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Abstract

Background: The emergence and re-emergence of viral haemorrhagic fevers (VHFs) is a growing concern worldwide. They are associated with major epidemics with an estimated 51–101 million cases each year, of which around 67 000 are fatal. In 2007, 13 countries in the Eastern Mediterranean Region reported VHF cases.

Aims: The main purpose of the study was to review the epidemiological situation in the Region vis-à-vis VHFs to obtain baseline epidemiological information for the establishment of the Emerging Dangerous Pathogen Laboratory Network (EDPLN).

Methods: A literature search was performed using PubMed, ProMED-Mail and GIDEON databases. Reported data included disease burden (reported cases and deaths), human prevalence (general population, high–risk groups), vectors and reservoirs. A scoring method was employed to divide countries into 4 groups (very highly, highly, medium and low affected countries).

Results: Very highly affected countries were Afghanistan, Egypt, Islamic Republic of Iran, Saudi Arabia and Sudan. Highly affected countries were Djibouti, Morocco, Oman, Pakistan, Tunisia and Yemen. Medium affected countries were Iraq, Somalia and United Arab Emirates. Low affected countries were Bahrain, Jordan, Lebanon, Libya, Palestine, Qatar and Syrian Arab Republic.

Conclusions: This study contributes in prioritizing countries to be part of EDPLN and in addressing specific needs related to outbreak investigations, surveillance and research.

Keywords: viral haemorrhagic fevers, Eastern Mediterranean Region, prevalence, Emerging Dangerous Pathogen Laboratory Network

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Introduction

Viral haemorrhagic fevers (VHFs) are among the most important pathogens that may cause public health emergencies of international concern (PHEIC) as defined by the International health regulations (2005) (IHR) (1). It is estimated that VHFs cause between 51 and 101 million (mostly dengue fever) cases each year, of which around 67 000 are fatal (2). The emergence and re-emergence of VHFs is a growing concern worldwide. They are associated with the occurrence of major epidemics with high case fatality rates. In the past 2 decades, the Eastern Mediterranean Region has witnessed several major outbreaks of different VHFs. In 2007, 13 countries of the Region reported VHF cases (3). Lack of timely laboratory diagnosis and functional epidemiological surveillance, inadequate infection control practices at health care facilities, lack of specific vaccines and weak vector control programmes could result in prolonged outbreaks.

The Global Health Security agenda is an effort between the government of the United States of America, other nations, international organizations and public and private stakeholders to

accelerate progress toward a world safe and secure from infectious disease threats and to promote global health security as an international priority. Developing and deploying novel diagnostics and strengthening laboratory systems are part of the strategy.

Early confirmation of VHF diseases requires specialized laboratories with appropriate biosafety levels, a capacity for accurate diagnosis of emerging viral pathogens and a functional regional network of laboratories to provide a service that covers all the countries in the Region. The World Health Organization (WHO) Emerging and Dangerous Pathogens Laboratory Network (EDPLN) is made up of global and regional networks of high security human and veterinary diagnostic laboratories (4). The EDPLN was established to assist WHO in enhancing both the readiness and the response of countries for timely laboratory detection and management of outbreaks of novel, emerging and re-emerging pathogens and in facilitating the transfer of safe and appropriate diagnostic technologies, practices and training to laboratories in affected countries, as outlined in the IHR (2005) (1).

The WHO Regional Office for Africa established its EDPLN networks in 2010 (5). Building the human and institutional capacities of designated laboratories for preparedness and response to emerging dangerous pathogens (EDP) (such as Ebola virus disease, MERS-CoV or Zika virus) is one of the priorities of the Member States of the Eastern Mediterranean Region. Currently, there are some laboratory networks in the Region operating under different clusters within the WHO Regional Office. These include the Poliomyelitis Laboratory Network (EPLN), Measles and Rubella Laboratory Network, Yellow Fever Laboratory Network, Japanese Encephalitis Laboratory Network, HPV Laboratory Network (LabNet), Rotavirus Laboratory Network, Invasive Bacterial Vaccine-Preventable Diseases (IB-VPD) laboratory network. However, diagnosis capacities for EDP remain extremely limited in most Member States. The issue is further exacerbated by the lack of WHO collaborating centres or reference laboratories in the Region with the capacity for and experience of EDP testing that could provide support and technical assistance to other countries. Hence there is an urgent need to establish a functional EDPLN system in the Region, providing reliable, accurate and timely diagnosis at all levels.

