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Abstract

Background: Zika virus infection (ZIKV) has caused major outbreaks in tropic and sub-tropic areas. No case from ZIKV has yet been reported in the countries of the Eastern Mediterranean Region (EMR) despite the presence of competent vector Aedes mosquitoes in many of these countries.

Aims: This study addresses appropriate surveillance strategies for early detection of ZIKV infection, which is important for EMR countries with established Aedes populations, but with no known or documented autochthonous transmission of ZIKV.

Methods: The WHO Regional Office for the Eastern Mediterranean developed a strategic framework for enhancing surveillance for ZIKV infection in EMR countries with established Aedes populations through a consultative process and review of available evidence.

Results: The framework calls for enhancing surveillance for early detection of ZIKV infection using a combination of both syndromic and event-based surveillance approaches.

Conclusions: Enhancing surveillance for ZIKAV would require no shift in the existing system. A number of considerations would be required to integrate this syndromic and event-based surveillance approaches within the existing system.

Keywords: Zika virus infection, Eastern Mediterranean Region, syndromic surveillance, Aedes, event-based surveillance

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Introduction

Zika virus (ZIKV), is an arbovirus transmitted primarily by Aedes mosquitos to humans, and has caused major outbreaks in French Polynesia, Brazil and elsewhere in tropic and sub-tropic areas in the past. (1–4). ZIKV causes mild and self-limiting infection in majority of patients but recent evidence indicates that ZIKV infection can be potentially associated with severe complications including congenital birth defects and neurological disorders such as microcephaly and Guillain-Barré syndrome. (5–10). In February 2016, the World Health Organization (WHO) declared the clusters of microcephaly and neurological disorders potentially associated with ZIKV as Public Health Emergency of International Concern (PHEIC) (11).

Although no ZIKV infection has yet been reported in the countries of the Eastern Mediterranean Region (EMR), competent disease vector Aedes mosquitoes are present in many countries in the Region (12,13) and a number of countries have reported outbreaks of dengue, chikungunya and yellow fever in the past, which are all transmitted by the same Aedes mosquitoes (13). In the globalized world, the risk of importation of ZIKV into EMR countries through a viraemic traveler returning from one of the ZIKV affected countries is a possibility, since it has happened in the recent past (14,15). Once the virus is introduced, the risk of local transmission of ZIKV remains high in EMR countries where Aedes populations and major arboviral disease outbreaks transmitted by the same Aedes species have occurred in the past (12,16–18). In the WHO's new country classification scheme for ZIKV, eight countries from the Eastern Mediterranean Region are included in Category 4, which means that a main competent vector is established in these countries with no known or documented autochthonous case of ZIKV infection (19). Considering that the Region is already besieged with so many health problems, including the fact that many of the countries within the WHO's Zika virus classification are chronically affected by fragility and conflict, it is imperative for early detection and timely response to any cluster of ZIKV infection. This will not only reduce the potential consequences of ZIKV infection but will also reduce the economic cost of health systems managing these severe complications of ZIKV infection.

In view of the threat of introduction of ZIKV infection, the WHO Regional Office for the Eastern Mediterranean (WHO/EMRO) launched a regional plan for enhancing preparedness and readiness measures for ZIKV infection to improve prevention, detection and response to the spread of the virus in the Region. One of the key priority activities of this plan was to recommend an effective surveillance strategy for early detection of the introduction, or any autochthonous transmission of ZIKV infection in EMR countries with competent Aedes species populations. This article describes the recommended strategy for enhancing surveillance systems for detection of ZIKV infection in settings where the Aedes mosquitoes are known to exist and no cases have so far been reported or documented.

Framework development for enhancing surveillance

To define an appropriate surveillance strategy for detection of clusters of ZIKV infection transmitted by Aedes mosquitoes, WHO/EMRO organized a consultative meeting for selected countries that are endemic for other arboviral infections in Islamabad, Pakistan during 14–16 November 2016. Senior level epidemiologists and disease surveillance officers working in these countries as well as a number of experts from WHO and WHO Collaborating Centers came together and reviewed the available evidence and data on the epidemiology and clinical manifestations of the ZIKV infection. A draft framework for enhancing surveillance systems in EMR countries with no known or autochthonous transmission of ZIKV infection was developed following this consultative process.

To follow up on the outcome of the regional consultative workshop, an expert group meeting was held 22–23 January 2017 in Cairo, Egypt, with the objectives of finalizing the framework and developing an algorithm for detection, verification and investigation process.

Framework for enhancing surveillance for detection of cluster of ZIKV infection

In areas where ZIKV infection is not endemic, early detection of a single case is highly improbable since over 80% of cases can be asymptomatic (20). Conventional indicator-based disease surveillance systems may not be able to pick up the first few cases since such systems rely on well-known diseases with specific case definitions and/or laboratory confirmation. More importantly, there is considerable overlapping of clinical symptoms (Table 1) between ZIKV and other arboviral diseases caused by the same Aedes species (20). There is also serologic cross-reactivity among arboviral diseases occurring in similar geographic areas. (4,21,22). In view of limitations of existing conventional disease surveillance systems to detect ZIKV infection in non-endemic settings, effective surveillance systems that are appropriate for resource-poor settings and can identify a potential cluster where laboratory capacity to detect the ZIKV is limited, should be the goal to prevent local transmission (12,23).

