Virology vigilance - an update on MERS and viral mutation and epidemiology for family doctors

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Abstract

This paper reviews aspects of virus mutation and spread generally as well as providing a review of the major viruses affecting people in the MENA and MESA regions.

Key words: virus, mutation, Middle East Respiratory Syndrome (MERS), Severe acute respiratory syndrome (SARS), Human Immunodeficiency Virus (HIV), rotavirus, Chikungunya, Ebola, avian flu, Marburg virus, rabies, dengue

Introduction

Viruses have been with mankind and the animal kingdom since recorded history and their aetiology is still not fully known.

Viruses are not cellular organisms and they may have either developed separately, or have been a precursor to cellular life; probably they are developing 'genetically' according to their own innate structure.

Throughout history the influenza viruses particularly, (having connections to simian life), have been the greatest everyday concern to man and Dengue viruses also take large numbers of lives in endemic areas.

Some viruses like smallpox, now eradicated, had been around for as long as recorded history - along with childhood viral complaints like rotavirus. Some scientists believe the Black Death (Bubonic plague) may have been an Ebola type virus.

While there are viruses specific to humans and particular animal species, the problematic viruses have become those that have spread from animals to humans due to mutation. Some of these mutations have then gone on to human to human transmission.

Even given better global communications has there been an actual increase in virus mutation and spread? In this past 100 years dramatic new viruses such as HIV, and Ebola, have emerged and spread rapidly among humans and have caused global concern; new strains of corona viruses such as SARS and MERS have been shown to spread rapidly and dramatically into new populations. We are yet to quantify if viruses spreading into new host populations may have an advantage and therefore greater impact on human health in geographical areas other than those in which the viruses originated.

The question for scientists and doctors to answer is, are these outbreaks just part of normal historical viral epidemiology or do they represent an advanced state of viral infection due to the virus's own increased virility or due to, for example, changes in our biosphere and the ecosphere of carriers (animals and birds) providing the virus better access into human hosts. Does human over- population of the planet, and human's greater proximity to concentrated animal populations (intensive animal husbandry) provide a new opportunity for both development of mutant strains and or the spread of such mutations globally into human populations in greater numbers?

If yes, we need to look generally at development and spread patterns in animal and human hosts of existing viruses and look equally at the possibility of development of new strains in certain environments.

It remains an ongoing problem and ongoing work for doctors, technicians and public health personnel, as well as global health organisations. Family doctors who are usually the first contacted and who live in the patient's local environment where the outbreak may have originated, particularly need to be alert not just for evidence and symptoms of existing strains but for pockets of new viral strains/mutations.

No part of the world is immune to either locally developed viral outbreaks or strains of viruses brought by travellers, or migrant workers into the local population.

Ideally and with proper scientific application we should be able to start to pinpoint risk factors/areas of risk of development of outbreaks (agricultural areas, specific climatic conditions, migration paths of wild animal and bird species) and put in strategies on the community level to contain, or better, prevent, outbreaks.

In this paper we also provide an update on MERS and other globally circulating viruses for regional family doctors who may have patients travelling to the Hajj, going on Ramadan holidays, and for those who will see patients who have travelled from endemic areas overseas.

Virus mutation

Accurate estimates of virus mutation rates are important to understand the evolution of the viruses and to combat them. However, methods of estimation are varied and often complex.

The mutation rate is a critical parameter for understanding viral evolution and has important practical implications. For example, the estimate of the mutation rate of HIV-1 demonstrated that any single mutation conferring drug resistance should occur within a single day and that simultaneous treatment with multiple drugs was therefore necessary. (1)

The viral mutation rate also plays a role in the assessment of possible vaccination strategies and it has been shown to influence the stability of live attenuated polio vaccines. At both the epidemiological and evolutionary levels, the mutation rate is one of the factors that can determine the risk of emergent infectious disease, i.e., pathogens crossing the species barrier.

Slight changes of the mutation rate can also determine whether or not some virus infections are cleared by the host immune system and can produce dramatic differences in viral fitness and virulence, clearly stressing the need to have accurate estimates. (1)

Future mutation rate studies should fulfil the following criteria:

- the number of cell infection cycles should be as low as possible,
- the mutational target should be large,
- mutations should be neutral or lethal or a correction should be made for selection bias.

