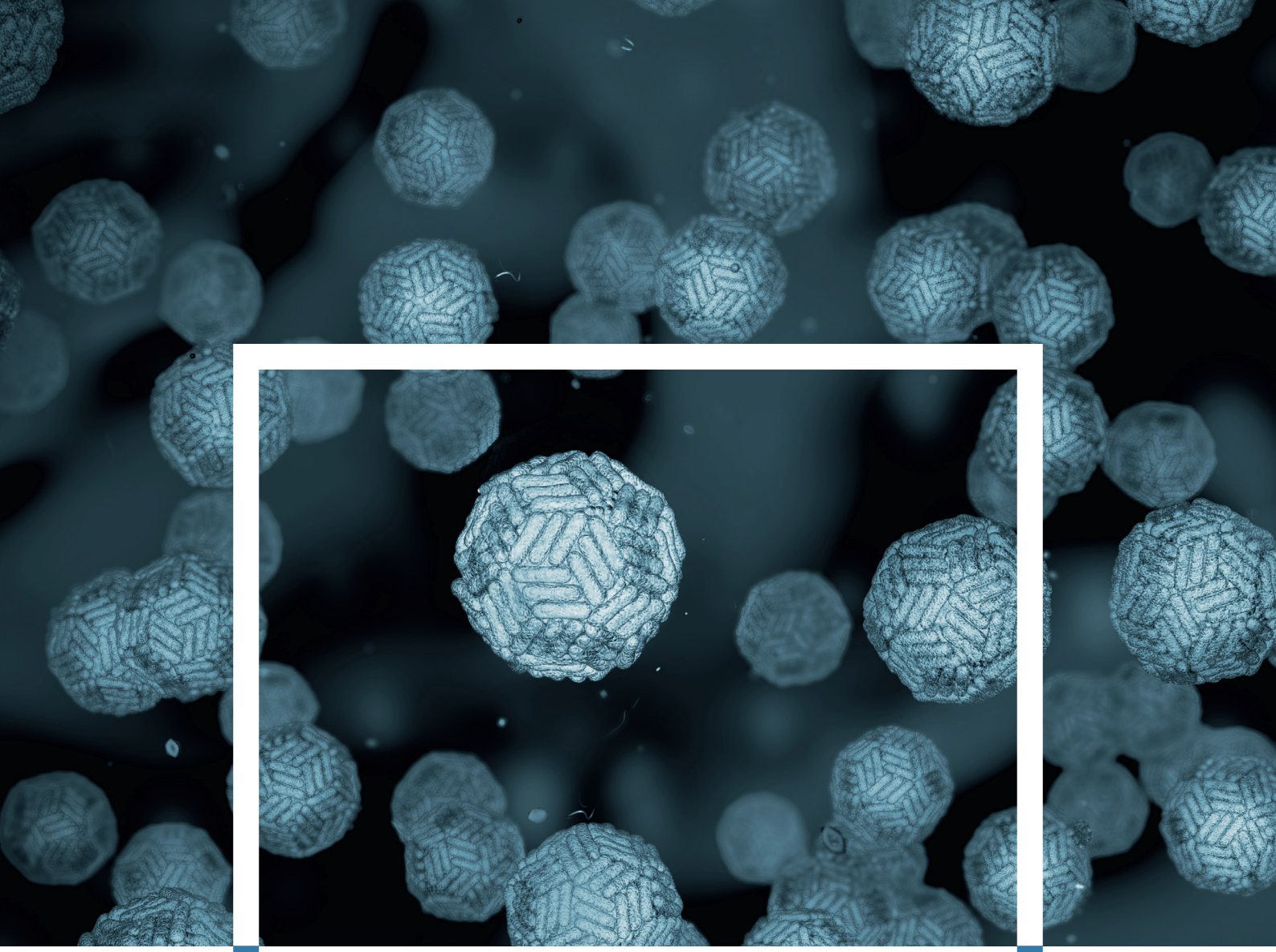

WHO guidelines for the prevention of sexual transmission of Zika virus

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ANNEXES

Acknowledgements

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Contributors to WHO guidelines for the prevention of sexual transmission of Zika virus

Guideline Development Group (GDG)

Chairperson: Gabriela Paz Bailey.

Members: Emma Aarons, Laith Abu-Raddad, Guilherme Calvet, Bidia Deperthes, Ousmane Faye, Hernando Gaitan Duarte, Susan Hills, Tippawan Liabsuetrakul, Otilia Mardh, Bill Potter, Nancy Santesso, Leo Yee Sin.

External Review Group (ERG): Thomas Jaenisch, Francis Ndowa, Cristina Pimenta.

WHO Secretariat: Nathalie Broutet, Sami Gottlieb, Edna Kara, James Kiarie, Caron Kim, Melanie Taylor, Anna Thorson, Teodora Wi, Eve Lackritz, Ornella Lincetto, Robyn Meurant, Stephanne Huguenot, Bernadette Murgue, Maeve de Mello, Rodolfo Gomez Ponce de Leon, Luis Castellanos.

Evidence Team: Nicola Low, Michel Counotte, Kaspar Meili.

Acronyms and abbreviations

CI	confidence interval
CrI	credible interval
DOI	Declaration of Interests
EU/EEA	European Union and European Economic Area
GBS	Guillain-Barré syndrome
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	Guidelines Review Committee
HIV	human immunodeficiency virus
IQR	interquartile range
PAHO	Pan American Health Organization
PHEIC	public health emergency of international concern
PICO	Population, Intervention, Comparator, Outcome
RNA	ribonucleic acid
RHL	Reproductive Health Library
RT-PCR	reverse transcriptase polymerase chain reaction
STI	sexually transmitted infection
USA	United States of America
WHO	World Health Organization

Executive Summary

Introduction

Zika virus is an arthropod-borne flavivirus, which is transmitted primarily by mosquitoes of the *Aedes* genus, but can also be transmitted through sexual intercourse. In 2016, the World Health Organization (WHO) concluded that Zika virus infection during pregnancy is a cause of congenital abnormalities, including microcephaly. The proportion of affected neonates born to mothers infected with Zika virus during pregnancy has not been established with certainty. Published estimates range from 6% of infants born to women with and without symptoms of possible Zika virus infection in the United States of America (USA) to 42% of infants born to women with symptoms of skin rash in pregnancy in Brazil. WHO also concluded that Zika virus can trigger Guillain-Barré syndrome (GBS), an immune-mediated neurological condition. A multi-country assessment estimated that two of 10 000 Zika virus infections result in GBS (95% credible interval (CrI): 0.5–4.5/10.000). Prevention of the sexual transmission of Zika virus can therefore prevent acute infection and neurological complications in a sexual partner, and prevention of transmission to a pregnant woman would prevent congenital Zika virus infection.

As of February 2018, 86 countries and territories have had evidence of Zika virus transmission and, as of January 2018, over 500 000 suspected cases had been reported in Latin America and the Caribbean. In the USA, as of 15 April 2018, 52 of 5672 reported cases of Zika virus disease were presumed to have been acquired through sexual transmission. In the European Union (EU) and European Economic Area (EEA), as of 13 March 2017, 20 of 1737 cases with a known route of transmission were acquired through sexual transmission.

Sexual transmission of Zika virus is much more likely from men to women than from women to men; and same sex transmission, from man to man, has only been documented once. Where documented, the longest time period between the onset of symptoms in one sexual partner and the onset of symptoms in the other is 44 days, with half of the sexual partners developing symptoms by 12 days. The longest time period that infectious Zika virus has been detected by viral culture in semen is 69 days. However, Zika virus genetic material in semen has cleared within 50 days in most cases; it is not known whether genetic material detected for longer durations represents infectious virus.

Recommendations for the prevention of sexual transmission of Zika virus need to take into account the risk of ongoing mosquito-borne transmission of Zika virus in geographic areas. In areas with ongoing transmission, people are much more likely to become infected by Zika virus through bites from infected mosquitoes, and the contribution of condom use to overall prevention of infection will be low. In areas with no autochthonous mosquito-borne Zika virus transmission, sexual transmission from returning travellers is one of the main routes of transmission. Travellers returning from areas with ongoing Zika virus transmission can therefore substantially reduce the risk of subsequent infections through the correct and consistent use of condoms. Areas with ongoing transmission are defined as regions with active circulation of mosquito-borne Zika virus. These are areas where disease surveillance detects circulation of Zika virus, in accordance with periodic epidemiological updates from WHO. In the absence of adequate disease surveillance, the definition of areas of ongoing transmission depends on the availability of local risk assessments. Adoption of the precautionary principle could result in designation of areas with known previous transmission as areas with ongoing transmission. Areas without ongoing transmission have no active circulation or suspected active circulation of Zika virus.

Rationale for the guidelines

WHO published interim guidelines on the prevention of sexual transmission of Zika virus in September 2016, based on a limited amount of evidence under an emergency process during a public health emergency of international concern (PHEIC). The body of evidence has grown considerably since then, and WHO experts concluded, at a meeting in March 2017, that the guidelines should be redeveloped under the formal WHO guideline process.

These guidelines contain updated recommendations on the prevention of sexual transmission of Zika virus, based on the best available evidence as of June 2018.

Rationale for the update of interim guidelines

At the time of the interim guidance issuance, very few data on sexual transmission of Zika virus were available and recommendations were developed under emergency response procedures. In March 2017, WHO convened an expert meeting to review the evidence and identify the research gaps surrounding sexual transmission of Zika virus. At this meeting, participants discussed a conceptual framework. The sexual transmission framework describes key events in sexual transmission of Zika virus between humans, based on variables and time periods that apply to all infectious diseases.

What is new in this guideline?

- For the new recommended duration for correct and consistent use of condoms or abstinence to prevent sexual transmission of Zika virus, a distinction is made between men and women, and the recommended duration has been reduced from six to three months for men, two months for women.
- The risk groups women or couples planning to conceive or having sex that could result in conception and pregnant women, are more explicitly targeted in these new recommendations.
- For this guideline, systematic reviews were conducted to assess available evidence on the sexual transmission of Zika virus and all evidence on effectiveness of condom use to prevent sexual transmission of Zika virus.

Goal and Objectives

The overall goal of these guidelines is to provide guidance and evidence-based recommendations about the prevention of sexual transmission of Zika virus. The absolute risks of different clinical complications of Zika virus are not fully known and the prevention measures may differ. Nevertheless, it is essential for individuals to have information about the risks of sexual intercourse as a mode of transmission in itself. These guidelines are informed by an update of the evidence underpinning the interim guidance and follow the requirements of the formal WHO guideline development process. The specific objectives are:

- to provide recommendations about the prevention of sexual transmission of Zika virus, rather than about the prevention of specific complications or about the prevention of mosquito-borne transmission;
- to update the interim guidelines in accordance with the formal WHO guidelines development process;
- to offer safe and effective options for the prevention of sexual transmission of Zika virus; and
- to provide evidence summaries about the risks of sexual transmission of Zika virus and the effectiveness of condoms for the prevention of sexual transmission of Zika virus.

Target audience

These guidelines aim to inform national and subnational policy makers, healthcare providers, other healthcare stakeholders and the general public.

Methods

These guidelines were developed as outlined in the *WHO handbook for guideline development*. Members of the Guideline Development Group (GDG), which includes experts in sexually transmitted infections, virology, epidemiology, gynaecology, condoms and sexual behaviour, developed key questions to guide the guideline development process. All members declared conflict of interests according to WHO procedure. For each key question, an evidence team from the University of Bern conducted systematic reviews, synthesized the retrieved evidence, and assessed its certainty using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. The GDG, based on an evidence-to-decision (EtD) framework, developed and finalized the recommendations and justifications during a web conference in May 2018 and through subsequent communication by email. After external review, these guidelines were published. Recommendations were formulated as "strong" or "conditional" using the evidence to decision framework. The strength of individual recommendations is annotated in after the recommendation in parentheses. The quality of the body of evidence was assessed Grading of Recommendations Assessment, Development and Evaluation (GRADE). After external review, these guidelines were published.

Recommendations

1. Recommendations for individuals living in areas with ongoing transmission of Zika virus:

1.1 Recommendations for all sexually active women and men

a) All **women and men** with Zika virus infection and their sexual partners, particularly pregnant women,[1] should receive information about the risks of sexual transmission of Zika virus (Strong recommendation, very low certainty of evidence).

b) All **women and men** should be offered a full range of contraceptives and be counselled to be able to make an informed choice about whether and when to prevent pregnancy in order to avoid possible adverse outcomes of Zika virus infection during pregnancy (Strong recommendation, best practice recommendation).

c) **Men** should be informed about the possible risk of sexual transmission of Zika virus during the **3 months** after known or presumptive infection.[2] Men should be informed about the correct and consistent use of condoms or abstinence during that time period to prevent Zika virus infection through sexual transmission (Conditional recommendation, low certainty of evidence).

d) **Women** should be informed about the possible risk of sexual transmission of Zika virus during the **2 months** after known or presumptive infection.[2] Women should be informed about the correct and consistent use of condoms or abstinence during that time period to prevent Zika virus infection through sexual transmission (Conditional recommendation, very low certainty of evidence).

1.2 Recommendations for women or couples planning to conceive or having sex that could result in conception

a) **Women** who have had sex that could result in conception, and do not wish to become pregnant due to concerns about Zika virus infection, should have ready access to emergency contraceptive services and counselling (Best practice).

b) **Women** should receive information about the possible risk of vertical transmission of Zika virus to the fetus. Women should avoid sex that could result in conception for **2 months** after known or presumptive infection,[2] to ensure that a possible Zika virus infection has cleared before becoming pregnant (Strong recommendation, very low certainty of evidence).

c) **Male** sexual partners should receive information about the possible risk of sexual transmission of Zika virus during the **3 months** after known or presumptive infection.[2] Men should use condoms correctly and consistently or abstain from having sex for that time period to prevent Zika virus infection through sexual transmission (Strong recommendation, low certainty of evidence).

d) Taking into account current and projected local transmission rates[3] of Zika virus, **women or couples** planning to conceive should be informed about the option to delay conception until the risk of Zika virus infection in the local area has substantially decreased, in accordance with local risk assessment (Conditional recommendation, very low certainty of evidence).

1.3 Recommendations for pregnant women[1] and their sexual partners

a) **Pregnant women** and their sexual partners should use condoms correctly and consistently, or abstain from sex for **the whole duration of the pregnancy**, to prevent Zika virus infection through sexual transmission and possible adverse outcomes of Zika virus infection during pregnancy (Strong recommendation, very low certainty of evidence).

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[1] Further guidance on Zika virus infection and pregnancy can be found in the WHO interim guidelines *Pregnancy management in the context of Zika virus infection* (available online at http://www.who.int/csr/resources/publications/zika/pregnancy-management/en/).

[2] After known or presumptive infection: After onset of symptoms compatible with Zika virus infection or, if asymptomatic, a positive test result for Zika virus. Most Zika virus infections are asymptomatic. Sexual transmission from a partner with asymptomatic Zika virus infection has been reported. Whether a person is infected or not may be hard to establish, given the low diagnostic accuracy of some available tests and the absence of resources for testing in some areas. Further guidance on the diagnosis of Zika virus infection can be found in the WHO interim guidance *Laboratory testing for Zika virus infection* (available online at http://www.who.int/csr/resources/publications/zika/laboratory-testing/en/).

[3] Local or projected transmission rates: In areas with high levels of current ongoing Zika virus transmission, delaying conception until the transmission rate decreases can reduce the risk of Zika virus infection during pregnancy.

2. Recommendations for individuals living in areas without ongoing transmission of Zika virus travelling to or from areas with ongoing Zika virus transmission

2.1 Recommendations for all sexually active women and men returning from areas with ongoing Zika virus transmission

a) All **women and men** travelling to or returning from areas with ongoing Zika virus transmission and their sexual partners, particularly pregnant women,[1] should receive information about the risks of sexual transmission of Zika virus (Strong recommendation, very low certainty of evidence).

b) All **women and men** travelling to or returning from areas with ongoing transmission of Zika virus should be offered a full range of contraceptives, and be counselled to be able to make an informed choice about whether and when to prevent pregnancy, in order to avoid possible adverse outcomes of Zika virus infection during pregnancy (Strong recommendation, very low certainty of evidence).

c) **Men** returning from areas with ongoing Zika virus transmission and their sexual partners should use condoms correctly and consistently, or abstain from sex for at least **3 months** after the last possible exposure,[4] to prevent Zika virus infection through sexual transmission (Strong recommendation, low certainty of evidence).

d) **Women** returning from areas with ongoing Zika virus transmission and their sexual partners should use condoms correctly and consistently, or abstain from sex for at least **2 months** after the last possible exposure,[4] to prevent Zika virus infection through sexual transmission (Strong recommendation, very low certainty of evidence).

2.2 Recommendations for women or couples planning to conceive, or having sex that could result in conception, and returning from areas with ongoing Zika virus transmission

a) **Women** returning from areas with ongoing Zika virus transmission should avoid sex that could result in conception for at least **2 months** after the last possible exposure[4] (Strong recommendation, very low certainty of evidence).

b) **Male** sexual partners returning from areas with ongoing Zika virus transmission should use condoms correctly and consistently, or abstain from sex for at least **3 months** after the last possible exposure,[4] to prevent Zika virus infection through sexual transmission and reduce the risk of conception (Strong recommendation, low certainty of evidence).

2.3 Recommendations for pregnant women[1] and their sexual partners travelling to or returning from areas with ongoing Zika virus transmission

a) **Pregnant women** and their sexual partners should use condoms correctly and consistently or abstain from sex for the **whole duration of the pregnancy** if the sexual partner is returning from areas with ongoing Zika virus transmission. This recommendation aims to prevent Zika virus infection through sexual transmission and possible adverse pregnancy and fetal outcomes (Strong recommendation, very low certainty of evidence).

b) **Pregnant women** should consider delaying nonessential travel to areas with ongoing Zika virus transmission (Conditional recommendation, very low certainty).

3. Recommendations about safer sex

WHO always recommends the use of safer sexual practices. Safer sex is a behavioural concept that promotes the reduction of sexual risk-taking behaviour. It emphasizes measures to reduce the risk of contracting or spreading sexually transmitted infections (STIs), including postponing sexual debut, nonpenetrative sex, correct and consistent use of male or female condoms, and reducing the number of sexual partners.

Men and women should receive counselling and be informed about safer sex. Health authorities should ensure affordable and equitable access to condoms and other contraception methods, especially in the context of Zika virus transmission and other STIs. The correct and consistent use of condoms reduces the risk of an unintended pregnancy as well as STIs, including the human immunodeficiency virus (HIV).

[4] After the last possible exposure: After the last day of stay in an area with ongoing Zika virus transmission or the last day of sexual contact with a possibly Zika virus-infected person.

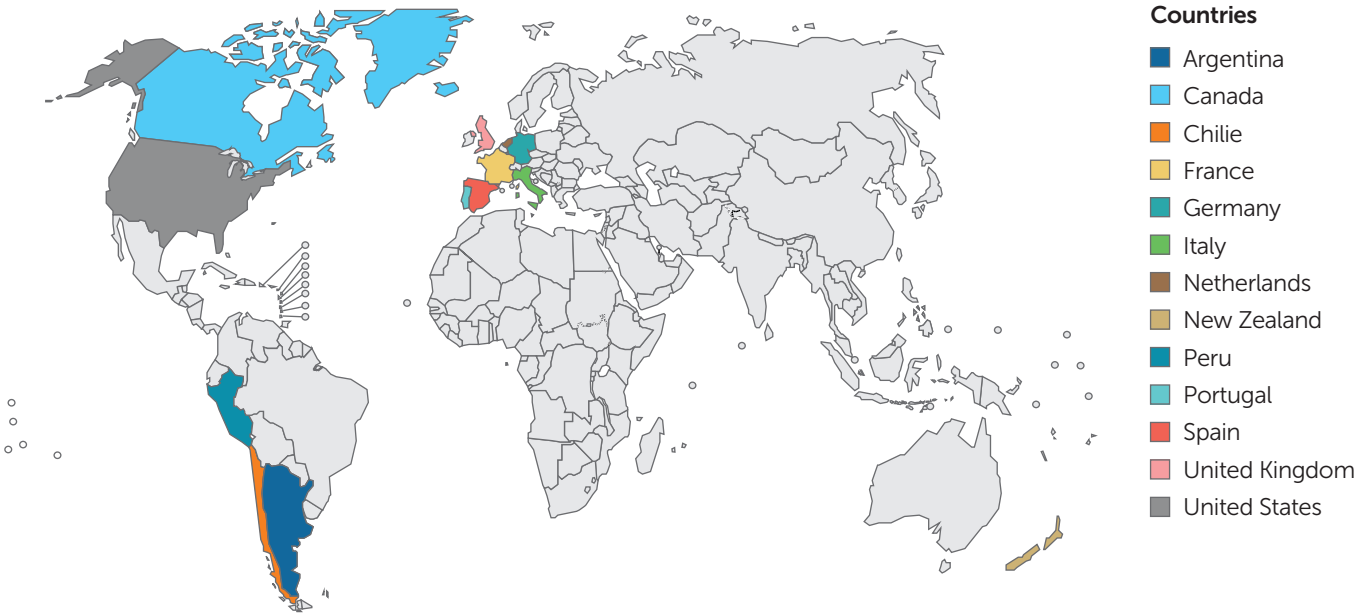
1. Introduction

1.1 Background

Zika virus was first discovered in Uganda when isolated from a rhesus monkey in 1947. Zika virus is a species of the genus Flavivirus, which also includes dengue virus. The 2015–2016 epidemic of Zika virus infection in South America drew international attention to Zika virus, when an association with babies born with microcephaly was suspected. The World Health Organization (WHO) declared a public health emergency of international concern (PHEIC) in response to the then unexplained clusters of microcephaly and Guillain-Barré syndrome (GBS). To respond to the PHEIC, WHO, Pan American Health Organization (PAHO) and partners developed the *Zika strategic response plan (1)*, which emphasized the role of research. In this context, the WHO *Zika Virus Research Agenda (2)* was developed, a key component of which was to characterize the virus and its potential effects. The last published *WHO Zika Virus Classification Table* from February 2018 *(3)* shows that 86 countries and territories have shown evidence of Zika virus transmission. In Latin America and the Caribbean, as of January 2018, over 220 000 locally transmitted cases of confirmed Zika virus infection and 583 000 suspected cases have been reported *(4)*. The real number of people with Zika virus infection is probably much higher because of the high proportion of asymptomatic cases *(5)*. In the United States of America (USA), as of 15 April 2018, 52 of 5672 reported cases of Zika virus disease were acquired through sexual transmission *(6)*. In the European Union (EU) and European Economic Area (EEA), as of 13 March 2017, 20 of 1737 cases with a known route of transmission were acquired through sexual transmission *(7)*. The primary transmission route of Zika virus is via mosquitoes of the *Aedes* genus. Sexual transmission of Zika virus was also accepted as a route of transmission that is more common than assumed before the outbreak in the Americas (Fig. 1) *(8)*.

