Epidemiology of Ebola virus disease

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Animals = reservoir of diseases

Zoonosis, also called zoonotic diseases, are diseases that can be transmitted from animals, whether wild or domesticated, to humans.

60% of pathogens are zoonotic and 3/4 of emerging diseases are zoonotic.

Human population 7.3 billions Farmed animals 24.4 billions

- Every person 2.5 chicken
- Every 5 persons 1 cow
- Every 7 persons 1 sheep
- Every 8 persons 1 pig
Most common zoonosis: influenza

Seasonal flu about 40 000 people dying each year in the European countries due to the seasonal influenza

6.2 million vaccinated in EU, about 9% of total population

ARS 2002 (coronavirus) 775 deaths in 17 countries

H1N1 2009 (swine flu): 2900 deaths in Europe, 15300 deaths in the rest of the world

H5N1 2013 (avian flu): 380 deaths in 15 countries

MERS 2012 -to date: 571 deaths in 26 countries
Epidemics

**Epidemic**: the spreading of an infectious disease rapidly and extensively, affecting many individuals in an area or a population at the same time.

**Pandemia**: when a new infectious disease appears against which the human population has no immunity, resulting in several simultaneous epidemics worldwide with high numbers of deaths and illness.

**Example**

1. Middle East Respiratory Syndrome (MERS) is a viral respiratory illness that is new to humans. It was first reported in Saudi Arabia in 2012 and has since spread to several other countries, including Europe.
2. Coronaviruses are a large family of viruses that can cause diseases ranging from the common cold to Severe Acute Respiratory Syndrome (SARS).
3. 26 countries have reported cases, the great majority is in Saudi Arabia.
4. Total cases 1595, deaths 571 (Arabia 688 cases, 282 deaths) (36% patients have died).
5. No vaccine or specific treatment is currently available. Treatment is supportive and based on the patient’s clinical condition.
Ebola virus

Filoviridae Family

Morphology: enveloped RNA filaments up to 14 000 nm, diameter 80 nm

Virus can survive in liquid or dried material for many days

Five different kind of viruses with different pathogenicity

Sensitive to sodium hypochlorite and other disinfectants

Pathogen of Group risk 4 which trigger special containment measures and barrier protection, particularly for health care workers
Epidemiological features of Ebola virus

- Fruit bats are considered natural reservoir; monkeys and chimpanzees can carry the virus.

Animal-to-person transmission: contact with living or dead infected animals (e.g. primates, bats) or material infected by animals

Person-to-person transmission: through direct contact with organs, blood and other bodily fluids (e.g. saliva, urine, vomit) of living or dead infected persons

Incubation period (the time from infection to the onset of symptoms) is between 2 to 21 days.

A person is infectious from the onset of symptoms and as long as their blood and secretions contain the virus (sometimes weeks sometimes months).

Burial ceremonies and health care settings without proper protection are particularly dangerous, underestimated until the 2014 outbreak.
Ebola outbreak

Although fruit bats are considered possible natural hosts of the Ebola virus, direct transmission to humans is rare. However, animals that may have come into contact with fruit dropped by infected bats, like chimps and gorillas, have been linked to spreading the disease in communities that eat them.

Range of fruit bats in Africa

Possible natural hosts:
- Hypsignathus monstrosus
  Hammer-headed fruit bat
- Epomops franqueti
  Franquet’s epauletted fruit bat
- Myonycteris torquata
  Little collared fruit bat

Other fruit bats

Past outbreaks

Range of chimpanzees and gorillas in Africa

- Chimpanzee populations
  Four sub-species of the common chimpanzee (Pan troglodyte)
- Gorilla populations
  Both Western and Eastern species

Since 1994, Ebola outbreaks from the EBOV and TAFV species have been observed in chimpanzees and gorillas.

