Emergencies

Zika causality statement

7 September 2016

Zika virus infection: update on the evidence for a causal link to congenital brain abnormalities and Guillain-Barré syndrome[1]

Update of WHO Statement published on 31 March 2016

Since 2013, an unexpected rise in the number of reported cases of the neurological disorder Guillain-Barré syndrome[2] (GBS) in French Polynesia, Brazil and other countries in the Americas led specialists to infer a link with an ongoing outbreak of Zika virus infection. Reports of unexpected increases in cases of microcephaly in north-eastern Brazil also led to the suggestion of a link to Zika virus infection in late 2015. On 1 December 2015, PAHO/WHO published an alert regarding the implications for public health of the detection of neurological syndromes and congenital malformations in the context of epidemic transmission of Zika virus in Brazil. On 1 February 2016, the World Health Organization (WHO) declared that the clusters of cases of microcephaly and neurological disorders occurring in areas with Zika virus transmission constituted a public health emergency of international concern.

Methodology

In February 2016, WHO and partners[3] developed a causality framework that defined questions about the relationship between Zika virus infection and each of two clinical outcomes: congenital brain abnormalities including microcephaly and GBS, according to 10 dimensions of causality[4]. In late February 2016, WHO commissioned systematic reviews of the scientific literature to determine whether the currently available evidence was sufficient to establish a causal link between Zika virus infection and each of the two potential complications. A team of researchers[3] conducted the systematic review of literature and selected studies available up to 30 May and synthesized the evidence in the structured causality framework[4]. The team[5] also assessed the quality of the evidence. WHO convened a multidisciplinary panel of experts to assess the methods and interpret the results of the systematic review. Finally, selected, non-systematically identified, studies up to 29 July 2016 were added to the systematic review.

Conclusions

The panel of experts[5] concluded:

1. The most likely explanation of available evidence from outbreaks of Zika virus infection and clusters of microcephaly is that Zika virus infection during pregnancy is a cause of congenital brain abnormalities including microcephaly;

2. The most likely explanation of available evidence from outbreaks of Zika virus infection and Guillain-Barré syndrome is that Zika virus infection is a trigger of GBS.

The expert panel recognizes that Zika virus alone may not be sufficient to cause either congenital brain abnormalities or GBS. It is not known whether these effects depend on as yet uncharacterized co-factors being present. Nor is it known whether dengue virus plays a part; dengue virus is carried by the same species of mosquito and has circulated in many countries during the same period.

Recommendations

The panel agreed that there is sufficient evidence to recommend increasing:

- public health actions to reduce the risk of the effects of Zika virus infection in pregnancy, and to provide appropriate care and support (for women who have been exposed;
- public health actions to reduce exposure to Zika virus infection for all people;
- public health actions to provide appropriate clinical care and rehabilitation and continuing care for all those with long term neurological conditions, such as acute clinical services and rehabilitation;
- surveillance and research into diagnostics, vaccines, treatments and vector control.

Key findings of the reviews

Microcephaly and other brain abnormalities before or present at birth

The systematic review team found 72 studies that directly addressed one or more specific questions about links between Zika virus and congenital brain abnormalities including microcephaly. Laboratory studies have shown that Zika virus can cross the placenta and replicate in human brain cells. Both population- and individual-level studies have demonstrated a temporal association between Zika virus exposure and microcephaly incidence. Clinical reports have shown the presence of Zika virus infection in pregnant women prior to the detection of fetal brain malformations. In these women other congenital infections and dengue virus infection had been excluded. Epidemiological studies have suggested a marked increase in the risk of brain abnormalities in fetuses and newborns when a woman acquires Zika virus infection during pregnancy, particularly when infection occurs during the first trimester. The exact magnitude of the association is not known yet, however one study from French Polynesia and on-going studies in Brazil (to be published) suggest that the risk of fetal brain abnormalities is likely to be many times greater for pregnant women with Zika virus infection than for those without.

Guillain-Barré syndrome

The systematic review team found 36 studies that directly addressed one or more specific questions about links between Zika virus and GBS. A temporal association between clinical symptoms of Zika virus infection and the onset of GBS was demonstrated in population- and individual-level studies in several countries. The most detailed evidence came from studies of the 2013-14 outbreak in French Polynesia, in

which around one in 4000 people with Zika virus infection were estimated to have developed GBS. A study comparing hospitalised patients with and without GBS found that the odds of having recent Zika virus infection were more than 30 times higher in the patients with Guillain-Barré syndrome. Several other infections that can trigger GBS were excluded, though many of the patients also had antibody reactivity to dengue viruses. The number of cases of GBS fell as the Zika virus outbreak ended.