WHO concluded in 2016 that there was a causal link between Zika virus infection and adverse pregnancy and congenital outcomes, including microcephaly, as well as with GBS, an immune-mediated condition of the peripheral nerves *(11)*. Zika virus infection during pregnancy can result in adverse congenital outcomes. The proportion of affected infants born to mothers with Zika virus infection in pregnancy has not been established with certainty. A range of birth defects reported to be associated with Zika virus were found in 6% (26/442) of infants in a study that included women with and without

Fig. 1. Countries from which presumed sexual transmission of Zika virus has been reported



Source: reports up to December 2016 from Moreira et al. 2017 *(9)*; reports up to September 2018 from Counotte et al. *(10)*

symptoms of possible Zika virus infection in the USA, and in 42% (49/117) of infants born to women with symptoms of skin rash in pregnancy in Brazil *(12, 13)*. In rare cases Zika virus infection can result in GBS. Two out of 10 000 infected cases resulted in GBS (95% credible interval (CrI): 0.5–4.5) *(14)*. WHO published an interim guidance document on the prevention of sexual transmission of Zika virus in September 2016, during the PHEIC *(15)*. The limited evidence available up to August 2016 consisted mainly of case reports from 13 countries in which Zika virus infection was diagnosed in a person living in an area without ongoing Zika virus transmission, but whose sexual partner had returned from an area with ongoing Zika virus transmission. These studies reported evidence of sexual transmission from symptomatic and asymptomatic men to their female partners, a woman to her male partner, a man to his male partner, and of longer detection of Zika virus in semen than in viral culture. Currently, male to female sexual transmission of Zika virus via vaginal sex is most commonly reported *(16–20)*, but female to male transmission via vaginal sex *(21)*, anal transmission *(22)*, and possibly oral transmission *(23, 24)* have also been reported.

The guidance recommended safer sex practices for six months for women and men returning from areas with ongoing Zika virus transmission.

1.2 Rationale for the update of interim guidelines

At the time of the interim guidance issuance, very few data on sexual transmission of Zika virus were available, and recommendations were developed under emergency response procedures. In March 2017, WHO convened an expert meeting to review the evidence and identify the research gaps surrounding sexual transmission of Zika virus *(25)*. At this meeting, participants discussed a conceptual framework. The sexual transmission framework describes key events in sexual transmission of Zika virus between humans, based on variables and time periods that apply to all infectious diseases (Fig. 2) *(26)*.

Infection of Zika virus through sexual contact is followed by an incubation period before symptoms, if any, develop. An infected person can transmit Zika virus to others for a certain duration of infectiousness, which might start before the onset of symptoms, if any. For those who develop symptoms, the serial interval is the period between the onset of symptoms in one individual and the onset of symptoms in their sexual partner. After the infection clears, individuals can become immune.

The sexual transmission framework provided a systematic approach to synthesise the evidence. Discussion about the sexual transmission framework helped to ascertain the time periods for which estimates are needed to make recommendations about the duration of protection, and to identify research gaps. The meeting participants agreed that the evidence should be updated to include studies published since August 2016 and the end of the PHEIC in November 2016. Most of the proposed members of the Guideline Development Group (GDG) took part in the expert meeting.

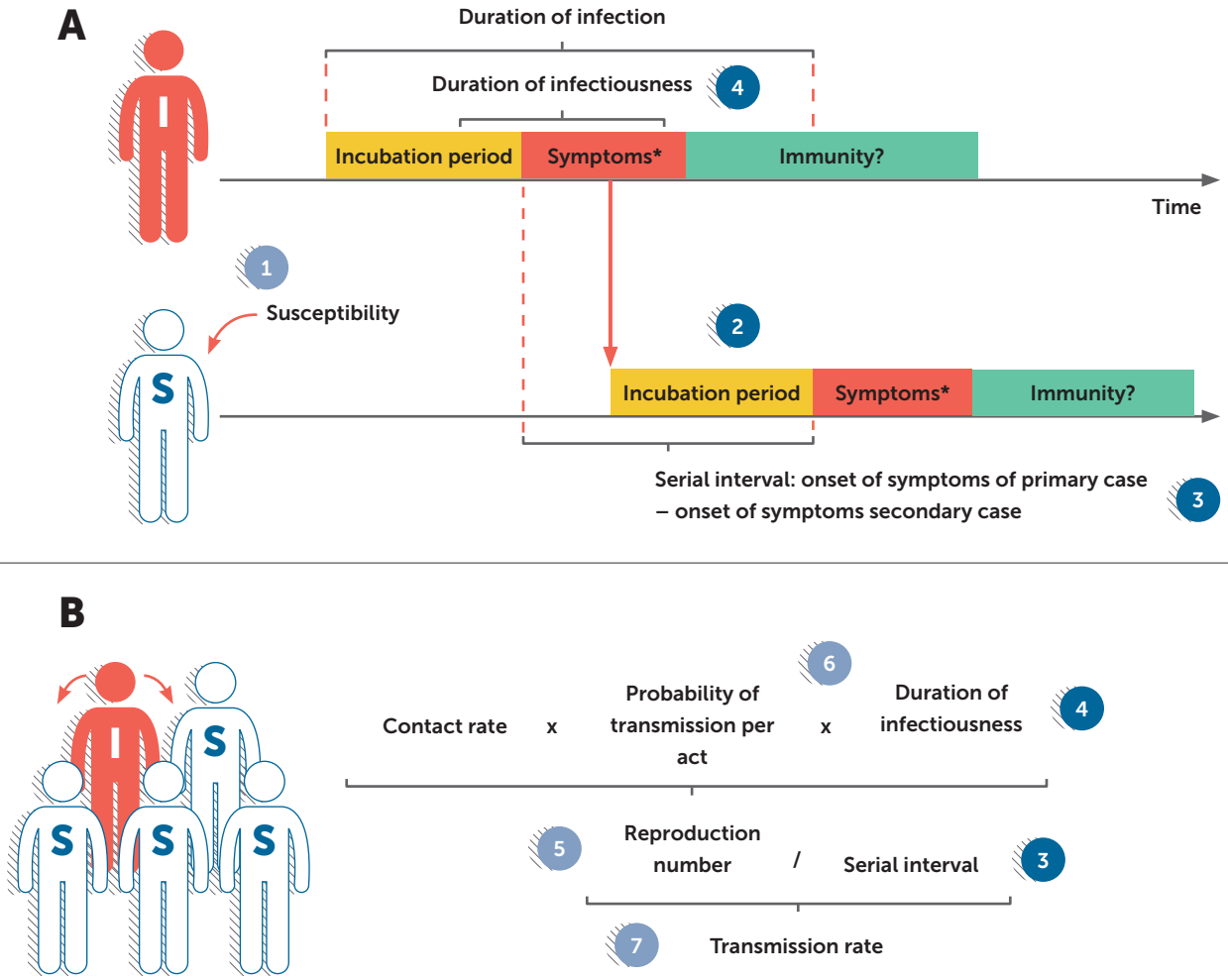
This update of the guidance follows the formal WHO guidelines development process *(27)*.

1.3 Timeline

Table 1. Timeline of guideline development

Step	Timeframe
Scoping, development of draft Population, Intervention, Comparator, Outcome statements (PICOs)	February–March 2017
Formation of guideline group, preliminary meeting, finalization of PICO questions	March 2017
Evidence retrieval, synthesis and appraisal	April 2017–March 2018
Preparation of documents for the GDG meeting	April 2018
Meeting of the GDG to finalize recommendations	25 May 2018
Document revised, reviewed and submitted to Guidelines Review Committee (GRC) for final clearances	31 October 2018

Fig. 2. A schematic representation of the sexual transmission of Zika virus and 7 key elements



The numbered circles show the seven key elements. Dark blue circles are elements for which evidence is based on empirical research. Light blue circles denote elements derived from mathematical modelling studies and in vivo studies. (A) Transmission between two individuals. The horizontal arrows show the time course of the disease for the primary infected individual (I), who is infected, and the secondary individual (S), who starts as susceptible (element 1). The vertical red arrow represents a Zika virus transmission event. *Zika virus infection results mostly in asymptomatic disease. (B) Relation between different elements at population level. Parameters describing transmission at a population level are the reproduction number, the result of the contact rate, the probability of transmission per act, and the duration of infectiousness. The transmission rate can be estimated using the reproduction number and the serial interval.

Source: adapted from Counotte et al. *(10)* [adapted with permission from WHO *(26)*].

1.4 Goals and objectives

The overall goal of these guidelines is to provide guidance and evidence-based recommendations about the prevention of sexual transmission of Zika virus. The absolute risks of different clinical complications of Zika virus are not fully known and the prevention measures may differ. Nevertheless, it is essential for individuals to have information about the risks of sexual intercourse as a mode of transmission in itself. These guidelines are informed by an update of the evidence underpinning the interim guidance, and follow the requirements of the formal WHO guideline development process.

The specific objectives are:

- to provide recommendations about the prevention of sexual transmission of Zika virus, rather than about

the prevention of specific complications or about the prevention of mosquito-borne transmission;

- to update the interim guidelines in accordance with the formal WHO guidelines development process;
- to offer safe and effective options for the prevention of sexual transmission of Zika virus; and
- to provide evidence summaries about the risks of sexual transmission of Zika virus and the effectiveness of condoms for the prevention of sexual transmission of Zika virus.

1.5 Target audience

The target audience comprises:

- national and subnational policy makers;
- implementers, and managers of national and subnational reproductive health and STI programmes;
- nongovernmental and other organizations and professional societies involved in the planning and management of services for those affected by Zika virus infection;
- healthcare providers; and
- general public.

1.6 Scope and structure of the guidelines

These guidelines present evidence-based recommendations for the prevention of sexual transmission of Zika virus. Countries can use these guidelines as a base for the development of locally adapted national guidelines. National guidelines should be adapted to consider the current status and future potential for local ongoing Zika virus transmission, the attitude and perceptions of residents regarding safer sex, and the capacity of health services and available resources.

The guidelines provide recommendations about the prevention of sexual transmission of Zika virus. The guidelines recognize that contraception that prevents pregnancy is the most important measure to prevent potential adverse outcomes of Zika virus infection in pregnancy. The guidelines also recognize that the prevention of mosquito-borne infection for pregnant women, and for women planning to conceive, is the most important measure for the prevention of Zika virus infection in areas with ongoing transmission of Zika virus *(28)*.

These guidelines apply to areas with ongoing and without ongoing transmission of Zika virus. For each category, they contain separate recommendations for:

- all sexually active women and men;
- women or couples planning to conceive or having sex that could result in conception; and
- pregnant women and their sexual partners.

1.7 Related WHO guidelines

The guidelines are related to the following guidance documents:

Prevention of sexual transmission of Zika virus, interim guidance update (15): As documented above, this is the interim guidance that was issued in the midst of the Zika virus outbreak and that followed the guidelines process in the emergency response setting.

Pregnancy management in the context of Zika virus infection, interim guidance update (28). This guidance was also issued as part of the emergency response to the Zika virus outbreak. It is relevant for all pregnant women residing in areas with ongoing Zika virus transmission, pregnant women exposed through travel to an area with ongoing Zika virus transmission, or pregnant women who have had unprotected sexual contact with an infected partner. The guidance provides recommendations for pregnancy care and management in the context of Zika virus transmission and congenital Zika virus infection, including recommendations on voluntary discontinuation of pregnancy and appropriate counselling. The importance of preventing mosquito-borne infection for pregnant women and women planning to conceive or having sex that could result in conception, and who are living in areas with ongoing transmission of Zika virus, is mentioned in these guidelines.

Laboratory testing for Zika virus infection, interim guidance (29): This guidance was also published following the PHEIC. It covers recommendations regarding the testing and diagnosis of Zika virus infections.

2. Methods

The methods documented in the *WHO handbook for guideline development (27)* were used to develop these guidelines. See Annex B for a detailed description.

2.1 Guideline Development Group (GDG)

The GDG consists of 13 members from different regions affected by Zika virus, with expertise in sexually transmitted infections (STIs), research, laboratory research, virology, epidemiology, gynaecology, condoms and sexual behaviour (Annex A), and came together in an in-person meeting and web conference. The GDG was involved in defining the key questions, assessing the reviewed evidence, developing the recommendations, and approving the final version of these guidelines.

2.2 Formulation of key questions

This updated guidance takes into consideration the questions that guided the interim guidance on prevention of sexual transmission of Zika virus and advances in the evidence. Two main questions framed the evidence synthesis in the interim guidance: (1) Can Zika virus be transmitted through sexual contact, and (2) How long does Zika virus persist in bodily fluids? Since then, there is now sufficient evidence that Zika virus can be transmitted through sexual intercourse. During the initial phase of the guideline development process, the GDG, the evidence team and the steering group collaborated to draft and finalize key questions. The key questions are:

(1) What is known about the risks of sexual transmission of Zika virus?

(2) Does consistent and correct condom use reduce transmission of Zika virus?

(3) When, and for how long, does one need to use a condom?

The sexual transmission framework (Fig. 2) provided the basis to structure the evidence for the key question (1). For key question (2), a Population, Intervention, Comparator, Outcome (PICO) was formulated. Because there were no randomized or non-randomized trials, evidence from key questions (1) and (2) were used to inform key question (3). Key question (3) determines the recommendations in these guidelines for different populations at risk and different geographical areas. See Annex B1 and Annex B2 for details.

2.3 Review of the evidence

The evidence team from the University of Bern conducted preplanned systematic reviews for key questions (1) and (2). A suitable range of data sources was searched for each question from April 2017 to March 2018, including PubMed and Embase. Two reviewers independently screened studies, performed data extraction and verification, and resolved discrepancies by consensus. The included evidence consists of cohort studies, case reports, case series, cohort studies, animal studies, mathematical modelling studies, laboratory studies and reviews. Included studies were synthesized narratively or using appropriate statistical methods. The quality of the included studies was assessed systematically using published tools for each study type. The evidence team used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework *(30)* to assess the overall certainty of the evidence for each key question. Table 2 displays the four grades that were used to attribute the certainty of the evidence.

See Annex C for a list of references of all included studies, Annex B for detailed descriptions of methods for each key question, and Annex B3 for the GRADE evidence profiles.

Table 2. The four evidence certainty grades *(30)*

Level	Name	Description
●●●●	High	The estimate reflects the true effect well
●●●○	Moderate	The estimate may differ from the true effect
●●○○	Low	The estimate is likely to differ from the true effect
●○○○	Very Low	The estimate is unlikely to reflect the true effect

2.4 From evidence to recommendations

Members of the GDG, the Guideline Steering Group (GSG) and the Evidence Team met in May 2018 in a web conference. After the presentation of the evidence, the GDG discussed the evidence and suggestions for recommendations guided by the evidence-to-decision (EtD) framework *(31)*. For each subgroup of affected people in areas with and without ongoing Zika virus transmission, the GDG considered the priority, benefits and harms, evidence certainty, outcome importance, the balance between desirable and undesirable effects, resource use, equity, acceptability and feasibility of the recommendation. Under guidance of the chairperson and the Steering Group, the GDG discussed until consensus was reached. For the recommendation on the duration of condom use for travellers returning from areas with ongoing Zika virus transmission, each present member of the GDG gave an opinion statement, followed by a discussion until consensus was reached.

Each recommendation was formulated as either "strong" or "conditional", as specified by the *WHO handbook for guideline development (27)*. This rating takes into account the certainty of the balance between desirable and undesirable consequences of recommendations. A very high certainty of a positive balance warrants a "strong" recommendation, whereas "conditional" recommendations are based on lower certainty of a positive balance. The strength of each recommendation is annotated in after the recommendation in parentheses and documented in the evidence to decision framework (Annex B4). Details about differences and implications for different target audiences are outlined in Table 3.

2.5 Management of conflicts of interests

According to the procedures described in the *WHO Handbook for guideline development (27)* and by the WHO Office of Compliance, Risk Management and Ethics in the *Guidelines for declaration of interests* (DOI) *(32)*, members of the GDG provided declaration of interests statements at the time of invitation to participate in updating the guidelines. At the beginning of the web conference, the GDG members were again asked to disclose any conflicts of interest.

After review of the DOI, it was concluded that there were no conflicts of interest (Annex A1). Therefore, there were no exclusions of any member from participating fully in the guideline development process.

WHO invited the general public to review the experts and stakeholders involved and provide feedback regarding any member deemed to have a significant conflict of interest with respect to the terms of reference for this group (https://www.who.int/reproductivehealth/publications/dvlpt-guideline-prevention-sexual-transmission-zika-virus/en/). Short biographies of individuals attending the Guideline Development Group meeting were posted online for two weeks for public notice. The short biographies were provided by the experts themselves. A generic email notification was provided and no response from the public has been received.

Table 3. Implications of recommendations worded strongly or conditionally. Adapted from the *WHO handbook for guideline development (27)*.

Audience	Strong recommendation (i.e. The man/woman should …)	Conditional recommendation (i.e. The man/woman should be informed …)
Patients	Most individuals in this situation would want the recommended course of action; only a small proportion would not. Formal decision aides are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Most individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Adherence to the recommendation could be used as a quality criterion or performance indicator.	Different choices will be appropriate for individual patients, who will require assistance in arriving at a management decision consistent with their values and preferences. Decision aides may be useful in helping individuals make decisions consistent with their values and preferences.
Policy-makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

3. Dissemination, updating and implementation of the guidelines

3.1 Dissemination and implementation

The guideline will be produced as a PDF file and distributed online and in print. Translation into Spanish (in collaboration with PAHO), French and Portuguese are planned, and have been budgeted for.

The digital versions will be available via the WHO websites and through the Reproductive Health Library (RHL, https://extranet.who.int/rhl). Print versions will be distributed to WHO regional and country offices, nongovernmental organization (NGO) partners, and professional associations.

The guidelines will be launched in several WHO areas through a dissemination meeting. WHO staff will look for opportunities during already planned country visits to discuss the implementation of the guidelines with country staff. Adaptation activities and implementation research may take place in select countries, based on need and interest to move ahead with recommendations.

3.2 Assessment of guideline usefulness, impact, and future updates

There will be an ongoing evaluation process over the first year of the guideline implementation, focusing on the accessibility, acceptance, use, impact, and generalizability of the guidelines. As an assessment of document uptake, the number of downloads of the document from the WHO websites will be monitored, as well as the number of hard copies of the guidance requested and distributed through the document centre.

After implementation, an evaluation of the impact of the guidelines will be undertaken in the form of an online survey. This will be conducted through WHO Regional and Country offices and through selected respondents of other user groups (e.g. professional societies, NGOs) in order to gauge utilization in-country and whether any of the recommendations in the guidelines have been implemented or influenced policy decisions. This evaluation will also include as assessment of uptake and barriers to effective implementation which will be important feedback for future modifications.

Evidence will be reviewed four years after the date of publication, and the need for updating of recommendations will be determined. This may be done earlier if evidence should significantly alter before then.

4. Recommendations for the prevention of sexual transmission of Zika virus

4.1 Background

These guidelines apply to the prevention of the sexual transmission of Zika virus through vaginal and anal sexual intercourse. The terms "women" and "men" refer to the biological sex of persons, as defined by female or male reproductive organs, regardless of gender identity.

"Women and men returning from areas with ongoing Zika virus transmission": Individuals travelling from areas with ongoing transmission to areas without ongoing transmission of Zika virus. This also includes travellers that travel to areas other than the area from where they originally started travelling, and travellers that previously resided in areas with ongoing Zika virus transmission; that is, travellers that are not "returning" in a strict sense.

Areas with ongoing Zika virus transmission: All subnational areas, territories and countries with ongoing transmission of Zika virus. Areas with ongoing Zika virus transmission are areas where disease surveillance detects circulation of Zika virus, in accordance with periodic epidemiological updates from WHO. In the absence of adequate disease surveillance, the definition of areas of ongoing transmission depends on the availability of local risk assessments. Adoption of the precautionary principle could result in designation of areas with known previous transmission as areas with ongoing transmission.

Areas without ongoing Zika virus transmission: All subnational areas, territories and countries without ongoing transmission of Zika virus.

Condoms, as used in these guidelines: Male and female condoms, in particular male latex condoms and condoms made of other polymer-based materials, but not condoms made of sheep intestines.

