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Editorial

Taking forward a 'One Health' approach for turning the tide against the Middle East respiratory syndrome coronavirus and other zoonotic pathogens with epidemic potential

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SUMMARY

The appearance of novel pathogens of humans with epidemic potential and high mortality rates have threatened global health security for centuries. Over the past few decades new zoonotic infectious diseases of humans caused by pathogens arising from animal reservoirs have included West Nile virus, Yellow fever virus, Ebola virus, Nipah virus, Lassa Fever virus, Hanta virus, Dengue fever virus, Rift Valley fever virus, Crimean-Congo haemorrhagic fever virus, severe acute respiratory syndrome coronavirus, highly pathogenic avian influenza viruses, Middle East Respiratory Syndrome Coronavirus, and Zika virus. The recent Ebola Virus Disease epidemic in West Africa and the ongoing Zika Virus outbreak in South America highlight the urgent need for local, regional and international public health systems to be be more coordinated and better prepared. The One Health concept focuses on the relationship and interconnectedness between Humans, Animals and the Environment, and recognizes that the health and wellbeing of humans is intimately connected to the health of animals and their environment (and vice versa). Critical to the establishment of a One Health platform is the creation of a multidisciplinary team with a range of expertise including public health officers, physicians, veterinarians, animal husbandry specialists, agriculturalists, ecologists, vector biologists, viral phylogeneticists, and researchers to co-operate, collaborate to learn more about zoonotic spread between animals, humans and the environment and to monitor, respond to and prevent major outbreaks. We discuss the unique opportunities for Middle Eastern and African stakeholders to take leadership in building equitable and effective partnerships with all stakeholders involved in human and health systems to take forward a 'One Health' approach to control such zoonotic pathogens with epidemic potential.

1. Introduction

The appearance, disappearance, and re-emergence of novel pathogens of humans with both epidemic potential and high mortality rates have threatened global health security for centuries.[1] Over the past few decades, notable new zoonotic infectious diseases of humans have been caused by pathogens arising from animal reservoirs, including West Nile virus, yellow fever virus, Ebola virus, Nipah virus, Lassa fever virus, hantavirus, dengue virus, Rift Valley fever virus, Crimean-Congo haemorrhagic fever virus, severe acute respiratory syndrome coronavirus (SARS-CoV), highly pathogenic avian influenza viruses, Middle East respiratory syndrome coronavirus (MERS-CoV), and Zika virus (ZKV).[2] The recent Ebola virus disease (EVD) epidemic in West Africa[3] and the ongoing ZKV outbreak in South America[4] highlight the urgent need for local, regional, and international public health systems to be better prepared.[5–8]

The unique opportunities for Middle Eastern and African stakeholders to take leadership in building equitable and effective partnerships with all stakeholders involved in human and health systems, to take forward a 'One Health' approach to control such zoonotic pathogens with epidemic potential, is highlighted here. In this article the example of MERS-CoV is used as an important case in point.

2. Need for newer approaches to control zoonotic diseases

The 2014–2015 EVD epidemic in West Africa showed that countries with weak health services and inadequate capacity to identify infectious disease outbreaks early are unable to respond appropriately to control the outbreak. International health agencies were too sluggish to effect an early resolution. There were no rapid point-of-care diagnostics, no specific treatments, no vaccines, and insufficient medical care facilities, teams, and trained staff, and furthermore the international responses were initially uncoordinated and unable to adapt policies and advice for a very different expression of the disease. As a consequence, aggressive community responses to inappropriate health interventions, foreign aid workers, and researchers unfamiliar with local cultural and health systems norms were common and life-threatening.[9,10] Research to find and evaluate new treatments and vaccines conducted during the EVD epidemic was also slow to start and was dominated by foreign groups with little involvement of local scientists.[7,9] The development and evaluation of experimental tools came too late to

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benefit the large majority of affected people. Some foreign aid workers and researchers were not familiar with local cultural and medical services norms and aroused local anxieties.[10]

The EVD epidemic highlighted the need for developing more comprehensive local, national, international, and global surveillance, as well as epidemic and outbreak preparedness response infrastructures. Multiple animal, human, and environmental factors are obviously playing a critical role in the evolution, transmission, and pathogenesis of zoonotic pathogens, and these require urgent definition to enable appropriate interventions to be developed for optimal surveillance, detection, management, laboratory analysis, prevention, and control in both human and animal populations.