Adhering to these criteria will help us to obtain a clearer picture of virus mutation patterns. (1)

There have been many laboratory-based investigations since the emergence of the new coronaviruses in 2012, but most of the parameters required for establishing scientifically the control measures that will protect against them have yet to be determined. Equally, the global distribution of the viruses in their animal reservoir has yet to be established. The approach to monitoring of virus mutation is to highlight particular questions that need to be answered for the purposes of preventing or treating these infections and diseases.

Tables 1-3, on the following page, provide a summary of data and investigations required for control or mitigation of virus spread.

Table 1: Information required from investigations for control or mitigation of a novel respiratory virus affecting humans

Reservoir of infections: animal, human, environmental
Modes of transmission to humans and effective prevention of transmission
Survival of the viruses in infectiousness doses in the environment
Method of spread: human-to-human
Setting when infections take place and procedures associated with transmission
Those at risk of infection: risk factors for transmission
Those most likely to transmit
Those at highest risk of severe disease
Population susceptibility
Incubation period
When cases are infectious and how this relates to symptoms
Reproductive number and serial interval
Clinical presentation and clinical spectrum
Antiviral susceptibility if any
Effectiveness of specific treatment and care strategies
Proportionate and effective infection control procedures

Table 2: What parameters are involved in virus spread?

Modes of transmission
Method of spread
Those at risk of infection
Setting when infections take place
Incubation period
When infectious
Reproductive number
Clinical presentation
Effective control measures
Those at highest risk of severe disease

Table 3: Specific public health questions regarding novel corona viruses that need to be answered

What do we need to know?
1. Where geographically are the human infections occurring worldwide?
2. What is the reservoir of the virus infection?
3. The estimated incubation period (from exposure to symptoms) and serial interval?
4. How infectious are these cases and what are the sources of infectious virus?
5. When are these cases infectious to others?
6. Are there any super-spreading events?
7. What do cases look like?
8. Who are the high risk groups?
9. How best to manage and treat the patients