The network will include national EDP reference laboratories among the 22 countries of the Region. It will serve for laboratory surveillance, detection of and response to EDP and as reference laboratories for confirmation of cases and capacity-building in all countries of the Region. Effective design of the laboratory network critically depends on the availability of information on the epidemiologic situation, patterns and hotspots of VHF in the Region.

The main purpose of this study was to review the epidemiological situation in the Eastern Mediterranean Region vis-à-vis VHFs to obtain baseline epidemiological information for the

establishment of the Emerging Dangerous Pathogen Laboratory Network.

Methods

Setting

The WHO's Eastern Mediterranean Region comprises 22 countries: Afghanistan, Bahrain, Djibouti, Egypt, Islamic Republic of Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syrian Arab Republic, Tunisia, United Arab Emirates and Yemen.

Viral haemorrhagic fevers

The present work does not address the exhaustive list of diseases which are diagnosed routinely: the target was biosafety levels 2 and 3 (BSL2/BSL3) diagnostic facilities. Viral haemorrhagic fevers served as a reference for the establishment of the EDPLN; they include Crimean–Congo haemorrhagic fever, dengue/dengue haemorrhagic fever, West Nile fever, Rift Valley fever, yellow fever, Hanta fever, Alkhurma haemorrhagic fever, tick-borne encephalitis and Ebola.

Literature review

A literature search was performed in PubMed, ProMED-Mail and GIDEON databases using country name and disease/virus specific terms. Additional sources of information included WHO and Centers for Disease Control and Prevention webpages. The analysis period was restricted to 1995–2015. All information/studies older than 1995 were excluded. Epidemiological information considered in this review included reported cases and deaths (including notable outbreaks), prevalence and seroprevalence studies among humans and/or accidental hosts and associated individual risk factors, vectors and reservoirs, environmental risk factors (e.g. flooding, drought) and geographical distribution (literature review available on request from the corresponding author). Data were analysed by country and by disease/virus. All available epidemiological information considered above was reported. Particular attention was paid to the date of the report/study, its location and its result (number of cases, seroprevalence/prevalence).

Analysis

The analysis aimed at identifying "hotspots" of VHF in the Region in order to inform the establishment of EDPLN. To our knowledge, there is no standardized method that applies to this particular objective, therefore, for the purposes of this study, a simple working method was established. This method consisted in using 6 epidemiological criteria (i.e. number of reported cases, number of reported deaths, prevalence in general population, prevalence in high–risk groups, prevalence in vectors and prevalence in reservoirs) to score each country.

Epidemiological criteria

For reported number of cases and deaths, the total number for each pathogen was approximated by adding all reported cases and deaths from the literature review. When numbers were approximated in the literature review (e.g. n > 500), the nearest rounded number was selected (e.g. n = 500). Outbreaks without a specified number of cases were not included in the calculation. Equine populations are not a reservoir for West Nile Fever viruses but rather an “end host”. As such, there were considered as human cases for the purposes of this study.

For the prevalence, estimates were separated between general population and high-risk groups among humans. Equine populations were considered as a high-risk group. Other high–risk groups included animal workers, military, people in care settings and sewage workers. The highest prevalence was selected if different estimates were available. This method does not aim to provide the true estimate but rather to compare countries with each other. Furthermore, calculation of a mean prevalence would need to weight each estimate by the total population, which was beyond the scope of this study.

For vectors and reservoir, the highest estimate was selected as well. Vectors included ticks, mosquitoes and fleas. Reservoirs included livestock, birds, rodents, dogs, camels and other mammals.

Cut-off values and score

The aim was to define a scoring system in order to compare countries on their VHF epidemiological criteria. First, we defined a cut-off value as the median value among all countries for each criterion and by pathogen. Then, the estimate for a criterion (number of cases or prevalence) was compared to this median value and a score was attributed. The scoring system was: 0 points when no data were available or the estimate was zero; 1 point when the estimate was greater than 0 but under the median value; 2 points when the estimate was equal to or greater than the median value. Finally, the total score for each country was calculated by combining the total score of the 6 criteria for all pathogens.

