ACM/1252

ADVISORY COMMITTEE ON THE MICROBIOLOGICAL SAFETY OF FOOD

INFORMATION PAPER

Zika virus – Risk assessment related to exposure via the food chain

A draft risk assessment on Zika virus and the food chain was discussed at the June 2016 meeting of the ACMSF (ACM/1220). Following comments made at that meeting the Newly Emerging Pathogens Working Group met on 22 November 2016 to consider a revised version produced by the Secretariat. The revised risk assessment agreed by the Working Group is attached for Members' information.

Secretariat
January 2017

23 November 2016

Zika virus – Risk assessment related to exposure via the food chain

Statement of purpose

- To assess the risk to consumers from Zika virus via food imported from Zika-endemic countries.

Hazard Identification

1. Zika virus (ZIKV) is an emerging mosquito-borne virus, first identified in Uganda in 1947 in rhesus monkeys. It was subsequently identified in humans in 1952 in Uganda and the United Republic of Tanzania. Outbreaks of ZIKV disease have been recorded in Africa, the Americas, Asia and the Pacific (WHO, 2016). Prior to 2015, ZIKV outbreaks occurred in areas of Africa, Southeast Asia, and the Pacific Islands. As surveillance for ZIKV improves, further cases are expected to be reported in these regions and previously unaffected countries, particularly in south and central America and the Caribbean, where the Aedes *aegypti* mosquito vector is present (HAIRS, 2016).

2. ZIKV is a member of the genus *Flavivirus* and family Flaviviridae (Dick *et al.,* 1952). The *Flaviviridae* are a family of positive, single-stranded, enveloped RNA viruses. They are found in arthropods, (primarily ticks and mosquitoes), and can occasionally infect humans. Members of this family belong to a single genus, *Flavivirus*, and cause widespread morbidity and mortality throughout the world (Centres for Disease Control and prevention, update 2014).

3. There are two main lineages of Flavivirus, the African and the Asian lineage (Kuno *et al.,* 1998, Faye *et al.,* 2014, Haddow *et al.,* 2012). ZIKV is transmitted by mosquitoes belonging to the genus *Aedes*, mainly *Aedes aegypti.*

4. ZIKV is not endemic in the UK. Without exception, cases reported have been associated with travel to Zika endemic countries. As of 23 November 2016, 263 travel-associated cases have been diagnosed since 2015. Of these, 178 are confirmed cases including: 134 PCR positive cases with virus detected, 44 cases with antibody evidence indicating recent infection (seroconversion) and 85 probable cases that have antibody evidence highly indicative of recent infection (Zika-specific IgM) (Public Health England).

5. Active Zika virus transmission has been reported in numerous countries. As of 21 November 2016, The Centre for Disease Control and Prevention

illustrated that fifty one countries in South America, Central America, the Caribbean and USA are affected. Ten countries in Asia, Oceania and the Pacific Islands are affected and in Africa, transmission is active in Cape Verde.

Exposure assessment

6. **Transmission in humans** - *Aedes aegypti* mosquitos are considered to be a primary vector of viral diseases such as the dengue fever, chikungunya and yellow fever and Zika. These mosquitos are most frequently found in tropical and subtropical areas of the world. In Europe, they are currently only present around the Black Sea coast, in Russia, Georgia and in Madeira. *Aedes albopictus* may also have a role as vector for ZIKV. This species has been found to colonise new areas via main highway routes, having moved across regions in vehicles and is expected to become established in northern France in the next few years (HAIRS, 2016). To date, there have been no reports of either species in the UK.

7. ZIKV is transmitted to humans mainly through the bite of an infected *Aedes* mosquito primarily *A. aegypti*. *A. aegypti* mosquitos which are primarily daytime biters and are most active for approximately two hours after sunrise and several hours before sunset.

8. Person-to-person transmission of ZIKV has not been widely reported. However, there is evidence that mother-to-child transmission can occur, most likely transplacentally or during the delivery by a viraemic mother (HAIRS, 2016). ZIKV has also been found in semen in a limited number of cases but there is no information relating to the length of time the virus may persist in this environment. The risk of sexual transmission of ZIKV has been reported to be low (HAIRS, 2016).

