Universidade de Lisboa

Faculdade de Farmácia

EVALUATION OF THE REGULATORY PREPAREDNESS FOR HEALTH THREATS AND HEALTH CRISIS

Rafael José Maia Amaral

Dissertation supervised by Professor Bruno Miguel Nogueira Sepodes
and co-supervised by Professor João Pedro Fidalgo Rocha

Master in Regulation and Evaluation of Medicines and Health Products

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ABSTRACT

In a globalized and highly interconnected world, infectious diseases of international concern are inevitable and unpredictable, hitting communities in devastating ways. When public health threats (re-)emerge, the public health system works towards mitigating their impact, reduce the death toll and any associated morbidity. Within it, the regulatory system has a critical role in responding to such threats, with pressure being applied to the development and access to medicinal products, vaccines and diagnostic tests as quickly as possible.

In this context, it is important to understand how the regulatory system is prepared, how it can accelerate the assessment and availability of therapeutic solutions and identify possible opportunities for improvement. This work presents a thorough analysis of the regulatory system's performance in recent Ebola health crises, followed by the identification of the current mechanisms put in place by the main Regulatory Authorities and possible opportunities for improvement.

The 2014-2016 West African Outbreak, the largest and deadliest Ebola outbreak in history so far, marked a turning point in regulatory and global health preparedness. Efforts across multiple stakeholders led to the accelerated development of Ebola virus vaccines and medicinal products, in a catastrophic environment. However, this outbreak also exposed weaknesses in the worldwide regulatory systems' capacity to respond rapidly and effectively to health threats. Only one vaccine clinical trial was able to gather enough data to assess efficacy during the outbreak, and several doubts on safety, tolerability or immunogenicity were left unanswered. Consequently, important lessons were discussed and considered thereafter, mainly the inclusion of clinical research in the plans for future health crisis and further integration in epidemic responses. Based on these lessons, the response to the second largest Ebola outbreak, two years later, was swift, more organized and better coordinated, culminating in the approval of the first vaccine against Ebola (a landmark moment in public health preparedness).

The analysis of the response to the Ebola outbreaks demonstrated the successful implementation of diversified regulatory mechanisms that fostered the development, early access and expedite assessment of medicinal products, vaccines and diagnostic tests, including priority review, conditional marketing authorization and rolling reviews. It also showcased the regulatory system's flexibility, response capacity and ability to embrace innovative solutions, while keeping the standards of quality, safety and efficacy.

Some opportunities for improvement exist within the current regulatory framework, including a more centralized coordination, better regulatory capacity and harmonization in low and middle-income countries, transparency and clearer communication. Despite these, the regulatory system seems capable and adequate to positively address both current and future public health crisis. It cannot stop them from occurring, but it can minimize their impact and protect our global health.

Keywords: Regulatory system, regulatory preparedness, health threats, health crisis, Ebola

RESUMO

Num mundo global e interconectado, as doenças infeciosas de âmbito internacional são inevitáveis e imprevisíveis, atingindo as comunidades de forma devastadora. Quando ameaças de saúde pública (re)emergem, o sistema de saúde pública trabalha para mitigar seu impacto, reduzir o número de mortes e a morbilidade associada. Dentro dos sistemas de saúde pública, o sistema regulamentar tem um papel crítico na resposta a estas ameaças, com pressão para o desenvolvimento e acesso a medicamentos, vacinas e testes de diagnóstico o mais rapidamente possível.

Neste contexto, é importante compreender a forma como o sistema regulamentar está preparado, como pode acelerar a avaliação e a disponibilização de soluções terapêuticas, e identificar oportunidades de melhoria. Este trabalho apresenta uma análise minuciosa do desempenho do sistema regulamentar nas recentes crises da saúde do Ébola, seguida pela identificação dos mecanismos atuais implementados pelas principais Autoridades Regulamentares e possíveis oportunidades de melhoria.

