there may be important uncertainty or variability in the values and preferences of pregnant women, mothers, family members, health-care practitioners, policy-makers and health-care providers (midwives) concerning infant feeding (including breastfeeding, breast-milk and their alternatives) when there is a risk of potentially transmissible Zika virus. The certainty of the evidence is low.

Balance of effects

The balance between desirable and undesirable effects favours breastfeeding compared with not breastfeeding.

Acceptability

No direct studies have evaluated the acceptability of breastfeeding or feeding of breast-milk to infants from a lactating woman infected with Zika virus. Nevertheless, the Guideline Development Group considered that breastfeeding or feeding breast-milk to infants from a lactating woman infected with Zika virus is acceptable to key stakeholders.

Because of some uncertainty about the transmission of Zika virus from the mother to the child through breast-milk, recommending breastfeeding for mothers infected with Zika virus represents a challenge. A comprehensive benefit-versus-harm assessment is still in progress, and alternatives should therefore not be ruled out based on the assumption of damage to the public image of breastfeeding by potential cases of Zika virus infection related to breastfeeding. Further, women infected with Zika virus who breastfeed or those who choose not to breastfeed could be potentially stigmatized. On the one hand, if they choose to breastfeed, women may be subject to stigma for fear of passing Zika virus to their children. On the other hand, women may feel compelled to formula-feeding in order to minimise any potential risk of infection. In doing so, they may experience guilt and dissatisfaction. A study among 890 mothers of infants who were formula feeding evaluated the predictors of emotional experiences related to their choice and found that overall, most women experienced negative emotions as a result of their decision to feed infant formula to their babies *(55)*. Guilt and stigma were directly associated with feeding intention and method, thus highlighting the need to address infant formula feeding in a more balanced, woman-centred manner, especially in the case of Zika virus.

Accurately understanding the values of members of the community is important in assessing the usefulness of a recommendation to breastfeed during a Zika virus outbreak. Raising awareness of the complex set of values around breastfeeding better equips health-care workers to support pregnant and lactating women with their infant-feeding choices, even in the context of an outbreak.

Resource implications

Based on the tool on the cost of not breastfeeding, 595 379 childhood deaths (6–59 months old) from diarrhoea and pneumonia and 974 956 cases of childhood obesity each year can be attributed to not breastfeeding *(56)*. For women, breastfeeding is estimated to have the potential to prevent 98 243 deaths from breast and ovarian cancer and type 2 diabetes each year. This has been estimated to have global health system treatment costs of US$ 1.1 billion annually, with an economic loss due to premature mortality among children and women of US$ 53.7 billion and a cognitive loss of US$ 285.4 billion annually.

The resources required include training personnel in advising lactating women to continue to breastfeed or feed from expressed and stored breast-milk, training in advising mothers not to breastfeed and on which alternatives to recommend and time for staff to provide counselling as part of the routine antenatal and postnatal care services.

Breastfeeding or feeding of breast-milk (any or exclusive) from a lactating woman infected (suspected, probable or confirmed) with Zika virus likely results in moderate savings compared with not breastfeeding among infants not infected with Zika virus. The certainty of evidence on costs is low. The cost–effectiveness of breastfeeding or feeding of breast-milk (any or exclusive) from a lactating woman infected (suspected, probable or confirmed) with Zika virus probably favours treatment compared with not breastfeeding among infants not infected with Zika virus.

Equity

Breastfeeding or feeding of breast-milk among infants from a lactating woman infected with Zika virus probably increases equity compared with not breastfeeding among infants not infected with Zika virus. Families may experience economic pressures because of the need to buy special food (*6,7*). The economic burden of formula feeding may exacerbate the socioeconomic standing of families with babies affected by congenital Zika syndrome. A small descriptive cross-sectional study among 25 mothers of live-born babies with confirmed diagnosis of congenital Zika syndrome in Brazil found inequities in the Zika virus epidemics, in which women with low income and lower social class were more often affected *(57)*.

Breastfeeding encompasses a complex set of behaviour, values, beliefs and social roles that interact with the implementation of actions to protect, promote and support breastfeeding. Continual screening of breastfeeding infants and lactating mothers could help to determine whether the expected benefits are likely to be distributed equitably in the community. These programmes could also help to identify any unwanted harm or adverse effect from potential transmission of the virus.

Feasibility

No studies have evaluated the feasibility of breastfeeding or feeding breast-milk to infants from a lactating woman infected with Zika virus. Using the HIV model, a qualitative study among 17 formula-feeding and 19 breastfeeding mothers in Burkina Faso explored the acceptability and feasibility of WHO's recommendation of infant-feeding options among mothers living with HIV *(58)*. Although exclusive breastfeeding for the first six months remains the most appropriate option for many mothers living with HIV in sub-Saharan Africa, its acceptability and feasibility are not very high.

The Guideline Development Group considered that understanding the values of members of the community is important in assessing the usefulness of a recommendation to breastfeed during a Zika virus outbreak. Individuals should agree with or be comfortable with the recommendation.

RECOMMENDATIONS

- 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 *(strong recommendation, very-low certainty of evidence)*.
- Infants fed with expressed breast-milk from 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 *(strong recommendation,very-low certainty of evidence)*.
- There is insufficient evidence to make a recommendation on breastfeeding or expressed milk from a lactating woman vaccinated against Zika virus, since no vaccine is available at this time.

Rationale

Breastfeeding has significant benefits for mothers and children, in low-, middle- and high-income countries *(59,60)*. 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, since it may prevent breast cancer, lengthen birth spacing and reduce the 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 *(59)*.

The systematic reviews described here show evidence of several case reports of Zika virus infection among breastfeeding infants and show evidence of Zika virus in the breast-milk. However, the current evidence is not sufficient to conclude that Zika virus can be transmitted through breastfeeding or feeding of breast-milk. The frequency of virus detection, virus kinetics and size of viral load of Zika virus in breast-milk are unknown.

No long-term complications have been documented for any of the cases described in the systematic reviews, although most studies have followed infants for short periods after birth.

Overall, the Guideline Development Group felt that there was minor variability in the values and preferences around breastfeeding in the context of Zika virus. Mothers and caregivers, when reassured about breastfeeding in the context of Zika virus, support and place a high value on breastfeeding in most communities. Given the evidence available, the benefits of breastfeeding for the infant and mother outweigh any potential risk of Zika virus transmission through breast-milk.

Remarks

- This recommendation is consistent with previous WHO recommendations on infant feeding in areas of Zika virus transmission *(1)*.
- Although Zika virus has been detected in human breast-milk, there is no clear evidence about the origin and a yet undefined risk of transmission to the infant through this route. Since Zika virus infection is mild for infants, the balance between desirable and undesirable effects favours breastfeeding compared with not breastfeeding.

2.2 Infant feeding among infants affected by complications associated with Zika virus: among infants (0–12 months old) affected by complications associated with Zika virus, what modifications in infant feeding practices compared with no modification or standard care can improve infant outcomes?

SUMMARY OF THE EVIDENCE

No eligible studies assessing modified infant feeding versus no modified infant feeding practices were identified. A qualitative systematic review was conducted to answer this question *(43)*. A total of 42 records were initially screened, but none met the inclusion criteria. However, data from eight observational studies were examined since they included important information related to the nutritional status, infant feeding practices and outcomes of infants exposed to Zika virus or diagnosed with congenital Zika syndrome. These studies may in turn guide future studies on modifying infant feeding practices *(61–68)*. All studies were conducted in Brazil.

In general, mean *z*-scores of weight-for-age, head circumference-for-age and height-for-age declined significantly among infants diagnosed with congenital Zika syndrome *(43)*, including infants hospitalized during the first days of life. Weight status was also affected by type of feeding, with lower weight among those fed orally compared with those fed with nasogastric or orogastric tube feeding or those fed infant formula compared with breast-milk (breastfeeding, expressed milk or milk bank). These children were more likely to present difficulties feeding, including choking and reflux, dysphagia and other swallowing disturbances and sucking difficulties *(43)*. Mouth breathing, excessive salivation, abnormal insertion of the upper labial frenulum, ogival palate, dental enamel defects and delay in dental eruption have also been reported. Feeding difficulties resulted in a decline in nutritional status and low caloric intake, with the variety of foods in their diet being very limited and lipid intake below the recommended daily allowances. Motor abnormalities and developmental delays that persisted in time beyond two-year follow-up periods were reported.