9. **Transmission in animals** - although humans are the main target for *A. aegypti,* these mosquitos have also been documented to bite dogs and other domestic animals, mostly mammals (CDC, 2016), though it was not reported whether infection results. There is also limited evidence from one study carried out in Indonesia in the late 1970s that horses, cows, carabaos (water buffaloes), goats, ducks, and bats could become infected with Zika, but there is no evidence that they develop disease or pose a risk for Zika virus transmission to humans (CDC, 2016).

10. It should also be noted that other members of the Flaviviridae family of viruses for example, West Nile virus, are also mosquito-borne with birds as the primary vertebrate reservoir hosts and therefore the possibility of transmission via products of food animals infected by mosquitos with ZIKV needs to be explored.

11. Komer *et al.,* (2003) exposed 25 bird species to West Nile virus by infectious mosquito bite. The authors reported that cloacal shedding of West Nile virus was observed in 17 of 24 species, and oral shedding in 12 of 14 species. Persistent West Nile virus infections were found in tissues

of 16 surviving birds. Contact transmission was observed among four species and, oral transmission in five species. The authors reported that this work demonstrated that certain bird species may become infected by West Nile virus after ingesting infected dead animals and infected mosquitoes, both part of the natural diet of some species. Komer *et al*., (2003) found that the viremia profiles generated by oral infection were essentially identical to those derived from mosquito-borne infection. This phenomenon was previously observed in American Crows that ingested West Nile virus-infected suckling mice and in mammals on several occasions. Other authors such as Langevin *et al*., (2001) were not able to infect chickens orally. West Nile virus outbreaks have also been reported in horses.

12. Oral infection appears to be an alternative transmission mechanism used by a number of different flaviviruses including West Nile virus. In a study conducted by Sbrana *et al*., (2005), adult hamsters were infected with West Nile virus via mosquito bite, needle inoculation, and ingestion. The hamsters were readily infected by all three routes. The level and duration of viremia, clinical manifestations, pathology, and antibody response in the hamsters following mosquito infection and needle inoculation were similar; after oral infection, the onset of viremia was delayed and the mortality was lower, but the level and duration of viremia, histopathology, and antibody response were similar to the other routes. The authors suggest that results from this and previously published studies indicate that a wide variety of animal species are susceptible to oral infection with West Nile virus and that orally infected animals develop a viremia and illness similar to that following the bite of infected mosquitoes.

13. It is evident that some flaviviruses are capable of infecting various animals. Although other animal species cannot be ruled out (**uncertainty**), at present, evidence suggests non-human primates are the only known reservoir for ZIKV (HAIRS, 2016).

Transmission via food

14. Many vector-borne diseases are zoonotic diseases, i.e. diseases that can be transmitted directly or indirectly between animals and humans. These include for example Lyme disease, tick-borne encephalitis, West Nile virus, Leishmaniosis and Crimean-Congo haemorrhagic fever. Some vector-borne diseases such as tick-borne encephalitis can be transmitted from animals to humans via infected food; in this case raw milk (EFSA 2015).

15. Zika virus disease outbreaks were reported for the first time from the Pacific in 2007 and 2013 (Yap and French Polynesia, respectively), and in 2015 from the Americas (Brazil and Colombia) and Cape Verde. Data relating to imports of meat from Latin America to the UK were obtained for 2015. Bovine, sheep, goat and horse meat imported from Latin America accounted for 28.8% of the total value (£) of meat imports to the UK, this is equivalent to 74311 tonnes. (Source: HMRC); therefore some

consideration must be given to the possibility of transmission of ZIKV via potentially infected livestock and products (meat/milk) imported from endemic countries. The country with the highest contribution in the area was Brazil, which alone contributed to 23.6% of the total value (£) of meat imports in the UK. Total imports of poultry entering the UK from Latin American countries in 2015 equated to 60931 tonnes (23.7% of total value (£) meat imports to the UK: Source HMRC). Brazil accounted for the highest proportion of imports to the UK.