4.2 Summary of the evidence

This section contains a summary of the evidence included in the systematic reviews conducted to inform the guidelines. The summary is structured according to the key questions, because the single recommendations are grounded on the synthesized evidence for key questions (1) and (2). For detailed results and methods of the systematic reviews conducted, see Annex B1 for key question (1) and Annex B2 for key question (2). Annex C contains a list of all studies included as evidence per key question.

Key question (1): What is known about the risks of sexual transmission of Zika virus?

Serial interval

The evidence includes 24 observational studies of Zika virus infections diagnosed in the partners of travellers returning from areas with ongoing Zika virus transmission *(16–24, 33–47)*. Amongst 23 cases of presumed sexual transmission, the evidence team documented a median serial interval of 12 days (interquartile range (IQR): 10–14.5, max. 44 days) between the onset of symptoms in the male traveller and the onset of symptoms in the female partner *(16–18, 20–23, 33, 35–37, 39, 45, 47)* (Table 1, Annex B3).

Presence of Zika virus in the male genital tract

Not all men with symptomatic Zika virus infection, who have been studied, had detectable viral RNA in semen at the time of sampling, and attempts to culture virus were often unsuccessful. In two cohort studies, both conducted in the USA, 31/55 (56%, 95% confidence interval (CI): 42–69) and 60/184 (33%, 95% CI: 26–40) men had Zika virus detected by reverse transcription polymerase chain reaction (RT-PCR) in any semen sample *(48, 49)*.

Amongst 110 men in whom Zika virus culture in seminal fluid was attempted *(10, 48, 50)*, no culturable virus was detected beyond 69 days after symptom onset (median 10 days, IQR: 1–20) *(20)*.

Ninety days after the onset of symptoms of Zika virus infection, (13.6%, 95% CI: 7.2–21.1) of men reported in case reports and case series had Zika virus detected in semen by RT-PCR *(10)*. In one prospective cohort study, Zika virus was detected by RT-PCR, 9% was positive at day 90 (95% CI: 3-20) *(49)*. In the collected case reports and case series, 15 out of 128 semen samples were positive after 90 days (11%, 95% CI: 2–11) *(45, 47, 51–57)*. The quantity of ribonucleic acid (RNA) in semen samples appears to decline over time *(58)*. The duration of viral RNA positivity detected with RT-PCR likely overestimates the presence of infectious virus in a semen sample *(58, 59)* (Table 1, Annex B3).

Presence of virus in female genital tract

The evidence team found only one case of symptomatic Zika virus infection in a male partner of a women returning from an area with ongoing Zika virus transmission. The serial interval was six days *(21)*. Among publications reporting detection of viral RNA in the female genital tract, the maximum duration was 37 days *(60)*. In one case report of a woman infected with human immunodeficiency virus (HIV), Zika virus was cultured in vaginal samples on day three after symptom onset *(61)*. The evidence team did not find any documented case of Zika virus infection in a female sexual partner of a women returning from an area with ongoing Zika virus transmission (Table 1, Annex B3).

Presence of virus in saliva

Twenty-two included studies reported RT-PCR detectability of Zika virus RNA in saliva. The median duration of Zika virus positivity of saliva was 6.8 days (95% CI: 4.3–9.6) based on measurements from 76 individuals in 22 reports *(10)*, with a maximum of 91 days *(52)*.

Incubation period

The incubation period for mosquito-borne Zika virus is estimated from modelling at 5.9 days (95% CrI: 4.4–7.6) with 95% of people developing symptoms within 11.2 days (95% CrI: 7.6–18) *(62)*. A similar incubation period, 3–14 days, was estimated based on analysis of 197 Zika virus-infected individuals *(63)* (Table 1, Annex B3).

Certainty of evidence

The certainty of the evidence ranged from very low to low, and not all parameters of the sexual transmission framework could be assessed: no evidence about susceptibility, the incubation period following sexual transmission, or the transmission rate was found.

Certainty of evidence about the serial interval, reproduction number due to sexual transmission, and proportion of cases due to sexual transmission was very low, and the certainty of evidence about the probability of transmission per sex act was low.

The evidence about the duration of infectiousness in the male genital tract is highly relevant to high relevance. The question of how long condom use should be recommended included cohort studies with low certainty, and case reports and case series with very low certainty. The certainty of evidence on duration of infectiousness in the female genital tract and saliva was very low (Table 1, Annex B3).

Key question (2): Does consistent and correct condom use reduce transmission of Zika virus?

No direct evidence was found on the minimal infectious dose for the sexual transmission of Zika virus, and no direct evidence was found on the effectiveness of condoms to prevent sexual transmission of Zika virus. Based on indirect evidence from the following: a total of 24 experimental studies comprising 15 laboratory studies on other viruses and virus-sized particles *(64–78)* and nine animal studies *(79–87)*; eight reviews comprising four systematic *(88–91)* and four non-systematic *(92–95)*; one modelling study *(96)*; and one pooled cohort study *(97)*, correct and consistent use of condoms prevents sexual transmission of Zika virus with an effectiveness that is comparable to the effectiveness of condoms to prevent the sexual transmission of HIV. Only two of the included studies reported on the effectiveness of female condoms, but the evidence team assumes that the effectiveness of female condoms can be compared to male condoms if used correctly. Thus, the guidelines include both male and female condoms as a measure to prevent the sexual transmission of Zika virus (Table 2, Annex B3).

Certainty of evidence

The certainty of the indirect evidence ranged from very low to moderate, and the overall certainty of the evidence for this outcome was assessed as very low, owing to indirectness.

Key question (3): When and for how long does one need to use a condom?

Because of the absence of direct evidence, the GDG used the combined evidence from key questions (1) and (2) to answer this question and formulate recommendations, after reaching consensus. See the EtD framework (Annex B4, 1. Areas with ongoing transmission, and 2. Areas without ongoing transmission) for details.

Limitations of the evidence in key questions (1), (2) and (3)

There was no evidence on the relationships between Zika virus RNA detection using RT-PCR, detection in viral culture, and duration of infectiousness.

The exact duration of the latent period of Zika virus is unknown. The virus can be transmissible before onset of the symptoms in men *(16)*. Whether or not this also applies to women is unknown.

How frequently asymptomatic Zika virus infection in a male or female returning traveller results in asymptomatic Zika virus infection in a sexual partner, or how frequently symptomatic Zika virus infection in a male or female returning traveller results in asymptomatic Zika virus infection in a sexual partner, is unknown.

There was no direct evidence on the effectiveness of condoms to prevent sexual transmission of Zika virus, and the minimal infectious dose of Zika virus for sexual transmission is unknown.

4.3 Recommendations

1. Recommendations for individuals living in areas with ongoing transmission of Zika virus:

1.1 Recommendations for all sexually active women and men

a) All **women and men** with Zika virus infection and their sexual partners, particularly pregnant women,[5] should receive information about the risks of sexual transmission of Zika virus (Strong recommendation, very low certainty of evidence).

b) All **women and men** should be offered a full range of contraceptives and be counselled to be able to make an informed choice about whether and when to prevent pregnancy in order to avoid possible adverse outcomes of Zika virus infection during pregnancy (Strong recommendation, best practice recommendation).

c) **Men** should be informed about the possible risk of sexual transmission of Zika virus during the **3 months** after known or presumptive infection.[6] Men should be informed about the correct and consistent use of condoms or abstinence during that time period to prevent Zika virus infection through sexual transmission (Conditional recommendation, low certainty of evidence).

d) **Women** should be informed about the possible risk of sexual transmission of Zika virus during the **2 months** after known or presumptive infection.[6] Women should be informed about the correct and consistent use of condoms or abstinence during that time period to prevent Zika virus infection through sexual transmission (Conditional recommendation, very low certainty of evidence).

1.2 Recommendations for women or couples planning to conceive or having sex that could result in conception

a) **Women** who have had sex that could result in conception and do not wish to become pregnant due to concerns about Zika virus infection should have ready access to emergency contraceptive services and counselling (Best practice).

b) **Women** should receive information about the possible risk of vertical transmission of Zika virus to the fetus. Women should avoid sex that could result in conception for **2 months** after known or presumptive infection,[6] to ensure that a possible Zika virus infection has cleared before becoming pregnant (Strong recommendation, very low certainty of evidence).

c) **Male** sexual partners should receive information about the possible risk of sexual transmission of Zika virus during the **3 months** after known or presumptive infection.[6] Men should use condoms correctly and consistently or abstain from having sex for that time period to prevent Zika virus infection through sexual transmission (Strong recommendation, low certainty of evidence).

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[5] Further guidance on Zika virus infection and pregnancy can be found in the WHO interim guidelines on *Pregnancy management in the context of Zika virus infection* (available online at http://www.who.int/csr/resources/publications/zika/pregnancy-management/en/).

[6] After known or presumptive infection: After onset of symptoms compatible with Zika virus infection or, if asymptomatic, a positive test result for Zika virus. Most Zika virus infections are asymptomatic. Sexual transmission from a partner with asymptomatic Zika virus infection has been reported. Whether a person is infected or not may be hard to establish, given the low diagnostic accuracy of some available tests and the absence of resources for testing in some areas. Further guidance on the diagnosis of Zika virus infection can be found in the WHO interim guidance *Laboratory testing for Zika virus infection* (available online at http://www.who.int/csr/resources/publications/zika/laboratory-testing/en/).

d) Taking into account current and projected local transmission rates[7] of Zika virus, **women or couples** planning to conceive should be informed about the option to delay conception until the risk of Zika virus infection in the local area has substantially decreased, in accordance with local risk assessment (Conditional recommendation, very low certainty of evidence).

1.3 Recommendations for pregnant women[1] and their sexual partners

a) **Pregnant women** and their sexual partners should use condoms correctly and consistently or abstain from sex for **the whole duration of the pregnancy** to prevent Zika virus infection through sexual transmission and possible adverse outcomes of Zika virus infection during pregnancy (Strong recommendation, very low certainty of evidence).

2. Recommendations for individuals living in areas without ongoing transmission of Zika virus travelling to or from areas with ongoing Zika virus transmission

2.1 Recommendations for all sexually active women and men returning from areas with ongoing Zika virus transmission

a) All **women and men** travelling to or returning from areas with ongoing Zika virus transmission and their sexual partners, particularly pregnant women,[5] should receive information about the risks of sexual transmission of Zika virus (Strong recommendation, very low certainty of evidence).

b) All **women and men** travelling to or returning from areas with ongoing transmission of Zika virus should be offered a full range of contraceptives and be counselled in order to assist them to make an informed choice about whether and when to prevent pregnancy in order to avoid possible adverse outcomes of Zika virus infection during pregnancy (Strong recommendation, best practice recommendation).

c) **Men** returning from areas with ongoing Zika virus transmission and their sexual partners should use condoms correctly and consistently, or abstain from sex for at least **3 months** after the last possible exposure[8] to prevent Zika virus infection through sexual transmission (Strong recommendation, low certainty of evidence).

d) **Women** returning from areas with ongoing Zika virus transmission and their sexual partners should use condoms correctly and consistently, or abstain from sex for at least **2 months** after the last possible exposure[8] to prevent Zika virus infection through sexual transmission (Strong recommendation, very low certainty of evidence).

2.2 Recommendations for women or couples planning to conceive, or having sex that could result in conception, and returning from areas with ongoing Zika virus transmission

a) **Women** returning from areas with ongoing Zika virus transmission should avoid sex that could result in conception for at least **2 months** after the last possible exposure[8] (Strong recommendation, very low certainty of evidence).

b) **Male** sexual partners returning from areas with ongoing Zika virus transmission should use condoms correctly and consistently, or abstain from sex for at least **3 months** after the last possible exposure,[8] to prevent Zika virus infection through sexual transmission and reduce the risk of conception (Strong recommendation, low certainty of evidence).

2.3 Recommendations for pregnant women[1] and their sexual partners travelling to or returning from areas with ongoing Zika virus transmission

a) **Pregnant women** and their sexual partners should use condoms correctly and consistently, or abstain from sex for the **whole duration of the pregnancy,** if the sexual partner is returning from areas with ongoing Zika virus transmission. This recommendation aims to prevent Zika virus infection through sexual transmission and possible adverse pregnancy and fetal outcomes (Strong recommendation, very low certainty of evidence).

b) **Pregnant women** should consider delaying nonessential travel to areas with ongoing Zika virus transmission (Conditional recommendation, very low certainty of evidence).

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[7] Local or projected transmission rates: In areas with high levels of current ongoing Zika virus transmission, delaying conception until the transmission rate decreases can reduce the risk of Zika virus infection during pregnancy.

[8] After the last possible exposure: After the last day of stay in an area with ongoing Zika virus transmission or the last day of sexual contact with a possibly Zika virus-infected person.

3. Recommendations about safer sex

WHO always recommends the use of safer sexual practices. Safer sex is a behavioural concept that promotes the reduction of sexual risk-taking behaviour. It emphasizes measures to reduce the risk of contracting or spreading STIs, including postponing sexual debut, non-penetrative sex, correct and consistent use of male or female condoms, and reducing the number of sexual partners.

Men and women should receive counselling and be informed about safer sex. Health authorities should ensure affordable and equitable access to condoms and other contraception methods, especially in the context of Zika virus transmission and other STIs. The correct and consistent use of condoms reduces the risk of an unintended pregnancy as well as sexually transmitted infections, including HIV.

4.4 Rationale for recommendations

Recommendations that apply to both areas with and without ongoing transmission

For **all individuals** living in areas with ongoing transmission or travelling to areas with ongoing transmission, the GDG decided to formulate a **strong recommendation** that all men and women should receive information about the risk of sexual transmission of Zika virus infection because information is a key component of prevention and for the successful implementation of the recommendations on condom use or abstinence (1.1a, 2.1a). The GDG also decided that free access to contraception and counselling to enable couples to make an informed choice about postponing conception in case of ongoing Zika virus transmission should be a **best practice recommendation** (1.1b, 1.2a, 2.1b).

For **women planning to conceive or having sex that could result in conception and their male partners**, and for **pregnant women**, the GDG decided to formulate a **strong recommendation** for condom use or abstinence given the potentially severe outcomes of congenital Zika virus infection (1.2b, 1.2c, 1.3a, 2.2a, 2.2b).

In **pregnant women and couples planning to conceive** the GDG formulated a **strong recommendation** to receive information and counselling regarding the sexual transmission of Zika virus owing to the possible severe consequences of congenital Zika virus infection (1.2b, 1.2c, 1.2d, 2.3a). The GDG judged that positive effects of condom use or abstinence may be small, owing to the likely small proportion of cases due to sexual transmission, except for the subgroup of pregnant women. However, the GDG favoured the intervention because of the very high certainty that the avoidance of the severe possible consequences of Zika virus infection in pregnant women outweighs the disadvantage of a short duration of condom use or abstinence. The GDG judged that acceptability of the recommendation amongst affected people might be challenging, with low compliance, and acknowledged that condoms may be perceived as a burden. However, condoms are already recommended and used for the prevention of conception and other STIs. Shorter durations of condom use may be more acceptable.

Recommendations that apply to areas with ongoing transmission

For **women and men** living in areas with ongoing transmission, the GDG formulated a **conditional recommendation** for condom use or abstinence (recommendation 1.1c, 1.1d). Condom use or abstinence generally has moderate desirable effects and small undesirable effects but the certainty of evidence is very low to low. The GDG judged the recommendations to require moderate resource use, to have a minor impact on health equity, varying acceptability among key stakeholders, and to be feasible to implement. There may be important variability on how individuals value the prevention of the sexual transmission of Zika virus: well informed individuals, couples planning to conceive, and pregnant women may value the prevention of sexual transmission of Zika virus. Travellers are a clearly defined and limited group of people. The GDG concluded that condom use or abstinence probably incurs negligible costs in travellers and the impact and health equity would probably not be impacted.

Recommendations that apply to areas without ongoing transmission

For **women and men** from areas without ongoing transmission, who are travelling back from areas with ongoing transmission of Zika virus, the GDC decided to formulate a **strong recommendation** for condom use or abstinence because of the very high certainty that the benefits of avoiding Zika virus infection outweighs the disadvantage of a short duration of condom use or abstinence although the certainty of evidence is very low to low (2.1 c, 2.1d). For **pregnant women**, the GDG formulated a **strong recommendation** to abstain from travelling to areas with ongoing transmission of Zika virus, owing to the severe possible outcomes from mosquito-borne infection. The GDG concluded that acceptability is likely high in this risk group, owing to the severity of the potential adverse congenital outcomes.

For a detailed rationale, see Annex B4 – Evidence to decision frameworks.

4.5 Research implications

Several research gaps were identified at the preliminary planning meeting in March 2017 *(98)*. The most relevant research gaps for these guidelines, and the understanding of the risk of the sexual transmission of Zika virus, are the quantification of the parameters of the sexual transmission framework (Fig. 2). The susceptibility, incubation period following sexual transmission, and transmission rate were not quantified (Table 1, Annex B3). For all other parameters: the serial interval; duration of infectiousness; the reproductive number due to sexual transmission; the probability of transmission per sex act; and the proportion of cases due to sexual transmission, the certainty of evidence was rated as either very low or low (Table 1, Annex B3). Well-designed, large-scale studies would help to address the absence of evidence, or to improve the evidence certainty.

For the assessment of condom effectiveness, direct epidemiological evidence regarding the sexual transmission of Zika virus is needed, as currently none is available (Table 2, Annex B3). The very low certainty of indirect evidence on condom effectiveness could be improved by results of current laboratory studies on condom effectiveness against Zika virus, and by evidence on the risk imposed by semen and other bodily fluids in case of Zika virus infection.

In addition, research on the following outstanding questions is needed to improve understanding of sexual transmission of Zika virus.

- Whether and how sexually transmitted Zika virus infection differs from mosquito-borne transmission: for example, is there a difference in the proportion or severity of adverse pregnancy and congenital outcomes?

- What are the differences between symptomatic and asymptomatic Zika virus disease in connection with sexual transmission: does the risk for sexual transmission vary with symptom status?

- How can diagnostic testing, virus isolation and sample collection be improved, and standardized testing and virus isolation?

- What is the role of immunity, hormones, co-existing STIs, and assessment of infectiousness of semen and other bodily fluids in the context of sexual transmission of Zika virus?

- What are properties of the Zika virus, such as sexual transmission efficiency and host adaptability?

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ANNEXES

CONTENTS

Acronyms and abbreviations

AFRO	African Region
AMRO	Region of the Americas
CDC	Centers for Disease Control and Prevention
CLAP	Centro Latinoamericano de Perinatología
CMV	cytomegalovirus
CT	cycle threshold
ECDC	European Centre for Disease Prevention and Control
EU/EEA	European Union and European Economic Area
EMRA	Eastern Mediterranean Region
EURO	European Region
FIOCRUZ	Fundação Oswaldo Cruz
GDG	Guideline Development Group
GRC	Guidelines Review Committee
HBV	hepatitis B virus
HIS	Health Systems and Innovation
HSV	herpes simplex virus
HSV1	herpes simplex virus type 1
HSV2	herpes simplex virus type 2
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISO	International Organization for Standardization
LILACS	Literatura Latino-Americana e do Caribe em Ciências da Saúde
MCA	maternal, newborn, child and adolescent health
MSM	men who have sex with men
NICE	National Institute for Clinical Excellence
NIH	National Institute of Health
PAHO	Pan-American Health Organization
PHE	Public Health England
PHEIC	public health emergency of international concern
PRISMA	preferred reporting items for systematic reviews and meta-analyses
SEARO	South-Eastern Asia Region
SMR	Unidad de Salud de la Mujer y Reproductiva
SRH	Department of Sexual and Reproductive Health and Research
STF	sexual transmission framework
STI	sexually transmitted infection
SYRCLE	SYstematic Review Center for Laboratory animal Experimentation
WHE	Health Emergencies Programme
WHO	World Health Organization
WPRO	Western Pacific Region
UK	United Kingdom
UNFPA	United Nations Population Fund
USA	United States of America

Annex A.
Guideline development teams

The work of developing the guideline was coordinated by the WHO Secretariat. The following are members of the WHO Steering Group.

Name	Department and Team	Affiliation
Nathalie Broutet	SRH, Sexual and Reproductive Health and Research	WHO
Sami Gottlieb	SRH, Sexual and Reproductive Health and Research	WHO
Edna Kara	SRH, Sexual and Reproductive Health and Research	WHO
James Kiarie	SRH, Sexual and Reproductive Health and Research	WHO
Caron Kim	SRH, Sexual and Reproductive Health and Research	WHO
Melanie Taylor	SRH, Sexual and Reproductive Health and Research	WHO
Anna Thorson	SRH, Sexual and Reproductive Health and Research	WHO
Teodora Wi	SRH, Sexual and Reproductive Health and Research	WHO
Eve Lackritz	Health Emergencies Programme (WHE)	WHO
Ornella Lincetto	Maternal, Newborn, Child and Adolescent Health (MCA)	WHO
Robyn Meurant	Health Systems and Innovation (HIS)	WHO
Stephanne Huguenot	Health Emergencies Programme (WHE)	WHO
Bernadette Murgue	Health Emergencies Programme (WHE)	WHO
Maeve de Mello	Department of Communicable Diseases and Health Analysis	PAHO/ WHO
Rodolfo Gomez Ponce de Leon	Centro Latinoamericano de Perinatología/Unidad de Salud de la Mujer y Reproductiva (CLAP/SMR)	PAHO
Luis Castellanos	Neglected Tropical and Vector-borne Diseases	PAHO

The Evidence Team worked closely with the WHO Secretariat throughout the process of developing the guidelines.

Name	Affiliation
Michel Counotte	University of Bern
Kaspar Meili	University of Bern
Nicola Low	University of Bern

The Guideline Development Group (GDG) was formulated to keep in mind the need to have varied expertise in the field of sexual transmission and infectious disease and to ensure geographic representation for regions and countries and of WHO Regions.

