Times to key events in Zika virus infection and implications for blood donation: a systematic review

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Objective To estimate the timing of key events in the natural history of Zika virus infection.

Methods In February 2016, we searched PubMed, Scopus and the Web of Science for publications containing the term Zika. By pooling data, we estimated the incubation period, the time to seroconversion and the duration of viral shedding. We estimated the risk of Zika virus contaminated blood donations.

Findings We identified 20 articles on 25 patients with Zika virus infection. The median incubation period for the infection was estimated to be 5.9 days (95% credible interval, CrI: 4.4–7.6), with 95% of people who developed symptoms doing so within 11.2 days (95% CrI: 7.6–18.0) after infection. On average, seroconversion occurred 9.1 days (95% CrI: 7.0–11.6) after infection. The virus was detectable in blood for 9.9 days (95% CrI: 6.9–21.4) on average. Without screening, the estimated risk that a blood donation would come from an infected individual increased by approximately 1 in 10 000 for every 1 per 100 000 person–days increase in the incidence of Zika virus infection. Symptom-based screening may reduce this rate by 7% (relative risk, RR: 0.93; 95% CrI: 0.89–0.99) and antibody screening, by 29% (RR: 0.71; 95% CrI: 0.28–0.88).

Conclusion Neither symptom- nor antibody-based screening for Zika virus infection substantially reduced the risk that blood donations would be contaminated by the virus. Polymerase chain reaction testing should be considered for identifying blood safe for use in pregnant women in high-incidence areas.

Introduction

In early 2016, the World Health Organization (WHO) declared a public health emergency of international concern because of the explosion in the number of people infected with the Zika virus in Central and South America and indications that the virus was responsible for an epidemic of microcephaly in Brazil.1 By 29 February 2016, at least half a million people in the Americas had been infected.2,3 Although the clinical disease is generally mild or asymptomatic,4 there is increasing evidence that Zika virus infection during pregnancy is linked to severe microcephaly in infants – there was a 10-fold increase in microcephaly cases in Brazil in the wake of the 2015 Zika virus epidemic.5 In adults, the infection has been linked to Guillain–Barré syndrome.6,7

The severity of these complications highlights the need to protect pregnant women from infection and to ensure that blood supplies remain safe, both in areas experiencing ongoing Zika virus transmission and in places with travellers returning from affected areas. There are concerns about potential transmission through blood transfusion because a large proportion of people infected with the virus remain asymptomatic,1 current diagnostic techniques are inadequate and the duration of viraemia and viral shedding are uncertain. In an outbreak in French Polynesia in 2013 and 2014, researchers found that 3% of asymptomatic blood donors were infected with the Zika virus and, in Brazil, several cases of possible viral transmission through blood transfusion were investigated in early 2016.8,9

As a result, some agencies, including WHO and the United States Food and Drug Administration, recommended deferring or halting blood donations from individuals within, or returning from, areas with active Zika virus transmission.9,10 Subsequently, Puerto Rico began importing blood components on 5 March 2016, though local donations resumed on 2 April 2016 after the Food and Drug Administration (FDA) approved an investigational nucleic acid test for the Zika virus.11

As temporary deferral or the banning of blood donations could result in severe shortages in blood supplies, research on the duration of viraemia and the time to antibody seroconversion is vital for quantifying the risk to blood supplies and for developing strategies for protecting them. Furthermore, better knowledge of the natural history of Zika virus infection, including the incubation period and infectious period, is essential for designing evidence-based surveillance systems and informing public health policy.12,13 Historically, estimates of the incubation period of even common diseases have been based on limited data. For instance, most of what we know about the incubation period of the respiratory syncytial virus is based on one observational and one experimental study, which involved fewer than 20 individuals in total.14,15 The situation does not necessarily improve as the prevalence of a disease increases because it becomes more difficult to establish the time range within which infection occurred. Previously, to make the best use of the limited data available, we developed an approach to estimating the incubation period and the distributions of other key variables in the natural history of an infectious disease from coarsely observed data.16,17,20 Using this approach, any case report that enables us to set bounds on the time of possible infection and the timing of an event of interest, such as symptom onset, seroconversion or viral clearance, can con-

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tribute to estimates of key variables in a statistically principled manner.

The aim of this study was to better characterize the natural history of Zika virus infection and to inform disease prevention, surveillance and blood supply safety strategies by applying an extension of this analytical approach to case reports collected through a systematic review of the literature. Using pooled data, we estimated the incubation period, the time to seroconversion and the duration of viral shedding from Zika virus infection.

**Methods**

We searched the PubMed, Scopus and Web of Science databases on 8 and 25 February 2016 (i.e. 7 and 24 days, respectively, after WHO’s declaration of a public health emergency of international concern) for publications containing the term Zika in any field. For our analysis, we included publications that provided information on: (i) the timing of symptoms in 25 persons; (ii) the timing of seroconversion in 22 persons; (iii) the duration of viral shedding in 22 persons.