The 22 countries were divided into 4 groups (very high, high, medium and low affected countries) according to their total score. We first calculated the median of the total score and the interquartile range. Then, we compared the total score of each country to the median and interquartile range values in order to classify each country into one of the 4 categories: low affected country when total score was between zero and the first quartile value; medium affected country when total score was greater than the first quartile value and under the median

value; high affected country when total score was greater than the median value and under the third quartile value; and very high affected country when total score was equal or greater than the third quartile value.

Results

Reported cases and deaths

Total numbers and median of reported cases and deaths for VHFs during 1995–2015 are summarized in Table 1 . Human cases for at least 1 pathogen were reported in 13 (59%) countries. Considering equine cases, 14 (64%) countries reported VHF cases. Reported cases ranged from 2 for Alkhurma fever in Egypt to more than 30 000 for dengue fever in Pakistan. While the highest number of actual reported cases was for dengue fever, the VHFs which had the widest geographical distribution were Crimean–Congo haemorrhagic fever, dengue and West Nile fever with 8 countries each. The median for reported cases ranged from 42 for Crimean–Congo haemorrhagic fever to 1454 for yellow fever. The total reported deaths ranged from 8 in the Islamic Republic of Iran to 720 in Yemen. While Crimean–Congo haemorrhagic fever had the widest geographical distribution among countries, dengue was responsible for the greatest number of deaths: the number of reported deaths ranged from 3 Crimean–Congo haemorrhagic fever cases in Egypt to more than 500 dengue cases in Pakistan.

Prevalence in the general population and in high–risk groups

The highest VHF seroprevalence in the general population and in high–risk groups during 1995–2015 is summarized in Table 2 . Only 7 countries (31.8%) reported data on seroprevalence for at least 1 pathogen in the general population. Seroprevalence ranged from 0% for Crimean–Congo haemorrhagic fever to 21.8% for dengue fever, both in Djibouti. Medians ranged from 2.1% for Rift Valley fever to 21.8% for dengue fever. Seroprevalence was most frequently reported for West Nile fever; seroprevalence was not reported at all for some diseases (yellow fever, Alkhurma, tick-borne encephalitis and Ebola). Twelve countries (54.5%) reported data on seroprevalence in high–risk groups for at least 1 pathogen, ranging from 2.4% for Crimean–Congo haemorrhagic fever in Oman to 81.8% for Rift Valley fever in Sudan, with a median of 36.0%.

Vectors and reservoirs

Highest and median prevalence of VHF among vectors (ticks, mosquitoes) and reservoirs (livestock, birds, rodents, camels) are summarized in Table 3 . Only 3 (13.6%) countries reported a prevalence for vectors, Islamic Republic of Iran (28% for Crimean–Congo haemorrhagic fever in ticks), Oman (13% for Crimean–Congo haemorrhagic fever in ticks) and Egypt (1.7% for West Nile virus in ticks). Additionally, 4 countries reported the presence of VHF viruses in vectors without prevalence estimates. The remaining 15 countries did not report the presence or prevalence of vectors.

Eleven (50%) countries reported data on reservoirs for at least 1 pathogen. For Yemen, no prevalence was reported, however, as more than 9000 deaths due to Rift Valley fever were reported among livestock, a prevalence of 50% was attributed to this country. Distribution ranged from 1% for West Nile virus in birds in Tunisia and Crimean–Congo haemorrhagic fever in livestock in Egypt to 75% for Crimean–Congo haemorrhagic fever in livestock in Afghanistan. The median ranged from 3.6% for Hanta virus to 20.5% for Crimean–Congo haemorrhagic fever.

Crimean–Congo haemorrhagic fever was also the most frequently reported VHF among the countries, followed by Rift Valley fever and West Nile fever.

Scoring

Scoring results for the 6 epidemiological criteria are presented in Table 4 . Total scores ranged from 0 for Bahrain, Libya, Palestine and Qatar to 26 for Saudi Arabia. The median score was 6.0, with an inter-quartile range from 1.0 to 11.75. Countries above the third quartile were Afghanistan, Egypt, Islamic Republic of Iran, Pakistan, Saudi Arabia and Sudan. Scores were calculated for 63 (47.7%) of the 132 possible scores (6 × 22). The information most frequently missing was prevalence in both the general population and in vectors, followed by prevalence in the reservoir.

