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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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Highlights

- The appearance, disappearance and re-emergence of pathogens of humans with epidemic potential and high mortality rates have threatened global health security for centuries.
- The recent Ebola Virus Disease (EVD) epidemic in West Africa illustrated that the global public health authorities should have been better prepared for them.
- The current ZKV outbreak is diverting the attention of public authorities and governments from other important infectious diseases which continue to threaten global public health security. One such disease lurking in the background is the Middle East Respiratory Syndrome (MERS).
- The emergence of the MERS-CoV in 2012 was the second time (after SARS-CoV) that a new coronavirus, highly pathogenic for humans emerged in the 21st century. Whilst most of MERS cases have been reported from the Middle East, MERS cases have been reported from 27 countries in all continents.
- MERS-CoV has been found in camel populations of eastern Africa and the Middle East and with millions of pilgrims visiting Saudi Arabia and returning home every year MERS-CoV the movement of the virus to new locations presents a real threat to global health security.
• With animal, human and environmental factors playing a critical role in its evolution, MERS-CoV represents a classical zoonoses.

• The reliable detection of intermittent MERS cases 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 serious and more collaborative and coordinated MERS-CoV response plan is required to better define MERS-CoV epidemiology, transmission dynamics, molecular evolution, optimal treatment and prevention measures and development of vaccines for humans and camels. The factors and operating conditions which promote the emergence and geographical spread of zoonotic viruses are complex and may be related to a single or chain of multiple events influenced by genetic evolution of the pathogen, environmental and climate changes, anthropological and demographic changes, movement and changes in the behavior of humans, animals and vectors.

• The One Health concept focus 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).

• A One Health approach is ideally suited for the MERS-CoV situation and requires close co-operation between those who provide human health, animal health and promote environmental and ecosystems health,
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, microbiologist, viral geneticists, 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. For the science to be effective requires appropriate policy and a conductive sociopolitical and economic framework for action.

The persistence of MERS-CoV four years since its first discovery creates major opportunities for Saudi Arabia or one of the other Middle Eastern countries to take leadership of One Health approaches to tackling new emerging and re-emerging infectious diseases with epidemic potential in their region.

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 safe and sustainable agricultural, systems especially for livestock in support of human development.
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 caused by pathogens arising from animal reservoirs (2) have included West Nile virus (WNV), Yellow fever virus (YFV), Ebola virus disease (EVD), Nipah virus (NV), Lassa Fever virus (LV), Hanta virus (HV), Dengue fever virus (DENV), Rift Valley fever (RVF) virus, Crimean-Congo haemorrhagic fever (CCHF) virus, severe acute respiratory syndrome coronavirus (SARS-CoV), Highly pathogenic avian influenza viruses, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and Zika virus (ZKV). The recent Ebola Virus Disease (EVD) epidemic in West Africa (3) and the ongoing Zika Virus (ZKV) outbreak in South America (4) highlight the urgent need for local, regional and international public health systems to be better prepared (5-8). We highlight here 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. In this article we give the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) as an important case in point.

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 affect 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 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 (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 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, 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, ecosystems, and environmental health sectors at 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 co-operation 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 (2) are on the radar of WHO, 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.

**WHO priority list of top ten emerging pathogens**

On December 10th 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 ten includes the new viral zoonotic pathogen of humans, Middle East Respiratory Syndrome coronavirus (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 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 sera from different geographical locations indicate that MERS-CoV has been circulating for several decades (Ref).
As of May 1st 2016, there have been 1,733 laboratory confirmed cases of MERS reported to the WHO (27) of which 628 have died (34% mortality). 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) regarding MERS-CoV (28).

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, 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 since the ban on live animal imports from Somalia in particular was lifted by Saudi Arabia in 2009/2010. Somalia now exports some 5 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 One Health approaches can be. Most 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, we have previously highlighted the need for increased vigilance and watchful surveillance for
MERS-CoV in sub-Saharan Africa (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 when MERS-CoV was imported by a traveler (agriculture businessman) to the Middle East resulting in 184 MERS cases with 33 deaths (31). The first case was reported on 20 May 2015 and over the ensuing three 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 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 and the genetic evolution of MERS-CoV strains infecting humans over the past year remains unknown. There is an urgent need for more sequencing studies MERS-CoV evolution in camels and humans with development of appropriate local capacity for these studies. The Kingdom of Saudi Arabia has kept proactive watchful MERS-CoV surveillance (33) with regular reports to WHO of MERS-CoV cases. 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.