Limitations of the evidence

- Publication bias may be occurring with researchers only offering studies with positive findings to journals. At this early stage of discovery of a new cause of disease, strong findings in favour of causation are more likely to be published than weak or contradictory findings. The systematic review process could not prevent publication bias but reduced the risk that only positive reports in favour of causation would be evaluated.
- There were methodological limitations in many studies reviewed. Uncertainties around the accuracy of diagnostic tests for Zika virus made interpretation of many studies problematic. Some studies have only reported preliminary findings and important gaps remain in both surveillance and research evidence. So far, epidemiological studies to calculate the strength of the associations with Zika virus infection have only been completed in French Polynesia, and have either not been completed or not conducted in other affected countries.
- Current evidence does not show which specific environmental and host factors interact with Zika virus to increase the risk of an affected pregnancy or of GBS or whether there are specific factors that also have an effect in certain places.
- The systematic review did not find studies that could determine whether or not Zika virus causes specific brain abnormalities not found with other congenital infections.
- Some characteristics of the cases of GBS differed from typical patterns described following other infections. Surveillance data have shown increased incidence rates of microcephaly or of GBS in some but not all countries that have experienced large outbreaks of Zika virus infection.

Implications for research

- Research questions to be addressed:
    - Research to define the biological mechanisms of causality and to further the development of vaccines, treatments and better vector control methods.
    - Cohort studies of the populations currently at risk are needed to determine both absolute and relative risks of a Zika-affected pregnancy, the role of co-factors and effect modifiers, and to determine whether there is a specific congenital Zika virus syndrome.
- The group is also working on methods to produce a living systematic review of the Zika causality framework that will incorporate new evidence as it becomes available – to combine rigour with timeliness for causality research.

Next steps

The use of the causality framework enables identification of areas where evidence quality needs to be improved and where more research is needed to address specific questions about the effects of Zika virus infection. The systematic review will be updated regularly to incorporate the rapidly expanding body of evidence about the causal relationships between Zika virus infection and congenital brain abnormalities, and

Guillain-Barré syndrome, and other potentially associated conditions.

Situation report 31 March 2016

Footnotes

[1] This statement is a standalone document that summarizes the position of WHO based on advice from an expert panel. Alongside this statement, a full manuscript and tables of evidence have been submitted to PlosMed. Please see the below related links.
[2] Guillain-Barré syndrome is an immune mediated neurological condition that usually occurs within a month of certain viral or bacterial infections. These infections can trigger the immunological pathways that end in the pattern of paralysis that is typical of GBS. In other words, a particular virus or bacteria does not cause GBS directly, but trigger mechanisms that result in the syndrome.
[3] Institute of Social and Preventive Medicine, University of Bern, Switzerland
[4] Bradford Hill, in 1965, proposed a list of nine aspects that could help decide whether causation is the most likely explanation for an association between and exposure and an outcome. The list has been modified over time and the systematic review team considered 10 aspects (referred to in this document as dimensions of causality): temporality (cause precedes effect); biological plausibility (and coherence with current biological knowledge of the proposed biological mechanisms); strength of association (measured as risk ratio, rate ratio, or odds ratio in cohort or case-control studies); consistency of associations across different study types, populations and times; exclusion of alternative explanations; dose-response relationship (biological gradient); cessation (reversal of an effect by experimental removal of, or observed decline in, the exposure); experimental evidence (from animal studies); analogous cause-and-effect relationships found in other diseases; and specificity of the effect.

[5] Expert panel members
pdf, 263kb

Full manuscript and tables of evidence, submitted to PlosMed

Microcephaly/Zika virus »

This page links all WHO information to its response on the Public Health Emergency of International Concern.

All situation reports

Related links

Zika virus

- Fact sheet: Zika virus
- Q&A: Zika virus
- More on Zika virus

Microcephaly

- Key facts: Microcephaly
- More on Microcephaly

Guillain–Barré syndrome

- Fact sheet: Guillain–Barré syndrome
- More on Guillain–Barré syndrome

Information in Portuguese

- Zika virus
- Women in the context of microcephaly and Zika virus disease

Epidemiological Update: Region of the Americas

- Neurological syndrome, congenital anomalies, and Zika virus infection