16. The amount of fresh produce imported from endemic countries in South and Central America is also not insignificant. Imports of fruits and vegetables in 2015, equated to 218,418 tonnes (27.1% of total fresh produce imported to the UK from Latin American countries). Argentina, Brazil, Chile, Guatemala and Peru were the countries exporting the highest amounts to the UK (Source: HMRC).

17. There is no evidence to suggest involvement of livestock in the epidemiology of ZIKV (APHA personal communication) but this is an uncertainty. There is no evidence to suggest infected food handlers or fresh produce imported from Zika-endemic countries play a role in virus transmission, although the virus has been reported to be present in saliva and urine of symptomatic individuals (Centres for Disease Control and Prevention, 2016) and cases with ZIKV infection can report gastrointestinal symptoms (uncertainty). (European Centre for Disease Control and Prevention factsheet, 2016). It is unclear whether the virus is present in the faeces of infected individuals (uncertainty). Organisations such as the WHO and CDC have not published any material relating to foodborne transmission of ZIKV suggesting it is unlikely that food plays a role (if any) in ZIKV infection.. Additionally, the EU has not placed any health restrictions on meat or fresh produce imports from Zika-endemic countries (Source: APHA).

18. The potential of transmission of ZIKV via illegally imported bush meat from Zika-endemic countries in Africa also warrants mentioning even though there is limited distribution to the UK, particularly given that non-human primates are the only known reservoir for ZIKV.

19. Viable ZIKV has been detected in saliva, urine (Bonaldo *et al*., 2016) and perhaps more significantly, high loads of ZIKV have been detected in human breast milk (Dupont-Rouzerol *et al*., 2016). This may raise the question on whether ZIKV is able to survive in bovine secretions particularly milk and therefore present some risk via foodborne exposure.

20. A recent review by Shukla et al., 2016, reviewed methods for detecting ZIKV and reported that liposome-based immunoassays show applicability in various areas of food chemistry, food microbiology, nano- biotechnology and diagnostic or clinical microbiology, for the detection of foodborne pathogens, toxins, and hazardous components in a variety of environmental and human samples. The authors stated that, in the near future, studies should aim to confirm the practical applications of liposome-

based virus detection assays in various food samples contaminated with foodborne viruses, including ZIKV.

21. Other less likely routes of transmission associated with food also warrant some acknowledgement.. Exposure to ZIKV by consumers or food handlers in the UK via infestation of food by viable infected mosquitos appears to be unlikely and there are no reports of transmission via this route, nonetheless it is not impossible that a small number of infected mosquitos may potentially survive transit from Zika-endemic countries and transmit the virus in this way (uncertainty). The possibility of precutaneous exposure to ZIKV via handling of infected food is also worthy of mention though is unlikely and no reports are present in the literature relating to this.

22. At a recent meeting of the American Association of Pharmaceutical Scientists in November 2016, a study was presented which documented that ZIKV can survive on hard, non-porous surfaces for up to eight hours, but possibly longer in a blood-containing environment. Disinfectants such as isopropyl alcohol and quaternary ammonium/alcohol were documented to be generally effective in killing the virus in this type of environment in as little as 15 seconds (Zhou, 2016). The study did not investigate survival beyond eight hours. Like many other viruses, it is likely that ZIKV is able to survive on inanimate objects for a period of time and is susceptible to disinfectants such as alcohol, but there is no indication at present to suggest unusual, prolonged or different survival characteristics to many other viruses or whether survival has any implication in terms of transmission for example, from an infected surface to a food handler.

