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LETTERS TO THE EDITOR

Spread of ZIKV and YFV to China: Potential implications

To the Editor,

Introduction

As reported recently, Zika virus (ZIKV) and other flaviviruses have been identified in different regions of the world leading to significant concerns for public health.[1—4] ZIKV disease is a well-known vector-borne disease which is transmitted by the *Aedes* mosquito genus, and it was recently discovered that sexual transmission of ZIKV was possible[5]. Human infections usually present mild symptoms, but for women who are pregnant or planning to be pregnant, ZIKV may cause microcephaly in the fetus.[6] The strong link of current ZIKV epidemics in South America to spiking cases of microcephaly in Brazil prompted the WHO to declare a global public health emergency on February 1, 2016 (http://apps.who.int/iris/bitstream/10665/204371/1/zikasitrep_12Feb2016_eng.pdf?ua=1). A relative to ZIKV, yellow fever virus (YFV) is also a member of the *Flaviviridae* virus family and is transmitted by the same mosquito species, *Aedes aegypti*.[7] Yellow fever has a long history. Although the virus itself is thought to have originated in Africa, the first recorded outbreak of YFV occurred in Barbados in 1647[8] and was followed by cases in Yukatan in 1648, New York in 1668, and Philadelphia in 1793, respectively. Since the 17th century epidemics have also spread to West Africa, other tropical and subtropical regions of the Americas as well as Europe. YFV was first isolated in 1927 from a patient.[9] The development of a vaccine in 1946 led to a notable reduction of the disease burden in endemic countries.[10] The common reported symptoms are fever, malaise, myalgia, headache, nausea and dizziness. Severe YFV infections cause prostration, liver damage, acute renal failure and central nervous system manifestations.[11]

Imported Zika virus and Yellow fever virus cases in China and clinical syndromes

By March 26th, 2016, China had twelve imported cases of ZIKV and six imported cases of YFV infections, which could cause major challenges for public health (Fig. 1, Tables S1 and S2). On February 6th, a 34-year-old Chinese male traveler returning from Venezuela was admitted to a local hospital in Ganxian, China and became the first confirmed case of a ZIKV infection in China (http://www.chinacdc.cn/mtbd_8067/201602/t20160214_125262.html). On March 12th, 2016, the first imported case of YFV was also first reported in China (http://www.nhfpc.gov.cn/). Of note, all six imported cases of YFV had a history of working in Angola and were not vaccinated before going there. Five of six YFV patients had fever and other mild clinical symptoms including malaise. Cases 1 & 2 had severe liver damage and case 6 had no syndrome. Cases 1 & 2 are in stable condition.

What is the big risk which could be caused by imported cases in developing countries such as China?

In 2015, due to a lack of timely and effective control measures, Brazil became the center of the ZIKV outbreak and potentially millions of Brazilians were infected.[12,13] In order to prevent such outbreaks and infection rates in China and other non-endemic countries, surveillance at country borders will be an important measure to prevent the import of ZIKV and YFV. For example, the second imported ZIKV case in China was caught early due to the detection of a fever when entering the country and was then confirmed as a ZIKV case (http://www.aqsiq.gov.cn/zjxw/zjxw/zjftpxw/201602/t20160215_461558.htm). Most people infected with ZIKV will not show any clear symptoms,[14] because the viremia is too short to detect viral RNA by PCR, and serologic tests for ZIKV can often be falsely positive because of cross-reaction with other flaviviruses such as Dengue virus and YFV.[15] So the development of a rapid, specific and sensitive diagnostic test is urgently needed in China, and it should be able to distinguish ZIKV from other viruses, particularly Dengue and Yellow fever virus infections.

In China, *Aedes* is broadly distributed in southern China (resulting in a large number of dengue cases). Here the warm weather and precipitation are ideal for promoting the population growth of *Aedes*,[16] and the risk of imported ZIKV and YFV spreading within these areas is large. Without proper measures to control ZIKV and YFV in southern China, imported cases run a high risk of becoming the source of an outbreak.

How important is it to prevent the outbreaks?