Name	Sex	Affiliation	Expertise	Country/ Region
Emma Aarons	F	Public Health England (PHE)	Virologist	UK/EURO
Laith Abu-Raddad	M	Cornell University in Qatar	Infectious disease epidemiology Biostatistics	Qatar/EMRO
Gabriela Paz Bailey	F	CDC	Researcher	USA/AMRO
Guilherme Calvet	M	FIOCRUZ	Researcher	Brazil/AMRO
Bidia Deperthes	F	UNFPA		
Ousmane Faye	M	Institut Pasteur		Senegal/AFRO
Susan Hills	F	CDC	Medical epidemiologist	USA/AMRO
Hernando Gaitan-Duarte	M	Clinical Research Institute, National University of Colombia	Researcher	Colombia/AMRO
Tippawan Liabsuetrakul	F	Prince of Songkla University	Obstetrician/ Gynaecologist	Thailand/SEARO
Otilia Mardh	F	ECDC	Epidemiologist	Sweden/EURO
Bill Potter	M	International consultant	Condom specifics	England/EURO
Nancy Santesso	F	McMaster University	Methodologist	Canada/AMRO
Leo Yee Sin	F	Institute of Infectious Disease and Epidemiology, Communicable Disease Centre, Tan Tock Seng Hospital		Singapore/WPRO

Peer Review Team

Name	Affiliation	Region	COI
Carolyn Deal	NIH	AMRO	None
Francis Ndowa	Senior International Consultant on STI and Gonococcal Antimicrobial Resistance	AFRO	None
Cristina Pimenta	Ministry of Health	AMRO	None
Thomas Jaenisch	Heidelberg University Hospital	EURO	None

Annex A1.
Conflicts of interest management and statements

Name	Affiliation	Conflicts of interest
Gabriela Paz Bailey	CDC, USA	None
Emma Aarons	PHE, UK	None
Otilia Mardh	ECDC, Sweden	None
Hernando Gaitan-Duarte	Clinical Research Institute, National University of Colombia, Colombia	None
Laith Abu-Raddad	Weill-Cornell University, Qatar	None
Tippawan Liabsuetrakul	Prince of Songkla University, Thailand	None
Bill Potter	International consultant	None
Nancy Santesso	McMaster University, Canada	None
Susan Hills	CDC, USA	None
Bidia Deperthes	United Nations Population Fund – UNFPA	None
Guilherme Calvet	Fiocruz, Brazil	None
Ousmane Faye	Institut Pasteur, France	None
Leo Yee Sin	Institute of Infectious Disease and Epidemiology, Communicable Disease, Tan Tock Seng Hospital, Singapore	None

Annex B. Detailed methods for guideline development

1. Key questions

(1) What is known about the risks of sexual transmission of Zika virus?

The risk of sexual transmission of Zika virus cannot be measured directly, and sexual transmission cannot be distinguished from mosquito-borne transmission in areas affected by Zika virus. This key question does not address a specific recommendation, but several issues that help to understand the sexual transmission of Zika virus. The evidence base for observed cases of sexual transmission of Zika virus and the persistence of the virus in bodily fluids consisted of case reports, case series and cohort studies. Data from laboratory studies, mathematical modelling and animal models provided supportive information.

The sexual transmission framework (Fig. 2, main text) shows the relationships between seven events and/or parameters involved in sexual transmission. As indicated below, the estimation of some of these was possible from available data:

1. Duration of infectiousness: case reports, case series, cohort studies of Zika virus persistence in bodily fluids
2. Probability of transmission per sex act: mathematical modelling
3. Reproductive number: mathematical modelling
4. Serial interval: case reports, case series, cohort studies
5. Transmission rate: could not be estimated
6. Incubation period: could be estimated
7. Susceptibility: could be estimated.

In addition, based on an updated systematic review of case reports and case series, we examined differences in the distribution of reported cases of sexual transmission by direction of transmission (male–female, female–male, male–male) and according to symptom status.

(2) Does consistent and correct condom use reduce transmission of Zika virus?

A PICO was formulated for this key question:

P – Zika virus-infected/exposed individuals who are having sexual intercourse with non-Zika virus-infected individuals

I – Use of a condom: this includes male and female condoms for a defined period of time that depends on the infectivity in the male and female reproductive tracts after onset of symptoms

C – Non-use of a condom/barrier method

O – Laboratory-confirmed Zika virus infection of the non-infected partner.

The evidence team examined data about Zika virus size and condom characteristics to obtain indirect evidence about condom protection.

(3) When and for how long does one need to use a condom?

This is the main key question that resulted in a recommendation for these guidelines. There were no randomized or non-randomized controlled trials in humans to address this question. Thus, this question was informed by the evidence gathered for key questions (1) and (2).

2. Evidence retrieval, synthesis and appraisal

The update of these guidelines required a thorough evidence review and its assessment using the GRADE process *(1)*. In accordance with the GRADE process, certainty of evidence, along with benefits and harms, values

and preferences, and resource implications, were taken into account to develop the recommendation statements.

The systematic reviews were externally commissioned. Contributors to the systematic reviews containing the evidence were not members of the GDG so that the latter could provide independent oversight of recommendations based on evidence assessment.

Two systematic reviews were conducted to address the key questions (1) and (2). For both the condom review and the review to inform the variables in the sexual transmission framework (Fig. 2), the following process was followed:

1) Literature search strategy

The following databases were searched from April 2017 to March 2018 without language filters. The search allowed an update of the review of reported cases of sexual transmission of Zika virus up to December 2016, published by Moreira and colleagues *(2)*.

- PubMed, EMBASE, OVID, LILACS
- Other databases and information sources: bioRxiv, Arxiv, PeerJ, WHO, PAHO, ECDC, CDC, Google, and Google Scholar

See Annex B1 for detailed search strategies for key question (1): What is known about the risks of sexual transmission of Zika virus?

2) Evidence included appropriate case control studies, interrupted time series, cohort studies, case reports, case series and mathematical modelling studies (for the sexual transmission framework review). Laboratory and animal studies were included where appropriate.

Data from studies meeting the inclusion criteria were extracted using piloted forms and spreadsheets. The evidence team evaluated the risk of bias in individual study designs using published tools. The United Kingdom's (UK's) National Institute of Health and Clinical Excellence (NICE) checklists were applied for case-control studies and cohort studies *(3)*. For in vivo studies the SYstematic Review Center for Laboratory animal Experimentation's (SYRCLE) risk of bias tool was used *(4)*. For mathematical modelling studies, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Questionnaire to Assess Relevance and Credibility of Modelling Studies was used *(5)*.

For each critical outcome, a summary of findings table based on the GRADEpro framework *(6)* was created. The GRADE approach to appraise the certainty of evidence was used for all the critical outcomes identified with the key questions and PICOs. A GRADE evidence profile was prepared for each outcome within all key questions.

For key questions (1), (2) and (3), it was expected that observational study designs of different types would dominate the evidence base. The evidence team applied the GRADE approach using published guidance. The general GRADE approach, in which evidence from observational studies begins as low certainty evidence, was applied. The level of certainty of the evidence was then upgraded, based on assessments of severity of study limitations, inconsistence, indirectness, imprecision and publication bias *(7)*. For mathematical modelling studies, an adaptation to the GRADE process was applied *(8)*.

For key question (2), the effectiveness of condoms, the GRADE approach was also applied, similarly as in a review of evidence about the sexual transmission of Ebola virus *(9)*.

3. Formulation of recommendations and decision-making

Draft recommendations formulated using the evidence synthesis and appraisal process described above, as well as the evidence profiles, were presented to the GDG for review, discussion and decision at a web conference on 25 May 2018.

Formulation of the recommendations took various factors into consideration, such as benefits and harms, values and preferences, feasibility, acceptability and resource use. These considerations were applicable for key question (3). In order to determine for how long one must practice safer sex, the GDG members factored in the following: the transmission data as provided by the evidence synthesis on key questions (1) and (2), relative values of risk of transmission compared to not wearing a condom, the values and preferences, and the feasibility and acceptability of condom use. Feasibility is a key consideration, considering that the previous recommendation of 6 months' condom use has raised concerns about adherence; for example, in cases of couples wanting to conceive.

Decision-making at the Guideline Panel Meeting was consensus-driven, based on discussion of the synthesized evidence. The chairperson worked to reach consensus during the web conference. Consensus was reached for all recommendations and justifications in these guidelines, and no vote was necessary.

4. Documentation and peer review

Early drafts of sections of the evidence were circulated to GDG members after the webinar to finalize the recommendations. Their feedback was incorporated.

The guideline was also reviewed by external peer reviewers for comments. Recommendations finalized by the GDG were not changed by external review other than providing clarity and readability. In addition, the external reviewers provided structured feedback on accuracy, presentation, and on the overall usefulness of the guideline.

The WHO Secretariat ensured that all recommendations in these guidelines do not contradict any recommendations made in the related WHO guidelines.

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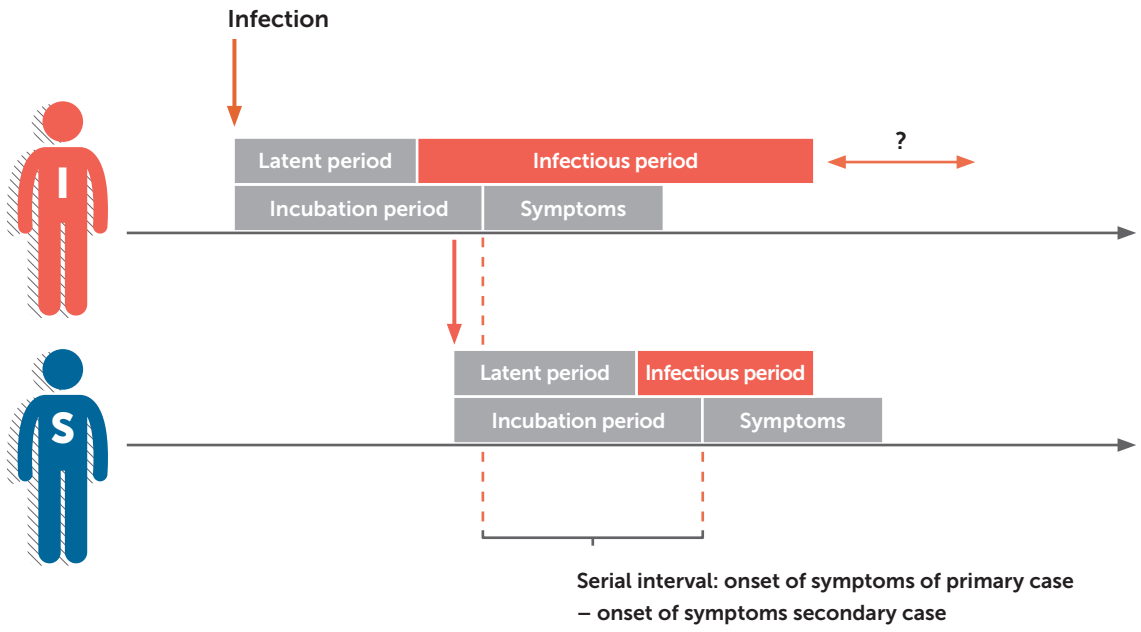
Annex B1.
Evidence review, key question (1): What is known about the risks of sexual transmission of Zika virus?

Here we present a summary of evidence about risks of sexual transmission, based on the sexual transmission framework as published by Counotte MJ et al. Sexual transmission of Zika virus and other flaviviruses – a living systematic review (https://doi.org/10.1371/journal.pmed.1002611).

1. Background

To inform a recommendation about the prevention of sexual transmission of Zika virus, we need to determine the infection transmission parameters. Fig. 1 summarises the relationships between the key parameters of transmission of an infectious disease.

Fig. 1. Relationships between important parameters in infection transmission



Source: adapted from Giesecke 2017 *(1)*.

The figure shows a hypothetical infectious period that starts before the onset of symptoms. Zika virus can possibly be transmitted before the onset of symptoms. The length of the latent period in asymptomatic infection is not known. The horizontal red arrow indicates the unknown duration of infectiousness through sexual transmission of Zika virus.

Based on Fig. 1, we developed a sexual transmission framework (STF) for Zika virus *(2)*, which includes additional parameters that can only be determined indirectly or through mathematical modelling. The full STF is described in Counotte et al. (2020) *(2)*.

1.1 Definitions: transmission parameters in Fig. 1

- **Incubation period:** the delay between exposure to the pathogen and the onset of symptoms.
- **Latent period:** the period between exposure and the onset of a subject becoming infectious. In a symptomatic infection, infectiousness can precede, coincide with, or follow symptom onset.
- **Serial interval:** the time between onset of symptoms in the first case and the second case. The serial interval is often used as a proxy for the generation time, which is the period between onset of infectiousness in the first and second case. The generation time often cannot be measured directly, but influences the speed of propagation of an outbreak *(3)*, so it is an important parameter in mathematical modelling.
- **Duration of infectiousness (also known as infectious period):** the time period for which an individual is capable of transmitting the disease to susceptible individuals.
- **Per sex act transmission risk:** the average proportion of couples in which sexual transmission of an infection will take place; a risk of 2% is equivalent to one transmission per 50 exposures or unprotected sex acts.

1.2 Context for inferences about duration of infectiousness

The duration of infectiousness cannot be observed directly and there are no large-scale observational studies that have assessed the risk of sexual transmission of Zika virus. Several variables can be used to inform an estimate of the duration of infectiousness.

- **Viral culture:** a positive viral culture result represents the presence of infectious virus. The infectious dose of Zika virus through sexual intercourse is not known. A negative viral culture result does not exclude infectiousness. Viral culture is not always available, is prone to sample decay and semen is cytotoxic *(4, 5)*. In mice, Duggal et al. (2017) could isolate virus using cell culture during the same period in which sexual transmission was observed; after this period, they could only detect Zika virus RNA for an extended period *(6)*.
- **Viral RNA:** the detection of Zika virus RNA using reverse transcriptase polymerase chain reaction (RT-PCR) *(7)* is much easier than detection in viral culture. In humans, the relationship between RT-PCR positivity and infectiousness for Zika virus has not been established. Atkinson et al. (2017) found cycle threshold (CT) values of 30 or lower in semen samples taken within 28 days of symptom onset in returning UK male travellers with Zika virus infection *(32)*.
- **Serial interval:** the time between the onset of symptoms in a first and secondary case. Extrapolation from information about the serial interval assumes that the duration of infectiousness is the same for asymptomatic and symptomatic infections. If Zika virus is not infectious before the onset of symptoms, the distribution of the serial interval can approximate the duration of infectiousness. If Zika virus can be transmitted before the onset of symptoms, the serial interval is a minimum estimate. It is not known whether the infectious period of Zika virus starts before the onset of symptoms. Ebola virus is not transmissible before the onset of symptoms.

2. Systematic review methods

We searched ten electronic databases from their earliest dates to 14 April 2018. The search strategy and protocol describing the review methods are published in the database PROSPERO (CRD42017060338) *(8)*.

2.1 Additional data

- For this report, we contacted corresponding authors of selected studies *(9-13)* to ask for additional information, or clarification about sexual transmission of Zika virus between partners. Gabriela Paz-Bailey provided updated data about the Puerto Rican cohort study of persistence of Zika virus in bodily fluids *(14)*.
- We also conducted a mathematical modelling study to estimate the per sex act transmission probability of Zika virus. This has been presented as a poster at the Epidemics 6 conference (Sitges, 2017) but the study has not yet been published.

2.2 Quality assessment: risk of bias and GRADE

We assessed the methodological quality of individual studies using specific checklists for each study type. For observational studies we used National Institutes of Health (NIH) Quality Assessment Tool for Case Series Studies *(15)* and the UK's NICE checklists for case-control studies and cohort studies *(16)*. For in vivo studies we used the risk of bias tool for animal studies *(17)* SYRCLE, and, for mathematical modelling studies, the ISPOR Questionnaire to Assess Relevance and Credibility of Modelling Studies *(18)*. We performed the assessment by a consensus-driven approach among multiple reviewers. We used the GRADE tool *(19, 20)* to assess the certainty of the body of evidence based on observational and in vivo studies. We adapted this approach for mathematical modelling studies, based on a WHO workshop about the use of mathematical modelling studies in guideline development *(21)*.

3. Summary of studies included in systematic review

We identified 1227 unique citations and included 109 publications identified by 14 April 2018 (Table 1).

3.1 Reports of Zika virus sexual transmission between partners

- US Centers for Disease Control and Prevention (CDC) reported that, of 52 out of 5672 cases of Zika virus infection (0.9%, 95% CI: 0.6–1.2%) were acquired through sexual transmission in the United States (US) *(73)*.

Table 1. Overview of study designs of included studies

Category	Publications on Zika virus
Epidemiological studies	
Case reports	44
Case series	17
Cohort studies	4
Outbreak or surveillance reports	1
Mathematical modelling studies	2
Basic research studies	
In vivo studies	35
In vitro studies	6
Review studies	-
Total publications	**109**
Publications used for serial interval and persistence of Zika virus	**51**
Reporting on sexual transmission between partners	24[a]
Reporting serial interval	14[a]
Reporting at least one measurement in bodily fluids of interest using RT-PCR or viral culture	48[a]

[a] One publication can report on multiple outcomes, e.g. serial interval and/or persistence and/or sexual transmission, so these numbers sum to more than 51.

- The European Centre for Disease Prevention and Control (ECDC) reported that, as of 13 March 2017, 20 out of 1737 cases of Zika virus (1.2%, 95% CI: 0.7–1.8) infection were acquired through sexual transmission in the European region *(74)*.

- We included 24 case reports or case series reporting on 36 couples *(9–13, 22–40)*. In 34 of 36 couples, transmission was from man to woman *(9–13, 22–25, 27, 28, 30–40)*. There was one report of female to male transmission *(29)* and one report of male to male transmission *(26)*, which we assume resulted from anal sexual intercourse.

- The findings that male–female transmission is more likely than female–male transmission are biologically plausible, given the longer persistence of Zika virus in male than female genital fluids (see below).

Supportive evidence from in vivo studies: In animal models, only male to female transmission of Zika virus was demonstrated; female to male transmission did not occur, despite exposure *(6)*. Oral transmission in non-human primates was only demonstrated in a small number of animals using high infectious doses, which do not occur naturally *(41)*.

3.2 Symptomatic and asymptomatic infections

- The primary case was symptomatic in 34 of 36 reports of sexually transmitted Zika virus infection. In two cases, the primary case was an asymptomatic man *(30, 31)*. In one case, this resulted in symptomatic infection in a woman; the other case in asymptomatic infection in a woman *(30)*, detected due to increased screening because of assisted reproduction treatment *(31)*.

- Asymptomatic Zika virus infection is more common than symptomatic infection. It is therefore unclear whether the high proportion of reports of Zika virus sexual transmission from symptomatic primary cases is due to under-reporting of infections from an asymptomatic primary case, resulting in asymptomatic Zika virus infection in the partner, or a lower level of transmission. We did not find studies showing that symptomatic status is related to a higher viral load in bodily fluids, or a higher per sex act probability of transmission.

- Sexual transmission of Zika virus where both partners are asymptomatic might go undetected.

4. Incubation period

We did not find any studies about the duration of the incubation period following infection through sexual transmission. For mosquito-borne transmission, the median incubation period was estimated at 5.9 days (95% CrI: 4.4–7.6), with 95% of people developing symptoms within 11.2 days (95% CrI: 7.6–18.0) *(42)*. A similar incubation period, 3–14 days, was estimated based on analysis of 197 Zika virus-infected individuals *(63)*.

5. Serial interval

We included 14 case reports or case series reporting on 24 couples in which a serial interval could be calculated *(11, 22–29, 32, 33, 38–40)* (Fig. 2). The median serial interval was 12 days (IQR: 10–14.5). The maximum serial interval was 44 days *(27)*. In another 10 reports on 12 couples, the serial interval could not be calculated *(9, 10, 12, 13, 30, 31, 34–37)*.

6. Duration of detection of Zika virus in bodily fluids

- We found case reports, case series and cohort studies reporting on the detection of Zika virus in bodily fluids. We describe the findings of case reports and case series separately from cohort studies, because the risks of bias differ between these study types.

- We included 48 case reports and case series describing 180 individuals who underwent diagnostic testing by RT-PCR or viral culture on semen, vaginal fluid or saliva at one or more time points *(4, 11, 25–28, 30–33, 38–40, 43–78)*.