The systematic review was conducted according to Meta-analysis of Observational Studies in Epidemiology group guidelines and Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines, where applicable. We abstracted the data necessary to estimate: (i) the incubation period of the Zika virus; (ii) the timing and duration of viral shedding; (iii) the time to a positive serum antibody test result. In particular, we obtained information that enabled us to determine upper and lower bounds on the time of: (i) exposure to the Zika virus; (ii) symptom onset; and (iii) sample collection for virological or antibody testing. The exact timing of events was used when possible; otherwise bounds on the timing of an event were derived from the information available (e.g. the dates of travel to an endemic region). For virological and serological tests, the test result was recorded and specific immunoglobulin-M serological test results were noted, when available. We also recorded basic demographic details, the type of sample collected (e.g. blood or urine) and, when available, the mode of viral transmission.

The bounds for the time of Zika virus infection were the earliest and latest possible times of exposure consistent with the case report. When no latest exposure time could be determined – for example, the patient developed symptoms in an endemic area – it was assumed to be the latest possible time of symptom onset – the time of symptom onset was specified to the nearest day in most case reports. The earliest possible time of seroconversion was considered to be immediately after the last negative serological test and the latest possible time was immediately before the first positive test. If only a positive serological test was reported, the earliest possible time of seroconversion was considered to be the same as the earliest possible time of exposure; when only a negative test was reported, seroconversion was considered to have occurred after the time of testing. Similarly, the earliest possible time of viral clearance, which was defined as no detectable virus in blood, was the time of the last positive virological test and the latest was the time of the first negative test. Missing virological test results were treated in the same way as missing serological test results.

**Statistical analysis**

For each observation of a time to a key event in the course of Zika virus infection (e.g. symptom onset, seroconversion or the end of viral shedding), we used the observed data to derive upper and lower bounds for the time of exposure and for the event. These censored observations were then used to fit separate distributions for each key event using an adaptation of previously described techniques. Briefly, Markov chain Monte Carlo methods were used to simultaneously fit the incubation period distribution (assuming a log-normal distribution) and the distribu-

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**Fig. 1.** Flowchart showing the selection of studies on natural history of Zika virus infection, 1956–2016

- 964 articles identified through literature search
- 948 titles and abstracts screened
- 18 full-text articles assessed for eligibility
- 20 articles included in the study, which contained information on:
  - the timing of symptoms in 25 persons
  - the timing of seroconversion in 22 persons
  - the duration of viral shedding in 22 persons

- 366 articles excluded
  - 268 not about Zika virus infection in humans
  - 98 did not include appropriate temporal data
- 120 articles excluded
  - 86 did not give sufficient information on the variables of interest
  - 12 reported perinatal viral transmission

Note: The full texts of 55 articles in French, Portuguese or Spanish were screened and none was found to contain relevant information.
tions of the time to immunoglobulin-M seroconversion (assuming a Weibull distribution) and the time to viral clearance (assuming a Weibull distribution) to the doubly interval-censored data. For the incubation period, we report the dispersion of the log-normal distribution as the exponential of the log-scale standard deviation — this metric was used by Sartwell to characterize the incubation period and has the property that 66% of incubation periods will lie between the values of the median ± dispersion and the median ± dispersion.23

Given a time of infection, the times to symptom onset, seroconversion and viral clearance were considered to be independently distributed. The mean incubation period and the times within which 5, 25, 50, 75 and 95% of patients who will develop symptoms are expected to do so were estimated. Details and software published elsewhere.24

We estimated the impact of the distributions of key variables on the safety of blood supplies for a constant incidence rate. The number of blood donors with a possible Zika virus infection in every 100 000 in the absence of screening was calculated as the daily incidence of infection per 100 000 multiplied by the mean time to viral clearance. This estimate was adjusted for symptom-based screening using the mean time to symptom onset and by assuming that 80% of those infected remain asymptomatic.23 In addition, the effect of screening based on serological tests was estimated using the mean time to the first of either seroconversion or viral clearance, which were assumed to be independent: patients who experienced seroconversion would be successfully excluded from donation by screening and those who cleared the virus would no longer be infectious. Analyses were performed using the JAGS program version 3.3 (GNU General Public License version 2) and the R statistical language (R Foundation, Vienna, Austria).25,26

Results

The literature search identified 964 articles containing the term Zika, of which 118 were selected for full text review (Fig. 1). We contacted the authors for four articles with insufficient information, none of which was included in the analysis. Finally, we extracted data from 20 articles on 25 patients infected with Zika virus, most of whom were infected after 2008 (Table 1).4,28–46 Most affected individuals were American or European residents, none was a child and 14 were male. Data were available on the time of symptom onset for 25 individuals, on 49 virological tests on 22 individuals and on 62 serological tests on 22 individuals. Twenty-three were infected while travelling in an endemic area, one via sexual transmission and one through experimental infection.

We estimated the median incubation period of Zika virus disease to be 5.9 days (95% credible interval, CrI: 4.4–7.6), with a dispersion of 1.5 days (95% CrI: 1.2–1.9). Hence, 5% of symptomatic cases would be expected to develop symptoms within 3.2 days of infection (95% CrI: 1.7–4.6), 25% within 4.6 days (95% CrI: 3.1–6.0), 75% within 7.6 days (95% CrI: 5.8–10.4) and 95% within 11.2 days (95% CrI: 7.6–18.0; Fig. 2).