Hazard Characterisation

23. ZIKV, is a member of the genus *Flavivirus* and family Flaviviridae (Dick *et al* 1952). There are three distinct groups of Flaviviruses, the mosquito borne viruses, tick borne viruses and those viruses with no known arthropod vector. The mosquito-borne group is the largest and most important medically and includes the Dengue viruses, West Nile virus, yellow fever virus and ZIKV. There are two groups of mosquito-borne flaviviruses; the oldest evolutionary group rely on lower primates as their host, and include Dengue viruses and Yellow Fever virus. The second group have birds as their principal vertebrate hosts and include West Nile virus and Japanese Encephalitis virus. The tick-borne group include Louping ill virus (including the British sub-type) and tick-borne encephalitis virus. (Gubler, 2012).

24. The Americas (making up the vast proportion of current known ZIKV affected countries), Pacific Islands and Africa (Cape Verde) are all areas where active ZIKV transmission is ongoing (CDC, 2016). *A. aegypti* would not survive longer than two or three days at temperatures below 14°C, although introduced individual mosquitoes might be able to survive for a few days or weeks in the summer months, the temperature is generally too low for *A. aegypti* to establish in the UK. The main vector responsible for

transmission of ZIKV is *Aedes aegypti,* which, in Europe, is only present around the Black Sea coast in Russia and Georgia as well as the island of Madeira. *Aedes albopictus* may also have a role as a vector for ZIKV. This species has entered Europe via highways using used tyres for carriage for example. *A. albopictus* has been reported in Paris for two consecutive years, and is expected to become established in further areas of northern France in the next few years (Medlock and Leach, 2015). To date, there have been no reports of either species being established in the UK (HAIRS, 2016).

25. For transmission of mosquito-borne flaviviruses to occur, vertebrate hosts are required to have viremia as defined by an ID_{50} of at least 10^4/ml to infect the arthropod at a blood meal (Gubler, 2012). Given the absence of information relating to food as a potential source of ZIKV, it is not surprising that the infectious dose for humans (if any) via ingestion has not been established.

26. Cheng (1958) investigated the stability of various mosquito-borne viruses in the presence of proteases (trypsin, chymosin and papain). While some flaviviruses were shown to be unaffected by proteases, hemagglutinin activity of ZIKV was largely destroyed by treatment with any of the enzymes. This may provide further support that the food chain is unlikely to be a mode of transmission of ZIKV.

27. A review of Flaviviruses (Monath, 1990) reported that Flavivirus infectivity and hemagglutinin are optimally stable at pH 8.4 to pH 8.8. The authors report that sensitivity to acid pH and to bile and enzymes generally precludes infection by the oral route. The authors also report that Flaviviruses are rapidly inactivated at high temperatures (at 50°C, 50% of infectivity is lost in 10 minutes).

28. Early studies by Dick (1952) also illustrated that ZIKV is sensitive to heat; these studies also reported on some other physical properties of ZIKV. The thermal death point of the virus was determined to be 58°C for 30 minutes in a mouse brain suspension. This suggests that cooking food for the standard 70°C for 2 mins is sufficient to destroy the virus. Infectious virus may be preserved up to 6 months in 50% glycerol and up to 30 months after drying. The particle size of the virus is estimated by the same author to be in the region of 30 to 45 nm.

29. An incubation period for ZIKV has not been determined yet but is likely to range between three to twelve days following the bite of an infected mosquito. Infection is largely asymptomatic (60-80%) and generally mild and self-limiting, lasting two to seven days. Symptoms of ZIKV infection are similar but usually milder than infection with dengue or chikungunya virus and may include fever, joint pain, itching, macular/papular rash, conjunctivitis/red eyes, headache, muscle pain and eye pain (HAIRS, 2016). Severe disease requiring hospitalisation is uncommon. Case fatality rate is low and mostly associated with underlying conditions. Diagnosis can be confirmed by RT-PCR. If serological tests are conducted, cross

reaction with related flaviviruses (e.g. dengue) is common. No specific anti-viral treatment or vaccine is available or usually required for ZIKV infection (HAIRS, 2016).