In these studies, some mothers reported difficulties breastfeeding infants with congenital Zika syndrome, possibly because of the dysphagia or mouth breathing, difficulty in swallowing and excessive salivation. Infants with congenital Zika syndrome also had a limited variety of foods in their diet and lipid intake below recommended allowances. Others reported using starch-rich meals to avoid choking. In another study, iron and other micronutrient supplementation and processed foods were more commonly used among children with congenital Zika syndrome compared with healthy children. Overall, infant feeding complications were more prevalent among infants with congenital Zika syndrome *(43)*. The prevalence of swallowing disturbances varied by study, and in some cases swallowing issues, choking and reflux were reported. There were reports of general swallowing disturbances, sucking difficulties and dysphagia.

ADDITIONAL CONSIDERATIONS

To expand on the evidence found in the systematic review, existing recommendations on dysphagia were explored. These recommendations include postural correction, thickened feeds, pacing and spoon placement technique *(69,70)*. Placement of a nasogastric or orogastric tube may be warranted because of feeding difficulty. Recommendations for avoiding gastroesophageal reflux include slow feeding, keeping the infant upright after meals and elevating the head of the bed with support under the mattress. Proper positioning is also an important modification for managing a child with abnormal tone.

In addition, other strategies for children with feeding and swallowing problems of nervous system origin include adjusting the child's environment (increasing or reducing stimuli depending on whether the child has hypotonicity or hypertonicity), sensory stimulation (direct stimulation of the lips and oral cavity and modifying foods and liquids regarding texture, volume, temperature and taste) and using adaptive equipment (one-way, slit-valve nipples, nosey cups and Maroon Spoons) *(70)*.

Desirable effects

The desirable anticipated effects of modifying infant feeding practices are large compared with no modification or standard of care for infants not infected with Zika virus.

Undesirable effects

The undesirable anticipated effects of modifying infant feeding practices are trivial compared with no modification or standard care among infants not infected with Zika virus.

Certainty of the evidence

No studies answering the question of interest were identified. Only indirect evidence was available from observational studies.

SUMMARY OF THE CONSIDERATIONS FOR DETERMINING THE DIRECTION AND STRENGTH OF THE RECOMMENDATIONS

These recommendations were informed by the evidence presented above, with explicit consideration of the factors listed next.

Certainty of the evidence

This is not applicable, since the systematic review conducted to answer this question did not identify any relevant studies. The observational studies providing information related to the nutritional status of infants affected by congenital Zika syndrome provided evidence of very-low certainty.

Balance of benefits and harm

The benefits of modifying infant feeding practices compared with no modification or standard of care far outweigh the potential risks.

Values and preferences

Qualitative systematic reviews were conducted to summarize and assess the values and preferences of relevant stakeholders (such as pregnant women, mothers, family members and health-care practitioners) concerning infant (0–2 years) feeding in the presence of: (1) congenital Zika syndrome (the direct evidence) *(43)*; (2) severe disability and nonprogressive, chronic encephalopathies (indirect evidence), which present with similar problems *(44)*. The review was expanded to other diseases in an attempt to understand the context of Zika virus *(53)*. This conceptual model could help to explore interrelationships between various factors in decision-making and to identify gaps in which issues have not yet been considered in the context of Zika virus. These reviews also informed the recommendation on support for primary caregivers of infants (0–12 months old) affected by complications associated with Zika virus.

a. Values and preferences of pregnant women, mothers, family members, health-care practitioners, policy-makers and health-care providers (midwives) concerning feeding when an infant has congenital Zika syndrome

Six publications on congenital Zika syndrome were found, all conducted in Brazil *(71–76)*. These publications included studies on parents and families with data collected through focus groups, videos, interviews or field notes (ethnographic). In general, the GRADE-CERQual assessment of confidence in the evidence related to infants with congenital Zika syndrome was very low, low or moderate *(41)*.

FEEDING PROBLEMS

The analysis of videos posted by family members showed that the family approached health-care professionals only "after a few days with their child, [when] mothers recognized abnormal infant behaviour, such as constant crying and difficulty swallowing".

FEAR OF CHOKING OR DIFFICULTY SWALLOWING

This theme appeared in five studies. Parents reported that their principal concern was that their child would choke and that they would be unsure how to manage this. Mothers in particular reported that

feeding almost always produced choking, which in turn produced fear and anxiety. An ethnographic study noted that "other women are notably more reluctant to participate in holding these babies, because they have problems in swallowing food, suffer frequent convulsions and, in general, present a very vulnerable condition".

PARENTS' KNOWLEDGE ABOUT FEEDING

Parents reported they did not know how to best feed their child. There was uncertainty and doubt regarding the best diet and the best way to feed their child. They also reported a lack of knowledge regarding how to manage choking or gagging. The need for guidance on infant feeding, especially on managing breastfeeding, feeding positions, weaning, types of foods to introduce first, spacing of diets, correct mode of food preparation, introduction of supplements, use of adequate pacifiers and specific need to learn first-aid techniques, was highlighted. Essential care is needed when administering food by nasogastric and nasoenteral tubes. Anecdotally, a study documented how a mother reported that her daughter acquired food-related bronchoaspiration pneumonia because of poor positioning while feeding. She was instructed to modify the consistency of the foods (to pasty) and to position the child with the body slightly inclined, with the legs lower in relation to the rest of the body. Mothers in one of the studies reported how doctors and other health-care professionals providing home visits did offer guidance and instruction about feeding.

FEAR, STRESS AND ANXIETY

Several parents reported fear and anxiety when the time came to feed their child. They were concerned that the child would choke or that they would suffocate the child while feeding. Such anxiety could affect other family members and the community in general.

DEMANDS ON THE MOTHER

Feeding a child with swallowing difficulties placed logistical and emotional burdens on the primary caregiver, which was almost always the mother. Demands on the mother were seen to hinder and limit the relationship between mothers and their children. Mothers reported difficulty in accepting the congenital anomaly of their child, which affected their daily habits and their bond with the child. Rejection was reportedly the main reason for abandonment; many mothers did not feel able to meet their children's constant need for care. Social exclusion and lack of support from the health-care system have caused many mothers to abandon their children, giving them up to the care of neighbours or grandparents.

All studies were from a single geographical region (north-eastern Brazil) and explored the views and experiences of mothers and fathers. These studies used different methods of data collection and included observation of parents and family as well as approaches that directly elicited their values and preferences. All studies were published between 2017 and 2019.

b. Values and preferences of pregnant women, mothers, family members, health-care practitioners, policy-makers and health-care providers (midwives) concerning feeding when infants with severe disability or nonprogressive, chronic encephalopathy experience feeding problems

Eight indirect studies *(77–84)* reported feeding difficulties among infants with severe disability and nonprogressive, chronic encephalopathy were assessed in the review as part of the indirect evidence *(44)*. One study was conducted in each of the countries Bangladesh, Brazil, Portugal and the United Kingdom and two in Australia and Ghana. Three studies focused exclusively on the mothers of infants with Down's syndrome; these studies used either interviews or focus groups. Another used in-depth interviews and field notes with parents whose babies had been in a neonatal intensive care unit and who experienced one or more feeding difficulties. The evidence base was of high certainty and with low threats to rigour across all domains. In general, the GRADE-CERQual assessment of confidence in the evidence related to infants with severe disability or nonprogressive, chronic encephalopathy was low or moderate *(41)*.

FRUSTRATION, STRESS AND BONDING CONCERNS WHEN FEEDING THEIR CHILD

Most studies reported that breastfeeding, expressing or bottle-feeding was overwhelming, time-consuming, exhausting and difficult. The difficulties experienced by mothers when feeding their children caused stress and frustration, as did the lack of "skilled help" and information available. Parents reported experiencing frustration that they could not feed in the way they wanted to, such as breastfeeding, and that interventions and advice often did not work. Among infants in neonatal intensive care units, mothers reported that the intervention was a helpful step for improving infant feeding and that family and professional support helped them to manage their feelings and to enhance their positive feelings and thus help in maintaining breastfeeding, without early weaning. Some mothers described how family members and friends often sought to provide support in lieu of health-care professionals.