The estimated mean time to seroconversion was 9.1 days (95% CrI: 7.0–11.6) after infection: 5% of cases would be expected to have detectable antibodies by 4.4 days (95% CrI: 1.3–7.0), 25% by 7.1 days (95% CrI: 4.0–9.2), 75% by 11.0 days (95% CrI: 8.7–14.6) and 95% by 13.7 days (95% CrI: 10.6–21.7; Fig. 3). The mean time to viral clearance was estimated to be 9.9 days (95% CrI: 6.9–21.4) after infection: 5% of cases would be expected to have no detectable virus by 2.4 days (95% CrI: 0.9–5.9), 25% by 5.8 days (95% CrI: 1.4–9.2), 75% by 12.7 days (95% CrI: 9.2–25.9) and 95% by 18.9 days (95% CrI: 13.6–79.4; Fig. 4).

Given that the estimated mean time to viral clearance from blood is 9.9 days, each 1 in 100 000 increase in the daily incidence of Zika virus infection would be associated with an increase in the proportion of infected blood donors of 9.9 per 100 000 (95% CrI: 6.9–21.4) if no screening were performed. Refusing donations from people with recent symptoms of a possible infection would decrease this risk by only 7% (relative risk, RR: 0.93; 95% CrI: 0.89–0.99), assuming that 80% of individuals with Zika virus infections are asymptomatic and given that those who develop symptoms are infectious but asymptomatic for an average of 5.9 days — here it is assumed that the Zika virus can be transmitted via blood from the moment of infection. Serological screening would reduce the risk by 29% (RR: 0.71; 95% CrI: 0.28–0.88) but improve the safety of blood supplies only marginally. In settings where the risk is solely from imported Zika cases, ensuring blood supply safety is easier. We estimated that, by 23.4 days (95% CrI: 14.3–154.3) after infection, 99% of cases would no longer have detectable virus in their blood. For these estimates, we assumed that a blood donation would be safe if there was no detectable virus in the donor’s blood. However, in four reported cases, a saliva, nasal or urine sample tested positive for the virus even though it was no longer detectable in blood (Table 1). Blood donation may, therefore, still pose a risk. Although few data were available on viral clearance in these fluids, we estimated that the latest positive saliva, nasal or urine test took place a mean of 12.0 days (95% CrI: 10.1–18.2) after infection.

Discussion

In June 2016, WHO reported that the incubation period of the Zika virus was uncertain but likely to be “a few days”.47 Similarly, the United States Centers for Disease Control and Prevention stated that the period was unknown but probably “a few days to a week” and the European Centre for Disease Prevention and Control estimated it was 3 to 12 days.48,49 Our analysis indicates that the incubation period is around 6 days and gives an estimate of the remaining uncertainty. In addition, we provide estimates of the times to seroconversion and viral clearance. Knowledge of these key variables in the natural history of Zika virus infection is important for designing and evaluating screening and surveillance protocols, as we illustrated in our analysis of screening for Zika virus infection in blood donors. Although the risk to blood supplies is quite low, it is proportional to the incidence of infection, which is hard to measure because many cases are asymptomatic. Screening for symptoms is important but only a direct antigen test can reduce risk. Our analysis indicates that antibody tests could reduce the risk of contaminated blood supplies by around 30%.

In practice, many countries and organizations recommend deferring blood donation until 28 days after the resolution of symptoms or after the time of a positive serological or virological test result for an asymptomatic individual, as recommended by WHO40 — the United States FDA recommended 28 days, the Brazil Ministry of Health recommended
Table 1. Characteristics of 25 reported patients with a Zika virus infection, worldwide, 1956–2016