30. A possible association between ZIKV infection in pregnancy and foetal microcephaly has been investigated since October 2015 when an unusual increase in cases of microcephaly were reported in Brazil. The WHO has stated that there is scientific consensus that Zika virus is a cause of microcephaly and also Guillain–Barré syndrome, based on a growing body of research (WHO 14 April 2016). http://www.who.int/emergencies/zika-virus/situation-report/14-april-2016/en/).

Risk characterisation

31. This risk assessment uses the EFSA risk level classification in order to describe the output. Further details can be found in Appendix 2.

32. Taking into account the above components of this assessment and considering the uncertainties that have been flagged; the risk of ZIKV infection via the food chain (from food imported to the UK from ZIKV endemic countries) is likely to be **negligible with a medium level of uncertainty**[1]. Three key uncertainties have been identified in this assessment: Very limited information relating to the ability of *A. aegypti* to infect animals other than non-human primates with ZIKV, non-human primates are the only known reservoir for ZIKV at present, a lack of information relating to the role of infected food handlers in transmission generally or via fresh produce from endemic countries, and a lack of information relating to the detection of ZIKV in faeces.

33. The assessment can be adapted as new information becomes available. In more general terms, it is also important to consider that the risk posed by ZIKV to a population depends on various factors including childhood exposure to the virus, being of childbearing age or pregnant. For example it is likely that in areas within Africa where ZIKV has been present for decades, there is a lower risk of illness in the population as a result of exposure to the virus through childhood, whereas in countries in S. America which have only recently reported ZIKV disease, the risk is likely to be higher. The risk to pregnant women for example is greater than for other groups in a population.

Uncertainties

Three key uncertainties associated with this assessment are outlined in Appendix 1.

[1] The estimation of overall uncertainty is based on current evidence; if further information becomes available; this will be noted and may or may not result in a change to the level of overall risk and uncertainty.

Overall risk

For thoroughly cooked meat and hygienically handled meat and fresh produce which has been stored correctly, the risk of infection with ZIKV via (handling and) consumption is considered to be **negligible**. Three medium level uncertainties were associated with this assessment and have been highlighted but are not currently considered to make a significant impact on the risk estimate.

Appendix 1: Key uncertainties

Exposure assessment- Although other species cannot be ruled out (**uncertainty - medium**), at present, evidence suggests non-human primates are the only known reservoir for ZIKV.

Exposure assessment- A lack of information relating to the role of infected food handlers in transmission of ZIKV generally or via fresh produce from endemic countries **(uncertainty-medium).**

Exposure assessment - A lack of information relating to the detection of ZIKV in faeces **(uncertainty- medium**).

Appendix 2: Risk estimation

Risk Level Classification

Probability Category	Interpretation
Negligible	**So rare that it does not merit to be considered**
Very Low	**Very rare but cannot be excluded**
Low	**Rare, but does occur**
Medium	**Occurs regularly**
High	**Occurs very often**
Very High	**Events occur almost certainly**

Table from EFSA (2006) modified from OIE (2004)

References

Bonaldo, M.C., Ribeiro, L.P., Lima, N.S., dos Santos, A.A.C., Menezes, L.S.R., DA Cruz, S.O.D., de Mello, L.S., Furtado, N.D., de Moura, E.E., Damasceno, L., da Silva, K.A.B., de Castro, G., Damasceno, L., Gerber, A.L., Almeida, L.G.P., Lourenco-de-Oliveira, Vasconcelos, A.T.R., Brasil, P. (2016) Isolation of infective Zika virus from urine and saliva of patients in Brazil.

Centres for Disease Control and Prevention May 2016. Comparison of test results for Zika Virus RNA in urine, serum, and saliva specimens from persons with travel-associated Zika virus disease — Florida, 2016
http://www.cdc.gov/mmwr/volumes/65/wr/mm6518e2.htm

Centres for Disease Control and Prevention, last updated June 2014. Flaviviridae.
http://www.cdc.gov/vhf/virus-families/flaviviridae.html

Centres for Disease Control and Prevention (2016). Zika and animals. http://www.cdc.gov/zika/transmission/qa-animals.html

Cheng, PY (1958). The inactivation of Group B arthropod-borne viruses by proteasaes. *Virology* 6: 129-136.