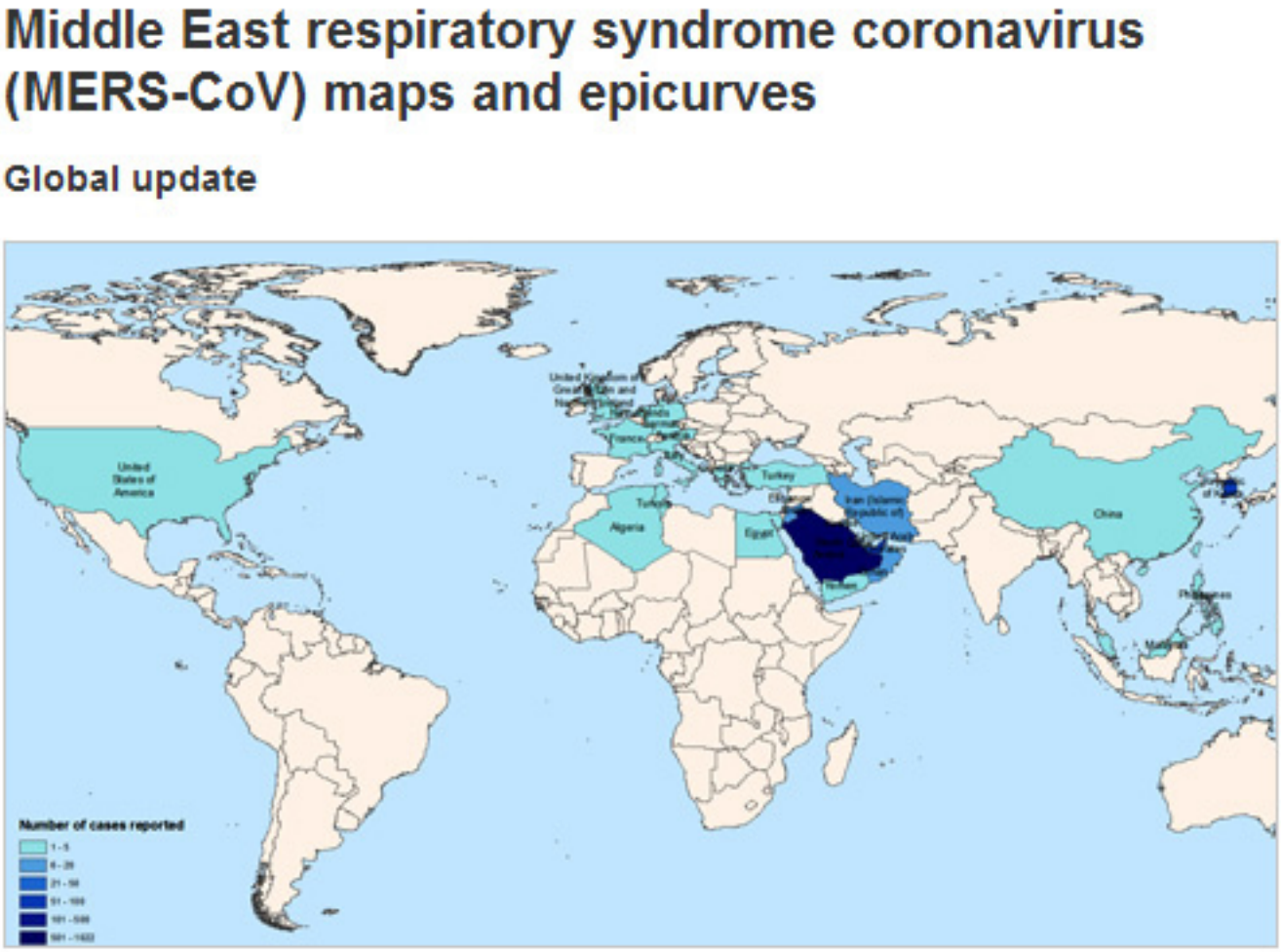
Dealing with virus outbreaks

Viruses cannot exist on their own and for survival they need to spread to another host. This is because the original host may either die or eliminate the infection. Some important routes of viral transfer include:

Route	Examples
Skin contact	HPV (warts)
Respiratory	SARS, Cold viruses, influenza, measles, mumps, rubella
Faecal-oral	Polio, Coxsackie, Hepatitis A, Rotavirus
Milk	HIV, HTLV-1, CMV
Trans-placental	Rubella, CMV, HIV
Sexually	Herpes 1 and 2, HIV, HPV, Hepatitis B
Insect vector	Yellow fever, Dengue fever
Animal bite	Rabies

Global and regional virus updates

MERS



Number of regional and global cases reported: Reproduced with permission from World Health Organization

Corona viruses are a large and diverse family of viruses that include viruses that are known to cause illness in humans. Middle East Respiratory Syndrome coronavirus (MERS-CoV) has never previously been detected in humans or animals but appears most closely related to coronaviruses previously found in bats. It is genetically distinct from the SARS coronavirus, and appears to behave differently.

The World Health Organization (WHO) first reported cases of Middle East Respiratory syndrome (MERS) coronavirus on 23 September 2012.

While Saudi Arabia has still recorded the highest number of MERS deaths, (over 400) the outbreak continues in South Korea with 33 deaths and 183 cases to mid June 2015.

All cases have lived in or travelled to the Middle East, or have had close contact with people who acquired the infection in the Middle East.

MERS Symptoms
- Most people become unwell quickly, with fever, cough, shortness of breath, leading to pneumonia.
- Other symptoms include muscle pain, diarrhoea, vomiting and nausea.
- There have also been people with mild symptoms or no symptoms at all. These people had close contact with others who were seriously ill.

How MERS spreads
- It appears to spread from an infected person to another person in close contact. The virus does not appear to spread easily from person-to-person and appears to spread only from people who are sick.
- Some people in the Middle East appear to have caught the disease from infected camels and bats. How this occurred is not well understood.

People with underlying illnesses that make them more vulnerable to respiratory disease may be at a higher risk.

How it is diagnosed
A laboratory test on fluid collected from the back of the throat or the lungs can diagnose MERS-CoV.

How it is treated
There is no vaccine for MERS-CoV but early and careful medical care can save lives.