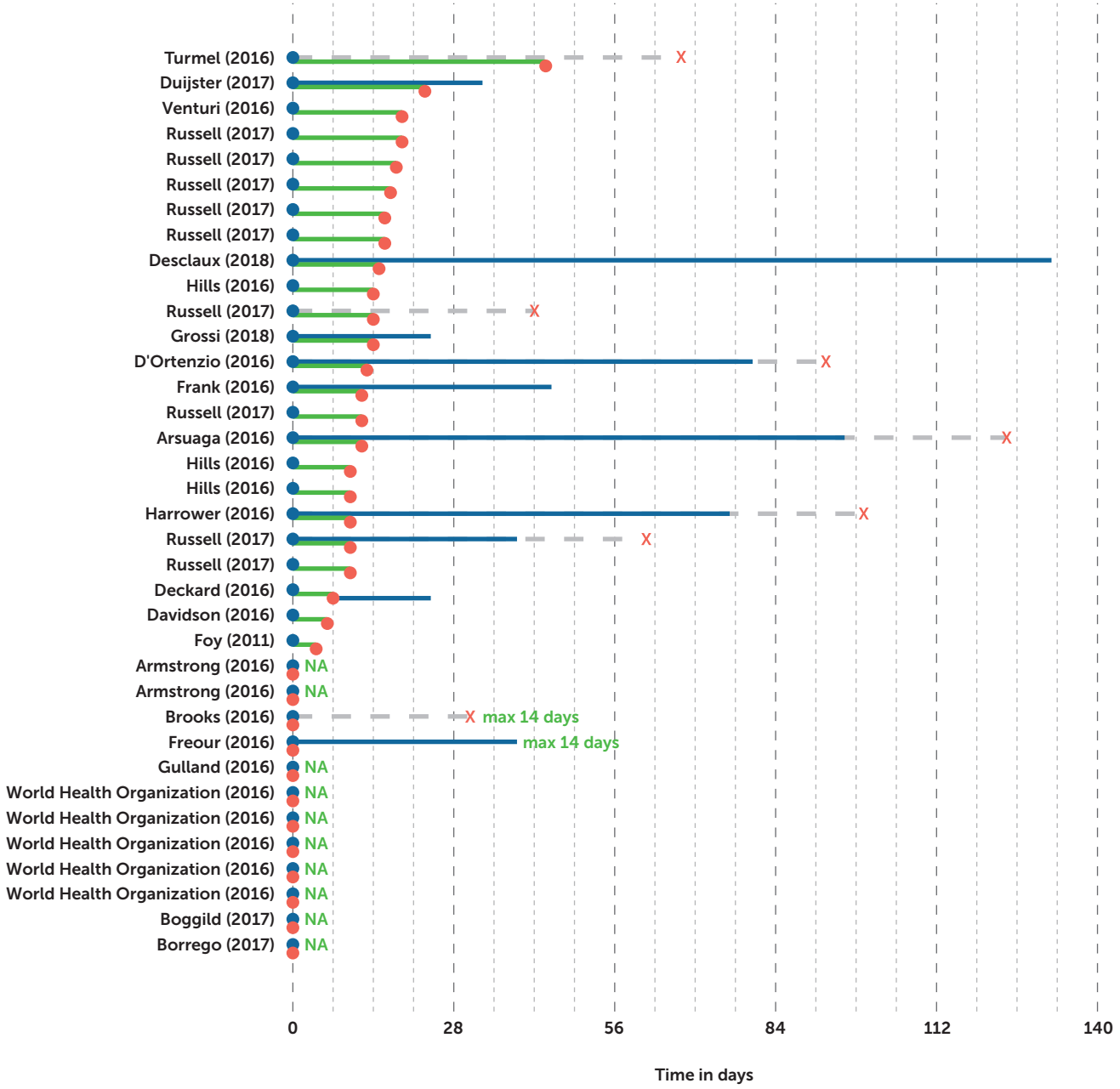
- We included two cohort studies. One reported on 150 women and men with symptomatic Zika virus infection in Puerto Rico *(14)*. One cohort study enrolled 184 men with symptomatic Zika virus infection returning to the USA from travel to another Zika virus-affected country, or who acquired Zika virus in the USA *(79)*.

6.1 Semen

Case reports and case series

- RT-PCR: the median duration of Zika virus RNA detection was 40 days (95% CI: 30–49) and the maximum was 370 days *(76)* (data available from 37 case reports and case series from 119 individuals, Fig. 4, panel A). Fig. 3 summarises the data from the individual cases.

Fig. 2 Findings from studies reporting on sexual transmission of Zika virus between couples



The name on the left is the study author; a total of 24 studies reported on 36 couples. Each line represents one couple (blue dots are men, pink dots are women). Green lines show the serial interval for 24 couples, blue lines show the duration of RNA detection in semen. Grey dashed lines represent the time between the last positive measurement and the first negative measurement (red X). There were no female samples with RNA detected in this dataset. Primary and secondary cases are symptomatic, except for the primary case of Brooks *(30)*, and both primary and secondary case of Freour *(31)*. Green NA are couples for which the serial interval was not reported. Green "max" followed by a number shows the maximum possible serial interval, based on information in the study report.

- Viral culture: the median duration of Zika virus detection was 10 days (95% CI: 1–20) (data from 22 men in 11 reports) and a maximum of 69 days *(33)* (Fig. 4, panel A).

Cohort studies

- RT-PCR: Paz-Bailey et al. reported that Zika virus RNA was detected in 31/55 men (56%, 95% CI: 42–69) in Puerto Rico, with a median duration of persistence of 34 days (95% CI: 28–41) in their preliminary report *(14)*. They are updating their preliminary report with additional patients and follow-up. As of 9 March 2018, "Zika virus RNA was detected by RT-PCR in 48/94 men. The median duration of persistence was 42 days (95% CI: 34–49), the 95 percentile was 119 days (95% CI: 100–139). The maximum RNA detection was 191 days." (G Paz-Bailey, personal communication, manuscript in preparation).

- Mead et al. reported that Zika virus RNA was detected in 60/184 men (33%, 95% CI: 26–40) in the US. The mean duration of persistence was 54 days (95% CI: 53–55). The median duration was not reported, but plotted at approximately 35 days.

- Viral culture: Paz-Bailey et al. reported successful virus isolation in only three semen samples with CT values ranging from 19–27, out of 40 samples tested with CT values ranging from 19–37. The time post-onset of these samples was not reported. Mead et al. reported that Zika virus could be cultured from only three out of 19 semen samples provided within 30 days after symptom onset; Zika virus was not culturable from any of the 59 samples provided after 30 days.

6.2 Female genital fluid and saliva

Case reports and case series

- RT-PCR: the median duration of detection of Zika virus RNA in any fluid from the female genital tract was 14 days (95% CI: 7–20) (data from 15 women in seven reports) and a maximum of 37 days *(74)* (Fig. 4, panel B).

- RT-PCR: the median duration of detection of Zika virus RNA in saliva was 7 days (95% CI: 4–11) with (data from 76 individuals in 23 reports) and a maximum of 91 days *(52)* (Fig. 4, panel C).

- Viral culture: there were too few data for analysis of viral culture specimens in female genital tract fluids and saliva.

Cohort studies

- Zika virus RNA was only detected in a few participants in saliva or vaginal fluids *(14)* and none by viral culture.

6.3 Risk of bias in observational studies

Studies varied widely in risk of bias and completeness of reporting (Counotte et al. (2020) *(2)*, S6 Table). Many studies reporting on transmission events did not use reliable diagnostic methods in both partners, potentially leading to misclassification bias. The median duration of Zika virus persistence was higher in case reports and case series than in the prospective cohort studies, indicating a bias towards publication of case reports with long persistence of Zika virus.

7. Other parameters related to Zika virus sexual transmission derived from modelling studies

7.1 Per sex act transmission probability

- We constructed a simple mathematical model, which we fitted to data about travellers returning to the USA (USA, 2016–2017).

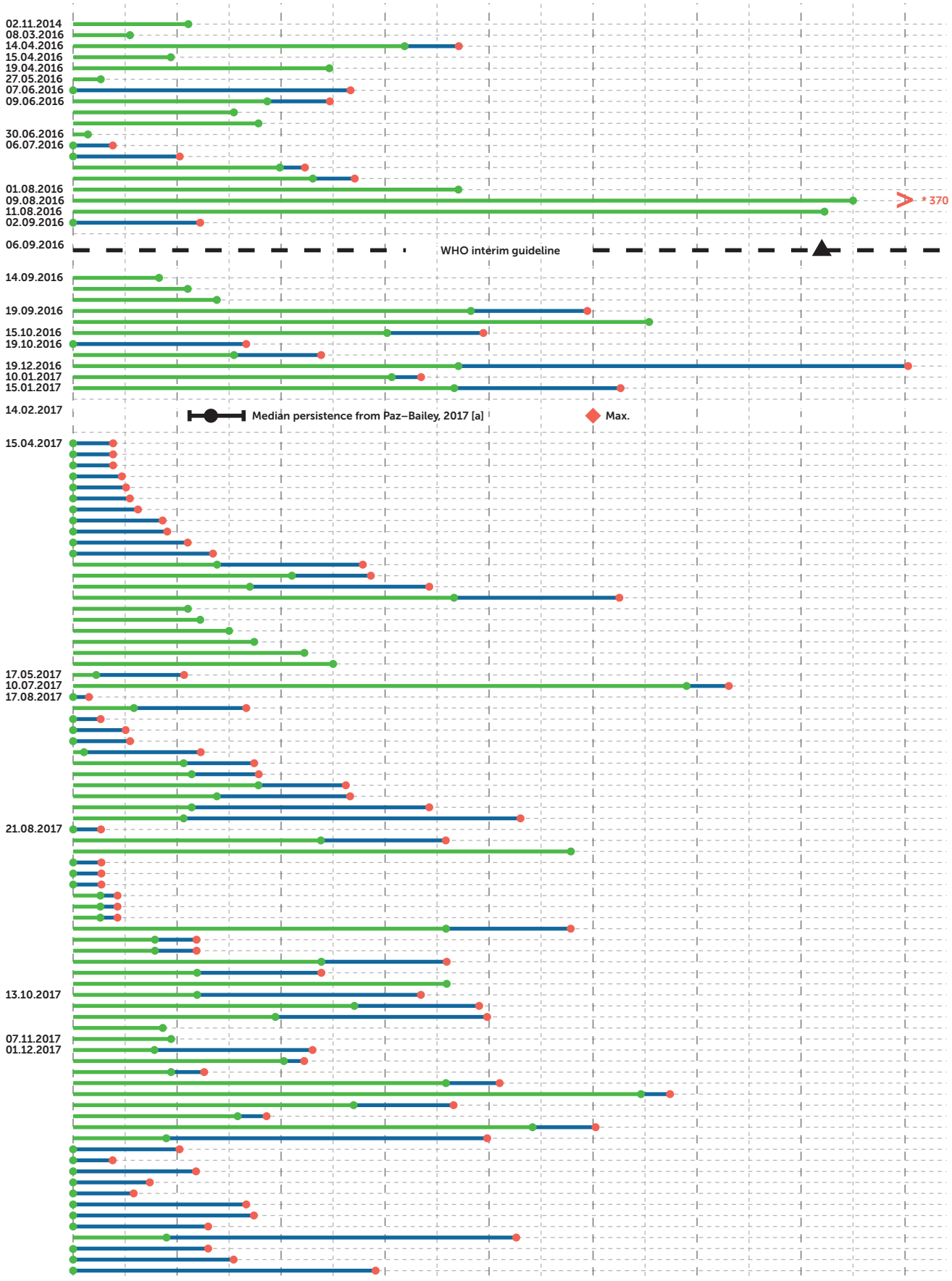
- We estimated the sex act transmission probability from male to female to be 1.6% (95% CI: 1.1–2.4) *(81)*.

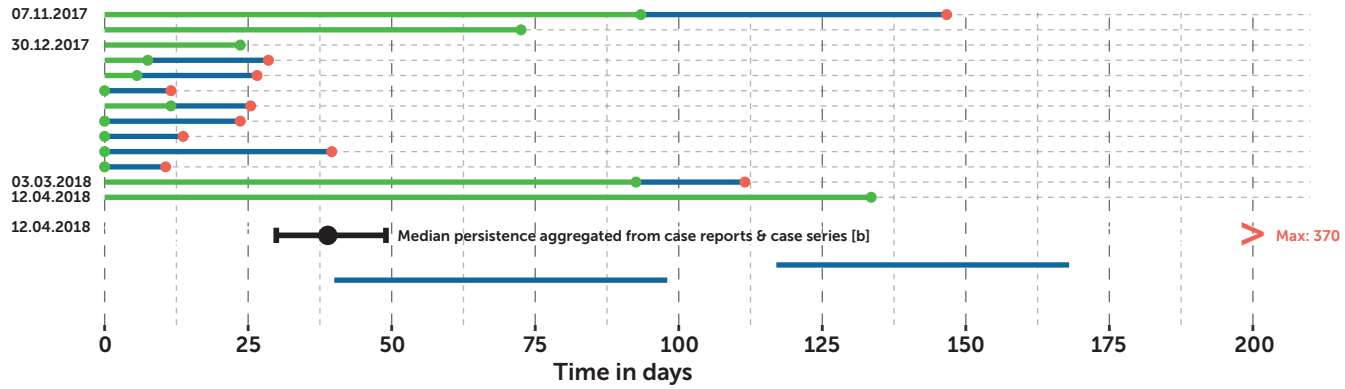
- If the average male is infectious for 50 days and sexual intercourse occurs 1.5 times per week on average (approximately 11 times intercourse in the 50 days), this would result in a transmission risk of 16%, that is, in 16 of 100 male–female sexual partnerships the man would transmit Zika virus to their female partner *(81)*. This estimate is uncertain and somewhat higher than an extrapolation from CDC data: 5000 Zika virus cases, 30% are sexually active men (n=1500), resulting in ~50 cases of sexual transmission (3.3%).

7.2 Reproduction number and the proportion of Zika virus infections resulting from sexual transmission

- We included two published mathematical modelling studies, both of which used a deterministic structure *(82, 83)*. Gao et al. used surveillance data from Brazil, Colombia and El Salvador *(82)*, Towers et al. used data from Colombia *(83)*.

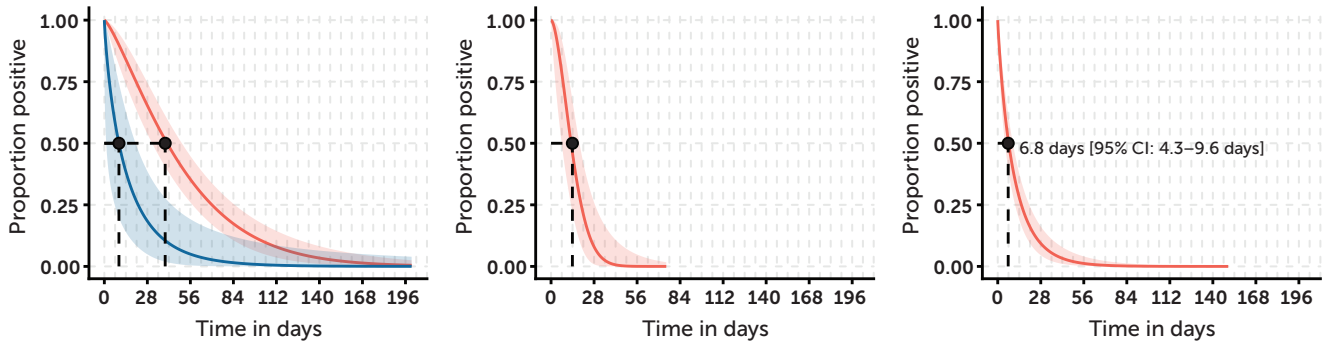
Fig. 3 Semen RT-PCR results from individual patients and aggregated data





Green lines represent the duration of RT-PCR positivity in individuals; green dots represent the last positive RT-PCR measurement or assumed positive status at symptom onset. Blue lines represent the interval between the last positive measurement and the first subsequent negative measure (red dot). The black dotted line shows timing of the publication of the WHO interim guidelines *(80)* and the advised suggested duration of protected sexual intercourse (6 months, black triangle). The black dots and whisker bars represents median aggregated values and 95% CIs for a prospective cohort *(14)*, and the aggregation of all available case reports and case series. Maximum values in these data sets are shown with a purple diamond or a red greater than symbol for values outside the range of the image. The labels on the Y-axis represent the time of publication of the studies, data is ordered in ascending order. Lines for which the date is not provided are from the same publication date as the line above.

Fig. 4. Weibull survival curves of the duration of Zika virus positivity in case reports and case series



Semen (panel A), female genital fluids (panel B), and saliva (panel C) diagnosed with RT-PCR (red curve) and viral culture (blue curve).

- Both studies derived the reproduction number for Zika virus sexual transmission: 0.136 (95% CI: 0.009–0.521) *(82)* and "likely below one" *(83)*. The two studies calculated the proportion of Zika virus infections resulting from sexual transmission as 3.04% (95% CI: 0.12–45.73) *(82)* and 23% (95% CI: 1–47) in Zika virus endemic regions *(83)*.

7.3 Risk of bias in mathematical modelling studies

For both modelling studies, the data used to populate the model was not suitable to derive the outcome. Surveillance data, on which these studies base their results, did not distinguish between vector-borne Zika virus and sexually transmitted Zika virus. The results of these studies did not provide information about the size of the risk of sexual transmission. External validation for both models is lacking.

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Annex B2.
Evidence review, key question (2): Does consistent and correct condom use reduce transmission of Zika virus?

1. Background

Assuming correct usage and otherwise ideal circumstances, the efficacy of condoms as a barrier depends on their physical properties. The materials used to make condoms have different physical properties. Most male condoms are made from latex, which can be obtained from plants or produced synthetically *(1, 2)*. Other materials used for male condoms are polyurethane *(3)* or membranes made from sheep intestines *(4)*. The female condom is made out of polyurethane or nitrile *(5)*. The diameter of the spherical Zika virus virions has been estimated by cryo-electron microscopy studies at 48 nm *(6)* and 50 nm *(7)*. We applied a virion diameter of 48 nm. We refer to sheep intestine-based condoms as natural condoms and other condoms as non-natural condoms.

1.1 Assessment of condom properties

- The International Organization for Standardization (ISO) defines the standards for the "freedom from holes" test, as well as physical properties of condoms – ISO 4074 for male latex condoms *(8)*, ISO 23409 for synthetic male condoms *(9)*, and ISO 25841 for female condoms *(10)* – manufacturing and testing (ISO 2859) *(11)*. The WHO/United Nations Population Fund (UNFPA) procurement specifications for male latex condoms *(12)* and female condoms *(13)* are based on the ISO standards 4074 and 25841, respectively.
- The mandatory freedom from holes test is either a water leak test where the condom is rolled and assessed for leakage, or a test where the flow of electric current through possible holes in condoms is assessed. For female condoms, only the water leak test is listed *(10)*H¿G . The ISO standards defines an acceptable quality level (AQL) of 0.25, meaning that the "great majority" of lots are accepted if at most 0.25% of condoms do not conform *(11)*.

2. Systematic review methods

Table 1 shows our four questions about the efficacy and effectiveness of condoms to prevent sexual transmission of Zika virus. We anticipated the absence of direct evidence, so we searched for evidence about the properties of condoms to prevent leakage of particles of a given size, and the risk that leakage would pose. We combined this evidence to assess the hypothesis that condoms are an effective barrier method to prevent Zika virus infection. We used studies about HIV – diameter 145 nm *(14)* – to infer the effectiveness of condom use in the prevention of the sexual transmission of Zika virus, because the evidence base for condom effectiveness against HIV is larger than for condom effectiveness against other viruses.

Table 1. Review questions for condom efficacy and effectiveness

Path of evidence	Question	
Direct evidence	1	Does condom use reduce the sexual transmission of Zika virus, compared with non-use?
Indirect evidence	2.1	What are the physical properties of condoms to act as an effective barrier for viral particles?
	2.2	What is the minimal amount of leaked Zika virus necessary to cause an infection through sexual intercourse?
	2.3	What is the effectiveness of condoms to prevent the sexual transmission of other viral infections?

Table 1 shows the sources of information.

Table 2. Overview of data sources for condom studies

	Direct evidence	Indirect evidence		
Question	**1** Condom effectiveness against Zika virus	**2.1** Physical properties of condoms	**2.2** Minimal infectious dose of Zika virus	**2.3** Condom effectiveness for other viral diseases
Search modes	Systematic, Systematic handsearch	Forward backward, non-systematic	Systematic, non-systematic, handsearch	Non-systematic
Data sources systematic	Embase, Pubmed, LILACS, WHO, CDC, ECDC, PAHO		Pubmed, Embase	
Data sources non-systematic		*(1, 3, 4, 15–22)*, Pubmed, Google, Google Scholar	Google, Google Scholar, Health Canada, Medscape	Pubmed, Google, Google Scholar
Number of included studies	0	18	9	9

Abbreviations: Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), World Health Organization (WHO), European Centre for Disease Prevention and Control (ECDC), Centers for Disease Control and Prevention (CDC), Pan American Health Organization (PAHO).

Risk of bias assessment

We assessed the quality of systematic reviews and reviews using risk of bias in systematic reviews (ROBIS) *(23)*, and observational studies, with the quality appraisal checklist for quantitative studies reporting correlations and associations by NICE *(24)*. For animal studies, we used the SYRCLE tool *(25)*. For laboratory studies that assessed the physical properties of condoms, we informally appraised quality based on characteristics of the experiments. We could not find formal tools to assess the risk of bias in laboratory studies assessing the physical properties of condoms. We provide a narrative summary of the potential bias in these studies. We used GRADE *(26)* to assess the overall certainty of evidence for each outcome.