| First author of publication (year) | Age (years) | Sex | Place of origin | Probable place of Zika virus infection | Year of exposure to the virus | Length of exposure period (days) | Possible time to symptom onset, range (days) | Possible time to seroconversion, range (days) | Possible time to viral clearance from serum, range (days) |
|-----------------------------------|-------------|-----|----------------|--------------------------------------|-----------------------------|--------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------------|
| Bearcroft (1956)°                 | 34          | Male| Europe         | Nigeria                              | ND                          | < 1°                          | 3–4                                         | < 39                                        | ND                                                |
| Chen (2016)°                      | 55          | Male| United States  | Costa Rica                           | 2015                        | 8                             | 3–12                                        | < 39                                        | ND                                                |
| Duffy (2009)°                     | ND          | Female| United States  | Yap Islands                          | 2007                        | 13                            | 7–21                                        | < 34                                        | ND                                                |
| Fonseca (2014)°                   | ND          | Female| Canada         | Thailand                             | 2013                        | 16                            | 1–18                                        | < 24                                        | 26–28                                             |
| Foy (2011)°                       | 36          | Male| United States  | Senegal                              | 2008                        | 24                            | 5–30                                        | < 33                                        | 33°                                               |
|                                     | 27          | Male| United States  | Senegal                              | 2008                        | 24                            | 4–29                                        | < 33                                        | 33°                                               |
|                                     | ND          | Female| United States  | United States†                        | 2008                        | 7                             | 3–11                                        | 15–34                                       | 16°                                               |
| Giner (2016)°                     | 51          | Female| Switzerland    | El Salvador, Guatemala                | 2015                        | 14                            | 3–18                                        | < 24                                        | 23                                                |
| Gyurech (2016)°                   | 44          | Female| Switzerland    | Brazil                               | 2015                        | 1                             | 4–17                                        | 19–23                                       | 23                                                |
| Korhonen (2016)°                  | 37          | Male| Finland        | Maldives                             | 2015                        | 183                           | 1–185                                       | ND                                          | < 191°                                            |
| Kutsuna (2014)°                   | 30–35       | Female| Japan          | Bora Bora                            | 2013–2014                   | 10                            | 5–16                                        | < 21                                        | < 21°                                             |
| Kwong (2013)°                     | 52          | Male| Australia      | Indonesia                            | ND                          | 9                             | 0–10                                        | ND                                          | 13–24                                             |
| Leung (2015)°                     | 27          | Male| Australia      | Indonesia                            | ND                          | 6                             | 2–9                                         | ND                                          | < 14                                              |
| Maria (2016)°                     | 60–69       | Female| France         | Martinique                           | 2015                        | 22                            | 1–24                                        | < 28                                        | ND                                                |
|                                     | 20–29       | Male| France         | Brazil                               | 2015–2016                   | 8                             | 0–9                                         | 17                                         | ND                                                |
|                                     | 50–59       | Male| France         | Colombia                             | 2015–2016                   | 29                            | 0–30                                        | 31–37                                       | ND                                                |
| Shinohara (2016)°                 | 40–45       | Male| Japan          | Thailand                             | 2014                        | 7                             | 1–9                                         | 10–14                                       | > 10°                                             |
| Simpson (1964)°                   | 28          | Male| Europe         | Uganda                               | ND                          | 76                            | 0–77                                        | < 78                                        | > 2°                                              |
| Summers (2015)°                   | 48          | Male| United States  | Bolivia (Plurinational State of), Chile, Easter Island, Ecuador, French Polynesia, Hawaii, Peru | 2013                        | 34                            | 0–35                                        | < 45                                        | ND                                                |
| Tappe (2015)°                     | 45          | Female| Germany        | Malaysia                              | 2014                        | 22                            | 5–28                                        | 29–33                                       | < 30                                              |
| Tappe (2014)°                     | 50–55       | Male | Germany        | Thailand                             | 2013                        | 12                            | 0–12                                        | < 22                                        | < 22                                              |
| Waehe (2014)°                     | 31          | Female| Norway         | Tahiti                               | 2013                        | 15                            | 0–16                                        | 20–52                                       | 20–52°                                             |
| Zammarachi (2015)°                | 60–65       | Male| Italy          | Brazil                               | 2015                        | 12                            | 0–13                                        | < 16                                        | < 16                                              |
|                                     | 30–35       | Female| Italy          | French Polynesia                      | 2013–2014                   | 19                            | 0–20                                        | 22–58                                       | > 22                                              |
|                                     | 30–35       | Male| Italy          | French Polynesia                      | 2013–2014                   | 19                            | 0–20                                        | 22–56                                       | < 23                                              |

ND: not determined.

° Viral clearance was defined as no detectable virus in blood.

°° Inoculation of a volunteer with the Zika virus.

°°° Viral shedding determined from mouse inoculation.

°° An equivocal test result was counted as a positive result.

°°°° Serum tested positive for the virus on polymerase chain reaction (PCR) testing but was negative on culture.

°°°°° Probable sexual transmission.

°°°°°° Serum tested negative for the virus on PCR testing but urine tested positive on PCR testing but was negative on culture.

°°°°°°° Serum taken from, a swab of, the site of the monkey bite tested negative for the virus on PCR testing but a nasopharyngeal swab tested positive on PCR testing.

°°°°°°°° Serum tested negative for the virus on PCR testing but urine tested positive on PCR testing at a later visit.

°°°°°°°°° Serum tested positive for the virus on PCR testing but urine tested positive on PCR testing at a later visit.
30 days and the Canadian Blood Services recommended 21 days.9,50,51 Our analysis indicated that well over 99% of people with a Zika virus infection will have no detectable virus in their blood after this period. However, since most laboratory testing will take place because symptoms are present, these recommendations essentially concern symptomatic screening, which we estimate will reduce the probability that a blood donor will have a Zika virus infection by less than 10%. Since it may not be practical to stop blood donations until a Zika virus epidemic has passed, countries may consider virological (i.e. nucleic acid) testing, particularly of blood for use in pregnant women. However, nucleic acid testing may not be perfect: we found one case in which a negative test result was followed by a positive test result, though this was in the context of perinatal transmission.52 In settings where the risk to blood donations comes solely from imported Zika cases, ensuring safety is far easier. We estimated that 99% of patients would no longer have detectable virus in their blood 23.4 days after infection. Although this figure was based on only a few observations, it can guide the deferral of blood donations: for example, donations could be accepted only 300 days after travel to a region where the Zika virus is endemic – this period is more than twice the upper 95% credible interval for viral clearance from 99% of affected patients.