Parents consistently reported uncertainty about whether they were making the best feeding choices for their children. When looking for information, they found either no answers or inconsistent guidance, leaving mothers unwilling to access services at all.

In all studies, the interaction with health-care professionals was seen as the most influential factor in feeding decisions. However, supported decision-making did not take place and parents often felt forced to adopt a particular approach, either breastfeeding, expressing or another intervention. Even when attention and support were provided, some parents considered it inadequate. They felt that health-care professionals did not encourage breastfeeding and did not provide accurate information. Mothers felt confused and demotivated about feeding practices.

Some mothers reported that the lack of knowledge and support from midwives and health visitors led them to choose not to access these services or to approach these staff members for advice or support. Health-care professionals were often insensitive to stress and other concerns, and parents report feeling that they have to find information on their own.

Some mothers felt a lack of control over the feeding decisions made for their child, whether it was to persist with breastfeeding, to stop breastfeeding or to adopt a combination of breastfeeding, expressing or bottle-feeding. Use of formula feeding was frequent, both as a supplement to breast-milk or alone. Other mothers reported greater control over feeding when admitted to a children's hospital compared with the maternity hospital and that seeking and finding useful information gave them a sense of autonomy.

c. Values and preferences of pregnant women, mothers, family members, health-care practitioners, policy-makers and health-care providers (midwives) concerning feeding with complex needs unrelated to transmissible disease (other than HIV)

A commissioned systematic review explored what is known about the values and preferences of pregnant women, mothers, family members, health-care practitioners, policy-makers and health-care providers (midwives) concerning infant feeding when there is a risk of a mother transmitting an infectious disease (other than HIV) to infants (0–2 years of age) *(53)*. The synthesis included eight qualitative studies *(85–92)*. Four studies focused on human T-cell lymphotropic virus type 1 (HTLV-1), three studies on Ebola and one study on influenza vaccination. The scientific evidence appears to suggest that infant feeding decisions are typically made in a context in which individual, family and community values and preferences exert considerable influence. The impact of such decisions is further moderated by available health and social care provision, the financial and economic situation of the mother and, in the context of viral transmission, the specific characteristics of the virus. The specific characteristics of the virus therefore represent a small but critical piece of the process of making infant feeding decisions. Nevertheless, values that affirm the overall superiority of breastfeeding, together with the acknowledged limitations of mixed feeding approaches, transcend the specific requirements of the virus, especially in resource-limited areas. Of great concern are perceptions that counsellors are poorly equipped to communicate appropriate choices, to override their own biases and preferences, to provide advice tailored to the mothers' social and economic circumstances and to communicate the benefits of exclusive breastfeeding over formula feeding and

mixed regimes. In general, the findings from this synthesis support moderate confidence, especially mothers' expectations, the consequent stigma and sadness associated with not being able to breastfeed and the perceived preference for advice and support from infectious diseases health-care personnel. In general, the GRADE-CERQual assessment of confidence in the evidence related to infant feeding with complex needs unrelated to transmissible disease (other than HIV) was low or moderate *(53)*.

ADDITIONAL CONSIDERATIONS

Important facilitators at the family and community levels may help to mitigate negative attitudes. Previous research on the perception of disability among mothers of children with disabilities living in resource-limited settings revealed that, although these mothers often experienced significant challenges in caring for their children (related to negative community attitudes), when they receive essential support from key members of their family and community, they have greater future aspirations for their child.

SUMMARY

Overall, there is may be important uncertainty or variability in the values and preferences of pregnant women, mothers, family members, health-care practitioners, policy-makers and health-care providers (midwives) concerning modifying infant feeding practices among infants affected by complications associated with Zika virus. The certainty of the evidence is low.

Balance of effects

The balance between desirable and undesirable effects favours modifications in infant feeding practices among infants affected by complications associated with Zika virus compared with no modification or standard of care.

Acceptability

No direct studies have evaluated the acceptability of modifying infant feeding practices among infants affected by complications associated with Zika virus. The eight observational studies of feeding among infants with severe disability or nonprogressive, chronic encephalopathy identified in the systematic review completed to answer this question highlight the need for early nutrition interventions and caregiver support among infants affected by Zika virus or diagnosed with congenital Zika syndrome to reduce the risk of diminished nutritional status over time for infants exposed to Zika virus or diagnosed with congenital Zika syndrome *(59)*. Modifying infant feeding practices among infants affected by complications associated with Zika virus is probably acceptable to key stakeholders.

Resource implications

The resources required include training staff, training materials and time for staff to provide nutrition and feeding counselling as part of the routine antenatal and postnatal care services. Resources are also needed for therapeutic instruments and adaptive equipment (one-way, slit-valve nipples, nosey cups and Maroon Spoons), nasogastric or orogastric tube feeding and medicines and special foods and thickeners.

Modifying infant feeding practices among infants affected by complications associated with Zika virus likely results in moderate costs compared with no modifications. The certainty of evidence on costs is low. The cost–effectiveness of modifying infant feeding practices among infants affected by complications associated with Zika virus probably favours treatment compared with no modifications.

Equity

No direct evidence was identified. During pregnancy, Zika virus infection raises ethical issues on civil and human rights related to reproduction and diagnosis of serious malformations during pregnancy and health disparities in preventing maternal and neonatal morbidity and mortality. Zika virus infection is also relevant to issues related to the global burden of the disease, international spread of infectious disease,

reporting biases and confidentiality of patients' health information, vector control, stigmatization, transport between regions, climate change and Zika virus vaccine research and future deployment.

Modifying infant feeding practices among infants affected by complications associated with Zika virus probably increases equity compared with not breastfeeding among infants not infected with Zika virus.

Feasibility

No direct evidence was identified. However, some of the recommendations on modifying infant feeding may be more feasible than others, such as postural correction; thickening of foods and modifications in volume, temperature and taste; adjusting the child's environment; and direct sensory stimulation. In contrast, placing a nasogastric or orogastric tube and using adaptive equipment may be less feasible.

Breastfeeding or feeding breast-milk to infants from a lactating woman infected with Zika virus is probably feasible.

RECOMMENDATIONS

- Among infants (0–12 months old) affected by complications associated with Zika virus infection, infant feeding practices should be modified (such as adjusting the environment, postural correction and thickening feeds) to achieve and maintain optimal possible infant growth and development *(strong recommendations, very-low certainty of evidence)*.

Rationale

No studies were found comparing modifying infant feeding practices compared with no modification or standard care to improve infant outcomes among infants (0–12 months old) affected by complications associated with Zika virus. However, indirect evidence showed that children affected by complications associated with Zika virus have a decline in nutritional status, evidenced by slower growth, lower food intake, less breastfeeding, more infant formula use and calorie and lipid intake below the recommended allowances. These may be related to the high frequency of choking and reflux among these children.

Remarks

The modifications to infant feeding would be similar to those of infants with similar symptoms regardless of whether these symptoms are associated with Zika virus or not.

2.3 Support for primary caregivers of infants (0–12 months old) affected by complications associated with Zika virus

SUMMARY OF THE EVIDENCE

No eligible studies assessing support for caregivers of infants affected by complications associated with Zika virus were retrieved. Three systematic reviews were used to inform this recommendation *(43,44,53)*. They covered the evidence on the perceived need for support for pregnant women, mothers, family members and health-care practitioners, policy-makers and health-care providers (midwives) concerning feeding when an infant has congenital Zika syndrome *(43)*; the perceptions of pregnant women, mothers, family members, health-care practitioners, policy-makers and health-care providers (midwives) concerning feeding when infants with severe disability or nonprogressive, chronic encephalopathy experience feeding problems *(44)* and those concerning infant feeding when there is a risk of the mother transmitting an infectious disease (other than HIV) to infants (0–2 years of age) *(53)*.

According to one of these studies, 80% of the mothers did not have a partner and 48% did not have a work-related income at the time of birth. More than 60% did not receive prenatal care before six months of pregnancy. Mothers with 12 or more years of education had infants with a higher mean weight-for-age *z*-score than mothers with less education, but only about 14% of the mothers had 12 or more years of education.