Since ZIKV and YFV are vector-borne diseases, the significant risk factor for these infections is the presence of the

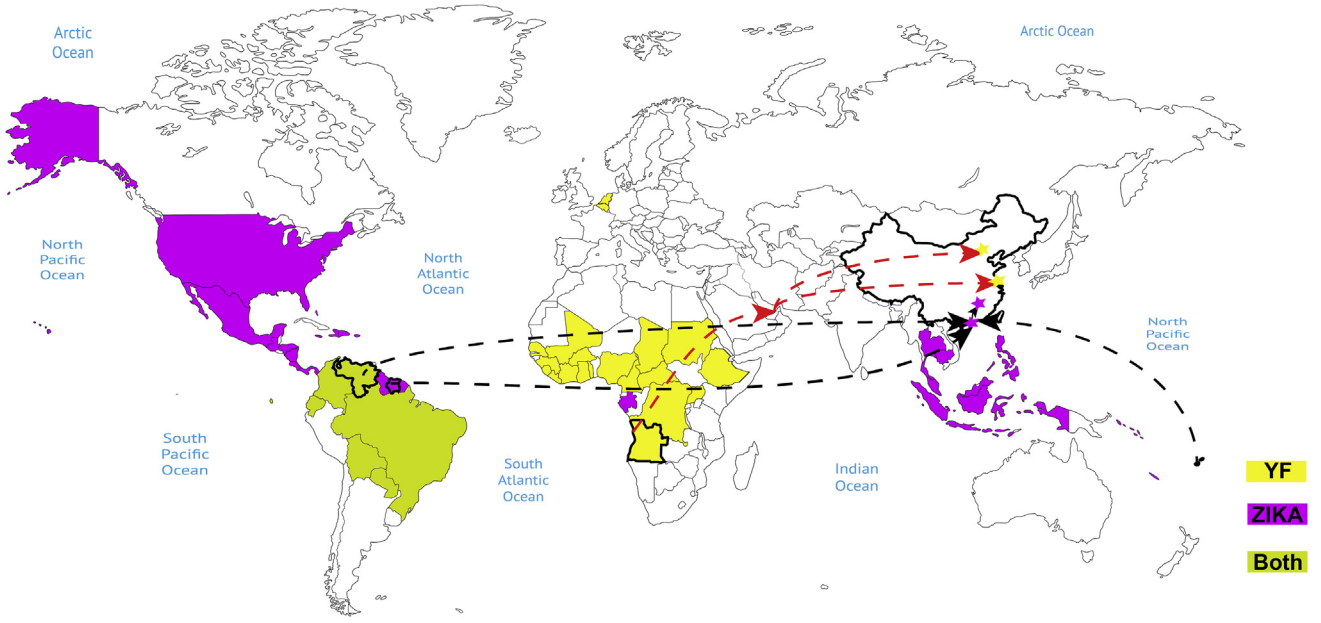

Figure 1 World map documenting all known imported Zika virus or Yellow fever cases to China and affected countries. Countries affected by Zika virus are shown in purple. Countries affected by Yellow fever virus are shown in yellow. Black arrows show Zika virus importations in China and red shows imported Yellow fever cases.

mosquito vector. Therefore, the people who reside in or who are traveling in an area where there is active transmission of those viruses, should protect themselves from mosquito bites. Therefore reducing the population of mosquito vectors through the use of mosquitocide at the community level is important to prevent the outbreaks.

China has a large population and is in a period of rapid economic development, which leads to frequent population exchange between China and other countries. The high rate of travel combined with southern China's natural climate and *Aedes* misquito population, make it imperative to prevent the import and spread of ZIKV and YFV in order to prevent future outbreaks in human populations. Fortunately, the development of new technology of China may become central to preventing ZIKV from entering the country. We need to take all necessary measures to control *Aedes* mosquitos before the weather becomes warm while applying strict border surveillance to prevent the importation of ZIKV and YFV into southern China.

Competing interests

The authors declare that they have no competing interests.

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Supplementary data

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References

1. Awate P, Yadav P, Patil D, Shete A, Kumar V, Kore P, et al. Outbreak of Kyasanur forest disease (monkey fever) in Sindhudurg, Maharashtra State, India, 2016. *J Infect* 2016 Jun;**72**(6):759—61. PubMed PMID: 26997635.
2. Buckingham SC. Tick-borne diseases of the USA: ten things clinicians should know. *J Infect* 2015 Jun;**71**:S88—96. PubMed PMID: WOS:000355828900014. English.
3. Chan JF, Choi GK, Yip CC, Cheng VC, Yuen KY. Zika fever and congenital Zika syndrome: an unexpected emerging arboviral disease. *J Infect* 2016 May;**72**(5):507—24. PubMed PMID: 26940504.
4. Wieten RW, Goorhuis A, Jonker EF, de Bree GJ, de Visser AW, van Genderen PJ, et al. 17D yellow fever vaccine elicits comparable long-term immune responses in healthy individuals and immune-compromised patients. *J Infect* 2016 Jun;**72**(6):713—22. PubMed PMID: 27017899.
5. Foy BD, Kobylinski KC, Chilson Foy JL, Blitvich 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. PubMed PMID: 21529401. Pubmed Central PMCID: 3321795.
6. Mlakar J, Korva M, Tul N, Popovic M, Poljsak-Prijatelj M, Mraz J, et al. Zika virus associated with microcephaly. *N Engl J Med* 2016 Mar 10;**374**(10):951—8. PubMed PMID: 26862926.
7. Barrett AD, Monath TP. Epidemiology and ecology of yellow fever virus. *Adv Virus Res* 2003;**61**:291—315. PubMed PMID: 14714435.