Our study highlights the need for a highly specific, simple and rapid Zika virus antigen test. As well as for screening donated blood, an antigen test could be used to monitor the incidence of Zika virus infection, to help provide advice for women considering becoming pregnant and to identify pregnant women at risk of a poor clinical outcome. In addition, saliva or urine could be used in diagnostic tests and research into the relationship between the presence of the virus in bodily fluids and the risk of disease transmission is also needed. Knowledge of the time between infection and the virus becoming detectable in various fluids is essential for ascertaining the ability of antigen testing to ensure the safety of blood and organ donations. Moreover, knowledge of the incubation period can help clinicians determine whether Zika virus infection should be considered in the differential diagnosis of febrile patients who have recently travelled abroad and a good estimate of the time to seroconversion can help optimize the timing of confirmatory testing. Knowing the time to viral clearance after a potential infection or exposure can indicate when it may again be safe to become pregnant. However, the time to clearance from seminal fluid remains unknown. Our analysis provides only a first step in determining the values of key variables in Zika virus infection as the small number of cases included means that there are substantial uncertainties and a potential for bias. Investigators should continue to collect data to refine and update our estimates and to provide information on other key variables in the disease’s natural history, such as the latent period (i.e. the time between being infected and becoming infectious). To assist that process, all our data and the analysis software we used are freely available to enable other investigators to contribute to this work or apply our methods to their own data.24

Our analysis necessarily involved several assumptions because the published data were not collected to assess key variables in Zika virus infection. First, we assumed that virological testing of blood or sera had a sensitivity of...

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**Fig. 2. Zika virus incubation period, pooled analysis of cases, 1956–2016**

Notes: An explanation of how time periods were derived is given in the methods section. The shaded areas indicate 95% credible intervals.

**Fig. 3. Zika virus seroconversion, pooled analysis of cases, 1956–2016**

Notes: An explanation of how time periods were derived is given in the methods section. The shaded areas indicate 95% credible intervals.
100% for detecting a Zika virus infection – however there is evidence that viral shedding can continue longer in urine and other bodily fluids and the virus may persist in the blood below the limit of detection. We also assumed that the time to seropositivity for the Zika virus was independent of previous infections – however it is probable that people who have had a prior flavivirus infection may seroconvert more quickly. Consequently, it is possible we overestimated the time to seroconversion because the majority of cases in our analysis were travellers returning to countries where flaviviruses were not endemic. Another limitation is that the majority of our data were from people presumed to have been infected through mosquito bites. The timing of key events may differ for other routes of infection (e.g. perinatal or sexual). Furthermore, all our cases were symptomatic – the time to seroconversion or viral clearance may be different in asymptomatic individuals and it is possible that cases reported in the literature may have been more severe than usual. Nevertheless, the principle limitation of our analysis was the small number of cases.

Despite these limitations, our analysis provides the most detailed, quantitative estimates to date of the timing of key events in the natural history of Zika virus infection. Our findings can help guide disease surveillance in both endemic areas and in returning travelers and can underpin research into the basic features of this pathogen.

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**Fig. 4.** Zika virus clearance, pooled analysis of cases, 1956–2016

![Zika virus clearance, pooled analysis of cases, 1956–2016](image-url)

Notes: An explanation of how time periods were derived is given in the methods section. The shaded areas indicate 95% credible intervals.
Objectif Estimer le chronométrage des événements clés de l’histoire naturelle de l’infection à virus Zika.

Méthodes En février 2016, nous avons recherché dans PubMed, Scopus et Web of Science des publications contenant le terme Zika. À l’aide des données rassemblées, nous avons estimé la période d’incubation, le laps de temps avant la séroconversion et la durée de l’excrétion virale. Nous avons estimé le risque que les dons de sang soient contaminés par le virus Zika.

Résultats Nous avons sélectionné 20 articles sur 25 patients atteints d’une infection à virus Zika. La période d’incubation moyenne pour l’infection était estimée à 5,9 jours (intervalle de crédibilité, IC, à 95%: 4,4–7,6), 95% des individus ayant développé des symptômes 11,2 jours (IC à 95%: 7,6–18,0) après l’infection. En moyenne, la séroconversion a eu lieu 9,1 jours (IC à 95%: 7,0–11,6) après l’infection. Le virus était détectable dans le sang pendant 9,9 jours (IC à 95%: 6,9–21,4) en moyenne. Nous avons estimé qu’en l’absence de dépistage, le risque qu’un don de sang provienne d’un individu infecté augmentait d’environ 1 pour 10 000 pour chaque augmentation de 1 pour 100 000 personnes–jours dans l’incidence de l’infection à virus Zika. Le dépistage fondé sur les symptômes peut réduire ce taux de 7% (risque relatif, RR: 0,93; IC à 95%: 0,89–0,99) et le dépistage des anticorps, de 29% (RR: 0,71; IC à 95%: 0,28–0,88).

Conclusion Dans le cas de l’infection à virus Zika, le dépistage fondé sur les symptômes peut aider à réduire considérablement le risque que les dons de sang soient contaminés par le virus. Un test basé sur l’amplification en chaîne par polymérase doit être considéré pour identifier le sang pouvant être utilisé sans danger pour les femmes enceintes dans les zones à forte incidence.
Resumen

Cronograma de los eventos clave de la infección por el virus de Zika e implicaciones para la donación de sangre: una revisión sistemática

Objetivo
Estimar el cronograma de los eventos clave en la historia natural de la infección por el virus de Zika.