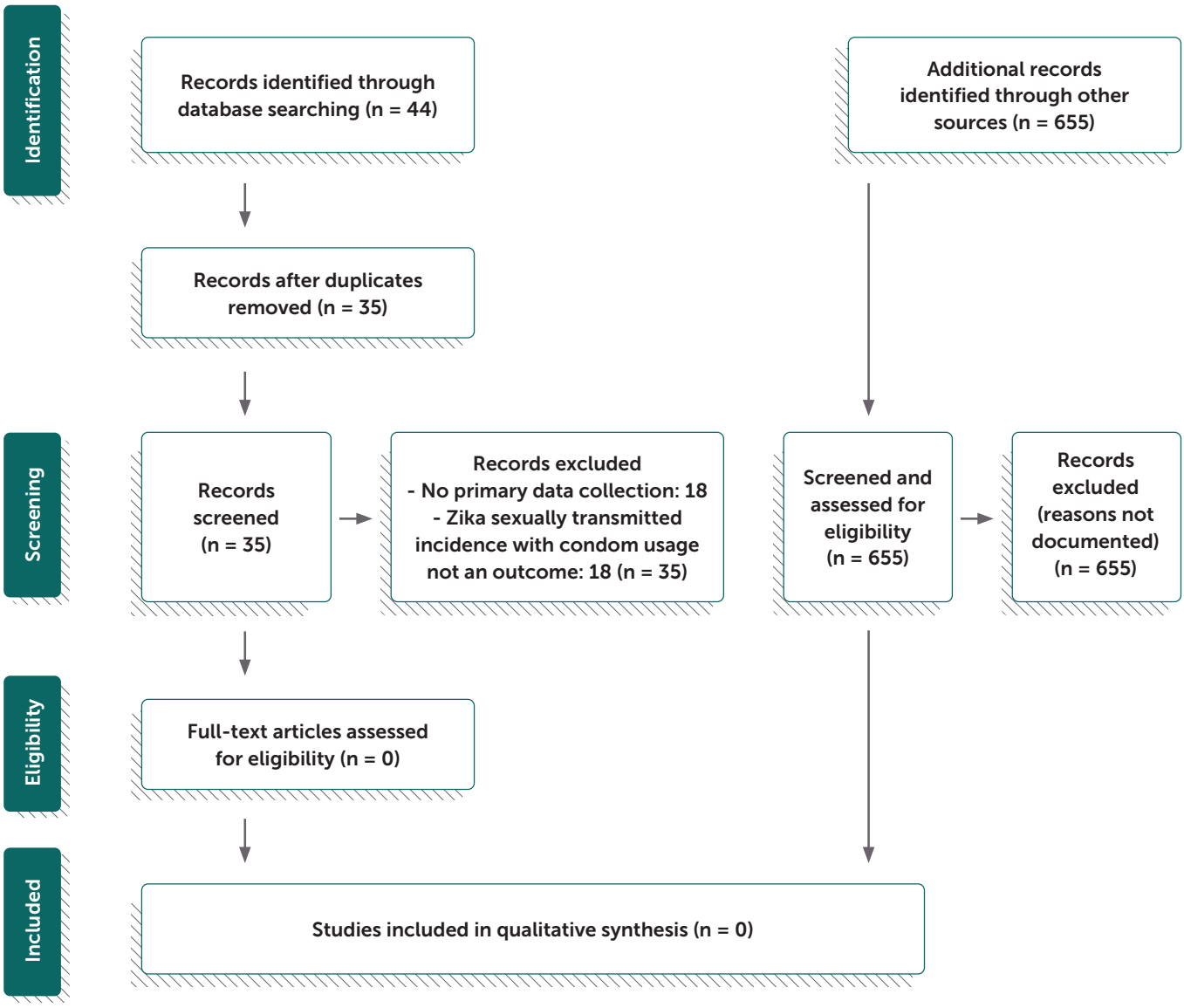
2.1 Direct evidence on the efficacy of condoms to prevent sexual transmission of Zika virus

We did not identify any direct evidence that assessed the condom effectiveness on the prevention of sexual transmission of Zika virus. None of 35 unique publications in Embase and PubMed met the eligibility criteria. None of 655 records on the websites of CDC, ECDC, PAHO and WHO met the eligibility criteria. See PRISMA flowchart in Fig. 1.

2.2 Indirect evidence, physical properties of condoms

- We extracted data about condom leakage from 13 in vitro studies with condoms: 11 about male condoms published

Fig. 1 PRISMA flowchart for direct evidence about the efficacy of condoms to prevent sexual transmission of Zika virus



Source: adapted from *(27)*.

from 1984 to 1994, one about female condoms published in 1990 *(28)*, and one about both male and female condoms in 2009 *(5)* (Fig. 2). We also included one in vitro study with latex and nitrile gloves *(29)*, two reviews *(30, 31)*, and one mathematical modelling study *(32)*.

- Leakage of condoms was tested using viral particles or proxies for viruses suspended in fluids. Five studies used the 27 nm bacteriophage ϕX174 for testing leakage *(3, 5, 21, 22)*, five used HIV (140 nm) *(19, 28, 33–35)*, four used herpes simplex virus (HSV1 and HSV2, 150–200 nm) *(1, 35, 36)*. Single studies used cytomegalovirus (CMV, 150–200 nm), hepatitis B virus (HBV, 42 nm), polystyrene microspheres (PMS, 110 nm), poliovirus type 1 (PV1, 27 nm), the 100 nm bacteriophage T7 and a type of murine retrovirus with unknown size (xenophobic type C mouse retrovirus, XTCMR).

The proportion of condoms that leaked varied between studies. In two of six studies that used particles smaller than Zika virus, none of the condoms leaked but sample sizes were small; poliovirus, 0/70 and 0/28 *(37)*; and HBV, 0/15 *(1)*. The largest study (n=546) found leakage in 3% (95% CI: 2–5) *(3)*. Proportions of leaking condoms were highest in the study by Voeller et al., but condoms in this study were five years old *(22)*.

Risk of bias assessment

We assessed a high risk of bias for lacking power size considerations (all included studies), manually performed experiments *(1, 19, 28, 33–37)*, lack of reporting detail *(19, 33, 39)*, old condoms *(22)*, or lack of control experiments *(1, 19, 33)*.

2.3 Indirect evidence, minimal infectious dose of Zika virus

See PRISMA flowchart (Fig. 3).

- We identified 16 unique publications in a search for studies about the minimal infectious dose of Zika virus in bodily fluids relevant to sexual transmission, but none provided any data.

- We identified 23 unique publications in a search for studies about the minimal infectious dose for sexual transmission of other viruses in humans. We included 13 after screening titles and abstracts but retained none after full text assessments. All studies were animal experiments.

- We included nine publications identified in the systematic review for review question 1 (Annex B1), which reported on the intravaginal or intrarectal dose of Zika virus in animal models. Seven studies used mouse models *(40–46)* and two used non-human primate models *(47, 48)*. All six studies that assessed Zika virus infection through intravaginal inoculation in mice used hormone treatment to induce diestrus *(40–42, 44, 45, 47)*. In non-human primates, a dose of log 4 to log 6 plaque forming units (PFU) *(47)* and log 7 PFU *(48)* led to successful intravaginal inoculation. The smallest dosages used to successfully infect immunodeficient diestrus mice were 1000 PFU *(43)* and 750 PFU *(45)*.

Risk of bias assessment

Reporting in all studies *(1, 19, 33–36)* was too poor to allow an assessment of the risk of bias using the SYRCLE tool.

2.4 Indirect evidence, condom effectiveness for prevention of non-Zika viral STIs

- We included five studies, all of which reported on the effectiveness of condoms to prevent HIV infection in "always" or "consistent" condom users compared with "never" users; one study pooled data from two cohort studies *(49)*, three conducted a meta-analysis *(15, 16, 50)*, and one narrative review *(51)*.

- In MSM serodiscordant couples, Smith et al. reported on prevention of HIV transmission among MSM, pooling data from two cohort studies based on participants in RCTs *(49)*. Condom effectiveness was 70.5% (95% CI: 58.2–79.2). A WHO meta-analysis estimated condom effectiveness against the sexual transmission of HIV in MSM at 64% (95% CI: 33–80, 5 studies, I^2 0%) *(50)*.

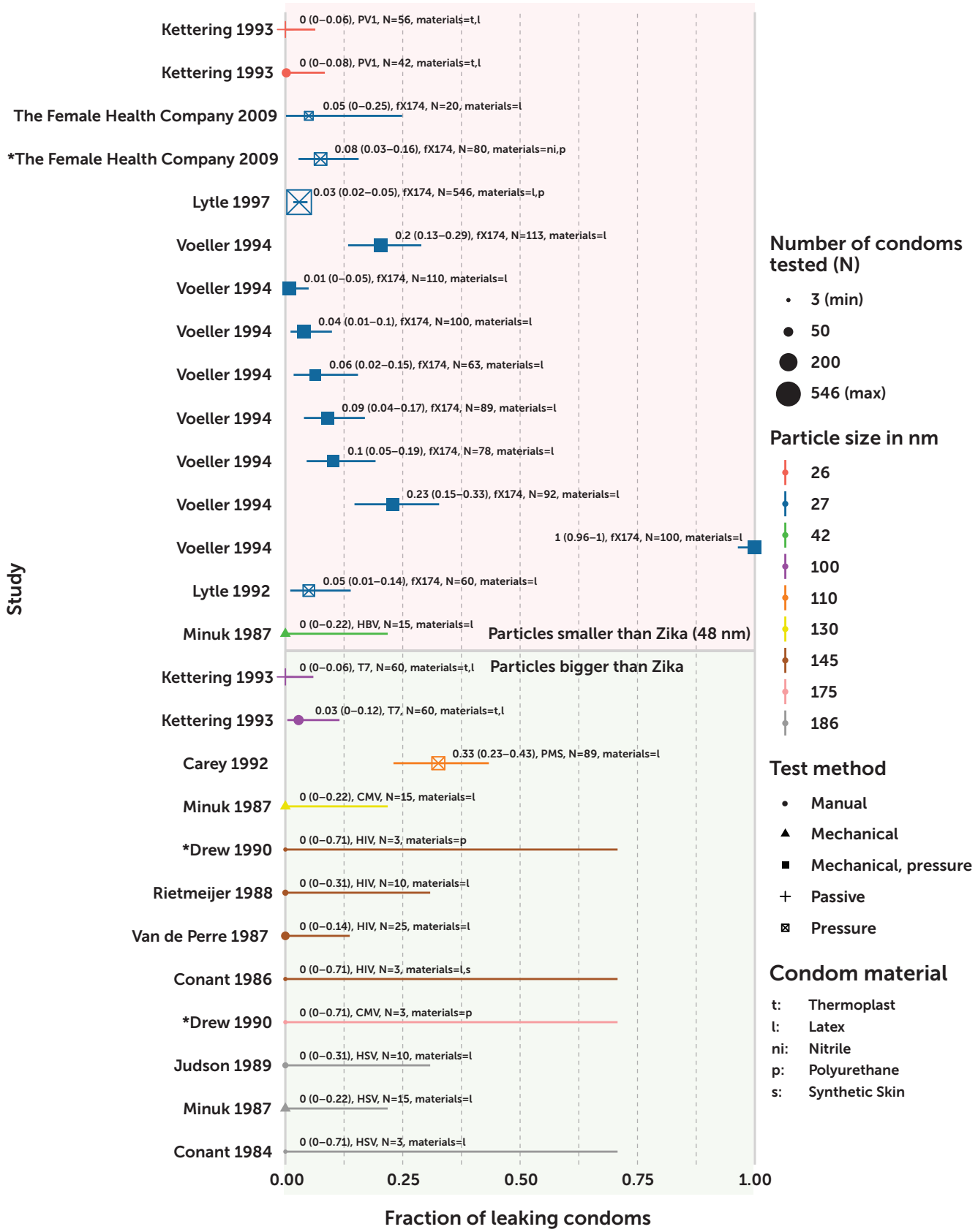
- In heterosexual serodiscordant couples: Giannou et al. estimated the effectiveness of male condoms at 71% (95% CI: 63–80, 17 studies, I^2 39%)*(16)*. Weller et al. estimated the effectiveness of male condoms at 80.2% (95% CI: 56.3–91.0). Three of five cohorts used to calculate the incidence among "never" condom users were also included in the calculation by Giannou et al. *(16)*. These estimates aggregate condom effectiveness over both vaginal and anal sex.

- Holmes et al. concluded in a narrative review that condoms are effective in protecting against HIV transmission *(51)*.

Risk of bias assessment

Using the ROBIS tool *(23)*, all systematic reviews were at high risk of bias because none assessed the risk of bias in individual studies. The study by Smith et al. *(49)* was limited by the representativeness of the study population, as it pooled data of RCT for an HIV vaccine and an HIV-behavioural intervention.

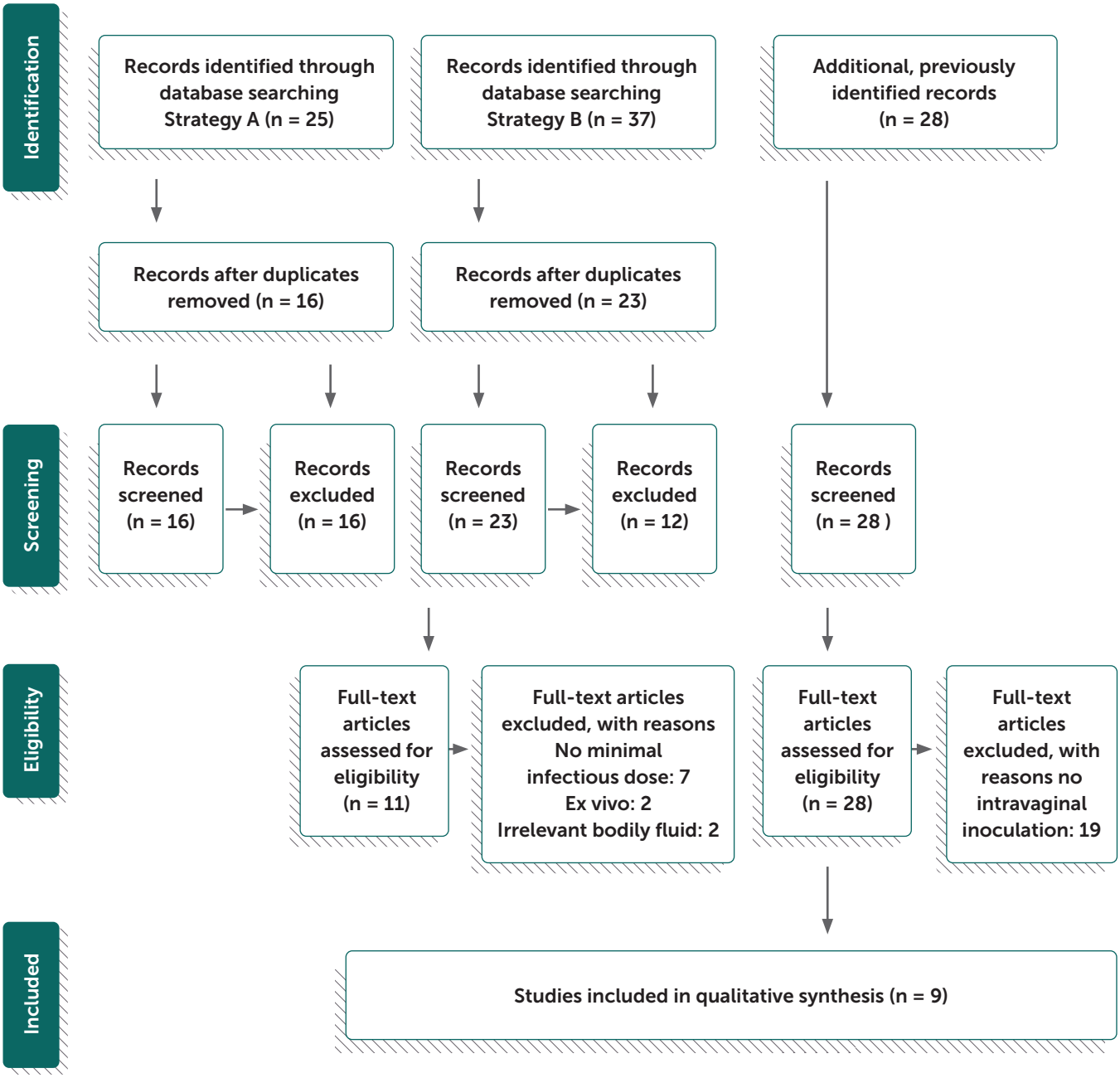
Fig. 2 Fraction of leaking condoms, stratified by particle size, and sorted from lowest to highest



Text at the top right position indicates the fraction of leaking condoms followed by Clopper–Pearson CIs *(38)*, the particle assessed, the number of condoms (**N**) tested, and the materials of the tested condoms. We report results stratified by brand for

Voeller et al. *(22)* because the fraction of leaking condoms showed large heterogeneity between brands. * Indicates leakage results of female condoms. All other results refer to male condoms. We excluded results from tests with spermicide-treated condoms. Abbreviations used: bacteriophage T7 (T7), bacteriophage ϕX174 (ϕX174), cytomegalovirus (CMV), herpes simplex type 2 (HSV2), HIV, hepatitis B virus (HBV), herpes simplex (HSV, type 1 and 2), polystyrene microspheres (PMS), poliovirus type 1 (PV1). We calculated confidence intervals for the leakage studies using Clopper–Pearson's exact method with the R package PropCIs *(38)*.

Fig. 3 PRISMA flow chart for indirect evidence, minimal infectious dose of Zika virus



Search strategy A was on Zika virus in bodily fluids, and search strategy B on other viruses in bodily fluids relevant to sexual transmission.

Source: adapted from *(27)*.

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Annex B3. GRADE evidence profiles

Table 1. GRADE evidence profile for outcomes in key question (1): What is known about the risks of sexual transmission of Zika virus?

Certainty assessment							Value	Certainty
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
1. Susceptibility								
	observational studies/ in vitro studies	not serious	not serious	serious	NA	not quantifiable	NA	NA
2. Incubation period following sexual transmission								
NA	NA	NA	NA	NA	NA	NA	NA	NA
3. Serial interval								
14	case reports/case series	serious	not serious	not serious	not serious	small sample size	12 days (IQR: 10–14.5)	●○○○ VERY LOW
4.1.a Duration of infectiousness: Male genital tract, RT-PCR (cohort studies)								
2	cohort study	not serious	not serious	serious	not serious	none	median: 34 days (95% CI: 28–41) – 35 days	●●○○ LOW
4.1.b Duration of infectiousness: Male genital tract, RT-PCR (case reports/case series)								
37	case reports/case series	serious	not serious	serious	not serious	reporting bias	median: 39.6 days (95% CI: 29.9–49.0)	●○○○ VERY LOW

Certainty assessment							Value	Certainty
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
4.2. Duration of infectiousness: Male genital tract, viral culture								
9	case reports/case series	serious	not serious	serious	not serious	small sample size	median: 11.6 days (95% CI: 1.1–20.9)	●○○○ VERY LOW
4.3. Duration of infectiousness: Female genital tract, RT-PCR								
7	case reports/case series	serious	not serious	serious	not serious	small sample size	median: 13.9 days (95% CI: 7.2–19.6)	●○○○ VERY LOW
4.4. Duration of infectiousness: Saliva, RT-PCR								
22	case reports/case series	serious	not serious	serious	not serious	small sample size	median: 6.8 days (95% CI: 4.3–9.6)	●○○○ VERY LOW
5. Reproduction number due to sexual transmission								
2	mathematical models	not serious	not serious	serious	serious	none	<1	●○○○ VERY LOW
6. Probability of transmission per sex act								
1	mathematical model	not serious	not serious	not serious	not serious	traveller population	1.6% (95% CI: 1.1–2.4)	●●○○ LOW
7. Transmission rate								
NA	NA	NA	NA	NA	NA	NA	NA	NA
8. Proportion of cases due to sexual transmission								
2	mathematical models	not serious	not serious	serious	serious	none	3.044% (95% CI: 0.123–45.73); 23% (95% CI: 1–47)	●○○○ VERY LOW

Table 2. GRADE evidence profile for outcomes in key question (2): Does consistent and correct condom use reduce transmission of Zika virus?

Certainty assessment							Value	Certainty
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
2.1 Physical properties of condoms: Leakage								
18	laboratory studies, reviews of laboratory studies, mathematical modelling study	not serious	serious	not serious	serious	heterogeneous methodology, old studies	Only a minority of condoms leak virus, substantial reduction of semen exposure even in case of breakage. Risk of leakage through non-detectable holes with very small diameters is low.	●○○○ VERY LOW
2.2 Minimal infectious amount								
9	in vivo studies	not serious	not serious	serious	serious	no direct evidence available	Only inoculation doses from animal studies. No evidence about Zika virus or other sexually transmitted viral diseases in humans.	●○○○ VERY LOW

Certainty assessment							Value	Certainty
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
2.3 Condom effectiveness for HIV								
6	systematic reviews	not serious	not serious	not serious	not serious	none	Between 71% (95% CI: 57–80, I^2: 39%) and 80.2% (95% CI: 56.3–91.0) in heterosexual couples. Between 64% (95% CI: 33–80, I^2: 0%) and 70.5% (95% CI: 58.2–79.2) in MSM.	●●●○ MODERATE
3. Effectiveness of condoms on the prevention of sexual transmission of Zika virus								
NA	combing the evidence from 2.1–2.3	not serious	not serious	serious	serious	no direct evidence available	"Comparable to the effectiveness of condoms in the prevention of HIV."	●○○○ VERY LOW

"Condom" refers to both male and female condoms, except for 2.3, which refers to evidence on male condoms.

Annex B4. Evidence-to-decision (EtD) frameworks

1. Areas with ongoing transmission

We present the information in the EtD framework using the guidance in a BMJ paper published by the GRADE Working Group: Alonso-Coello et al. (https://dx.doi.org/10.1136/bmj.i2016 and appendices, listed under "Related content" on the BMJ website) *(1)*.

Question
Key question (3): When and for how long does one need to use a condom to prevent the sexual transmission of Zika virus? **Subgroup:** People in areas with ongoing transmission of Zika virus.

Question details	
Patients	People in areas with ongoing transmission of Zika virus Subgroups: - Men and women - Men and women who have sex that could result in conception - Pregnant women
Option	Use of male or female condoms
Comparison	No condom use
Main outcomes	Sexual transmission of Zika virus
Setting	Area with ongoing Zika virus transmission
Perspective	Clinical recommendation – population perspective
Conflict of interests	[To be completed]
Background	Zika virus has been confirmed to be sexually transmissible. New evidence about the duration of persistent detection of Zika virus by culture or viral RNA in the male and female genital tract make it opportune to update the previous interim guidelines on the prevention of sexual transmission of Zika virus.