Although the additional support to caregivers was not addressed, these data highlight that primary caregivers and parents may need additional support to meet the feeding challenges of infants with complications associated with Zika virus and to promote adequate growth and development. Primary caregivers and parents of infants with complications associated with Zika virus may also have other social, education and financial challenges that could impact growth and development outcomes among their children. A cross-sectional qualitative study of children one to two years of age with congenital Zika syndrome and their caregivers found that facilities and rehabilitation services provided a care network that enabled mothers to meet the needs of their children, including stimulation to develop motor and cognitive skills and thereby to reduce disability.

Evidence is lacking in the literature on the efficacy of providing additional support to primary caregivers of infants affected by Zika virus complications and its relationship to infant feeding complications, morbidity, mortality, growth and development outcomes. Additional support may include respite care, medical support, caregiving competence support and financial support. As infants and children affected by Zika virus and congenital Zika syndrome mature, it is imperative to understand how primary caregiver support would affect the growth and development outcomes to design appropriate care recommendations and support programmes.

ADDITIONAL CONSIDERATIONS

The caregivers of children with special health-care needs report negative effects on their health, finances and social-related domestic areas of their lives *(44)*. These caregivers may also report greater rates of depression. Stigma and discrimination are common barriers faced by children affected by Zika virus and their caregivers, negatively affecting their ability to seek educational services and access health care. Early interventions for children at risk of developmental delays can improve cognitive and motor-related outcomes. Support for caregivers of infants with congenital Zika syndrome may be a protective factor for long-term optimal nutritional status, attaining developmental milestones and enhancing the quality of life.

Desirable effects

The desirable anticipated effects of additional support for caregivers of infants for improving feeding among infants affected by complications associated with Zika virus are large compared with no additional support or standard care.

Undesirable effects

The undesirable anticipated effects of additional support for caregivers of infants for improving feeding among infants affected by complications associated with Zika virus are trivial compared with no additional support or standard care.

Certainty of the evidence

No studies answering the question of interest were identified. Only indirect evidence was available from observational studies. Confidence in the findings regarding parental uncertainty on how best to feed their child was moderate, but confidence in all other findings was categorized as low or very low.

SUMMARY OF THE CONSIDERATIONS FOR DETERMINING THE DIRECTION AND STRENGTH OF THE RECOMMENDATIONS

These recommendations were informed by the evidence presented above, with explicit consideration of the factors listed next.

Certainty of the evidence

This is not applicable, since the systematic review conducted to answer this question did not identify any relevant studies. The certainty of the evidence from observational studies providing information related to the nutritional status of infants affected by congenital Zika syndrome is of very low certainty.

Balance of benefits and harms

The benefits of additional support for caregivers of infants for improving feeding among infants affected by complications associated with Zika virus compared with no additional support or standard care far outweigh the potential harm.

Values and preferences

The qualitative systematic reviews on values and preferences regarding breastfeeding when there is potential transmission of a mother-to-child transmissible disease other than HIV *(53)* found that financial factors play an important role in the decisions of mothers on infant feeding, especially when feeding choices have cost implications or when the mother faces potential loss of income because of either caring responsibilities or her own health status. Parents also expressed frustration at the inability of health-care professionals to provide sufficient support and information. Even where counselling is provided, counsellors may not consider the mothers' social and economic circumstances when offering support and advice. New mothers highly appreciated those who provided accurate advice that would protect their baby and trustworthy alternatives and facilities in hospitals to enable non-public infant feeding, thereby reducing exposure to any perceived stigma that they might experience from a failure to be seen breastfeeding.

SUMMARY

Overall, there may be important uncertainty or variability in the values and preferences of pregnant women, mothers, family members, health-care practitioners, policy-makers and health-care providers (midwives) concerning feeding when (1) an infant has congenital Zika syndrome; (2) when infants experience problems with feeding and swallowing because of a condition; or (3) an infant has complex needs unrelated to transmissible disease. The certainty of the evidence is low.

Balance of effects

The balance between desirable and undesirable effects favours the additional support for caregivers of infant for improving infant feeding among those affected by complications associated with Zika virus compared with no additional support or standard care.

Acceptability

A review discussing considerations for family support and services for children with congenital Zika syndrome *(43)* suggested the following family implications: (1) the severity of the impact on children with obvious abnormalities at birth, coupled with the anticipation of a lifetime of caregiving and financial burdens; (2) uncertainty about the unfolding consequences, both for obviously affected children and for exposed children with no symptoms at birth; (3) a lack of specialized professional knowledge about the course of the disease or treatment options; and (4) social isolation, a lack of social or community support and potential stigma. These implications imply that these families will require extensive support for health-care services and other types of services as well as information and surveillance.

Additional support for the caregivers of infants affected by complications associated with Zika virus is probably acceptable to key stakeholders.

Resource implications

An ethnographic study assessed the experience of parents of children with Zika-related microcephaly as they sought information, support and service provision in Brazil. This study highlighted that lack of resources becomes more intense for these families, especially when mothers stop working to take care of the baby and have growing needs for medicines, expensive special food and therapeutic instruments to address the issues in deglutition, ambulation, posture, vision etc. Mothers who were unable to maintain exclusive breastfeeding had to purchase infant formula. Parents highlighted lack of support from the government as the main cause of mothers' hopelessness towards their children. Parents with better financial circumstances had additional health insurance to address the shortcomings of the social care services.

Additional support for caregivers of infants affected by complications associated with Zika virus likely results in moderate costs compared with no additional support or standard care. The certainty of evidence on costs is low. The cost–effectiveness of additional support for caregivers of infants affected by complications associated with Zika virus probably favours treatment compared with no additional support or standard care.

Equity

No direct evidence was identified. In Brazil and the rest of South America, wealthier communities appear better prepared to face Zika virus than poorer ones to deal with the potential for Zika virus infection and its associated complications. Aside from the increased risk of having a child with microcephaly, inequalities remain when accessing health care, socioeconomic support and/or reproductive care. A small descriptive cross-sectional study among 25 mothers of babies with confirmed diagnosis of congenital Zika syndrome in Brazil showed inequities in the Zika virus epidemics, with women with low income and lower social class being more severely affected *(54)*. Investing resources to control the Zika virus spread and prevent future outbreaks seems to be needed, especially in areas with low income.

Feasibility

Additional support for caregivers of infants affected by complications associated with Zika virus is probably feasible based on previous experiences with other congenital syndromes similar to congenital Zika syndrome.

It is imperative to ensure that personnel providing advice and counselling to lactating women know the main aspects related to Zika virus and congenital Zika syndrome. A study *(93)* assessed the knowledge, attitudes and counselling practices of general practitioners and gynaecologists in Amman, Jordan. The study, conducted between 2016 and 2017, included 119 participants who completed a structured paper-based questionnaire on their knowledge of Zika virus transmission, prevention measures, diagnosis and treatment. Participants had a mean knowledge score of 32.4 ± 2.4 (of 42 points possible). Although participants were generally aware of the causes, major routes of transmission and main symptoms of Zika virus, almost all thought that Zika virus is transmitted through breastfeeding. In addition, about 56% failed to identify that casual direct contact between individuals is not a route of Zika virus transmission.

RECOMMENDATIONS

- Mothers and caregivers of infants affected by complications associated with Zika virus (such as feeding difficulties) should receive skilled support from health-care workers to initiate and sustain optimal infant feeding practices *(strong recommendation, very-low certainty of evidence)*.

Rationale

No studies were found comparing additional support for the caregivers of infants (0–12 months old) affected by complications associated with Zika virus for improving infant feeding compared with no additional support or standard care. However, indirect evidence showed that most mothers of infants affected by complications associated with Zika virus did not have a partner and did not receive prenatal care before six months of pregnancy. Many did not have work-related income at the time of birth, had higher depression scores, greater financial and childcare challenges and spent more time providing health care at home. Primary caregivers and parents may need additional support to address the feeding challenges of infants with complications associated with Zika virus and to promote adequate growth and development. Primary caregivers and parents of infants with complications associated with Zika virus may also have other social, educational and financial challenges that could affect growth and development outcomes among their children.

Remarks

- This recommendation is consistent with previous WHO recommendations on protecting, promoting and supporting breastfeeding in facilities providing maternity and newborn services *(94)* and on counselling women to improve breastfeeding practices *(95)*.