Métodos
En febrero de 2016, se realizaron búsquedas en PubMed, Scopus y la Web of Science en bases de datos que incluyeran el término Zika. Agrupando datos, se estimó el periodo de incubación, el momento de la seroconversión y la duración de la excreción del virus. Se estimó el riesgo de donaciones de sangre contaminadas con el virus de Zika.

Resultados
Se identificaron 20 artículos sobre 25 pacientes infectados por el virus de Zika. El periodo medio de incubación de la infección se estimó a 5,9 días (intervalo crítico, ICr del 95%: 4,4–7,6), y el 95% de las personas que desarrollaron síntomas lo hicieron 11,2 días (ICr del 95%: 7,6–18,0) tras la infección. De media, la seroconversión se produjo 9,1 días (ICr del 95%: 7,0–11,6) tras la infección. El virus se podía detectar en la sangre durante 9,9 días (ICr del 95%: 6,9–21,4) como promedio. Sin exámenes, el riesgo previsto de que una donación de sangre proviniera de un individuo infectado aumentó a, aproximadamente, 1 de cada 10 000 por cada incremento de 1 de cada 100 000 personas por día en la incidencia de la infección por el virus de Zika. Las pruebas basadas en anticuerpos en un 29% (RR: 0,71; ICr del 95%: 0,28–0,88).

Conclusión
Ni las pruebas basadas en anticuerpos ni las de anticuerpos en una infección por el virus de Zika redujeron considerablemente el riesgo de que las donaciones de sangre estuviesen contaminadas por el virus. Debería realizarse la prueba de reacción en cadena de la polimerasa para identificar la seguridad sanguínea para su uso en mujeres embarazadas en zonas de altos niveles de incidencia.

Referencias

1. WHO Director-General summarizes the outcome of the Emergency Committee regarding clusters of microcephaly and Guillain–Barré syndrome [Internet]. Geneva: World Health Organization; 2016. Available from: https://www.who.int/mediacentre/news/statement/2016/emergency-committee-zika-microcephaly/en/ [cited 2016 Aug 8]

2. Cumulative Zika suspected and confirmed cases reported by countries and territories in the Americas, 2015–2016. Updated as of 25 February 2016. Washington & Geneva: Pan American Health Organization & World Health Organization, 2016. Available from: http://aais.paho.org/php/viz/ed_zika_cases.asp [cited 2016 Feb 28]

3. Protocolo de vigilancia e resposta à ocorrência de microcefalia. Versão 1.3. Brasilia: Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Vigilância das Doenças Transmissíveis; 2016. Available from: http://www.saude.gov.br/public/media/2gZjINSpZwmb3b/1010001160222060026.pdf [cited 2016 Aug 17]. Portuguese.

4. Duffy MR, Chen TH, Hancock WT, Powers AM, Kooi JL, Lanciotti RS, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. N Engl J Med. 2009 Jun 11;360(24):2536–43. doi: http://dx.doi.org/10.1056/NEJMoa0805715 PMID: 19516034

5. Zika virus microcephaly and Guillain–Barré syndrome. Situation report. 26 February 2016. Geneva: World Health Organization, 2016. Available from: http://www.who.int/mediacentre/news/statements/2016/emergency-committee-zika-microcephaly/en/ [cited 2016 Jun 14].

6. Cao-Lormeau V-M, Blake A, Mons S, Lastère S, Roche C, Vanhomwegen E, et al. Zika virus microcephaly and Guillain–Barré syndrome. Situation report. 26 February 2016. Washington & Geneva: Pan American Health Organization & World Health Organization, 2016. Available from: http://aais.paho.org/php/viz/ed_zika_cases.asp [cited 2016 Feb 28]

7. Protocolo de vigilância e resposta à ocorrência de microcefalia. Versão 1.3. Brasilia: Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Vigilância das Doenças Transmissíveis; 2016. Available from: http://www.saude.gov.br/public/media/2gZjINSpZwmb3b/1010001160222060026.pdf [cited 2016 Aug 17]. Portuguese.

8. Duffy MR, Chen TH, Hancock WT, Powers AM, Kooi JL, Lanciotti RS, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. N Engl J Med. 2009 Jun 11;360(24):2536–43. doi: http://dx.doi.org/10.1056/NEJMoa0805715 PMID: 19516034

9. Zika virus microcephaly and Guillain–Barré syndrome. Situation report. 26 February 2016. Geneva: World Health Organization, 2016. Available from: http://www.who.int/mediacentre/news/statements/2016/emergency-committee-zika-microcephaly/en/ [cited 2016 Jun 14].

10. Maintaining a safe and adequate blood supply during Zika virus outbreaks. Interim guidance. February 2016. WHO/ZIKV/HS/16.1. Geneva: World Health Organization; 2016. Available from: http://apps.who.int/iris/bitstream/10665/204436/1/WHO_ZIKV_HS_16.1_eng.pdf?ua=1 [cited 2016 Aug 17].