Dick GW, Kitchen SF, Haddow AJ. (1952) Zika virus. I. Isolations and serological specificity. *Trans R Soc Trop Med Hyg*. Sep; 46(5):509-20.

Dupont-Rouzeyrol, M., Biron, A., O'Connor, O., Huguon, E., Descloux, E. (2016) Infectious Zika virus particles in breast milk. The Lancet Mar; 387 (10023): 1051.

European Centre for Disease Control and Prevention (ECDC) factsheet. Last updated 8 March 2016. http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/factsheet-health-professionals/Pages/factsheet_health_professionals.aspx

Scientific Opinion on the public health risks related to the consumption of raw drinking milk (2015). European Food Safety Authority (EFSA). http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/3940.pdf

Faye O, Freire CC, Iamarino A, Faye O, de Oliveira JV, Diallo M, et al. Molecular Evolution of Zika Virus during Its Emergence in the 20(th) Century. *PLoS Negl Trop Dis*. 2014;8(1):e2636.

Gubler, DJ (2012) Molecular Virology and control of Flaviviruses, Novartis Instutute for tropical diseases, Singapore. Chapter 1: Flaviviruses, past present and future. https://books.google.co.uk/books?id=BRnIYiTaEOgC&pg=PA1&lpg=PA1&dq=Gubler+flavivirus&source=bl&ots=13dumRMBRb&sig=Cq1RtDKkIhKGJ0CsJPo1cf2Pb7k&hl=en&sa=X&ved=0ahUKEwiSm4qV1rbNAhVBD8AKHQWXBgAQ6AEISjAG#v=onepage&q=Gubler%20flavivirus&f=false

Haddow AD, Schuh AJ, Yasuda CY, Kasper MR, Heang V, Huy R, et al. (2012) Genetic characterization of Zika virus strains: geographic expansion of the Asian lineage. *PLoS Negl Trop Dis*. 6(2):e1477.

Human Animal Infections and Risk Surveillance (HAIRS) group (2016). Qualitative assessment of the risk that Zika virus presents to the UK population. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/520878/Zika_virus_risk_assessment_v2.pdf

Komar N, Langevin S, Hinten S, Nemeth N, Edwards E, Hettler D, Davis B, Bowen R and Bunning M. (2003). Experimental Infection of North American Birds with the New York 1999 Strain of West Nile Virus. *Emerg Infect Dis* March 9 (3): 311-322.

Kuno G, Chang GJ, Tsuchiya KR, Karabatsos N, Cropp CB. (1998) Phylogeny of the genus Flavivirus. *J Virol*. Jan; 72(1):73-83.

Langevin SA, Bunning M, Davis B, Komar N. (2001) Experimental infection of chickens as candidate sentinels for West Nile virus. *Emerg Infect Dis* (7): 726–9.

Medlock JM and Leach SA. (2015) Effect of climate change on vector-borne disease risk in the UK. *Lancet Infectious Diseases* 2015 Jun;15(6):721-30.

Monath, TP (1990). Flaviviruses. Virology Second Edition Chapter 27.

Sbrana E, Tonry JH, Xiao SY, Amelia P. A. Da Rosa, T, Higgs S and Tesh RB. (2005) Oral transmission of West Nile Virus in a hamster model. *Am. J. Trop. Med. Hyg*. 72(3): 325–329

Shukla, S., Hong, S.Y., Chung, S.H. and Kim, M (2016) Rapid Detection Strategies for the Global Threat of Zika Virus: Current State, New Hypotheses, and Limitations. Frontiers in Microbiology 7(1685): 1-15.

WHO 2016 Zika Virus fact sheet updated 2 June 2016
http://www.who.int/mediacentre/factsheets/zika/en/

Zhou, S.S., (2016) Study presented at the November 2016 meeting of the American Association of Pharmaceutical Scientists.
https://www.eurekalert.org/pub_releases/2016-11/aaop-rfz111116.php