3. METHODS

The recommendations were developed using standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development (39)*. In summary, the process included:

- identifying the priority question and critical outcomes;
- retrieving evidence;
- assessing and synthesizing evidence;
- formulating the recommendations; and
- planning for disseminating, implementing, evaluating the impact of and updating the recommendations.

Contributors to the guideline

WHO Guideline Steering Committee

The WHO Guideline Steering Committee (Annex 4) managed the updating process and comprised WHO staff members from the Departments of Nutrition and Food Safety; Immunization, Vaccines and Biologicals; Maternal, Newborn, Child and Adolescent Health and Ageing; Reproductive Health and Research; and Gender, Equity and Human Rights and from each WHO regional office. The WHO Guideline Steering Committee drafted the key questions in PICO format, identified the systematic review team and guideline methodologist and the Guideline Development Group and external review groups. The WHO Guideline Steering Committee supervised the synthesis and retrieval of evidence, organized the Guideline Development Group meetings, drafted and finalized the guideline document and managed the guideline dissemination, implementation and impact assessment.

Guideline Development Group

The members of the Guideline Development Group (Annex 5) had expertise cutting across thematic areas and clinical practice, policy and programmes relating to infectious diseases, neonatology, infant feeding and nutrition policies. The members of the Guideline Development Group were identified in a way that ensured geographical representation and absence of significant conflicts of interest. There was an aim to ensure gender diversity, although potential group members were not consulted on this aspect.

Fifteen external experts and relevant stakeholders were invited to participate as members of the Guideline Development Group for updating this recommendation. They were a diverse group with expertise in research, guideline development methods and clinical policy and programmes relating to infant health and nutrition.

WHO convened two online Guideline Development Group meetings. At the first online meeting (11 April 2019), the Guideline Development Group provided input into the scope of the guideline, the key questions that were going to be addressed and the outcomes that would guide the evidence reviews and focus the recommendations. During the second online meeting (9–and10 December 2019), the Guideline Development Group members reviewed, deliberated and achieved consensus on the strength and direction of the recommendations presented here. They reviewed the balance between the desirable and undesirable effects and the overall certainty of supporting evidence, values and preferences of stakeholders, resource requirements and cost–effectiveness, acceptability, feasibility, human rights and equity.

Evidence Synthesis Group

Several systematic reviews were commissioned to inform this guideline *(42–44)*. Others were identified in the literature (*29,30,45*). The WHO Guideline Steering Committee reviewed and provided input into each review. Investigators from Cornell University reviewed the evidence on Zika virus transmission through breast-milk or feeding breast-milk from a lactating woman infected with Zika virus. Investigators from the University of Sheffield conducted qualitative reviews on the views of pregnant women, mothers, family members, health-care practitioners, policy-makers and health-care providers (midwives) concerning infant feeding (including

breastfeeding, breast-milk and their alternatives) when there is a risk of potentially transmissible Zika virus and about the parental attitudes to infant feeding difficulties associated or special needs of infants with congenital Zika syndrome and other similar syndromes (Guillain-Barré, microcephaly and swallowing difficulties). Investigators from Florida International University conducted reviews on the specific infant (0–12 months) feeding recommendations among those affected by complications associated with Zika virus and about the support needed for caregivers of infants (0–12 months) affected by complications associated with Zika virus. Annex 6 presents the systematic review teams.

Identifying critical outcomes

The critical and important outcomes were aligned with the Sustainable Development Goals. These outcomes were initially identified through a search of key sources of relevant published systematic reviews and setting priorities among outcomes by the Guideline Development Group panel that took place during the first online Guideline Development Group meeting. All the outcomes were included in the scope of this publication for evidence searching, retrieval, grading and formulation of the recommendation. Annex 1 lists the priority questions and the critical and important outcomes considered in this guideline.

Identifying and retrieving evidence

Several systematic reviews were conducted to answer the questions and were the primary source of evidence for these recommendations. These included reviews on (1) evidence related to the presence of Zika virus in breast-milk and transmission through breast-milk to help to inform global guidelines on infant feeding; (2) a systematic review of modified feeding practices and additional primary caregiver support to improve outcomes among infants 0–12 months old exposed to Zika virus or diagnosed with congenital Zika syndrome; and two qualitative evidence synthesis reviews of the values and preferences of pregnant women, mothers, family members, health-care practitioners, policy-makers and health-care providers (midwives) concerning feeding when there is a risk of mother-to-child transmission of (3) Zika virus; and (4) infectious diseases (other than HIV) to an infant (0–12 months old) or toddler (1–2 years old).

Formulating recommendations

The WHO Guideline Steering Committee used the evidence profiles to summarize the evidence from the systematic reviews. The evidence summary and corresponding GRADE tables and GRADE-CERQual evidence profiles along with other related documents for assessing values and preferences, resource requirements, cost–effectiveness, acceptability, feasibility and equity were provided in advance to Guideline Development Group members before the second online meeting. They were invited to submit comments electronically before the meeting using the online tool QuestionPro®.

The discussion points around each of the key questions are presented, covering the following contents:

- summary of the evidence from systematic reviews for each of the interventions; and
- summary of considerations for determining the direction and strength of the recommendations, which includes:
    - the certainty of the evidence;
    - the balance of benefits and harm;
    - values and preferences (of pregnant women and mothers);
    - acceptability (to health-care workers and lay or peer counsellors);
    - resource implications;
    - equity; and
    - feasibility.

- At the end of each section, a short summary brings together:
  - the recommendation;
  - the rationale;
  - additional remarks to be considered in implementing the recommendations.

The Guideline Development Group agreed on three options for the types of recommendations:

- recommended;
- context-specific recommendation (recommended only in specific contexts); and
- not recommended.

In this framework, the size of the effect is judged as important, less important, or not important. This decision is a judgement call and focuses on the importance to the end-users (decision-makers, health-care providers, health service users and end-beneficiaries) rather than on statistical significance.

The Guideline Development Group members and other participants were then invited to attend the second online Guideline Development Group meeting. Guideline Development Group members reviewed and discussed the balance between the desirable and undesirable effects of the intervention and the overall certainty of supporting evidence, values and preferences of stakeholders, resource requirements and cost–effectiveness, acceptability, feasibility and equity, before finalizing the recommendations and remarks by unanimous consensus.

Managing conflicts of interest

WHO, in compliance with the WHO guidelines for declaration of interests for WHO experts *(46)* and in collaboration with the Department of Compliance and Risk Management and Ethics, managed the potential conflicts of interest. All potential members of the Guideline Development Group were asked to fill in and sign the standard WHO declaration of interests and confidentiality undertaking forms. Updated curricula vitae were also required from the prospective members of the Guideline Development Group, since they engage in their individual capacity and not as institutional representatives.

The WHO Guideline Steering Committee reviewed the declaration-of-interest statements in conjunction with the curricula vitae for all Guideline Development Group members. Information from the Internet or media was gathered to identify any public statements made or positions held by the prospective Guideline Development Group members and experts on breastfeeding counselling. These were assessed for intellectual bias that may be perceived to or actually affect impartiality. All concerns or potential issues were discussed with the WHO Office of Compliance, Risk Management and Ethics. All potential conflicts of interest were managed on a case-by-case basis.

To strengthen public trust and transparency in connection with this guideline, the names and brief biographies of individual members of the Guideline Development Group for this guideline were published in the WHO website two weeks before each meeting to allow time for "public notice and comment".

The following members of the Guideline Development Group declared interests that were further discussed with the Office of Compliance, Risk Management and Ethics. They were assessed to merit full participation in the meeting after publicly disclosing their interests at the start of the meeting to all meeting participants and in the guideline publication. They fully participated in discussions and were included in all decision-making processes. Aside from their research and programme experiences and sources of funding, they were asked to specifically declare the following.

J.P. Dadhich declared that he owns and is paid for by the Breastfeeding Promotion Network of India. This association has worked in the field of infant nutrition and other related issues in India since 1992 in various programmes and activities. This declared interest was discussed with the Office of Compliance, Risk Management and Ethics and it was decided to allow him to fully participate in the meeting after publicly disclosing his participation in the Breastfeeding Promotion Network of India during presentations in the Guideline Development Group meeting.

All other Guideline Development Group members declared no conflicts of interest.