11. Vasquez AMSM, Sapiano MR, Basavaraju SV, Kuehnert MJ, Rivera-Garcia B. Zika virus in the Americas: transmission dynamics and implications for blood safety. J Med. 2009 Jun 11;360(24):2536–43. doi: http://dx.doi.org/10.1016/S0140-6736(16)00562-6 PMID: 26948433

12. Fraser C, Riley S, Anderson RM, Ferguson NM. Factors that make an infectious disease outbreak controllable. Proc Natl Acad Sci USA. 2004 Apr 20;101(16):6146–51. doi: http://dx.doi.org/10.1073/pnas.0307506101 PMID: 15071187

13. Lessler J, Brookmeyer R, Reich NG, Cummings DA, Perl TM. Identifying the probable timing and setting of respiratory virus infections. Infect Control Hosp Epidemiol. 2010 Aug;31(8):809–15. doi: http://dx.doi.org/10.1086/655023 PMID: 20569117

14. Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DA. Incubation periods of acute respiratory viral infections: a systematic review. Lancet Infect Dis. 2009 May;9(5):291–300. doi: http://dx.doi.org/10.1016/S1473-3099(09)70069-6 PMID: 19393959

15. Reich NG, Perl TM, Cummings DA, Lessler J. Visualizing clinical evidence: citation networks for the incubation periods of respiratory viral infections. PLoS One. 2011 Apr 29;6(4):e19496. doi: http://dx.doi.org/10.1371/journal.pone.0019496 PMID: 21553933

16. Reich NG, Lessler J, Cummings DA, Brookmeyer R. Estimating incubation period distributions with coarse data. Stat Med. 2009 Sep 30;28(22):2769–84. doi: http://dx.doi.org/10.1002/sim.3659 PMID: 19598148

17. Rudolph KE, Lessler J, Moloney RM, Kmuhs B, Cummings DA. Incubation periods of mosquito-borne viral infections: a systematic review. Am J Trop Med Hyg. 2014 May;90(5):882–91. doi: http://dx.doi.org/10.4269/ajtmh.13-0403 PMID: 24639305

18. Lessler J, Reich NG, Cummings DA, Nair HP, Jordan HT, Thompson N, New York City Department of Health and Mental Hygiene Investigation Team. Outbreak of 2009 pandemic influenza A (H1N1) at a New York City school. N Engl J Med. 2009 Dec 31;361(27):2628–36. doi: http://dx.doi.org/10.1056/NEJMoa0906089 PMID: 20042754

19. Lee RM, Lessler J, Lee RA, Rudolph KE, Reich NG, Perl TM, et al. Incubation periods of viral gastroenteritis: a systematic review. BMC Infect Dis. 2013 Sep;13(1):446. doi: http://dx.doi.org/10.1186/1471-2334-13-446 PMID: 24068685

20. Azman AS, Rudolph KE, Cummings DA, Lessler J. The incubation period of cholera: a systematic review. J Infect. 2013 May;66(5):432–8. doi: http://dx.doi.org/10.1016/j.jinf.2012.11.013 PMID: 23201968
21. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000 Apr 19;283(15):2008–12. doi: http://dx.doi.org/10.1001/jama.283.15.2008 PMID: 10786670

22. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.

23. Santwell PE. The distribution of incubation periods of infectious disease. Am J Hyg. 1950 May;51(3):310–8. PMID: 15413610

24. ZikaLitReview. San Francisco: GitHub, Inc.; 2016. Available from https://github.com/HopkinsIDD/ZikaLitReview [cited 2016 Sep 12].

25. Lessler J, Chaisson LH, Kucirka LM, Bi Q, Grantz K, Salje H, et al. Assessing the global threat from Zika virus. Science. 2016 Aug 12;353(6300):aaf1816. doi: http://dx.doi.org/10.1126/science.aaf1816 PMID: 27417495

26. Plummer M. JAGS: Just another Gibbs sampler. 2016. Available from: https://sourceforge.net/projects/mcmc-jags/ [cited 2016 Aug 17].

27. The R project for statistical computing. Vienna: The R Foundation; 2016. Available from: https://www.R-project.org/ [cited 2016 Aug 17].

28. Bearcroft WG. Zika virus infection experimentally induced in a human volunteer Trans R Soc Trop Med Hyg. 1956 Sep;50(3):442–8. doi: http://dx.doi.org/10.1016/0035-9203(56)90090-6 PMID: 13389887

29. Chen LH. Zika virus infection in a Massachusetts resident after travel to Costa Rica: a case report. Ann Intern Med. 2016 Apr 19;164(8):574–6. doi: http://dx.doi.org/10.7326/M16-0075 PMID: 26864175

30. Fonseca K, Meatheral B, Zara D, Drebout M, MacDonald J, Pabbaraju K, et al. First case of Zika virus infection in a returning Canadian traveller. Am J Trop Med Hyg. 2014 Nov;91(5):1035–8. doi: http://dx.doi.org/10.4269/ajtmh.14-0151 PMID: 25294619

31. Foy BD, Kobylinski KC, Chilson Foy JI, Bitvich BJ, Travassos da Rosa A, Haddow AD, et al. Probable non-vector-borne transmission of Zika virus, Colorado, USA. Emerg Infect Dis. 2011 May;17(5):880–2. doi: http://dx.doi.org/10.3201/eid1705.100999 PMID: 21529401