An important need exists for establishing long-term, sustainable, trusting and meaningful and equitable collaborations between the animal, human, ecosystem, and environmental health sectors at the local, national, and international levels. These should include sustainable political and funder support for developing human and laboratory capacity and training that enables effective human–animal health cooperation leading to proactive surveillance, early detection of potential pandemic pathogens, and rapid initiation of public health prevention and control guidelines and interventions. Whilst a long list of pathogens with epidemic potential are on the radar of the World Health Organization (WHO),[2] ideally 'prevention is better than cure' and new pathogens should be dealt with at the animal source, tackling the drivers and triggers of pathogen evolution and emergence. This requires close cooperation between human and animal health systems and an appreciation of human impacts on the environment at all levels and easy access to adequate laboratory facilities.

3. WHO priority list of the top 10 emerging pathogens

On December 10, 2015 an expert panel convened by WHO prioritized a list of emerging pathogens "considered likely to cause severe outbreaks in the near future, and for which no, or insufficient, preventive and curative solutions exist".[11,12] The list of the top 10 includes the new viral zoonotic pathogen of humans MERS-CoV,[13,14] which was first isolated from a patient who died of a severe respiratory illness in a hospital in Jeddah, Saudi Arabia in June 2012.[15]

The emergence of MERS-CoV in 2012[15] was the second time (after SARS-CoV[16]) that a highly pathogenic coronavirus of humans emerged in the 21st century.[17] A strong link between human cases of MERS-CoV and dromedary camels has been established through several studies.[18–26] MERS-CoV is endemic in the camel populations of East Africa and the Middle East[21,25,26] and presents a constant threat to human health in both regions. Retrospective studies using stored serum from different geographical locations have indicated that MERS-CoV has been circulating for several decades.[25] As of May 1, 2016, there have been 1733 laboratory-confirmed cases of MERS reported to the WHO,[27] with a mortality of 34% (628 cases died). Whilst most MERS cases have been reported from the Middle East (a large proportion from Saudi Arabia), MERS cases have been reported from 27 countries in all continents.[27] The WHO has held nine meetings of the Emergency Committee (EC) for MERS-CoV.[28]

4. The persistent and lurking epidemic threat of MERS-CoV

Since evidence of sustained human-to-human transmission of MERS-CoV in the community is lacking, the WHO currently does not recommend travel restrictions to the Middle East. However, MERS-CoV remains a major global public health threat with continuing reports of new human MERS cases in Saudi Arabia, where millions of pilgrims from over 184 countries travel throughout the year.[29] Furthermore, a more intensive farm-based camel livestock system has emerged and there is a large, well-established trade in camels between countries at the Horn of Africa and countries in the Middle East. This has increased significantly, particularly following the lifting of the ban on live animal imports from Somalia by Saudi Arabia in 2009/2010. Somalia now exports some five million live animals every year to the Gulf Arab States (including 77 000 camels), making it the single biggest exporter of live animals in the world. The positive experience of reviving Somalia's livestock export industry through increased investment in animal disease prevention and control strategies highlights how effective the 'One Health' approach can be. Most of the African countries do not have the resources, expertise, or capacity, including laboratory facilities, to have active surveillance for MERS-CoV in place. In light of this, the need for increased vigilance and watchful surveillance for MERS-CoV in Sub-Saharan Africa has been highlighted previously.[30] Such an initiative could be supported through investments by countries that import large numbers of camels and other livestock from the region.