Syndromic surveillance approach for early detection

There was a consensus that the goal of an appropriate surveillance strategy for EMR countries with no known or documented autochthonous transmission of ZIKV infection would be to detect early a “cluster” of suspected ZIKV cases. Owing to overlapping symptoms and clinical manifestations, single or first few suspected cases of ZIKV infection are likely to be missed. As such, a syndromic surveillance approach would be the best fit since the focus here is to detect a “cluster” on the basis of early symptoms of cases using a syndromic case definition before clinical diagnosis or laboratory confirmation is made. In the context of syndromic surveillance

approach, warning signs (Table 2) remain important aspects for early detection of diseases that present themselves initially with mild clinical manifestations, while the evidence for any specific clinical or laboratory marker is weak or not available.

After a review of the main epidemiological and clinical characteristics and existing case definitions of Zika, dengue and chikungunya, a working case definition for a suspected “case” and “cluster” was developed for use for a syndromic approach. (Table 3). Using such a syndromic case definition, health workers, even at the primary health care level, can alert/report the cluster corresponding to the case definition of clusters. This will then trigger steps for conducting field investigation by the district level surveillance officials as well as collecting more detailed epidemiological and clinical information in a line list and also collecting samples for laboratory confirmation. Blood samples should be collected preferably from acute febrile patients during the viraemic phase within 5 days of illness onset and should be sent for serological tests and reverse transcription polymerase chain reaction (RT-PCR). The laboratory confirmation tests should be considered in patients with acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis who live in or have traveled to an area with ongoing transmission in the 2 weeks preceding the illness onset. The possible diagnostic tests for confirming the presence of one of the targeted arboviral diseases should be available in the reference laboratory of the country.

Event-based surveillance for detection of ZIKV infection

In countries where event-based surveillance (EBS) systems have been functioning as part of national disease surveillance systems for early detection of health threats, including other arboviral diseases, such systems can also be used for detection of ZIKV infection. The strategy here would be to use the existing non-conventional sources of information related to other arboviruses such as dengue or chikungunya as well as other important information sources that may be specific to ZIKV infection. As the neurological manifestations potentially associated with ZIKV infection may appear late, identification of excess numbers of Guillain-Barré syndrome (GBS) or incidence of congenital birth defects and microcephaly in health facilities regarded as “excess” or “unusual”, should be a trigger for further investigation to rule out or confirm its association with ZIKV infection. In accordance with the source of information, the verification processes should consider establishing formal channels of communication for validation at national or local level.

A generic algorithm for detection of ZIKV infection using a syndromic case definition approach and event-based surveillance approach is presented in Figure 1 .

Discussion

Syndromic surveillance is now being used in many countries, specifically in resource limited settings for the early detection of outbreaks and clusters of health events. (24–27). The system relies on early stage of illness (symptomatic period) and uses both clinical and alternative data sources (28). In the case of ZIKV infection where majority of cases are either asymptomatic or present with mild infection and considerable overlapping of clinical symptoms with other diseases such as dengue, chikungunya, influenza, measles and malaria (29), the goal of the surveillance system in the countries where these diseases are endemic should be to detect a "cluster" of febrile syndromes and not a "case" using a more broader and sensitive syndromic case definition. It is plausible that detection of a "case" will lead to unnecessary resource-intensive and time-consuming procedures, while detection of a cluster can lead to a series of specific field investigations leading to verification and laboratory testing either to confirm (or dismiss) the existence of ZIKV circulation. In parallel, entomological surveillance needs to be purposeful and aligned to periodical risk assessment to detect high densities of competent vectors in high-risk areas (30). The entomological surveillance should be directed in high-risk areas not only to detect high densities of competent vectors, but also to assess the probability and efficiency of transmission of ZIKV from mosquitoes to human by detecting the virus and assessing the infectivity of mosquito vectors through appropriate molecular diagnostic tests.

On the basis of this rationale, the syndromic surveillance approach is highly recommended in EMR countries where indigenous transmission is low or absent or not documented, since the cost for establishing such a system is reasonable, supplements the functions of the existing surveillance system in the country, and has been ideally used to detect a new health event elsewhere (31,32). It is expected that using a syndromic approach, the warning signs of an impending outbreak of ZIKV infection would be detected early on, leading to further field investigation for confirmation.

The framework also suggests to enhance syndromic surveillance in only those geographic areas of the countries which are known to be habitats for Aedes population. These areas should also be targeted for enhanced entomological surveillance in order to detect early any evolving signs of high densities of competent vectors. Active surveillance for detection of high density of competent vectors should be conducted in and around areas where a single or preferably a cluster of cases of chikungunya, dengue and yellow fever has been detected or suspected in the past. The algorithm presented in the framework is only for verification purposes. It starts with case definitions to be used for detection purpose and flows in a stepwise manner, and include steps for verification and response as well as setting a clear pathway for laboratory confirmation of the collected sample.