Using the scoring results on prevalence in humans and accidental hosts, countries were divided into 3 groups (high, medium and low relative prevalence). Countries with the highest relative prevalence for VHFs were Afghanistan, Djibouti, Egypt, Islamic Republic of Iran and Saudi Arabia. Countries with a medium relative prevalence for VHFs were Kuwait, Morocco, Oman, Pakistan, Sudan and Tunisia. Low affected countries were Bahrain, Iraq, Jordan, Lebanon, Libya, Palestine, Qatar, Somalia, Syria, United Arab Emirates and Yemen.

Using the scoring results on prevalence in vectors and reservoirs, countries were divided into 3 groups (high, medium and low relative prevalence). Countries with the highest relative prevalence for VHFs in vectors/reservoirs were Egypt, Islamic Republic of Iran, Oman, Morocco and Saudi Arabia. Countries with a medium relative prevalence for VHFs in vectors/reservoirs were Afghanistan, Kuwait, Lebanon, Somalia Sudan, Syrian Arab Republic, Tunisia and Yemen. Countries with a low relative prevalence for VHFs in vectors/reservoirs were Bahrain, Djibouti, Iraq, Jordan, Libya, Pakistan, Palestine, Qatar and United Arab Emirates.

Discussion

Global classification

Our scoring results for VHFs allowed for dividing the 22 countries from the East Mediterranean Region into 4 groups (very high, high, medium and low affected countries). This global classification should help in prioritizing countries to be part of EDPLN. Nevertheless, each country had specific epidemiological patterns of VHF: while some countries were more affected by outbreaks, others had higher prevalence among risk groups, vectors or reservoirs. Accordingly, specific recommendations for outbreak investigations, surveillance and research are addressed.

Outbreak investigation

Likewise, for the scoring results on disease burden only (reported cases and deaths), countries were divided into 4 groups. Each country had specific epidemiological patterns of VHF. However, some pathogens were common between neighbouring countries. Cross-border investigations should be particularly relevant for the following borders and pathogens:

Afghanistan, Islamic Republic of Iran and Pakistan borders: dengue fever and Crimean–Congo haemorrhagic fever;

Saudi Arabia and Yemen border: Rift Valley fever, dengue fever, Alkhurma haemorrhagic fever;

United Arab Emirates and Oman border: Crimean–Congo haemorrhagic fever.

By providing laboratory capacity, EDPLN should enhance the possibility of increasing outbreak investigations. This support might include mobile laboratory capacities, including mobile BSL3 and the rapid diagnostic test (RDT) for field investigation of VHF outbreaks. The EDPLN should play a critical role in building a roster for a multidisciplinary team during outbreak investigations. The One Health initiative should be used as an opportunity for this purpose as well as the IHR (1).

Emerging dangerous pathogens surveillance

By providing laboratory capacity, EDPLN should enhance the ability of countries to strengthen and/or set up laboratory surveillance in the general population and high–risk groups. According

to the scoring results on prevalence in humans and accidental hosts, countries were divided into 3 groups (high, medium and low relative prevalence). By providing laboratory capacities, EDPLN should also enhance the capacity of countries to strengthen and/or set up laboratory surveillance in animals. According to the scoring results on prevalence in vectors and reservoirs, countries were divided into 3 groups (high, medium and low relative prevalence). The role of livestock (Crimean–Congo haemorrhagic fever, Rift Valley fever, rickettsia and leptospirosis) and camels (MERS-CoV) as reservoirs for many VHFs makes livestock/camels an important focus and target for EDP surveillance. Since VHFs are almost always zoonotic, there is a need for focused surveillance at the human, livestock and wildlife interface. It is essential for EDPLN to conduct further serological studies in collaboration with the animal health sector. Environmental investigation (e.g. water and food storage) may also help in public health decisions.