The epidemic potential of MERS-CoV was recently illustrated by a large outbreak in hospitals in Seoul, the Republic Korea, in mid-2015: MERS-CoV was imported by a traveller to the Middle East (an agriculture businessman), resulting in 184 MERS cases with 33 deaths.[31] The first case was reported on May 20, 2015 and over the ensuing 3 weeks, the number of secondary, tertiary, and perhaps quaternary cases of MERS from this single patient rose rapidly, resulting in the largest MERS case cluster occurring outside the Middle East. The unprecedented outbreak was attributed to poor infection control measures at the hospitals.[30] Sequencing studies of the MERS-CoV isolate showed genetic recombination of MERS-CoV in the case exported from Korea to China.[32] However, recombination is a frequent event in MERS-CoV and the Korean outbreak is unlikely to represent a special form of the virus. Nonetheless, the potential evolution of MERS-CoV into a more virulent form needs to be monitored closely.

Research on sequencing seems to have stagnated and there have been no further sequences published from new human MERS cases reported from the Middle East. Furthermore, the genetic evolution of MERS-CoV strains infecting humans over the past year remains unknown. There is an urgent need for more sequencing studies on MERS-CoV evolution in camels and humans, with the development of appropriate local capacity for these studies. The Kingdom of Saudi Arabia has kept proactive watchful MERS-CoV surveillance with regular reports to the WHO of MERS-CoV cases.[33] The WHO and ministries of health of Middle Eastern countries continue watchful surveillance of the MERS-CoV situation, and the watchful anticipation is that MERS-CoV may disappear with time like SARS-CoV. However, with the continuing, regular reports of community cases of MERS-CoV from Saudi Arabia,[27] there are no signs of this happening in the near future and lessons must be learnt from the Korean outbreak.[34] Whilst there is a growing camel livestock industry in the region, elimination of the virus is unlikely in the short term.

5. Urgent action required for more coordinated, collaborative multidisciplinary MERS-CoV research

Several animal, human, and environmental factors are obviously playing a critical role in the repeated movement of MERS-CoV from camels to humans. The disease ecology remains largely unknown. Urgent definition is required to enable appropriate interventions to be developed for optimal surveillance, laboratory detection, management, prevention, and control in both human and animal populations. Whilst several ad hoc research studies have been conducted and findings published over the past 4 years, more comprehensive investments in tackling MERS-CoV have not been forthcoming. There remain huge knowledge gaps on MERS-CoV.

Much of the information that we have about the source of MERS-CoV infections is based on small local studies and it is difficult to develop general country-wide policies without a clear understanding of the zoonotic problem. Questions remain, for example are new local MERS outbreaks in Saudi Arabia always seeded by the same type of human exposure to camels? Are there particular regions of Africa that provide infected camels to Saudi Arabia? Or is there a general risk from all regions? Is there a way to efficiently control the entry of infected camels? Are animal vaccination strategies economically viable given the large number of imported animals and the frequency of the infection?

A clear policy in which full virus genome sequences are generated from every outbreak in the country and in which virus from subsets of imported camels is routinely screened and sequenced after 2 years, would provide incredibly useful information about the transmission patterns of the virus and how to stop it. Certainly the resources and expertise to perform this sequence monitoring are available and only governmental support is needed to run such a survey. The cost of such a survey would be far less than the management costs and grief associated with a single hospital outbreak. Numerous priority research questions regarding MERS-CoV (basic science, epidemiology, management, and development of new diagnostics, biomarkers, treatments, and vaccines) in both humans and camels, highlighted 2 years ago by the WHO MERS expert groups[35] and by others,[36] remain unanswered. These have again been raised recently, highlighted by calls from Saudi Arabian health care staff and scientists[37,38] and by yet another WHO MERS expert group, which has defined a "Roadmap for Research and Product Development against MERS-CoV".[39]

6. Human, animal, and environmental factors

In 2000 the WHO set up the Global Outbreak Alert and Response Network (GOARN)[40] for better coordination of surveillance efforts across the globe. It networks 150 institutions and partner agencies, with cooperation with other agencies such as Public Health England and the US Centers for Disease Control and Prevention (CDC) and consortia such as the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC).[41] Recent consortia such as GLOPID-R aim to bring together research funding organizations on a global scale to facilitate an effective research response within 48 h of a significant outbreak of a new or re-emerging infectious disease with pandemic potential.[42] The past 4 years has seen outbreaks of Ebola virus, ZKV, and MERS-CoV,[2–4,13] which indicate that the global community needs to seriously reflect on what is critically missing from current political, scientific, and public health agendas, and how to delineate what is required at the national, regional, and global levels to prevent future epidemics.