Decision-making process

During the meeting, the Guideline Development Group reviewed and discussed the evidence summary and reviewed the preliminary judgements and comments posted by all members in the online form. In addition to evaluating the balance between the desirable and undesirable effects of the intervention and the overall certainty of the evidence, the Guideline Development Group applied additional criteria based on the GRADE evidence-to-decision framework *(47)* to determine the direction and strength of the recommendations. These criteria included stakeholders' values, resource implications, acceptability, feasibility and equity. Considerations were based on the experience and opinions of members of the Guideline Development Group and supported by evidence from a literature search when available. Evidence-to-decision tables were used to describe and synthesize these considerations.

The final decisions were made using the online tool. All members were invited to revisit the wording of the draft recommendations. No member expressed opposition to the recommendations. There was unanimous consensus.

Document preparation

Before the online meeting, the WHO Guideline Steering Committee prepared a draft version of GRADE evidence profiles, GRADE-CERQual evidence profiles, the evidence summary and other documents relevant to the Guideline Development Group deliberations. The draft documents were made available to participants two weeks before the meeting for their comments. Questions were posted online for all members to write in the judgement of the different sections included in the evidence-to-decision framework. During the meeting, these documents were discussed and comments were taken into account to modify the documents. Following the meeting, the questions were revised and all members were invited to deliberate and reach consensus.

Peer review

A preliminary version of the final document was sent for peer review to five external independent experts who were not involved in the Guideline Development Group (Annex 7) . The peer reviewers did not participate in any decision-making process. The name and affiliations of peer reviewers are provided as an acknowledgement and by no means indicate their endorsement of the recommendations in this guideline. The acknowledgement of the peer reviewers does not necessarily represent the views, decisions or policies of the institutions with which they are affiliated. The WHO Guideline Steering Committee evaluated the inputs of the peer reviewers for inclusion in this document. After the meeting and external peer review, the modifications made by the WHO Guideline Steering Committee to the document consisted only of correcting factual errors and improving language to address any lack of clarity.

4. DISSEMINATION AND IMPLEMENTATION OF THE RECOMMENDATIONS

The guideline will be disseminated through WHO regional and country offices, health ministries, professional organizations, WHO collaborating centres, other United Nations agencies, nongovernmental organizations and others. This guideline will also be available on the WHO website at the WHO Department of Nutrition and Food Safety site. The guideline will also be routinely disseminated during meetings or scientific conferences attended by WHO staff members. Social media channels will be used to increase awareness of the updated recommendation.

UNICEF and WHO lead the a Global Breastfeeding Collective to increase political commitment for breastfeeding – one of the smartest investments a country can make *(96)*. The initiative aims to increase early initiation, exclusive breastfeeding for the first six months of life and continued breastfeeding for up to two years or beyond, together with appropriate, adequate and safe complementary foods. This initiative will help disseminate the recommendations of this guideline.

The executive summary of the guideline may be translated into the other five United Nations languages and disseminated through the WHO regional offices. Specialized technical assistance will be provided to any WHO regional office willing to translate the full guidelines into any of these languages and support countries in implementation for impact.

All stakeholders involved in providing care for infants in regions with Zika virus transmission at the international, national and local levels should consider disseminating and implementing the recommendations presented herein.

Improving the implementation of these recommendations requires policy development and stronger regulatory frameworks on breastfeeding.

5. RESEARCH GAPS

The Guideline Development Group identified important knowledge gaps that need to be addressed through primary research, which may affect these recommendations. More research is needed related to the resources, feasibility, acceptability and equity of modifying the feeding of infants affected by complications associated with Zika virus and on the type of additional support to provide to caregivers of these infants, since no direct evidence was found. The following questions were identified as requiring urgent priority:

- determining the viral load needed for the infection to pass through breast-milk;
- understanding the views of pregnant women, mothers, family members, health-care practitioners, policy-makers and health-care providers (midwives) on infant feeding when there is a risk of potentially transmissible Zika virus;
- how breastfeeding or feeding breast-milk to infants from a lactating woman infected with Zika virus affects health equity;
- evaluating the acceptability or feasibility of breastfeeding or feeding of breast-milk among infants from a lactating woman infected with Zika virus;
- how infant feeding modifications affects important infant outcomes among those affected by complications associated with Zika virus and evaluating the resources, feasibility, acceptability and equity of these modifications; and
- how additional support and follow-up for caregivers affects improving infant feeding among those affected by complications associated with Zika virus and evaluating the resources, feasibility, acceptability, continuity and equity of this support.

6. APPLICABILITY ISSUES

Implementing recommendations to breastfeed or feed breast-milk to all infants born to mothers with suspected, probable or confirmed Zika virus infection or who reside in or have travelled to areas with ongoing Zika virus transmission requires staff training and staff time to provide counselling as part of the routine antenatal and postnatal care services.

Implementing interventions on infant feeding modification and additional support for caregivers among infants affected by complications associated with Zika virus requires resources for staff training for advising mothers on how to modify infant feeding and staff time to provide counselling as part of the routine postnatal care services, medicines, special foods and thickeners, therapeutic instruments and adaptive equipment (one-way, slit-valve nipples, nosey cups and Maroon Spoons) and nasogastric or orogastric tube feeding.

7. MONITORING AND EVALUATING THE IMPLEMENTATION OF THE GUIDELINE

The recommendations should be monitored at the health-service level as part of broader efforts to monitor and improve the quality of health care for children. Continuous screening of both mothers and infants in areas of Zika virus transmission should help to identify potential harm or adverse events. It is important to include data disaggregated by socioeconomic variables to understand which groups are more affected or vulnerable to the outbreak or may need more support for breastfeeding or infant feeding.

8. UPDATING THE GUIDELINE

WHO will continue to monitor research developments in infant feeding in areas of Zika virus transmission, especially the availability of a Zika virus vaccine in the market. WHO will follow the dynamic system of giving priority to normative global goods for country impact and will maintain literature surveillance to respond rapidly to any changes in the epidemiology of Zika virus transmission along with any emerging evidence relevant to ensure that accurate, relevant and up-to-date guidance is available to Member States and their partners globally.

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ANNEX 1. QUESTIONS ON INFANT FEEDING IN AREAS OF ZIKA VIRUS TRANSMISSION IN POPULATION, INTERVENTION, CONTROL, OUTCOMES (PICO) FORMAT

1. Among infants not infected with Zika virus, does breastfeeding (any or exclusive) or feeding of breast-milk from a lactating woman infected with Zika virus, compared with not breastfeeding, increase the risk of Zika virus transmission to the infant?

Population

Infants (0–11 months) not infected with Zika virus

Subgroups

- By infant classification:
  - Low birth weight (<2500 g) versus no low birth weight
  - Preterm (<37 completed weeks of gestation) versus term
  - Presence or absence of congenital anomaly
  - Not exposed to HIV, exposed and uninfected or infected by HIV

Intervention

- Breastfeeding or feeding with breast-milk from lactating women with (suspected, probable or confirmed) Zika virus infection

Subgroups

- By infection status of the woman:
  - Suspected infection (based on symptoms of people living in or visiting areas with Zika virus transmission and/or *Aedes* mosquito vectors)
  - Probable infection (by detection of IgM antibodies in blood)
  - Confirmed infection (by RT-PCR for Zika virus on urine and blood)
  - Recovered from infection (the virus has cleared her body)
- By timing of maternal infection:
  - Any time during pregnancy (but not acutely ill at the time of delivery)
  - Acutely ill at the time of delivery (within two weeks before or after the onset of labour)
  - Infected postnatally (two weeks after birth or beyond)
- By presence of the infectious agent in:
  - Breast-milk
  - Skin, blood, sweat, saliva or respiratory droplet
- A woman vaccinated against Zika virus

Comparator

- Not breastfeeding
- No intake of breast-milk
- Intake of untreated breast-milk (unpasteurized and not heat-treated; without direct breastfeeding)
- Intake of pasteurized or heat-treated breast-milk
- Intake of artificial feeding (ready-to-use infant formula)

Outcomes

Infant outcomes

- Suspected, probable or confirmed case of Zika virus infection among infants
- Adverse symptoms or events (not typically associated with the infection)
- Long term effects on the infant:
- Growth, such as body mass index (BMI)-for-age, head circumference-for-age, weight-for-length
- Developmental, such as sitting without support, hands-and-knees crawling, standing with assistance, walking with assistance, standing alone and walking alone
- Cognitive, such as communication

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2. Among infants (0–12 months old) affected by complications associated with Zika virus (P), what modifications in infant feeding practices (I) compared with no modification or standard of care (C) can improve infant outcomes (O)?