The silent introduction of ZIKV infection can be picked up by an existing EBS system of a country if the data sources for EBS become tuned to the nature and clinical manifestations of

ZIKV infection in humans. In addition to using data from nonconventional sources (e.g., media news, reports, stories, rumours etc.) could be useful (33,34). In case of detecting ZIKV transmission, the existing EBS of a country should focus on all established data sources that may represent early signs of arboviruses, but in particular the system should be geared to collecting information on the complications of ZIKV infection such as congenital Zika syndrome and GBS. The information in this phase of the process should be gathered by 'triage', e.g., cluster of fever and conjunctivitis (or others clinical symptoms/syndromes) or death from arboviral disease or syndrome, unusual increase in deaths particularly in an array of fever and conjunctivitis (or other clinical symptoms/syndromes), and unexpected and excess microcephaly signs among recently born babies. A multi-sectoral approach is also required for EBS and should rely on sources of information beyond the traditional health system sources (35).

Several strategic requirements need to be considered to implement an enhanced surveillance system for ZIKV infection. Syndromic definitions for early detection of any cluster or outbreak need to be validated constantly. Risk communication to improve the level of knowledge among health workers and the population at risk is helpful in order to consider the diagnosis of ZIKV infection when experiencing an acute febrile illness. Travel history within the past 2 weeks of acute febrile illness is an important marker that should not be overlooked.

Finally, such a system must be an integral part of the country's existing disease surveillance and reporting system. Experience has shown that incorporating both syndromic and EBS systems into existing surveillance systems could be useful and realistic for detection of ZIKV infection (36). In order to do so, there is a need to include ZIKV infection as one of the newly emerging notifiable disease conditions, establish a case definition, and train public health professionals on the use of syndromic and EBS system approach. While integrating the surveillance system for ZIKV infection within the existing disease reporting system in the country, data from the existing AFP surveillance system, as well as from any other surveillance system to detect and monitor the trend of GBS, microcephaly or other congenital birth defects, should be used for verification purpose. Relying on these existing reporting systems with adequate laboratory network support could prove to be decisive (37-39). In order to ensure the sustainability of the performance of the surveillance system, the quality of the data reported should be monitored rigorously. Consequently, the system needs to collect data that are more sensitive than specific, and both primary and secondary sources of data need to be explored for triangulation and verification.

Future direction

The emergence of Zika and other arboviral diseases in recent years has posed formidable challenges to public health, disease control and particularly the conventional disease surveillance system. Novel surveillance approaches including both the syndromic and EBS need to be implemented at country levels, which would also serve to fulfill the real-time

surveillance function as required by International Health Regulations (2005). In malaria endemic countries, one of the important considerations would be to establish an integrated vector control management system for arboviruses, leveraging on the existing malaria control programme and infrastructure for greater efficiency measure. An integrated vector control management sysytem should seek to reduce the potential breeding sites; this would mean that vector populations should be kept as low as practically possible throughout the year, particularly in their habitats until an outbreak occurs.

The proposed framework for enhancing surveillance for ZIKV infection highlighted the importance of defining surveillance strategies for the detection of clusters of ZIKV infection in EMR countries with established Aedes populations. High-risk countries need to roll out this framework in order to reduce the threat of the introduction of ZIKV. According to the prevailing surveillance systems and situations of each country, the at-risk countries should make arrangements for establishing such systems including setting mechanisms for collaboration and communication within health sectors as well as among other sectors. Such systems once functional can also be used for early detection of other arboviral diseases outbreaks, including the detection of other emerging and novel infectious diseases.

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Renforcement de la surveillance pour le dépistage précoce de l’infection par le virus Zika : stratégies destinées aux pays de la Région de la Méditerranée orientale

Résumé

Contexte : L’infection par le virus Zika est à l’origine d’importantes flambées épidémiques dans les régions tropicales et subtropicales. Aucun cas d’infection par le virus Zika n’a encore été signalé dans les pays de la Région de la Méditerranée orientale malgré la présence, dans nombre d’entre eux, de moustiques compétents du genre Aedes, vecteurs du virus.

Objectifs : La présente étude porte sur les stratégies de surveillance à mettre en œuvre pour le dépistage précoce de l’infection par le virus Zika, particulièrement important dans les pays de la Région de Méditerranée orientale où des populations d’Aedes sont établies mais dans lesquels aucune transmission autochtone de ce virus n’est connue ou documentée à ce jour.

Méthodes : Par l'intermédiaire d'un processus consultatif et d'examen des données disponibles, le Bureau régional de l'OMS pour la Méditerranée orientale a développé un cadre stratégique en vue d'améliorer la surveillance de l'infection par le virus Zika dans les pays de la Région de Méditerranée orientale où sont établies des populations d'Aedes.

Résultats : Afin de dépister de façon précoce l'infection par le virus Zika, ce cadre préconise une meilleure surveillance en recourant à la fois à la surveillance syndromique et basée sur les événements.

Conclusions : Le renforcement de la surveillance du virus Zika n'impliquerait pas le changement du système actuel. Un certain nombre d'aspects devraient être pris en compte afin d'intégrer ces approches de surveillance syndromique et basée sur les événements dans le système existant.

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