The factors and operating conditions that promote the emergence and geographical spread of zoonoses are complex and may be related to a single event or chain of multiple events influenced by the genetic evolution of the pathogen, environmental and climate changes, anthropological and demographic changes, and movement and behaviour of humans, animals, and vectors. With animal, human, and environmental factors playing a critical role in its evolution, MERS-CoV requires more close collaboration between human and animal health systems and university academics to reduce the risk of pandemic spread.[43] Moreover, a better understanding of the agricultural dynamics involved in its persistence and spread in camels and studies on interactions between hosts in the environment are urgently needed. The intermittent detection and reporting of MERS cases in the community and sporadic nosocomial MERS-CoV outbreaks will require a more coordinated response plan to study clinical cases, conduct translational basic science and clinical trials research, and perform longitudinal sequencing studies from human and camel MERS-CoV isolates. A more collaborative MERS-CoV response plan is required to better define MERS-CoV epidemiology, transmission dynamics, molecular evolution, laboratory capacity, optimal treatment and prevention measures, and development of vaccines for humans and camels.[44] A better understanding of the prevailing disease ecology and investigations into the dynamics of infectious agents in wildlife could act as a better means of preventing outbreaks in livestock and people at source.

7. The 'One Health' approach to tackling MERS-CoV and other zoonotic diseases

The 'One Health' concept is an important concept that focuses on the relationship and interconnections between humans, animals, and the environment, and recognizes that the health and wellbeing of humans is intimately linked to the health of animals and their environment (and vice versa).[45–49] A balanced ecological approach improves understanding of the true threat of novel pathogens and helps to avoid costly, poor, and inappropriate responses to new diseases. In many cases, solutions can be found through altered development pathways and are not inevitably requiring of costly, unsustainable technical and pharmaceutical interventions. Thus it is ideally suited to the MERS-CoV situation in which camels, humans, and environmental factors are central to its persistence and evolution.

Since the Kingdom of Saudi Arabia is host to millions of pilgrims each year travelling from all continents,[29] tackling the threat of MERS and other infectious diseases with epidemic potential will require enhanced closer cooperation between those who provide human health, animal health, and environmental health services, locally, nationally, regionally, and internationally: the Middle Eastern, European, African, Asian, and American governments, veterinary groups, the WHO, the Food and Agriculture Organization (FAO), the African Union, the United Nations International Children's Emergency Fund (UNICEF), The World Bank, Office International des Epizooties (OIE), CDC, Public Health England, the newly formed Africa CDC, and funding agencies among others. They should now demonstrate increased commitment towards local, national, and global multidisciplinary collaborative efforts to secure optimal health for people, animals, and the environment. Global efforts need to be focused on establishing the capability for and strengthening of surveillance systems in developing countries, particularly in Africa where emerging and re-emerging zoonoses are a recurrent problem. A prime emphasis should be on developing awareness and response capacity in all countries and on promoting interdisciplinary collaboration and coordination. Critical to the establishment of a well-functioning 'One Health' platform is the creation of a multidisciplinary team with a range of expertise, including public health officers, physicians, veterinarians, animal husbandry specialists, agriculturalists, ecologists, vector biologists, viral geneticists, and researchers, with easy access to adequate laboratory facilities, who will collaborate in order to learn more about zoonotic spread between animals, humans, and the environment and to monitor, respond to, and prevent major outbreaks.