**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 into humans. The disease ecology remains largely unknown. These require urgent definition 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 four years, more comprehensive investments into 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. 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 we generated full virus genome sequences from every outbreak in the country and routinely screened and sequenced the virus from subsets of imported camels, after 2 years would provide incredibly useful information about the transmission patterns of the virus and how to stop it. Certainly we have the resources and expertise to perform this sequence monitoring and we need only the governmental support to run such a survey. Certainly 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 two 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 both Saudi Arabian healthcare staff and scientists (37,38) and by yet another WHO MERS expert group which defines a ‘Roadmap for Research and Product Development against MERS-CoV’ (39).

**Human, animal and environmental factors**

In 2000 the WHO setup the Global Outbreak Alert and Response Network (GOARN), (40) for better coordination of surveillance efforts coordinated across the globe. It networks 150 institutions and partner agencies with co-operation with other agencies such as Public Health England and the USA Centers for Disease Control and Prevention and consortia such as the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) (41). Recent consortia such as GloPID-R (42) aim to bring together research funding organizations on a global scale to facilitate an effective research response within 48 hours of a significant outbreak.
of a new or re-emerging infectious disease with pandemic potential. The past four years has seen outbreaks of EVD, ZKV and MERS-CoV (2-4,13) which indicate that 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 national, regional and global levels to prevent future epidemics. The factors and operating conditions which promote the emergence and geographical spread of zoonoses are complex and may be related to a single or chain of multiple events influenced by genetic evolution of the pathogen, environmental and climate changes, anthropological and demographic changes, movement and behavior of humans, animals and vectors. With animal, human and environmental factors playing a critical role in its evolution, MERS-CoV requires more close collaborations between human and animal health systems and university academics to reduce the risk of pandemic spread (43) and 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.
‘One Health’ approach for tackling MERS-CoV and other zoonotic diseases

The One Health concept (45-49) is an important concept which focusses on the relationship and interconnections between Humans, Animals and the Environment, and recognizes that the health and well being of humans is intimately linked to the health of animals and their environment (and vice versa). 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 for the MERS-CoV situation where 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 co-operation between those who provide human health, animal health and environmental health services, locally, nationally, regionally and internationally: Middle Eastern, European, African, Asian, American governments, Veterinary Groups, the WHO, 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), US-Centers for Diseases Control (CDC), Public Health England, and the newly formed Africa CDC and Funding Agencies among others. They should now demonstrate increased commitments towards local, national and global multidisciplinary collaborative efforts for securing 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, agriculturalists, ecologists, vector biologists, viral geneticists, and researchers to co-
operate with easy access to adequate laboratory facilities, collaborate to learn more about
zoonotic spread between animals, humans and the environment and to monitor, respond to
and prevent major outbreaks.

Capacity building for surveillance, outbreak response and associated research

There is an urgent and critical need for to build up sustainable public health program and rapid
response capability for outbreaks of zoonotic pathogens in the Middle East and in low income
countries and especially in Africa. Importantly there is a need for capacity development
programs 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. This include national or regional laboratory
facilities as surveillance needs laboratory support to be meaningful. 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 geographical network of equitable and enduring South-South and North-South partnerships.

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

The persistence of MERS-CoV four years since its first discovery creates major opportunities for each of the Middle Eastern and African countries to take leadership of One Health approaches with a view to bringing them under regional and global umbrellas, to tackling 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 of sentinel surveillance systems in sub-Saharan African 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 animal 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, neurologic, hemorrhagic, gastro-enteric, and sepsis-like presentation) should be developed so that clinical protocols may be rapidly adapted for any major outbreak during mass gatherings. This should include 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 surveillance and response to emerging infectious diseases 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 and 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's been over four 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 imports of live animals increasing from sub-Saharan Africa, the potential risk of global spread will be ever present, especially if mutations or recombinations in MERS-CoV occurs. A major One Health initiative (50) to tackle MERS-CoV at source in animal populations is thus required. 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.

**Author declarations**

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