There is a need for differential diagnoses for VHFs. An appropriate algorithm and syndromic approach needs to be developed and harmonized within the EDPLN. An example would be the development of multiplex panels for screening and confirmation of suspected VHF cases using the Integrated Disease Surveillance and Response case definition. A referral system for confirmation has been proposed for AFRO EDPLN (5).

Research

Information was scarce for many pathogens and countries, highlighting the need to perform operational research on VHFs. Discrepancies were noticed between criteria inside countries. For example, Afghanistan had a large number of cases but information on vectors and reservoirs was weak. This is an indication of the potential for research. Recommendations on research include performing, in order of priority:

prevalence studies in humans: for Crimean–Congo haemorrhagic fever (Iraq), for dengue fever and Rift Valley fever (Somalia);

vector and reservoir studies for Crimean–Congo haemorrhagic fever (Afghanistan, Iraq, Pakistan), dengue fever (Afghanistan, Pakistan, Somalia, Yemen), West Nile Fever (Afghanistan, Pakistan) and Rift Valley fever (Yemen).

Limitations

Analyses were based on available information, mainly from PubMed, ProMED-Mail and GIDEON databases. These 3 sources of information are reliable and well known. While

ProMED-mail and GIDEON are robust and sensitive mechanisms for the discovery of emerging disease outbreaks involving humans, animals and plants around the world (6), PubMed is a robust and specific mechanism for publishing data on surveillance and research. Other databases were not used. Some data might not have been captured because they were not included among our data sources. Embase is somewhat similar to PubMed, however, it has more of a European focus and concentrates to a greater degree on the pharmacological literature. The Cochrane Library is a collection of databases that bring together in one place research on the effectiveness of health care treatments and interventions, so it was not appropriate for our study. Furthermore, by using few key words for searching, we remained very sensitive among the 3 databases we used. It is worthwhile noting that reliability of data was prioritized for this work, and that unreliable data sources might lead to erroneous estimates.

Unpublished surveillance data from ministries of health were not included. While they would have improved the completeness of our study for some countries, it would have been difficult to combine both data sources (published and unpublished) without possible double counting.

Another challenge was to summarize each criterion. Although outbreaks were reported, the number of cases and deaths were not always reported. Numbers were reported from different sources with probable double counting. Some numbers were simple estimations while others were confirmed cases. For this study, confirmed cases were used when available. For prevalence, general population and high–risk groups, as well as vectors and reservoirs were separated because they should provide 2 distinct indicators. Information on the general population and among vectors was so scarce that a single criterion might have been an option. The challenge was finally to find the right balance between having a single criterion that might not capture all available information and too many criteria that might not inform our objective.

Another issue was the methodology for scoring each criterion. Although today there are a number of published tools to guide the process of setting priorities, only a few publications describe the methodology in sufficient detail and transparency to allow reproducibility or adaptation in other settings (7–9). The concept of hotspots in infectious disease epidemiology varies widely in current research, and may include aspects, such as incidence or prevalence, transmission efficiency or risk, or probability of disease emergence (10). For our study, the objective was neither to assess socioeconomic level nor health system capacity, but rather the disease burden and its potential transmission in order to compare multiple diseases between multiple countries. Therefore, we used a working method for the specific purposes of this study. The aim was to compare countries according to available information rather than trying to provide absolute and precise estimates. The median value of available information for each pathogen was used with this aim. This method has the advantage of being simple and reproducible. Other methods include the use of spatiotemporal techniques and geographic information systems (11–13). But the objective in those studies is to assess factors responsible

for outbreak emergence and spread in a specific area. Furthermore, it is rare to have a complete databases with geopositioning of all cases, such as the one for Crimean–Congo haemorrhagic fever (14). Compared to the method used in Germany (15,16), our methodology did not weight each criterion: the availability of the data alone weighted each criterion. Alternatively, weighting would require a Delphi process, which was not possible for this study.

Conclusion

The results of this study highlighted hotspots for VHFs in the Region, including Afghanistan, Egypt, Islamic Republic of Iran, Saudi Arabia and Sudan. This global classification should help in prioritizing countries to be part of EDPLN. Nonetheless, each country had specific epidemiological patterns of VHFs. Accordingly, recommendations for outbreak investigations, surveillance and research were separately addressed.

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Competing interests: None declared.

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