8. Capacity building for surveillance, outbreak response, and associated research

There is an urgent and critical need to build a sustainable public health programme and rapid response capability for outbreaks of zoonotic pathogens in the Middle East and in low-income countries, especially in Africa. Importantly there is a need for capacity development programmes designed to strengthen research training and build career pathways for the best and brightest post-doctoral researchers, including PhD and masters students working at the

interface of humans, animals, and environment. These should include national or regional laboratory facilities, as surveillance requires laboratory support to be meaningful. The development of human and animal health research leaders will create a critical mass of local research capacity and the development of self-funding research environments in African universities and research institutes. This capacity growth could be facilitated through the further development and support of a geographical network of equitable and enduring South–South and North–South partnerships.

9. Need for more effective political and scientific engagement to eradicate the threat of MERS-CoV and other zoonotic diseases

The persistence of MERS-CoV 4 years since its first discovery has created major opportunities for each of the Middle Eastern and African countries to take leadership of the 'One Health' approach with a view to bringing this under regional and global umbrellas, to tackle new emerging and re-emerging infectious diseases with epidemic potential. This will also devolve current dominance of the global health agenda by Western groups and consortia and allow equitable partnerships to be established with long-term sustainability. The past year has seen some progress in research into MERS-CoV, but there remains a need for a more effective, coordinated, and multidisciplinary 'One Health' consortium to take forward MERS-CoV research on priority areas already defined by Saudi scientists[37,38] and the WHO MERS Committee.[39] The establishment of regional 'One Health' Centres of excellence in the Middle East (under the League of Arab States) and at specific geographical locations in West, Central, East, and Southern Africa could make an important difference in mitigating the risks and factors that pose a risk to both human and animal health. Furthermore, any operational plan developed will contribute to strengthening the sentinel surveillance systems in Sub-Saharan Africa in the preparedness and response to potential outbreaks. Regional centres should be sufficiently empowered to manage the spectrum of 'One Health' approaches to zoonotic disease control in humans and animals, from behaviour change and social interventions for prevention to surveillance of infections and antimicrobial resistance, and preparedness and response to outbreaks.

A model for the major syndromes (respiratory, neurological, haemorrhagic, gastro-enteric, and sepsis-like presentations) should be developed so that clinical protocols may be adapted rapidly for any major outbreak during mass gatherings. This should include the development and introduction of innovative and smart platforms for data sourcing, sample collection, and analysis, in order to give clinicians and public health workers continuously updated information on which clinical decisions may be based. There is a pressing need to develop and strengthen the national ethics and medicines regulatory frameworks in Sub-Saharan Africa in order to strike a balance between the public health interest, the interests of the pharmaceutical industry, and ethical values. Parallel initiatives across Africa and the tropics could be harmonized to create regional networks that can serve as a repository for expert 'One Health' advice on agriculture, sustainable livestock, and the links to human development. There are several ongoing important initiatives on developing 'rapid response' and broader 'One Health' capacity development groups in Europe, Asia, and the Americas to assist in the surveillance and response to emerging infectious disease threats.

The public health systems of West African countries failed with the Ebola epidemic, and the response from the WHO and the international community was very slow and uncoordinated. This led to thousands of people, including over 500 health care workers, losing their lives. The factors governing the appearance and disappearance of new coronaviruses affecting humans are complex and it has been over 4 years since the first patient died of MERS-CoV. MERS cases continue to be reported throughout the year from the Middle East. There is a large MERS-CoV camel reservoir and there is no specific treatment or vaccine. The precise pathway from infected camel to the recurring MERS hospital outbreaks needs to be understood in order to devise effective control measures. With 10 million people visiting Saudi Arabia every year for Umrah and/or Hajj and the increasing importation of live animals from Sub-Saharan Africa, the potential risk of global spread will be ever-present, especially if mutations or recombinations in MERS-CoV occur. A major 'One Health' initiative to tackle MERS-CoV at source in animal populations is thus required.[50] Middle Eastern and African governments should now work more closely together and increase collaborative efforts with international partners and global public health authorities if we are to prevent yet another global zoonotic pandemic.

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