Key facts
- Middle East respiratory syndrome (MERS) is a viral respiratory disease caused by a novel coronavirus (MERS-CoV) that was first identified in Saudi Arabia in 2012.
- Coronaviruses are a large family of viruses that can cause diseases ranging from the common cold to Severe Acute Respiratory Syndrome (SARS).
- Typical MERS symptoms include fever, cough and shortness of breath. Pneumonia is common, but not always present. Gastrointestinal symptoms, including diarrhoea, have also been reported.
- Approximately 36% of reported patients with MERS have died.
- Although the majority of human cases of MERS have been attributed to human-to-human infections, camels are likely to be a major reservoir host for MERS-CoV and an animal source of MERS infection in humans. However, the exact role of camels in transmission of the virus and the exact route(s) of transmission are unknown.
- The virus does not seem to pass easily from person to person unless there is close contact, such as occurs when providing unprotected care to a patient.

Between 1 and 4 June 2015, the National IHR Focal Point for the Kingdom of Saudi Arabia notified WHO of 5 additional cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infection, including 1 death. Contact tracing of household and healthcare contacts is ongoing for these cases.

In patients with suspected pneumonia or pneumonitis with a history of recent residence or travel (in the 14 days prior to symptom onset) in the Middle East*, or close contact with confirmed or probable cases, the following is recommended:

1. The patient should be placed in a single room if available and standard and transmission-based precautions implemented (contact, droplet and airborne), including the use of personal protective equipment (PPE).
2. The relevant state/territory public health unit/ communicable diseases branch must be notified urgently of any suspected (and probable or confirmed) cases in order to discuss patient referral and coordinate management of contacts.

Note: Transiting through an international airport (<24hours duration, remaining within the airport) in the Middle East is not considered to be risk factor for infection.

Are GPs/FPs at risk from MERS-CoV?
Many confirmed cases have occurred in healthcare-associated clusters, and there have been a large number of cases in healthcare workers, but mainly in hospital settings as has predominantly, if not exclusively, been the case in South Korea.

The particular conditions or procedures that lead to transmission in hospital are not well known. However, lapses in infection control were known to have occurred for seven healthcare workers who acquired the infection from cases in Saudi Arabia.

Patient Pre-travel advice, travel restrictions, periods of peak travel
The WHO does not currently recommend any restrictions to travel due to the MERS-CoV outbreak.

Travellers should be aware of the importance of personal hygiene including frequent hand washing, avoiding close contact with animals and with people who are suffering from acute respiratory infection, and should be advised to seek medical attention as soon as possible if they feel unwell. They should also follow usual food hygiene practices for travellers, including avoiding drinking raw milk or eating food that may be contaminated with animal secretions or products unless they are properly washed, peeled or cooked.

What are the recommended isolation and PPE recommendations for patients in hospital?
In summary, transmission-based precautions for suspected, probable and confirmed cases should include:

- Placement of confirmed and probable cases in a negative pressure room if available, or in a single room from which the air does not circulate to other areas

- Airborne transmission precautions, including routine use of a P2 respirator, disposable gown, gloves, and eye protection when entering a patient care area
- Contact precautions, including close attention to hand hygiene
- If transfer of the confirmed or probable case outside the negative pressure room is necessary, asking the patient to wear a surgical face mask while they are being transferred and to follow respiratory hygiene and cough etiquette.

Ebola

Ebola is spread through contact with blood or other body fluids, or tissue from infected people or animals. The known strains vary dramatically in their fatality rates. The Bundibugyo strain fatality rate is up to 50 percent, and it is up to 71 percent for the Sudan strain, according to WHO.

Less than two months after Liberia was declared Ebola-free by the World Health Organization, the virus is back in the country.

Even when the outbreak diminished in Liberia, neighboring Guinea and Sierra Leone have continued to see 20 to 27 cases a week since late May 2015, according to the WHO. There have been more than 11,000 total deaths from the outbreak since it began in March 2014.

Ebola Situation Report - 8 July 2015
There were 30 confirmed cases of Ebola virus disease (EVD) reported in the week to 5 July 2015: 18 in Guinea, 3 in Liberia, and 9 in Sierra Leone.

Ebola Situation Report - 1 July 2015
There were 20 confirmed cases of Ebola virus disease (EVD) reported in the week to 28 June, the same as the previous week. Weekly case incidence has been between 20 and 27 cases for 5 consecutive weeks. In Guinea, 12 cases were reported from 3 prefectures: Boke, Conakry, and Forecariah.