Priority

Is the problem a priority?

☐ Don't know ☒ Varies ☐ No ☐ Probably No ☐ Probably Yes ☐ Yes

Evidence

The probability of male to female transmission per sex act is probably low (1.6%, 95% CI: 1.1–2.4, Annex B3, Table 1).

According to modelling studies, the proportion of cases due to sexual transmission is probably low in areas with ongoing transmission (3.044%, 95% CI: 0.123–45.73, 23% 95% CI: 1–47, Annex B3, Table 1).

Additional considerations

Maternal Zika virus infection has been identified as a cause of congenital disorders such as microcephaly, and of GBS in adults.

The urgency and recognition of priority to update guidance on the prevention of the sexual transmission of Zika virus depends on the current global and regional incidence of Zika virus transmissions.

Benefits and harms

How substantial are the desirable effects?

☐ Don't know ☐ Varies ☐ Trivial ☐ Small ☒ Moderate ☐ Large

The evidence presented here shows the expected protection afforded by condom use for the recommended period following exposure/infection (3 months for men, 2 months for women).

Evidence

Median serial interval is 12 days (IQR: 10–14.5) *(2)*.

Aggregated case reports and case series *(2)*:

- 13.6% (95% CI: 7.2–21.1) of men were RT-PCR positive for Zika viral RNA in semen 90 days after symptom onset
- 1.2% (95% CI: 0–81) of men had culturable virus in semen 90 days after symptom onset
- 0% (95% CI: 0–0.2) of women were RT-PCR positive for Zika viral RNA in the female genital tract 60 days after symptom onset.

Cohort studies:

- Mead et al. *(3)*: 17% of men were estimated to have Zika viral RNA in semen 90 days after symptom onset
- Paz-Bailey et al. *(4)*: 9% (95% CI: 3–20) of men were estimated to have Zika viral RNA in semen 90 days after symptom onset.

The incubation period for sexual transmission of Zika virus is unknown; the incubation period for mosquito-borne transmission of Zika virus is 3–14 days *(5)*.

The condom effectiveness to prevent sexual transmission of Zika virus is comparable to condom effectiveness against HIV transmission (Annex B3, Tables 1 and 2).

Additional considerations

In areas with ongoing transmission the majority of the transmission is mosquito-borne.

How substantial are the undesirable effects?

☐ Don't know ☐ Varies ☐ Trivial ☒ Small ☐ Moderate ☐ Large

Evidence

No evidence included.

Additional considerations

For some people, using condoms correctly and consistently or being abstinent for prolonged periods may be difficult.

Certainty of the evidence

What is the overall certainty of the evidence of effects?

☐ No included studies ☒ Very low ☐ Low ☐ Moderate ☐ High

Evidence
Very low to low (Annex B3, Tables 1 and 2).

Additional considerations
None

Outcome importance

Is there important uncertainty about or variability in how much people value the main outcomes?

☒ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ☐ No important uncertainty or variability

Evidence
No evidence included.

Additional considerations
It depends on how well informed people are about the sexual transmission of Zika virus. If people are well informed, there may be less variability.
Subgroups of pregnant women and couples planning to conceive likely value outcome more highly than other subgroups.
In an outbreak situation, people may value the outcome more highly.

Balance

Does the balance between desirable and undesirable effects favour the option or the comparison?

☐ Don't know ☐ Varies ☐ Favours the comparison ☐ Probably favours the comparison
☐ Does not favour either the option or the comparison ☒ Probably favours the option ☐ Favours the option

Evidence
No evidence included.

Additional considerations
Owing to the likely small proportion of cases due to sexual transmission, positive effects of condom use or abstinence may be small, except for the subgroup of pregnant women.

Resource use

How large are the resource requirements (costs)?

☐ Don't know ☐ Varies ☐ Large costs ☒ Moderate costs
☐ Negligible costs or savings ☐ Moderate savings ☐ Large savings

Evidence
No evidence included.

Additional considerations
Highest cost may be programme costs and implementation costs, including personnel. Possibility of synergies with existing programmes.
Higher costs than in areas without ongoing transmission.
Other requirements might include the cost of condom procurement, promotion and distribution activities.

What is the certainty of the evidence of resource requirements (costs)?

☒ No included studies ☐ Very low ☐ Low ☐ Moderate ☐ High

Evidence

Additional considerations

Does the cost effectiveness of the intervention favour the intervention or the comparison?

☒ Don't know ☐ Varies ☐ Favours the comparison ☐ Probably favours the comparison
☐ Does not favour either the option or the comparison ☐ Probably favours the option ☐ Favours the option

Evidence
No evidence included.

Additional considerations
Life-term costs of congenital birth disorders such as microcephaly could be very high (care and productivity loss).

Equity

What would be the impact on health equity?

☐ Don't know ☒ Varies ☐ Reduced ☐ Probably reduced
☐ Probably no impact ☐ Probably increased ☐ Increased

Evidence
No evidence included.

Additional considerations
One month difference in duration of recommended condom-use or abstinence between men and women is not major.
Health equity reductions due to differences in the availability, accessibility and affordability of male and female condoms and information on their use.

Acceptability

Is the intervention acceptable to key stakeholders?

☐ Don't know ☒ Varies ☐ No ☐ Probably No ☐ Probably Yes ☐ Yes

Evidence
No evidence included.

Additional considerations
Condoms are already used for the prevention of conception and other STIs. Acceptability in affected people possibly challenging with low compliance and condoms may be perceived as a burden. Shorter durations may be more acceptable. Needs to be accompanied by strong messaging support.

Feasibility

Is the intervention feasible to implement?

☐ Don't know ☐ Varies ☐ No ☐ Probably No ☒ Probably Yes ☐ Yes

Evidence
No evidence included.

Additional considerations
Production, distribution and availability of condoms already established. Challenges related to acceptability, compliance and implementation may arise with patients, healthcare workers and programme managers. Possibility to link with existing programmes.

Justification

The prevention of sexual transmission of Zika virus has moderate benefits in general, but the benefits in the subgroups of pregnant women and women who have sex that could result in conception are higher. This is because Zika virus infection in pregnant women can cause adverse pregnancy outcomes and congenital disorders in fetuses.

Therefore, the GDG concluded that people living in areas with ongoing transmission should consider prevention of the sexual transmission of Zika virus by using condoms or abstinence for 3 months for men and 2 months for women after known or presumptive infection, despite low to very low certainty of evidence. Pregnant women should use condoms or abstain from sex for the duration of pregnancy, in addition to following precautions for prevention of mosquito-borne infections. The GDG decided to formulate a conditional recommendation for condom use or abstinence, given the low contribution of sexual transmission to the total transmission in areas with ongoing transmission. For the subgroup of pregnant women and women or couples who are having sex that could result in conception, the GDG decided to formulate a strong recommendation for condom use or abstinence, given the potentially severe outcomes of congenital Zika virus infection.

Subgroup considerations

Pregnant women, as well as couples wanting to conceive and women who have sex that could result in conception, are likely to value the outcome of the prevention of sexual transmission of Zika virus more highly than other men and women. Similarly, the balance of positive effects is likely to be higher for these subgroups, and acceptability of condom use or abstinence may be higher. On the other hand, the burden of condom use may be higher for people who are planning to conceive.

Implementation considerations

To increase acceptability of condom use, the recommendations should be accompanied by strong messaging support.

2. Areas without ongoing transmission

We present the information in the EtdD framework using the guidance in a BMJ paper published by the GRADE Working Group: Alonso-Coello et al. (https://dx.doi.org/10.1136/bmj.i2016 and appendices, listed under "Related content" on the BMJ website) *(1)*.

Question

Key question (3): When and for how long does one need to use a condom to prevent the sexual transmission of Zika virus?
Subgroup: People in areas without ongoing transmission of Zika virus.

Question details

Patients	People in areas without ongoing transmission of Zika virus, who return from areas with ongoing transmission or are exposed through sexual contact Subgroups: - Men and women - Men and women who have sex that could result in conception - Pregnant women
Option	Use of male or female condoms
Comparison	No condom use
Main outcomes	Sexual transmission of Zika virus
Setting	Area without ongoing Zika virus transmission
Perspective	Clinical recommendation – population perspective
Conflict of interests	[To be completed]
Background	Zika virus has been confirmed to be sexually transmissible. New evidence about the duration of persistent detection of Zika virus, by culture or viral RNA in the male and female genital tract, make it opportune to update the previous interim guidelines on the prevention of sexual transmission of Zika virus.

Priority

Is the problem a priority?

☐ Don't know ☐ Varies ☐ No ☒ Probably No ☐ Probably Yes ☐ Yes

Evidence
The probability of male to female transmission per sex act is probably low (1.6%, 95% CI: 1.1–2.4, Annex B3, Table 1).

Additional considerations
Maternal Zika virus infection has been identified as a cause of congenital disorders such as microcephaly, and of Guillain-Barré syndrome in adults.
Current guidelines recommending longer durations of condom use could result in non-adherence to advice about condom use.
The urgency and recognition of the priority to update guidance on the prevention of the sexual transmission of Zika virus depends on the current global and regional incidence of Zika virus transmissions.

Benefits and harms

How substantial are the desirable effects?

☐ Don't know ☐ Varies ☐ Trivial ☐ Small ☒ Moderate ☐ Large

The evidence presented here shows the expected protection afforded by condom use for the recommended period following exposure/infection (3 months for men, 2 months for women).

Evidence

Median serial interval is 12 days (IQR: 10–14.5) *(2)*.

Aggregated case reports and case series *(2)* (S3 Text):

- 13.6% (95% CI: 7.2–21.1) of men were RT-PCR positive for Zika viral RNA in semen 90 days after symptom onset
- 1.2% (95% CI: 0–81) of men had culturable virus in semen 90 days after symptom onset
- 0% (95% CI: 0–0.2) of women were RT-PCR positive for Zika viral RNA in the female genital tract 60 days after symptom onset.

Cohort studies:

- Mead et al. *(3)*: 17% of men were estimated to have Zika viral RNA in semen 90 days after symptom onset
- Paz-Bailey et al. *(4)*: 9% (95% CI: 3–20) of men were estimated to have Zika viral RNA in semen 90 days after symptom onset.

The incubation period for sexual transmission of Zika virus is unknown; the incubation period for mosquito-borne transmission of Zika virus is 3–14 days *(5)*.

The effectiveness of condoms for the prevention of sexual transmission of Zika virus is comparable to condom effectiveness against HIV transmission (Annex B3, Table 1 and 2).

Additional considerations

Reduction in the burden of condom use due to shorter duration compared to previous guidelines might increase adherence and acceptability.

How substantial are the undesirable effects?

☐ Don't know ☐ Varies ☐ Trivial ☒ Small ☐ Moderate ☐ Large

Evidence

No evidence included.

Additional considerations

For some people, using condoms correctly and consistently or being abstinent for prolonged periods may be difficult.

Certainty of the evidence

What is the overall certainty of the evidence of effects?

☐ No included studies ☒ Very low ☒ Low ☐ Moderate ☐ High

Evidence

Very low to low (Annex B3, Tables 1 and 2).

Additional considerations

None

Outcome importance

Is there important uncertainty about or variability in how much people value the main outcomes?

- ☒ Important uncertainty or variability
- ☐ Possibly important uncertainty or variability
- ☐ Probably no important uncertainty or variability
- ☐ No important uncertainty or variability

Evidence
No evidence included.

Additional considerations
Depends on how well informed people are about the sexual transmission of Zika virus. If people are well informed, there may be less variability.
Subgroup of pregnant women and couples planning to conceive likely value outcome more highly than other subgroups.
The burden of condom use may be larger for couples planning to conceive where one partner frequently stays in areas with ongoing transmission, and returns for periods shorter than the recommended duration of condom use or abstinence.

Balance

Does the balance between desirable and undesirable effects favour the option or the comparison?

- ☐ Don't know
- ☐ Varies
- ☐ Favours the comparison
- ☐ Probably favours the comparison
- ☐ Does not favour either the option or the comparison
- ☐ Probably favours the option
- ☒ Favours the option

Evidence
No evidence included.

Additional considerations
Short duration of condom use or abstinence compared to possible severe consequences in pregnant women.

Resource use

How large are the resource requirements (costs)?

- ☐ Don't know
- ☐ Varies
- ☐ Large costs
- ☐ Moderate costs
- ☒ Negligible costs or savings
- ☐ Moderate savings
- ☐ Large savings

Evidence
No evidence included.

Additional considerations
Compared with interim recommendations, the balance is in favour of a reduced period of condom use.
Resource requirements include costs of condoms. Highest cost may be programme costs and implementation costs, including personnel. Possibility of synergies with existing programmes.
Other requirements might include the cost of condom procurement, promotion and distribution activities.

What is the certainty of the evidence of resource requirements (costs)?

- ☒ No included studies
- ☐ Very low
- ☐ Low
- ☐ Moderate
- ☐ High

Evidence

Additional considerations

Resource use (cont.)

Does the cost effectiveness of the intervention favour the intervention or the comparison?

☐ Don't know ☐ Varies ☐ Favours the comparison ☐ Probably favours the comparison
☐ Does not favour either the option or the comparison ☒ Probably favours the option ☐ Favours the option

Evidence
No evidence included.

Additional considerations
Life-term costs of congenital birth disorders, such as microcephaly, could be very high (care and productivity loss).

Equity

What would be the impact on health equity?

☐ Don't know ☐ Varies ☐ Reduced ☐ Probably reduced
☒ Probably no impact ☐ Probably increased ☐ Increased

Evidence
No evidence included.

Additional considerations
A 1 month difference in duration of recommended condom use between men and women is small. Health equity reductions due to differences in the availability, accessibility and affordability of male and female condoms and information on their use.

Acceptability

Is the intervention acceptable to key stakeholders?

☐ Don't know ☒ Varies ☐ No ☐ Probably No ☐ Probably Yes ☐ Yes

Evidence
No evidence included.

Additional considerations
Condoms already used for the prevention of conception and other STIs. Acceptability in affected people possibly challenging with low compliance, as condoms may be perceived as a burden. Shorter durations may be more acceptable. Needs to be accompanied by strong messaging support.

Feasibility

Is the intervention feasible to implement?

☐ Don't know ☐ Varies ☐ No ☐ Probably No ☒ Probably Yes ☐ Yes

Evidence
No evidence included.

Additional considerations
Production, distribution and availability of condoms already established. Challenges related to acceptability, compliance and implementation may arise with patients, healthcare workers and programme managers. Possibility to link with existing programmes.

Justification

The prevention of sexual transmission of Zika virus has moderate benefits in general, but the benefits in the subgroups of pregnant women and women who have sex that could result in conception are higher. This is because Zika virus infection in pregnant women can cause adverse pregnancy outcomes and congenital disorders in fetuses.

Therefore, the GDG concluded that the sexual transmission of Zika virus, by travellers returning from areas with ongoing Zika virus transmission, should be prevented by recommending the use of condoms or abstinence during 3 months for men and 2 months for women, despite low to very low certainty of evidence. Pregnant women should use condoms or abstain from sex for the duration of pregnancy. The GDG decided to formulate a strong recommendation for condom use or abstinence, as sexual transmission is the main risk for infection in areas without ongoing transmission. For the subgroup of pregnant women and women or couples who are having sex that could result in conception, the GDG decided to formulate a strong recommendation for condom use or abstinence, given the potentially severe outcomes of congenital Zika virus infection.

Subgroup considerations

Pregnant women, as well as couples wanting to conceive and women who have sex that could result in conception, are likely to value the outcome of prevention of sexual transmission of Zika virus more highly than other men and women. Similarly, the balance of positive effects is likely to be higher for these subgroups, and acceptability of condom use or abstinence may be higher. On the other hand, the burden of condom use may be higher for people who are planning to conceive, especially for people who frequently stay overseas.

Implementation considerations

Public health authorities should implement these recommendations for travellers.

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Annex C. List of references for reviewed evidence in key questions (1) and (2)

1. Key question (1): Included studies describing sexual transmission in couples

Author (year) *(ref.)* study design	Transmission	Persistence*
Turmel (2016) *(1)* case report	Male–female sexual transmission in 1 couple Country of residence: France; returning traveller from: Martinique Serial interval: 44 days	Semen (RT-PCR) measurements available in 1 patient
Duijster (2017) *(2)* case report	Male–female sexual transmission in 1 couple Country of residence: Netherlands; returning traveller from: Unknown Serial interval: 23 days	Semen (RT-PCR) measurements available in 1 patient
Venturi (2016) *(3)* case report	Male–female sexual transmission in 1 couple Country of residence: Italy; returning traveller from: Thailand Serial interval: 19 days	No persistence measured
Russell (2017) *(4)* case series	Male–female sexual transmission in 9 couples Country of residence: United States; returning traveller from: Multiple countries (Colombia, Costa Rica, El Salvador, Haiti, Puerto Rico, and Suriname) Serial interval: 14, 10, 10, 18, 12, 16, 17, 19, 16 days	Semen (RT-PCR) measurements available in 2 patients
Desclaux (2018) *(5)* case report	Male–female sexual transmission in 1 couple Country of residence: France; returning traveller from: Martinique Serial interval: 15 days	Semen (RT-PCR) measurements available in 1 patient
Hills (2016) *(6)* case series	Male–female sexual transmission in 3 couples Country of residence: United States; returning traveller from: Unknown Serial interval: 14-15, 10, 10 days	No persistence measured

Author (year) *(ref.)* study design	Transmission	Persistence*
Grossi (2018) *(7)* case report	Male–female sexual transmission in 1 couple Country of residence: Italy; returning traveller from: Dominican Republic Serial interval: 14 days	Saliva (RT-PCR) measurements available in 2 patients Semen (RT-PCR) measurements available in 1 patient
D'Ortenzio (2016) *(8)* case report	Male–female sexual transmission in 1 couple Country of residence: France; returning traveller from: Brazil Serial interval: 13 days	Saliva (RT-PCR) measurements available in 2 patients Semen (RT-PCR) measurements available in 1 patient Semen (culture) measurements available in 1 patient
Frank (2016) *(9)* case report	Male–female sexual transmission in 1 couple Country of residence: Germany; returning traveller from: Puerto Rico Serial interval: 12 days	Saliva (RT-PCR) measurements available in 2 patients Semen (RT-PCR) measurements available in 1 patient
Arsuaga (2016) *(10)* case report	Male–female sexual transmission in 1 couple Country of residence: Spain; returning traveller from: Maldives Serial interval: 12 days	Semen (RT-PCR) measurements available in 1 patient Semen (culture) measurements available in 1 patient
Harrower (2016) *(11)* case report	Male–female sexual transmission in 1 couple Country of residence: New Zealand; returning traveller from: Samoa Serial interval: 10 days	Semen (RT-PCR) measurements available in 1 patient
Deckard (2016) *(12)* case report	Male–male sexual transmission in 1 couple Country of residence: United States; returning traveller from: Venezuela Serial interval: 7 days	Saliva (RT-PCR) measurements available in 2 patients Semen (RT-PCR) measurements available in 1 patient
Davidson (2016) *(13)* case report	Female–male sexual transmission in 1 couple Country of residence: United States; returning traveller from: Unknown Serial interval: 6 days	No persistence measured
Foy (2011) *(14)* case report	Male–female sexual transmission in 1 couple Country of residence: United States; returning traveller from: Senegal Serial interval: 4 days	No persistence measured
Armstrong (2016) *(15)* case series	Male–female sexual transmission in 2 couples Country of residence: United States; returning traveller from: Unknown Serial interval: NA	No persistence measured
Brooks (2016) *(16)* case report	Male–female sexual transmission in 1 couple Country of residence: United States; returning traveller from: Dominican Republic Serial interval: NA	Semen (RT-PCR) measurements available in 1 patient

Author (year) *(ref.)* study design	Transmission	Persistence*
Freour (2016) *(17)* case report	Male–female sexual transmission in 1 couple Country of residence: France; returning traveller from: Martinique Serial interval: NA	Semen (RT-PCR) measurements available in 1 patient
Gulland (2016) *(18)* case report	Male–female sexual transmission in 1 couple Country of residence: United Kingdom; returning traveller from: Unknown Serial interval: NA	No persistence measured
World Health Organization (2016) *(19)* case report	Male–female sexual transmission in 1 couple Country of residence: Chile; returning traveller from: Unknown Serial interval: NA	No persistence measured
World Health Organization (2016) *(20)* case report	Male–female sexual transmission in 1 couple Country of residence: Peru; returning traveller from: Unknown Serial interval: NA	No persistence measured
World Health Organization (2016) *(21)* case report	Male–female sexual transmission in 1 couple Country of residence: Portugal; returning traveller from: Brazil Serial interval: NA	No persistence measured
World Health Organization (2016) *(22)* case series	Male–female sexual transmission in 2 couples Country of residence: France; returning traveller from: Brazil Country of residence: Argentina; returning traveller from: Colombia Serial interval: NA	No persistence measured
Boggild (2017) *(23)* case report	Male–female sexual transmission in 1 couple Country of residence: Canada; returning traveller from: Unknown Serial interval: NA	No persistence measured
Borrego (2017) *(24)* case report	Male–female sexual transmission in 1 couple Country of residence: Spain; returning traveller from: Brazil Serial interval: NA	No persistence measured

*The detection of viral RNA or culturable virus on one or more timepoints.