Population

Infants affected by complications associated with Zika virus

Subgroups

- By age of the infant:
  - 0 to <6 months
  - 6–12 months

Intervention

- Modification in infant feeding practices (such as postural correction, adjustment of the environment or thickening feeds) as age appropriate

Comparator

No modification in infant feeding practices or standard of care

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Outcomes

- Infant feeding complications such as swallowing dysfunction or dysphagia (difficulty breathing with feeding, coughing or choking during feeding or extended feeding times), irritability or regurgitation
- All-cause, infant mortality from birth until 12 months of age
- Infant hospital admissions from birth until 12 months of age
- Growth outcomes as assessed from WHO growth curves (BMI-for-age; head circumference-for-age; and weight-for-length measures).
- Gross motor development milestones by age (sitting without support; hands-and-knees crawling; standing with assistance; walking with assistance; standing alone; and walking alone)

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3. Should primary caregivers of infants (0–12 months old) affected by complications associated with Zika virus (P) receive additional support for improving infant feeding (I) compared with no additional support or standard of care (C) to improve infant outcomes (O)?

Population

Primary caregivers of infants (0–12 months old) affected by complications associated with Zika virus

Subgroups

- Caregivers of:
  - 0 to <6 months
  - 6–12 months

Intervention

Additional support to improve feeding practices (any support including but not limited to social support, respite care (planned or emergency temporary care provided to caregivers of a child), medical support and financial support)

Comparator

No additional support (standard of care)

Outcomes

- Infant feeding complications such as swallowing dysfunction or dysphagia (difficulty breathing with feeding, coughing or choking during feeding or extended feeding times), irritability or regurgitation
- All-cause, infant mortality from birth until 12 months of age
- Infant hospital admissions from birth until 12 months of age
- Growth outcomes as assessed from WHO growth curves (BMI-for-age; head circumference-for-age; weight-for-length measures).
- Gross motor development milestones by age (sitting without support; hands-and-knees crawling; standing with assistance; walking with assistance; standing alone; and walking alone)

ANNEX 2. GRADE SUMMARY OF FINDINGS TABLES

A. Are children breastfeeding from a mother diagnosed with Zika virus positively diagnosed with Zika virus infection?

Patient or population: Breastfeeding children from women with suspected, probable or confirmed Zika virus infection
Setting: Areas of Zika virus transmission
Intervention: Children breastfeed from a woman with Zika virus infection
Comparison: Not breastfeeding children

Outcomes	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
Confirmed Zika virus infection among children breastfeeding from a woman with suspected, probable or confirmed Zika virus infection	7 (3 observational studies)	⨁⊖⊖⊖ VERY LOW[a]	Three studies provided evidence. One report was not considered due to ambiguous results. The cases reported by two reports were not breastfeeding and therefore were not included in this outcome. The child reported by one report was never breastfed, and the case reported by another was exposed in utero to Zika virus and was born with congenital Zika syndrome, and these two studies were therefore excluded from this analysis.
Confirmed Zika virus infection among children breastfeeding from a woman with suspected, probable or confirmed Zika virus infection: cohort study	6 (1 observational study)	⨁⊖⊖⊖ VERY LOW[b]	One report refers to a cohort study including women with confirmed Zika virus infection. Only an abstract was identified by the search and it reported on six women with Zika virus detected in breast-milk by RT-PCR.

Explanations

[a] Downgraded for risk of bias, imprecision and publication bias.
[b] Downgraded for risk of bias, imprecision and publication bias.

B. Is Zika virus detected in breast-milk samples from women with suspected, probable or confirmed Zika virus (Zika virus) infection?

Patient or population: women with suspected, probable or confirmed Zika virus infection
Setting: areas of Zika virus transmission
Intervention: children breastfeed from a woman with Zika virus infection
Comparison: not breastfeeding children

Outcomes	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
Presence of Zika virus in breast-milk from women with suspected, probable or confirmed Zika virus infection by RT-PCR	10 (6 observational studies)	⨁⊖⊖⊖ VERY LOW[a]	One study reported two mother and child pairs, while three studies reported one mother and child pair each. One study reported four mother and child pairs, only one of the mother's breast-milk tested positive for Zika virus infection. There was a one mother and child pair, in which exposure occurred at the 9th gestational week and the breast-milk sample was positive for Zika virus at the 36th gestational week.
Presence of Zika virus in breast-milk from women with suspected, probable or confirmed Zika virus infection by RT-PCR: cohort study	27 (1 observational study)	⨁⊖⊖⊖ VERY LOW[b]	There was a cohort study including women with confirmed Zika virus infection. Only an abstract was identified by the search, and it reported on 6 women with Zika virus detected in breast-milk by RT-PCR.
Presence of Zika virus in breast-milk from women with suspected, probable or confirmed Zika virus infection detected by cell culture	5 (5 observational studies)	⨁⊖⊖⊖ VERY LOW[a]	One study reported two mother-and-child pairs, Three studies reported one mother-and-child pair each. Cavalcanti 2017 reported four mother-and-child pairs; only one of the mother's breast-milk tested positive for Zika virus infection and was subsequently tested by cell culture.

Explanations

[a] Downgraded for risk of bias, imprecision and publication bias.
[b] Downgraded for risk of bias, imprecision and publication bias.

ANNEX 3. REVIEW OF CONGENITAL ZIKA SYNDROME – GRADE CERQUAL EVIDENCE PROFILES

A. Feeding infants with congenital Zika syndrome *(1)*

Summary of review finding	Studies contributing to the review finding	GRADE-CERQual assessment of confidence in the evidence	Explanation of GRADE-CERQual assessment
Parents report that they often do not know how best to feed their child with microcephaly because the child frequently chokes and has difficulty swallowing	*(2–7)*	Moderate confidence	Six studies with minor or moderate concerns about coherence, adequacy, relevance and methodological limitations (only six studies, but all are recent and conducted in the region in Brazil, the main location of congenital Zika syndrome)
Parents and others report that feeding a child with swallowing difficulties makes them stressed and anxious, even if they possess information on how to manage this: they fear that they might be doing or do something wrong, and that they might suffocate the child	*(2,4–7)*	Low confidence	Four studies with minor concerns about coherence because the link between the data and findings is very clear, but moderate concerns about methodological limitations, adequacy and relevance (all three studies are very recent and conducted in the one region in Brazil that is the main location of congenital Zika syndrome)
Mothers report that problems with feeding can affect bonding with their child	*(7)*	Very-low confidence	One study with serious or moderate concerns about methodological limitations, coherence, adequacy and relevance
Mothers report that the burden of feeding, which can be time-consuming and stressful, falls on them	*(4)*	Very-low confidence	One study with serious or moderate concerns about methodological limitations, coherence, adequacy and relevance
Parents feel that the information provided to them by health professionals is mostly inadequate	*(4,7)*	Very-low confidence	Two studies with serious or moderate concerns about methodological limitations, coherence, adequacy and relevance
Families value training where given	*(6,7)*	Very-low confidence	Two studies with serious or moderate concerns about methodological limitations, coherence, adequacy and relevance.
Families experience economic pressures because of the need to buy special food	*(6,7)*	Very-low confidence	Two studies with serious or moderate concerns about methodological limitations, coherence, adequacy and relevance