Sources: International Union for Conservation of Nature and Natural Resources (IUCN); World Wide Fund for Nature (WWF); World Health Organization.
Clinical presentation of the Ebola virus disease

Sudden onset of flu-like illness: fever, muscle pain, weakness, headache and sore throat

Followed by various clinical symptoms, including:
- gastrointestinal - abdominal pain, anorexia, diarrhoea, vomiting; hypovolemic shock
- neurological - headaches, confusion;
- vascular - conjunctival/pharyngeal injections;
- cutaneous - maculopapular rash and
- respiratory - cough, chest pain, shortness of breath

One week later, haemorragic manifestations in >50% of patients:
- bloody diarrhoea/vomiting, nosebleeds, petechiae, ecchymosis and puncture bleeding, fatal internal hemorrhage
Laboratory confirmation assays

**Detection and sequencing of viral RNA in blood** (by quantitative PCR) from onset of fever up to 10-12 days
Can be negative during the two first days of illness

**Viral isolation:** only conducted in laboratories of Biological Safety Level 4
From onset of fever up to 8-10 days

**Serology:** blood tests for detection of specific immunoglobulins (IgM and IgG)
No validated assays
History of Ebola virus disease

1976: epidemics of severe haemorrhagic fever simultaneously in the Democratic Republic of Congo and Sudan
The new virus was identified and named after a small river

Several Ebola viruses identified:
- Zaire and Sudan (1976) in Congo and Sudan
- Tai Forest (1994) in Ivory Coast
- Bundibugyo (2007) in DRC
- Reston (1989) in the Philippines: non-pathogenic for humans

Up to 2012 outbreaks in Congo, DRC, Gabon, Sudan and Uganda
In total 2387 cases and 1590 deaths reported
Biggest outbreaks of Ebola

- Sudan 1976: 284 cases - 151 deaths
- Democratic Republic of Congo 1976: 318 cases – 280 deaths
- Democratic Republic of Congo 1995: 315 cases - 254 deaths
- Uganda 2000: 425 cases - 224 deaths
- Democratic Republic of Congo 2007: 530 cases – 380 deaths
Factors leading to the Ebola Outbreaks (Source PLOS Neglected Tropical Diseases)
The largest ever documented outbreak of Ebola Virus Disease both in terms of numbers and geographical spread

Sierra Leone, Liberia and Guinea  Cases 28 476  Deaths 11 298
Other countries  Cases 36  Deaths 15

The first outbreak of Ebola Virus in West Africa

Zaïre ebolavirus related but distinct from the previous isolations in Africa

An area is declared Ebola-free when there has been no cases for a 42-day period (the double of the incubation period of 21-days)
Ebola epidemic in West Africa – How did it start?
Events of Ebola epidemic in West Africa (1)

March 2014: Guinea notified WHO about rapidly evolving outbreak. First cases indeed in December 2013 (population: 10.6 millions)

Late March 2014: Cases reported in Liberia (population: 4 millions)

April 2014: Cases reported also in Sierra Leone (6.2 millions)

July 2014: An imported case in Nigeria from Liberia - Subsequent local transmission

Aug 2014: WHO declared ”Public Health Event of International Concern (PHEIC)”

9 Aug 2014: One confirmed case in Senegal – native of Guinea - No local transmission

8 Sep 2014: United Nations Security Council declared ”threat to international peace and security”
16 Sep 2014: The first imported case in the USA from Liberia

6 Oct 2014: A confirmed case in Spain

9 Oct 2014: Health worker at Texas hospital tested positive for Ebola (had provided care for the first imported case); few days later a second case

7 Oct 2014: WHO declares outbreak in Senegal over (13.6 millions)

9 Oct 2014: WHO declares outbreak in Nigeria over (174 millions)

3 Oct 2014: Mali reports its first confirmed case of EVD: a child originally from Guinea, dies in Kayes hospital

3 Oct 2014: USA reports its fourth case of EVD medical aid worker
Events of Ebola epidemic in West Africa (3)

8 Oct 2014: WHO approved a new Ebola vaccine trial

2 Nov 2014: UN worker medically evacuated from Sierra Leone to France

21 Nov 2014: WHO declares outbreak in the Democratic Republic of Congo over (67.5 millions)

5 Nov 2014: Two additional cases in Mali
Events of Ebola epidemic in West Africa (4)

Dec 2014: UN peace corp worker medically evacuated from Liberia to Netherlands

9 Dec 2014: a UK health worker coming back from affected areas tested positive for Ebola

18 Jan 2015: WHO declares Mali Ebola free (15,3 millions)

May 2015: WHO declares Liberia Ebola free

2 May 2015: an Italian nurse coming back from Sierra tested positive for Ebola

20 June 2015: the Italian nurse has been declared Ebola free. All his contacts have ended 21-days follow-up
Experimental therapies used to treat Ebola

Prioritized for consideration based on the availability of NHP efficacy data with a filovirus challenge and justification for a human dose based on clinical data of the product or comparable products within that class.