O surto de 2014-2016 na África Ocidental, o maior e mais mortífero surto de Ébola até ao presente, marcou um ponto de viragem na capacidade de preparação e resposta global e regulamentar. Os esforços conjugados de vários stakeholders levaram ao desenvolvimento acelerado de vacinas e medicamentos para o Ébola, num contexto catastrófico. No entanto, este surto expôs também fraquezas na capacidade de resposta rápida e efetiva dos sistemas regulamentares às ameaças de saúde pública. Durante o surto, apenas um ensaio clínico foi capaz de reunir dados suficientes para avaliar a eficácia de uma vacina, e várias dúvidas sobre segurança, tolerabilidade ou imunogenicidade ficaram sem resposta. Como consequência, muitas lições foram discutidas e tidas em conta posteriormente, com destaque para a inclusão da investigação clínica nos planos para futuras crises de saúde e maior integração nas respostas às epidemias. Com base nessas lições, a resposta ao segundo maior surto de Ébola, dois anos depois, foi rápida, mais organizada e melhor coordenada, culminando na aprovação da primeira vacina contra o Ébola (um marco na capacidade de preparação em saúde pública).

A análise da resposta aos surtos de Ébola demonstrou a implementação bem-sucedida de mecanismos regulamentares diversificados, que promoveram o desenvolvimento, o acesso antecipado e a avaliação rápida de medicamentos, vacinas e testes de diagnóstico, incluindo revisão prioritária, autorização condicional de introdução no mercado e revisões contínuas. Esta análise também mostrou a flexibilidade do sistema regulamentar, a sua capacidade de resposta e capacidade de adotar soluções inovadoras, mantendo os padrões de qualidade, segurança e eficácia.

Existem algumas oportunidades de melhoria no atual quadro regulamentar, incluindo uma coordenação mais centralizada, melhor capacidade regulamentar e harmonização nos países em desenvolvimento, maior transparência e comunicação mais clara. Apesar disso, o sistema regulamentar parece capaz e adequado para lidar positivamente com atuais e futuras crises de saúde pública. Não obstante não poder impedir a sua ocorrência, pode minimizar os seus impactos e proteger a saúde global.

Palavras-chave: Sistema regulamentar, preparação regulamentar, ameaças de saúde pública, crises de saúde pública, Ébola

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LIST OF ABBREVIATIONS

ACEUL	Advisory Committee for Emergency Use Listing
Ad5	Human *adenovirus* type 5
Ad26	Human *adenovirus* type 26
AMRH	African Medicines Regulatory Harmonization
AVAREF	African Vaccine Regulatory Forum
BLA	Biologics License Application
CAT	Committee for Advanced Therapies
CBRN	Chemical, Biological, Radiological and Nuclear Emergency
CDC	Centers for Disease Control and Prevention
CEPI	Coalition for Epidemic Preparedness and Innovations
CHMP	Committee for Medicinal Products for Human Use
CMV	*Cytomegalovirus*
COMP	Committee for Orphan Medicinal Products
CTA	Clinical Trials Application
DRC	Democratic Republic of Congo
EDQM	European Directorate for the Quality of Medicines & HealthCare of the Council of Europe
EFPIA	European Federation of Pharmaceutical Industries and Associations
EIND	Emergency Investigational New Drug
EMA	European Medicines Agency
ERF	Emergency Response Framework
EUA	Emergency Use Authorization

EUAL	Emergency Use Assessment and Listing
EUL	Emergency Use Listing
EVD	Ebola Virus Disease
FDAAA	Food and Drug Administration Amendments Act
GOARN	Global Outbreak Alert and Response Network
HHS	Secretary of the US Health and Human Services
HMA	Head of Medicines Agencies
ICMRA	International Coalition of Medicines Regulatory Authorities
IFRC	International Federation of the Red Cross
IHR	International Health Regulations
IMI	Innovative Medicines Initiative
IND	Investigational New Drug
INSERM	Institut National de la Santé et de la Recherche Médicale
JIKI	Efficacy of Favipiravir Against Ebola
LSHTM	London School of Hygiene & Tropical Medicine
MCM	Medical Countermeasure
MERS	Middle East Respiratory Syndrome
MEURI	Monitored Emergency Use of Unregistered and Experimental Interventions
MHRA	Medicines and Healthcare Products Regulatory Agency
MSF	Médecins Sans Frontières
NHP	Nonhuman Primates
NIAID	National Institute of Allergy and Infectious Diseases
NTD	Neglected Tropical Disease
OCHA	United Nations Office for the Coordination of Humanitarian Affairs