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2. Key question (1): Included studies used for semen results and Weibull curves aggregated estimates

Author (year) *(ref.)* study design	Measurements
Hearn (2014) *(1)* case report	Semen (RT-PCR) measurements available in 1 patient
Mansuy (2016) *(2)* case report	Semen (RT-PCR) measurements available in 1 patient Semen (culture) measurements available in 1 patient
D'Ortenzio (2016) *(3)* case report	Saliva (RT-PCR) measurements available in 2 patients Semen (RT-PCR) measurements available in 1 patient Semen (culture) measurements available in 1 patient
Deckard (2016) *(4)* case report	Saliva (RT-PCR) measurements available in 2 patients Semen (RT-PCR) measurements available in 1 patient
Atkinson (2016) *(5)* case report	Semen (RT-PCR) measurements available in 1 patient Semen (culture) measurements available in 1 patient
Jang (2016) *(6)* case report	Saliva (RT-PCR) measurements available in 1 patient Semen (RT-PCR) measurements available in 1 patient Semen (culture) measurements available in 1 patient
Turmel (2016) *(7)* case report	Semen (RT-PCR) measurements available in 1 patient
Reusken (2016) *(8)* case report	Saliva (RT-PCR) measurements available in 1 patient Semen (RT-PCR) measurements available in 1 patient

Author (year) *(ref.)* study design	Measurements
Freour (2016) *(9)* case report	Semen (RT-PCR) measurements available in 1 patient
Frank (2016) *(10)* case report	Saliva (RT-PCR) measurements available in 2 patients Semen (RT-PCR) measurements available in 1 patient
Wu (2016) *(11)* case series	Saliva (RT-PCR) measurements available in 4 patients Semen (RT-PCR) measurements available in 1 patient
Huits (2016) *(12)* case series	Saliva (RT-PCR) measurements available in 1 patient Semen (RT-PCR) measurements available in 4 patients
Mansuy (2016) *(13)* case report	Semen (RT-PCR) measurements available in 1 patient
Nicastri (2016) *(14)* case report	Saliva (RT-PCR) measurements available in 1 patient Semen (RT-PCR) measurements available in 1 patient Semen (culture) measurements available in 1 patient
Barzon (2016) *(15)* case report	Saliva (RT-PCR) measurements available in 1 patient Semen (RT-PCR) measurements available in 1 patient
Brooks (2016) *(16)* case report	Semen (RT-PCR) measurements available in 1 patient
Torres (2016) *(17)* case series	Semen (RT-PCR) measurements available in 3 patients
Arsuaga (2016) *(18)* case report	Semen (RT-PCR) measurements available in 1 patient Semen (culture) measurements available in 1 patient
Mansuy (2016) *(19)* case report	Semen (RT-PCR) measurements available in 1 patient
Harrower (2016) *(20)* case report	Semen (RT-PCR) measurements available in 1 patient
Russell (2017) *(21)* case series	Semen (RT-PCR) measurements available in 2 patients
Oliveira Souto (2016) *(22)* case report	Semen (RT-PCR) measurements available in 1 patient Semen (culture) measurements available in 1 patient
Froeschl (2017) *(23)* case report	Saliva (RT-PCR) measurements available in 1 patient Semen (RT-PCR) measurements available in 1 patient Semen (culture) measurements available in 1 patient
Gaskell (2017) *(24)* case report	Semen (RT-PCR) measurements available in 1 patient
Paz-Bailey (2017) *(25)* cohort study	Semen (RT-PCR) measurements available in **55** patients **Outcome:** 150 women and men with symptomatic Zika virus infection in Puerto Rico. Zika virus was detected in semen by RT-PCR in 31/55 men, with a median duration of persistence of 34 days (95% CI: 28-41 days). Zika virus RNA was only detected in a few participants in saliva or vaginal fluids.

Author (year) *(ref.)* study design	Measurements
Atkinson (2017) *(26)* case series	Semen (RT-PCR) measurements available in 21 patients Semen (culture) measurements available in 11 patients
Percivalle (2017) *(27)* case report	Saliva (RT-PCR) measurements available in 1 patient Semen (RT-PCR) measurements available in 1 patient Semen (culture) measurements available in 1 patient
Duijster (2017) *(28)* case report	Semen (RT-PCR) measurements available in 1 patient
de Laval (2017) *(29)* case series	Semen (RT-PCR) measurements available in 12 patients
Joguet (2017) *(30)* case series	Semen (RT-PCR) measurements available in 15 patients
Grossi (2018) *(31)* case report	Saliva (RT-PCR) measurements available in 2 patients Semen (RT-PCR) measurements available in 1 patient
Garcia-Bujalance (2017) *(32)* case series	Semen (RT-PCR) measurements available in 4 patients Semen (culture) measurements available in 2 patients
Sanchez-Montalva (2018) *(33)* case series	Saliva (RT-PCR) measurements available in 7 patients Semen (RT-PCR) measurements available in 6 patients Female genital tract (RT-PCR) measurements available in 5 patients
Biava (2018) *(34)* case series	Semen (RT-PCR) measurements available in 2 patients
Barzon (2017) *(35)* case series	Saliva (RT-PCR) measurements available in 25 patients Semen (RT-PCR) measurements available in 9 patients
Cassuto (2018) *(36)* case report	Semen (RT-PCR) measurements available in 1 patient
Desclaux (2018) *(37)* case report	Semen (RT-PCR) measurements available in 1 patient
Mead (2018) *(38)* cohort study	Semen (RT-PCR) measurements available in **184** patients **Outcome:** 184 symptomatic Zika virus-infected men from the United States. Zika virus was detected in semen by RT-PCR in 60/184 men. The mean time to Zika virus RNA clearance was 54 days (95% CI: 53-55). The median duration was not reported, but plotted at approximately 35 days.
Studies not reporting on persistence in semen	
Barzon (2016) *(39)* case report	Saliva (RT-PCR) measurements available in 1 patient
Bonaldo (2016) *(40)* case series	Saliva (RT-PCR) measurements available in 5 patients
Jang (2016) *(6)* case report	Saliva (RT-PCR) measurements available in 1 patient Semen (RT-PCR) measurements available in 1 patient Semen (culture) measurements available in 1 patient

Author (year) *(ref.)* study design	Measurements
Prisant (2016) *(41)* case report	Female genital tract (RT-PCR) measurements available in 1 patient
Nicastri (2016) *(42)* case report	Saliva (RT-PCR) measurements available in 1 patient Female genital tract (RT-PCR) measurements available in 1 patient
Murray (2017) *(43)* case report	Saliva (RT-PCR) measurements available in 1 patient Female genital tract (RT-PCR) measurements available in 1 patient
Prisant (2017) *(44)* case series	Female genital tract (RT-PCR) measurements available in 5 patients
Froeschl (2017) *(23)* case report	Saliva (RT-PCR) measurements available in 1 patient Semen (RT-PCR) measurements available in 1 patient Semen (culture) measurements available in 1 patient
Visseaux (2016) *(45)* case report	Female genital tract (RT-PCR) measurements available in 1 patient
Suy (2016) *(46)* case report	Female genital tract (RT-PCR) measurements available in 1 patient
Fonseca (2014) *(47)* case report	Saliva (RT-PCR) measurements available in 1 patient
Iovine (2017) *(48)* case report	Saliva (RT-PCR) measurements available in 1 patient
Sun (2017) *(49)* case series	Saliva (RT-PCR) measurements available in 8 patients
Huits (2017) *(50)* case series	Semen (RT-PCR) measurements available in 15 patients
Jia (2018) *(51)* case series	Saliva (RT-PCR) measurements available in 7 patients

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3. Key question (2): Included studies for physical properties of condoms

Author (Year) *(ref.)* Study design	Characteristics methods	Characteristics included data/ tested units	Results
Conant (1984) *(1)* laboratory study	Method: Manual Particles: HSV2	3 male non-natural condoms 3 male natural condoms	
Conant (1986) *(2)* laboratory study	Method: Manual Particles: HIV, XTCMR	8 male non-natural condoms (2 excluded – spermicide treated) 2 male natural condoms	
Minuk (1987) *(3)* laboratory study	Method: Manual Particles: HPV, HSV, CMV	45 male non-natural condoms 9 male natural condoms	
Van de Perre (1987) *(4)* laboratory study	Method: Manual Particle: HIV	5 male non-natural condoms 1 male natural condom	
Rietmeijer (1988) *(5)* laboratory study	Method: Manual Particle: HIV	30 male non-natural condoms (20 excluded – spermicide treated)	
Judson (1989) *(6)* laboratory study	Method: Manual Particle: HIV, HSV2	70 male non-natural condoms (60 excluded – tested with *Chlamydia trachomatis*)	
Drew (1990) *(7)* laboratory study	Method: Manual Particles, CMV, HIV	6 female non-natural condoms	
Carey (1992) *(8)* laboratory study	Method: Pressure Particle: PMS	89 male non-natural condoms	(See Annex B2. Figure 2)
Lytle (1992) *(9)* laboratory study	Method: Pressure Particle: ϕX174	60 male non-natural condoms 19 male natural condoms	(See Annex B2. Figure 2)
Kettering (1993) *(10)* laboratory study	Method: Passive and Manual Particles: T1, PV1	116 male non-natural condoms (14 excluded – acidic effect)	(See Annex B2. Figure 2)
Voeller (1994) *(11)* laboratory study	Method: Mechanical and Pressure Particle: ϕX174	702 male non-natural condoms	(See Annex B2. Figure 2)
Lytle (1997) *(12)* laboratory study	Method: Pressure Particle: ϕX174	470 male non-natural condoms	(See Annex B2. Figure 2)

Author (Year) *(ref.)* Study design	Characteristics methods	Characteristics included data/ tested units	Results
The Female Health Company (2009) *(13)* laboratory study	Method: Pressure Particle: ϕX174	60 male non-natural condoms 40 female non-natural condoms	(See Annex B2. Figure 2)
Müller (2016) *(14)* Laboratory study	Method: Passive Particle: Zika virus	3 latex and nitrile glove fingertip	0 glove leaked
Carrey (1999) *(15)* Review	Review of condom laboratory studies	Results from Lytle 1997 *(12)* used to calculate leakage for different type of condom defects	Condoms without detectable holes: 1.3% leak ≥ 1e-6 ml 0.9% leak ≥ 1e-5 ml 0.2% leak ≥ 1e-4 ml
Lytle (1999) *(16)* Review	Review of condom laboratory studies	Several non-systematically identified studies	Detectable holes in condoms are more relevant than undetectable holes. Risk for HBV may be higher than for HIV due to higher infectivity.
NIAID (2001) *(17)* Review	Review of condom laboratory studies	Risk of leakage in different scenarios based on previous results. *(12, 15, 16, 18)*	Risk of semen exposure: 3.3 ml without condom 1 ml in case of breakage (Risk 2/100) 10e-2 ml in case of detectable holes (Risk 1/400) 10e−6 ml in case of non-detectable holes (Risk 0.23) 0 ml otherwise
Das (2001) *(19)* Mathematical modelling	Numerical fluid dynamics modelling to calculate risk of leakage in different scenarios in an intercourse situation		HBV virion (42 nm) passage 18 to 60 through elliptical, 1 µm high slits 80,000 through elliptical, 5 µm high slits 2e7 through elliptical, 20 µm high slits HIV virion (110 nm) pasage: Low through eliptical slits with height <20 µm 70 through elliptical, 20 µm high slits

Abbreviations: bacteriophage ϕX174 (ϕX174), bacteriophage T7 (T7), cytomegalovirus (CMV), hepatitis B virus (HBV), herpes simplex type 2 (HSV2), herpes simplex type not specified (HSV), human immunodeficiency virus (HIV), the National Institute of Allergy and Infectious Diseases (NIAID) poliovirus type 1 (PV1), polystyrene microspheres (PMS), xenotropic type c mouse retrovirus (XTCMRV), Zika virus

Method: Test method used to assay virus leakage. Manual means that condoms containing virus were tested by manually simulating intercourse, for example, inside a syringe. Pressure means that virus-containing condoms were tested while pressurized. Passive means that virus-containing condoms were not subjected to additional stress.

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4. Key question (2): Included studies for minimal infectious dose

Author (Year) *(ref.)*	Model	Dose	Cycle	Outcome summary
Yockey (2016) *(1)*	Mouse, intravaginal	2.5e4-5.2e5 PFU	Diestrus, induced (depo provera)	6/6 WT mice showed no severe disease after inoculation of 2.5e4 PFU. 6/6 IFNAR deficient mice died after inoculation of 5.2e5 PFU.
Khan (2016) *(2)*	Mouse, intravaginal	2e4 FFU	Diestrus, induced (depo provera)	6/6 WT mice showed Zika virus replication in lower female reproductive tract after inoculation.
Tang (2016) *(3)*	Mouse, intravaginal	1e5-1e6 FFU	Estrus and Diestrus, induced (hormone treatment)	5/5 diestrus AG129 mice died after inoculation with 1e5 PFU. 4/4 estrus AG129 mice survived after inoculation with 1e5 PFU with no clinical manifestations. 5/5 diestrus LysMCre+IFNAR$^{fl/fl}$ mice showed clinical symptoms but survived inoculation of 1e6 PFU. 5/5 estrus LysMCre+IFNARfl/fl mice survived after inoculation with 1e5 PFU with no clinical manifestations.
Duggal (2017) *(4)*	Mouse, intravaginal	1) 1e3 PFU inoculation 2) mean peak titter in infectious semen 1e4.2 PFU day 12 pi and 1e3.8 PFU day 9 pi	Random stages of cycle	3/5 of inoculated AG129 pregnant female mice infected. 2/9 of inoculated AG129 non-pregnant female mice infected. Infectious semen collected from uteri of CD-1 mice after mating. AG129 Male mice were mated again to other AG129 females, resulting in sexually transmitted infections.
Hastings (2017) *(5)*	Mouse, intravaginal	1.5e5 PFU	Diestrus, induced (depo provera)	6/6 Axl -/- showed Zika virus replication in vaginal tract. 6/6 WT mice showed Zika virus replication in vaginal tract.
Uraki (2017) *(6)*	Mouse, intravaginal	750 PFU	Diestrus, induced (depo provera)	3/5 Ifnar1$^{-/-}$ mice in diestrus infected. 0/3 Ifnar1$^{-/-}$ mice in estrus infected.
Martinez (2017) *(7)*	Mouse, intrarectal	3.4e6 PFU	NA	6/6 male AG129 ifnar1 -/- mice infected.

Author (Year) *(ref.)*	Model	Dose	Cycle	Outcome summary
Carroll (2017) *(8)*	NHP, intravaginal	1e4–1e6 PFU (7-day intervals between repeated inoculations)	Various	1 RM infected after 1 1e4 PFU inoculation. 1 RM infected after 1 1e5 PFU inoculation. 1 RM infected after 2 1e6 PFU inoculations. 1 RM infected after 5 1e6 PFU inoculations. 1 RM infected after depo provera, 1 1e4 PFU inoculation. 1 RM infected after depo provera, 1 1e5 PFU inoculation.
Haddow (2017) *(9)*	NHP, intravaginal	1e7 PFU	No information found	2/4 of rhesus macaques infected 2/4 of cynomolgus macaques infected

Abbreviations: wild type mice (T), rhesus monkey (RM), non-human primate (NHP); plaque forming units (PFU); focus forming units (FFU); not applicable (NA).

AG129: Lack IFNAR and IFNGR receptors, LysMCre+IFNAR$^{fl/fl}$: Lack IFNAR in myeloid cells, AXL -/-: Lack Axl receptor, CD-1: outbred albino mice.

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5. Key question (2): Included studies for condom effectiveness

Author (year) *(ref.)* Study design	Population	Pathogen	Condom type and use	Result	Size
Vijayakumar (2006) *(1)* Systematic review	Heterosexual couples	"STIs"	Female condom	"Randomized interventions addressing effectiveness [of female condom use] against STIs have not yielded consistent data", "two studies found promising decreases in sexually transmitted infection (STI) incidence with the introduction of the female condom"	5 randomized clinical trials
Smith (2015) *(2)* Cohort based on analysis of two randomized clinical trial data sets	MSM (serodiscordant)	HIV	Male condom, always vs never use	Male condom use "always use" compared to "never use" reduces HIV transmission in MSM by 70.5% (95% CI: 58.2–79.2)	Subset of 3 490 trial participants over 9 246 bi-annual visits
Weller (2002) *(3)* Systematic review with meta-analysis	Heterosexual couples (serodiscordant)	HIV	Male condom, always vs never use	Male condom use "always use" compared to "never use" reduces HIV transmission in heterosexual couples by 80.2% (95% CI: 56.3%-91.0%) "always use compared with never use"	964.3 total person years in "always use" from 13 cohorts, 243.3 person years "never use" from 5 cohorts
Giannou (2016) *(4)* Systematic review with meta-analysis	Heterosexual couples (serodiscordant)	HIV	Male condom, always vs never use	Male condom "always use" compared to "never use": 71% (95% CI: 57–80, I^2: 39%) effective against HIV transmission	17 studies with a total of 5 713 HIV serodiscordant heterosexual couples
WHO (2011) *(5)* Systematic review with meta-analysis	MSM	HIV	Male condom, consistent use vs never use	Male condom use "consistent" compared to "never" use reduces HIV transmission by 64% (95% CI: 33–80, I^2: 0%) in MSM	5 studies with 8 827 participants
Holmes (2004) *(6)* Review	Condom users	HIV	Condom use, heterogeneous definitions of condom use over the different included studies	Authors conclude that they identified evidence suggesting condom usage is associated with: "reduced transmission of HIV"	1 community-based controlled trial for HIV

Abbreviations used: human immunodeficiency virus (HIV), men having sex with men (MSM), sexually transmitted infections (STI).

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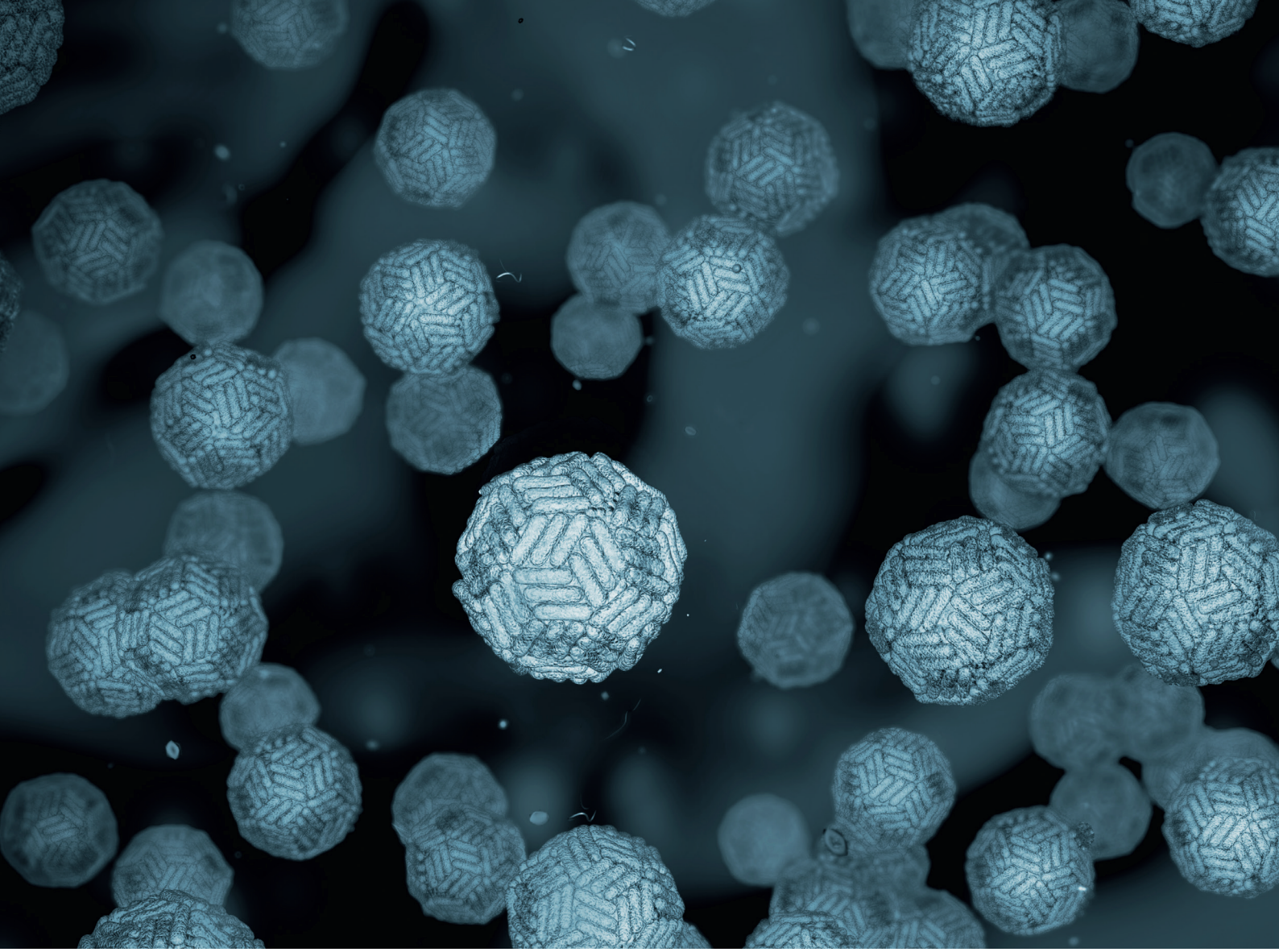

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For more information, please contact:

Department of Sexual and Reproductive Health and Research
World Health Organization
Avenue Appia 20, CH-1211 Geneva 27, Switzerland
E-mail: reproductivehealth@who.int
Twitter: @HRPresearch
Website: www.who.int/reproductivehealth

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