Chikungunya virus

While not fatal, this virus can have a chronic disabling effect and it has spread rapidly around the globe.

Chikungunya is ravaging the Caribbean, having affected 24 Caribbean nations and possibly more than 850,000 people worldwide, including 185 Americans (in New Jerseyans). Chikungunya virus is most often spread to people by Aedes aegypti and Aedes albopictus mosquitoes. These are the same mosquitoes that transmit dengue virus.

- The only way to prevent chikungunya is to prevent mosquito bites, such as by using repellant.
- Several vaccines are in the developmental stage but none are in the licensing stage.
- Generally, more South Jersey counties have a higher risk because they have more Asian Tiger Mosquitoes.

It is predicted that chikungunya virus will spread through rest of the globe this year (2015).

- Prior to 2013, chikungunya virus outbreaks had been identified in countries in Africa, Asia, Europe, and the Indian and Pacific Oceans.
- In late 2013, the first transmission of chikungunya virus in the Americas was identified in Caribbean countries and territories. Local transmission means that mosquitoes in the area have been infected with the virus and are spreading it to people.
- Since then, local transmission has been identified in 44 countries or territories throughout the Americas with more than 1.2 million suspected cases reported to the Pan American Health Organization from affected areas.

Symptoms
- Most people infected with chikungunya virus will develop some symptoms.
- Symptoms usually begin 3-7 days after being bitten by an infected mosquito.
- The most common symptoms are fever and joint pain.
- Other symptoms may include headache, muscle pain, joint swelling, or rash.
- Chikungunya disease does not often result in death, but the symptoms can be severe and disabling.
- Most patients feel better within a week. In some people, the joint pain may persist for months.
- People at risk for more severe disease include newborns infected around the time of birth, older adults (>65 years), and people with medical conditions such as high blood pressure, diabetes, or heart disease.
- Once a person has been infected, he or she is likely to be protected from future infections.

SARS

Severe acute respiratory syndrome. No outbreaks since May 2004 China

Avian Flu

Avian influenza A (H7N9) is a subtype of influenza viruses that have been detected in birds in the past. This particular A (H7N9) virus had not previously been seen in either animals or people until it was found in March 2013 in China.

However, since then, infections in both humans and birds have been observed. The disease is of concern because most patients have become severely ill. Most of the cases of human infection with this avian H7N9 virus have reported recent exposure to live poultry or potentially contaminated environments, especially markets where live birds have been sold. This virus does not appear to transmit easily from person to person, and sustained human-to-human transmission has not been reported.

WHO risk assessment of human infection with avian influenza A (H7N9) virus
On 23 February 2015 WHO conducted a risk assessment in accordance with the WHO recommendations for rapid

risk assessment of acute public health events the summary can be found below.

Risk assessment
This 23 February 2015 risk assessment was conducted in accordance with WHO's published recommendations for rapid risk assessment of acute public health events and will be updated as more information becomes available.

Overall, the public health risk from avian influenza A(H7N9) virus has not changed since the assessment published on 2 October 20142.

What is the likelihood that additional human cases of infection with avian influenza A (H7N9) viruses will occur?
The understanding of the epidemiology associated with this virus, including the main reservoirs of the virus and the extent of its geographic spread among animals, remains limited. However, it is likely that most human cases were exposed to the H7N9 virus through contact with infected poultry or contaminated environments, including markets (official or illegal) that sell live poultry. Changes to hygiene practices in live poultry markets have been implemented in many provinces and municipalities. Since the virus source has not been identified nor controlled, and the virus continues to be detected in animals and environments in China, further human cases are expected in affected and possibly neighbouring areas.

What is the risk of international spread of avian influenza A (H7N9) viruses by travellers?
On 27 and 31 Jan 2015, Canada reported 2 cases of human infection with avian influenza A (H7N9) in travellers returning from China. These travellers had mild symptoms and only reported indirect contact with poultry. On 12 February 2014, Malaysia reported one human case with avian influenza A (H7N9) virus infection. The patient was a Chinese resident who travelled to Malaysia while sick, and was most likely exposed in China. No further cases were reported in Malaysia linked to this case.

It is possible that further similar cases will be detected in other countries among travellers from affected areas, although community-level spread in these other countries is unlikely.