oSOC	optimized Standard of Care
PAHPRA	Pandemic and All-Hazards Preparedness Reauthorization Act
PDUFA	Prescription Drug User Fee Act
PEC	Product Evaluation Committee
PHE	Public Health Emergency
PHEIC	Public Health Emergency of International Concern
PHEMCE	US HHS Public Health Emergency Medical Countermeasures Enterprise
PMDA	Pharmaceuticals and Medical Devices Agency
PREVAC	Partnership for Research on Ebola Vaccination
PREVAIL	Partnership for Research on Ebola Vaccines in Liberia
PRIME	(European Medicines Agency's) Priority Medicines
PRV	Priority Review Voucher
SAGE	WHO Strategic Advisory Group of Experts
SARS	Severe Acute Respiratory Syndrome
SAWP	Scientific Advice Working Party
STAC-EE	WHO Science and Technical Advisory Committee on Emergency Ebola Interventions
STRIVE	Sierra Leone Trial to Introduce a Vaccine Against Ebola
TPP	Target Product Profiles
UN	United Nations
UNDP	United Nations Development Program
UNFPA	United Nations Population Fund
UNICEF	United Nations International Children's Emergency Fund
UNMEER	United Nations Mission for Ebola Emergency Response
US FDA	United States Food and Drug Administration

USA	United States of America
VEBCON	African and European VSV-Ebola Consortium
VSV	Vesicular Stomatitis Virus
WFP	United Nations World Food Program
WHO	World Health Organization
ZEBOV	*Zaire ebolavirus*

1. Introduction

In a globalized and highly interconnected world, infectious diseases of international concern, capable of causing severe health crisis, are inevitable and unpredictable. The widespread of such impactful public health threats is intimately related with global mobilization, population growth, urbanization, interaction with new ecosystems or climate change. When an outbreak erupts, other factors come into play that may affect its progression, impact, duration and control, including political and healthcare policies, and existence of adequate public health systems and infrastructures. (Klain November 2018)

In the past 20 years we have witnessed the emergence of serious infectious diseases outbreaks, with some evolving to the category of pandemics: the Severe Acute Respiratory Syndrome (SARS) caused by the Coronavirus SARS-CoV; the pandemic Influenza (novel H1N1 strain); the Middle East Respiratory Syndrome (MERS) caused by the Coronavirus MERS-CoV; the Ebola virus disease; the Zika virus disease; the COVID-19 pandemic caused by the new Coronavirus SARS-CoV-2. (WHO Website [1] May 2020) These public health threats can hit communities with significant impact, affecting the population's health and causing loss of lives, both directly and indirectly (by affecting other disease control programs, or the capacity to receive essential healthcare). Negative repercussions on the economy are usually significant, with economic recessions and increased poverty.

The safeguard of global health security is, therefore, imperative and should be acknowledged and addressed by all countries and International Health Organizations. Within it, the global regulatory system has a critical role in managing health crisis. Thus, it must be fully prepared, flexible and responsive to act quickly to public health threats. Its importance lies in the capacity of applying regulatory mechanisms that foster the development of medicinal products to attack the health threat and/or control its spreading, accelerate their assessment and approval, whilst maintaining their quality, safety and efficacy. (Heymann, et al. May 2015) But is the regulatory system effectively prepared? Did it evolve from lessons learned from previous health crisis? Are the regulatory mechanisms in place enough and positive? And what else needs to be enforced and planned while other, or the same, health threats might (re-)emerge?