B. Feeding among infants with severe disability or nonprogressive, chronic encephalopathy *(8)*

Summary of review finding	Studies contributing to the review finding	GRADE-CERQual assessment of confidence in the evidence	Explanation of GRADE-CERQual assessment
Parents report that they often do not know how best to feed their child	*(9,10)*	Moderate confidence	Two studies with minor concerns about coherence and methodological limitations. The data are rich, but there are serious concerns about adequacy (only two studies) and relevance (only from high-resource settings]
Parents report that feeding an infant who has difficulty feeding can be time-consuming and demanding	*(10–13)*	Moderate confidence	Five studies with minor or moderate concerns about coherence and methodological limitations: four studies are of high quality and the data from all studies are rich. Minor concerns about adequacy because there are five studies, and about relevance because these studies were with two exceptions (Brazil and Ghana) conducted in high-income settings (United Kingdom and Australia]
Parents experience frustration, stress and bonding concerns when feeding their child is problematic	*(10–13)*	Moderate confidence	Six studies with minor concerns about coherence, and minor or moderate methodological limitations. The data are rich. Minor concerns about adequacy with six studies and about relevance because studies were conducted across diverse socioeconomic settings
Parents feel that the information provided to them by health professionals is mostly inadequate; parents feel that the support provided to them by health professionals is mostly inadequate	*(9–12,14)*	Moderate confidence	Five studies with minor concerns about coherence and minor or moderate methodological limitations: the studies are high quality and the data are rich. Minor concerns about adequacy with five studies, and moderate concerns about relevance because these studies were mostly conducted in a particular socioeconomic context (Australia, Ghana, Portugal and the United Kingdom)
Parents report feeling they have to seek information themselves	*(9,14)*	Low confidence	Two studies with minor concerns about coherence; and minor or moderate methodological limitations: the studies are high quality and the data are rich. There are moderate concerns about adequacy and relevance because there are only two studies from resource-limited settings
Parents report a general lack of control	*(9–12,14)*	Moderate confidence	Four studies with minor concerns about coherence and minor or moderate methodological limitations: the studies are high quality and the data are rich. Moderate concerns about adequacy because there is only five studies but minor concerns about relevance because they are from across multiple settings (Australia, Brazil, Portugal and the United Kingdom)
Infant's weight gain can be the overwhelming focus both for them and for health professionals	*(9,10,13)*	Moderate confidence	Three studies with minor concerns about coherence and methodological limitations: the studies are mainly high quality and the data are rich. Moderate concerns about adequacy because there are three studies and about relevance because these studies were conducted in a particular socioeconomic context (Australia and the United Kingdom)
Training can alleviate concerns with choking and positioning may avoid risk of vomiting	*(10,12,13,15,16)*	Moderate confidence	Five studies with minor concerns about coherence, and minor or moderate methodological limitations. The data are rich. Minor concerns about adequacy with seven studies and about relevance because studies were conducted across diverse socioeconomic settings

Summary of review finding	Studies contributing to the review finding	GRADE-CERQual assessment of confidence in the evidence	Explanation of GRADE-CERQual assessment
In situations of poverty, feeding problems are exacerbated by lack of resources to buy nutritious food, limited time and facilities for cooking special recipes and lack of access to rehabilitation and health services. Mothers may lack welfare financial assistance or support from the fathers	*(12,13,15,16)*	Moderate confidence	Four studies with minor concerns about coherence and minor or moderate methodological limitations: three studies are high quality and the data in all studies are rich. Moderate concerns about adequacy since there are only four studies. Relevance has only minor concern, with three studies from a low-resource socioeconomic context

C. Infant feeding with complex needs unrelated to transmissible disease (other than HIV) *(17)*

Summary of review finding	Studies contributing to the review finding	GRADE-CERQual assessment of confidence in the evidence	Explanation of GRADE-CERQual assessment
Factors relating to the individual			
Lactating women lack knowledge about risk of transmission of HTLV-1 and influenza vaccination from mother-to-child by breastfeeding	*(18–20)*	Low	Three studies (French Guiana, Japan and Sierra Leone). There are moderate concerns about coherence and serious concerns about methodological limitations, adequacy and relevance (one study was HTLV-1 and one on influenza vaccination)
New mothers were strongly influenced by the information and advice on mother-to-child transmission provided by specialist infectious diseases health-care staff	*(19,21,22)*	Moderate	Three studies (two Brazil and one French Guiana). Moderate concerns about methodological limitations, coherence, adequacy and relevance (all studies only consider HTLV-1)
New mothers feel empowered by this information and advice			
New mothers report that when information and advice is given by health staff with specialist expertise, this gives them confidence in their choices	*(21,22)*	Moderate	Two studies (both Brazil). Moderate concerns about methodological limitations, coherence, adequacy and relevance (all studies only consider HTLV-1)
New mothers maintain strong expectations about the need to breastfeed if they are to form bonds with their baby	*(21–24)*	Moderate	Four studies (three Brazil and one Guinea). Minor concerns over coherence, and moderate concerns about methodological limitations, relevance and adequacy

Summary of review finding	Studies contributing to the review finding	GRADE-CERQual assessment of confidence in the evidence	Explanation of GRADE-CERQual assessment
Mothers experience stigma as a consequence of not being able to breastfeed	*(18,19,21,22)*	Moderate	Four studies (two Brazil, one French Guiana and one Sierra Leone). There are moderate concerns about methodological limitations, coherence, adequacy and relevance (all studies only consider HTLV-1)
Mothers' health can affect their ability to breastfeed	*(18,23,25)*	Low	Three studies (Brazil, Guinea and Sierra Leone). There are moderate concerns about methodological limitations and coherence and serious concerns about adequacy and relevance
Community-related factors			
Health decision-makers and managers reported a prevalent view in the community that failure to breastfeed indicated contagion or infection	*(21,22)*	Low	Two studies (both Brazil). Minor concerns over coherence, moderate concerns about methodological limitations but serious concerns about adequacy and relevance (such as HTLV-1 and Brazil only)
According to health decision-makers and managers, those in the community believed that alternatives to breastfeeding were not trustworthy	*(24)*	Low	One study (Guinea and Sierra Leone) of a single condition (Ebola). Minor concerns about methodological limitations and coherence but serious concerns about adequacy and relevance
Health system factors			
Women and new mothers report a lack of knowledge among non-infectious diseases health staff about certain conditions with a risk of mother-to-child transmission by breastfeeding (such as HTLV-1)	*(18,19,21,22,24)*	Moderate	Five studies (two Brazil and one each French Guiana, Guinea and Sierra Leone). Minor concerns about coherence, and moderate concerns about methodological limitations, adequacy and relevance (all studies only consider HTLV-1 or Ebola and only from a single perspective)
New mothers appreciate facilities that provide privacy for infant feeding because they are not exposed to observation by others and therefore are less likely to experience stigma from being identified as having a transmissible disease	*(22)*	Low	One study (Brazil) with minor concerns about coherence, moderate concerns about methodological limitations, but serious concerns about adequacy and relevance (such as only HTLV-1)

Summary of review finding	Studies contributing to the review finding	GRADE-CERQual assessment of confidence in the evidence	Explanation of GRADE-CERQual assessment
Health decision-makers and managers' report that establishing trust between providers and mothers is important if established practices on infant feeding are to be successfully challenged when there is a disease outbreak (such as Ebola)	*(18,24,25)*	Low	Three studies (Guinea and Sierra Leone). There are minor concerns about methodological limitations, moderate concerns about coherence and serious concerns about adequacy and relevance
Health decision-makers and managers' report that it is important for alternatives to breastfeeding to be available and trustworthy if established practices of exclusive breastfeeding are to be challenged	*(18,24)*	Low	Two studies (Guinea and Sierra Leone) of a single condition (Ebola). There are minor concerns about methodological limitations, moderate concerns about coherence and serious concerns about adequacy and relevance
Socioeconomic factors			
Mothers report that the cost of alternatives to breast-milk can be prohibitive	*(18,19)*	Low	Two studies (French Guiana and Sierra Leone) of HTLV-1 and Ebola. There are minor concerns about coherence, moderate concerns about methodological limitations in one study and serious concerns about adequacy and relevance

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SYSTEMATIC REVIEW 2

Carroll C, Booth A, Campbell F, Relton C. What are the implications of Zika virus for infant feeding? A synthesis of qualitative evidence concerning congenital Zika syndrome (CZS) and comparable conditions. PLoS Negl Trop Dis. 2020;14:e0008731.

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SYSTEMATIC REVIEW 3

Martinez SS, Pardo-Hernandez H, Palacios C. Feeding modifications and additional primary caregiver support for infants exposed to Zika virus or diagnosed with congenital Zika syndrome: a rapid review of the evidence. Trop Med Int Health. 2020;25:1353–61.

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SYSTEMATIC REVIEW 4

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