Flu viruses
During a typical flu season, up to 500,000 people worldwide will die from the illness, according to WHO. But occasionally, when a new flu strain emerges, a pandemic results with a faster spread of disease and, often, higher mortality rates.

There are four types of virus that cause seasonal flu in humans. Every year, drug developers try to predict which strains are likely to dominate in the next flu season so as to create an effective flu vaccine.

A good understanding of the rate and pattern of virus evolution helps these predictions, as one of the authors, Dr. Ian Barr, of the World Health Organization (WHO) Collaborating Centre for Reference and Research on Influenza in Melbourne, Australia, explains:

"This work represents another piece in the complex puzzle of influenza virus circulation and human infections and provides insights that will help develop better influenza vaccines that match strains circulating in the community."

The four viruses that cause seasonal flu in humans are: influenza A viruses H3N2 and H1N1, and influenza B viruses Yamagata and Victoria.

The viruses cause similar symptoms - for instance sudden fever, tiredness and weakness, dry cough, headache, chills, muscle aches, sore throat - and they evolve in similar ways.

But what has not been well understood is their different patterns of spread around the world and what influences them.

H1N1 and B viruses persist locally between epidemics.

Marburg virus

Scientists identified Marburg virus in 1967, when small outbreaks occurred among lab workers in Germany who were exposed to infected monkeys imported from Uganda. Marburg virus is similar to Ebola in that both can cause hemorrhagic fever, meaning that infected people develop high fevers and bleeding throughout the body that can lead to shock, organ failure and death.

The mortality rate in the first outbreak was 25 percent, but it was more than 80 percent in the 1998-2000 outbreak in the Democratic Republic of Congo, as well as in the 2005 outbreak in Angola, according to the World Health Organization (WHO).

Rabies

Although rabies vaccines for pets, which were introduced in the 1920s, have helped make the disease exceedingly rare in the developed world, this condition remains a serious problem in India and parts of Africa.

It destroys the brain, but there is a vaccine against rabies, and we have antibodies that work against rabies, so if someone gets bitten by a rabid animal they can be treated,

If a patient doesn't get treatment, there's a 100 percent possibility they will die.

HIV

In the modern world, the deadliest virus of all may be HIV. It is still the biggest killer. An estimated 36 million people have died from HIV since the disease was first recognized in the early 1980s.

Powerful antiviral drugs have made it possible for people to live for years with HIV. But the disease continues to devastate many low- and middle-income countries, where 95 percent of new HIV infections occur. Nearly 1 in every 20 adults in Sub-Saharan Africa is HIV-positive, according to WHO.

Dengue

Dengue virus first appeared in the 1950s in the Philippines and Thailand, and has since spread throughout the tropical and subtropical regions of the globe. Up to 40 percent of the world's population now lives in areas where dengue is endemic, and the disease - with the mosquitoes that carry it - is likely to spread farther as the world warms.

Dengue sickens 50 to 100 million people a year, according to WHO. Although the mortality rate for dengue fever is lower than some other viruses, at 2.5 percent, the virus can cause an Ebola-like disease called dengue hemorrhagic fever, and that condition has a mortality rate of 20 percent if left untreated.

Rotavirus

Two vaccines are now available to protect children from rotavirus, the leading cause of severe diarrheal illness among babies and young children. The virus can spread rapidly, through what researchers call the fecal-oral route (meaning that small particles of feces end up being consumed).

Although children in the developed world rarely die from rotavirus infection, the disease is a killer in the developing world, where rehydration treatments are not widely available.

The WHO estimates that worldwide, 453,000 children younger than age 5 died from rotavirus infection in 2008. But countries that have introduced the vaccine have reported sharp declines in rotavirus hospitalizations and deaths.

The future

The severity of viral outbreaks will largely depend on the local, regional and global response to them. Early vigilance by public health authorities and family doctors in endemic areas, particularly, are the greatest preventive measure along with hygienic practices of people, especially those living in close proximity to animal or bird carriers and those in hospital situations.

Global measures will need to be enacted early and up to date information made available to limit spread when it does occur.

Ideally, as in the case of smallpox which was declared eradicated in 1980 following a global immunization campaign led by the World Health Organization, we can start to tackle both the initial outbreaks and the spread of the more life threatening viruses.

This takes money and global will.

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