1- Targets the virus before it enters the cell
   **Zmapp**  A cocktail of three monoclonal antibodies, which block or neutralises the virus by binding to or coating a different site on the covering or “envelope” of the virus  
   **Hyperimmune globulin** Antibodies that can neutralize the different EVD strains.

2- Interferes with viral production
   **TKM 100802Ebola**  Target two essential viral genes to stop the Ebola from replicating.  
   **AVI 7537**  Sarepta Molecules that bind viral RNA, blocking gene function.  
   **Favipiravir T705**  Disrupts enzymes that the virus uses to make copies of himself.  
   **BCX4430 Biocryst** Disrupts enzymes that the virus uses to make copies of himself.  
   **Brincidofovir**  Disrupts enzymes that the virus uses to make copies of himself.

3- Prevents virus from exiting host cells

4- Bolsters human cells
   **Interferons**  Induce an antiviral state in exposed cells and regulates the immune system.

5- Testing existing drugs approved for other purposes
   **All drugs**  Screening all licensed drugs.

6- Whole blood transfusions and convalescent plasma

Source: Adapted from the Washington Post, Oct 7, 2014

Source: Current treatment approaches for EVD in European hospitals. WHO Ebola Clinical Team. Nahoko Shindo MD PhD, Coordinator, Epidemic Clinical Management, World Health Organization, Department of Pandemic and Epidemic Disease.
Development of Ebola virus disease vaccines

Vaccines best instrument to fight a new pandemia

Presently no vaccines to protect against EVD licensed for use in humans

Clinical trials for several candidate vaccines are in various phases

A safe and effective vaccine is hoped for early 2016

Main problem in vaccine development: lower levels of transmission so not enough people at risk to evaluate efficacy.
Clinical pipeline now

CLINICAL TRIALS

5 Jan 2015
Ad26/MVA

2 Sep 2014
ChAd3 +/- MVA

12 Feb 2015
VLP

17 Oct 2014
rVSV-ΔG

Chinese Ad5 candidate – no NHP efficacy data

Source: Clinical Pipeline now, from Ebola Vaccine Development. What went well. What lessons can be learned for vaccine R&D before the next emergency and for when the next emergency occurs? By Vasee Moorthy MD PhD
Vaccines in Clinical trials

1. VSV-EBOV, developed by NewLink Genetics and Merck Vaccines USA in collaboration with the Public Health Agency of Canada, is now tested in Phase II and III Clinical trials in Guinea, Sierra Leone and Liberia.

2. ChAd3-ZEBOV, developed by GlaxoSmithKline (GSK) in collaboration with the US National Institute of Infectious Diseases.

3. Johnson & Johnson, in association with Bavarian Nordic, has developed a 2-dose vaccination approach for Ebola using different vaccines for the first and second doses which has been tested in Phase I Clinical trials. The two vaccine candidates are known as Ad26-EBOV and MVA-EBOV.

4. Novavax, a biotech company in the US, has developed a recombinant protein Ebola vaccine candidate based on the Guinea 2014 Ebola virus strain and has completed a Phase I human clinical trials in Australia.

5. An additional vaccine candidate has recently finished early stage human clinical testing in China.
Projection of economic losses for 2015

Guinea  
US$ 540 million

Liberia  
US$ 180 million

Sierra Leone  
US$ 920 million

Total three Countries  
US$ 1.640 billion

Sub-Saharan Africa  
US$ 550 million

Source: World Bank, January 2015
What to expect now?

- In the last three months transmission of the virus geographically confined to several small areas in Western Guinea and Sierra Leone (case incidence at 5 confirmed cases or fewer per week), marking a transition to a distinct, third phase of the epidemic.

- Three new confirmed cases of Ebola virus disease were reported in the week to 18 October, all of which were reported in Guinea. Hundreds of contacts remain under follow-up in Guinea and few contacts in Sierra Leone: so there is still a risk of further cases among both registered and untraced contacts.

- Aim is to drive case incidence to zero, and ensure a sustained end to EVD transmission.

- Risk of a reintroduction either from an area of active transmission or from an animal reservoir, or re-emergence of virus from a survivor.

- Vaccines will bring the real solution.