8. McNeill JR. Yellow jack and geopolitics: environment, epidemics, and the struggles for empire in the American tropics, 1650–1825. *OAH Mag Hist* 2004;**18**(3):9–13.
9. Staples JE, Monath TP. Yellow fever: 100 years of discovery. *JAMA* 2008 Aug 27;**300**(8):960–2. PubMed PMID: 18728272.
10. Aseffa A. Viral diseases in Ethiopia: a review. *East Afr Med J* 1993 Oct;**70**(10):624–6. PubMed PMID: 8187657.
11. Gardner CL, Ryman KD. Yellow fever: a reemerging threat. *Clin Lab Med* 2010 Mar;**30**(1):237–60. PubMed PMID: 20513550. PubMed Central PMCID: 4349381.
12. Bogoch II, Brady OJ, Kraemer MU, German M, Creatore MI, Kulkarni MA, et al. Anticipating the international spread of Zika virus from Brazil. *Lancet* 2016 Jan 23;**387**(10016):335–6. PubMed PMID: 26777915.
13. Ai JW, Zhang Y, Zhang W. Zika virus outbreak: 'a perfect storm'. *Emerg Microbes Infect* 2016;**5**:e21. PubMed PMID: 26956448.
14. Samarasekera U, Triunfol M. Concern over Zika virus grips the world. *Lancet* 2016 Feb 6;**387**(10018):521–4. PubMed PMID: 26852261.
15. Petersen E, Wilson ME, Touch S, McCloskey B, Mwaba P, Bates M, et al. Rapid spread of Zika virus in the Americas — implications for public health preparedness for mass gatherings at the 2016 Brazil Olympic Games. *Int J Infect Dis* 2016 Mar;**44**:11–5. PubMed PMID: 26854199.
16. Jin LQ, Li D. A recent survey of mosquito fauna in Guangdong Province, southern China, with a review of past records [corrected]. *Med Vet Entomol* 2008 Dec;**22**(4):359–63. PubMed PMID: 19120964.

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Audit of guidelines for antimicrobial management of cellulitis across English NHS hospitals reveals wide variation

Cellulitis is a common condition managed by a wide range of clinicians. Guidelines for the management of cellulitis are variable and are based on evidence predominantly from studies of skin and soft tissue infections and on expert opinion.[1–5] Anecdotal discussions with clinicians and reviews of hospital guidelines within the UK have highlighted that there is significant variation in its management. In order to quantify the heterogeneity in the management of limb cellulitis we undertook an audit of guidelines from 23 acute NHS Trusts in England.

The majority of acute Trusts (15/23 (65.2%)) were categorised as district general hospitals. There were no clear definitions for non-severe and severe cellulitis and 3 guidelines did not mention severity. For non-severe cellulitis 17 recommended oral flucloxacillin alone as the first choice; one guideline recommended oral penicillin, but that flucloxacillin should be used if there was broken skin; a second guideline recommended either oral penicillin or amoxicillin or flucloxacillin; a third recommended a combination of amoxicillin and flucloxacillin. Two guidelines made recommendations for the first line management of patients with cellulitis known to be colonised with MRSA; either the addition of doxycycline to flucloxacillin, or the use of doxycycline and rifampicin.

Where dosing recommendations were made for non-severe cellulitis; 10 guidelines recommended oral flucloxacillin at a dose of 500 mg; five guidelines recommended a dosing range of 500 mg–1 g; four guidelines recommended flucloxacillin at a dose of 1 g all six-hourly.

A variety of antimicrobial agents were recommended for non-severe cellulitis in patients with allergies to penicillin. Some guidelines offered more than one option, depending on the nature and severity of the reported allergy. Overall, clarithromycin was the most common agent recommended (13/23 (56.5%)), followed by clindamycin (7/23 (30.4%)) and doxycycline (6/23 (26.1%)). In guidelines recommending clindamycin there was variation in the recommended dose and frequency of administration; 300 mg eight-hourly (one guideline), 300 mg six-hourly (one guideline), 450 mg eight-hourly (one guideline), 450 mg six-hourly (two guidelines)