32. Ginier M, Neumayr A, Günther S, Schmidt-Chanasit J, Blum J. Zika without symptoms in returning travellers: What are the implications? Travel Med Infect Dis. 2016 Jan-Feb;14(1):16–20. doi: http://dx.doi.org/10.1016/j.tmaid.2015.12.012 PMID: 26876061

33. Gyurech D, Schilling J, Schmidt-Chanasit J, Cassinotti P, Kaeppeli F, Dobec M. False positive dengue NS1 antigen test in a traveller with an acute symptomatic dengue infection. J Travel Med. 2016 Jan-Feb;23(1):16–20. doi: http://dx.doi.org/10.1111/jtm.12208 PMID: 25996909

34. Tappe D, Nachtigall S, Kapaun A, Schnitzler P, Günther S, Schmidt-Chanasit J. Zika virus infection imported into Switzerland. Swiss Med Wkly. 2016 02 02;156(2):5092016 PMID: 25294677

35. Zammarchi L, Stella G, Mantella A, Bartolozzi D, Tappe D, Günther S, et al. Zika virus infection imported into Italy: clinical, immunological and virological findings, and public health implications. J Clin Virol. 2015 Feb;63:32–5. doi: http://dx.doi.org/10.1016/j.jcv.2014.12.005 PMID: 25606000

36. Zika virus. Fact sheet. Geneva: World Health Organization; 2016. Available from: http://www.who.int/mediacentre/factsheets/zika/en/ [cited 2016 Feb 28].

37. Symptoms, testing and treatment. Atlanta: Centers for Disease Control and Prevention; 2016. Available from: http://www.cdc.gov/zika/symptoms/ [cited 28 Feb 2016].

38. Factsheet for health professionals. Solna: European Centre for Disease Prevention and Control; 2016. Available from: http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/factsheet-health-professionals/Pages/factsheet_health_professionals.aspx [cited 2016 Feb 28].

39. Nota técnica que define critérios de seleção para doadores em relação à transmissão do vírus Zika. Brasília: Ministério da Saúde, 2016. Available from: http://portalsaude.saude.gov.br/index.php/o-ministerio/principal/secretarias/sas/transplantes/noticias-transplantes/22713-nota-tecnica-que-define-criterios-de-selecao-para-doadores-em-relacao-a-transmissao-do-virus-zika [cited 2016 Jun 14].

40. New blood donation rules protect Canadian blood supply from Zika virus. Ottawa: Canadian Blood Services, 2016. Available from: https://www.blood.ca/en/media/new-blood-donation-rules-protect-canadian-blood-supply-from-zika-virus [cited 2016 Feb 28].

41. Srinohara K, Kutsuna S, Takaishi T, Moi ML, Reda M, Kotaki A, et al. Zika fever imported from Thailand to Japan, and diagnosed by PCR in the urines. J Travel Med. 2016 Jan 18;23(1):tao011. doi: http://dx.doi.org/10.1093/jtm/tao011 PMID: 26783128

42. Simpson DI. Zika virus infection in man. Trans R Soc Trop Med Hyg. 1964 Jul;58(4):335–8. doi: http://dx.doi.org/10.1016/0035-9203(64)90201-9 PMID: 1417544

43. Summers DJ, Acosta RW, Acosta AM. Zika virus in an American recreational traveler. J Travel Med. 2015 Sep–Oct;22(5):338–40. doi: http://dx.doi.org/10.1111/jtm.12208 PMID: 25996909

44. Wæhre T, Maagard A, Tappe D, Cadar D, Schmidt-Chanasit J. Zika virus infection after travel to Tahiti, December 2013. Emerg Infect Dis. 2014 Aug;20(8):1412–4. doi: http://dx.doi.org/10.3201/eid2008.140302 PMID: 25062427

45. Zammarchi L, Tappe D, Fortuna C, Remoli ME, Günther S, Venturi G, et al. Zika virus infection in a traveller returning to Europe from Brazil, March 2015. Euro Surveill. 2015 06 11;20(23):21153. doi: http://dx.doi.org/10.2807/1560-7917.EU2015.20.23.21153 PMID: 26084316

46. Tappe D, Rissland J, Gabriel M, Emmerich P, Günther S, Held G, et al. First case of laboratory-confirmed Zika virus infection imported into Europe, November 2013. Euro Surveill. 2014 Jan 30;19(4):20685. doi: http://dx.doi.org/10.2807/1560-7917.EU2014.19.4.20685 PMID: 24507467

47. Kino-Blacksheep et al. Zika virus infection experimentally induced in a human volunteer Trans R Soc Trop Med Hyg. 1956 Sep;50(3):442–8. doi: http://dx.doi.org/10.1016/0035-9203(56)90090-6 PMID: 13389887

48. Soto S, Cao-Lombardo V, Haddow AD, et al. Probable non-vector-borne transmission of Zika virus, Colorado, USA. Emerg Infect Dis. 2011 May;17(5):880–2. doi: http://dx.doi.org/10.3201/eid1705.100999 PMID: 21529401

49. Zika virus infection imported into Switzerland. Swiss Med Wkly. 2016 02 02;156(2):5092016 PMID: 25294677

50. Zika virus infection imported into Switzerland. Swiss Med Wkly. 2016 02 02;156(2):5092016 PMID: 25294677