This work aims to understand how the regulatory system is prepared to manage threatening situations that negatively affect public health, how it can accelerate medicinal products' assessment and access, and identify possible opportunities for improvement within the regulatory framework.

It does so by first assessing the regulatory system's performance during the 2014-2016 West African Ebola Outbreak (which marked a turning point in regulatory and global health preparedness), describing the major Regulatory Authorities' mechanisms and finally concluding on the overall regulatory system preparedness and its capability to reduce the burden of health threats.

2. Ebola

The Ebola virus disease (EVD), previously known as Ebola hemorrhagic fever, is a severe zoonotic viral disease most commonly affecting humans and nonhuman primates. It is caused by an infection with a group of viruses within the genus *Ebolavirus*: Ebola (species *Zaire ebolavirus*), Sudan, Taï Forest, Bundibugyo, Reston and Bombali. The first four viruses cause disease in humans, whereas Reston virus is only known to cause disease in nonhuman primates and pigs. It is unknown if Bombali virus causes disease in humans and/or animals. (WHO Website [2] February 2020) (CDC Website [1] November 2019)

The Ebola virus is a lipid-enveloped, glycosylated, non-segmented negative strand RNA virus, with 19 kb in length. The genome, presented in Figure 1, contains seven genes that encode for a nucleoprotein (NP), a glycoprotein (GP - that can also be expressed in a soluble form, sGP), a RNA-dependent RNA polymerase (L) and four structural proteins (VP24, VP30, VP35 and VP40). The envelope glycoprotein is responsible for the receptor binding and fusion with the host cell membrane, while other structural genes play an inhibitory role on the host's innate and adaptative immune response. (Ansari September 2014)

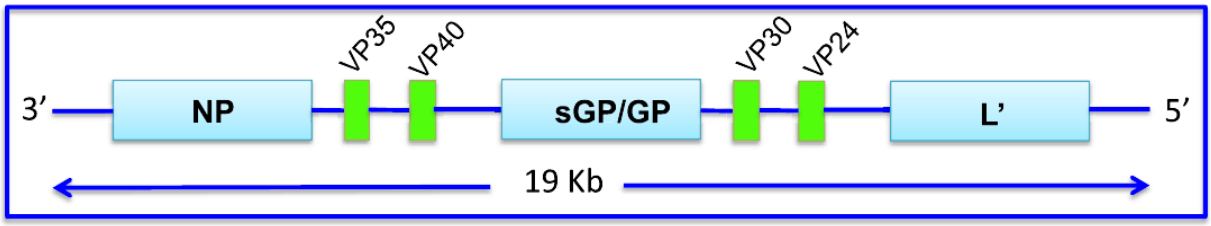


Figure 1: Ebola virus genome (Ansari September 2014)

Evidence suggests that fruit bats are the reservoir hosts for the Ebola virus, and that can transmit it to other animals and humans (spillover event). Humans can also be infected by direct contact with the blood, body fluids and tissues of other infected animals, such as nonhuman primates. Subsequently, the virus can spread from human to human, potentially affecting a large number of people. (WHO Website [2] February 2020) (CDC Website [2] November 2019)

Ebola virus is often found in several human secretions during the acute phase of the infection, including saliva, feces, vomit, sweat, semen, breast milk, tears and nasal blood. Human-to-human transmission can, therefore, occur through direct contact with blood or body fluids (or objects contaminated with them) of a person who is sick with or has died from EVD, with the virus getting in through broken skin or mucous membranes in the eyes, nose or mouth. Sexual contact is another, particularly worrying, means of human-to-human transmission, as the Ebola virus can remain for a long period of time in the semen of a patient who has recovered from EVD and has no symptoms of severe illness. (WHO Website [2] February 2020) (CDC Website [2] November 2019)

The spread of Ebola virus does not happen until a person develops symptoms of EVD, which is related with the incubation period of the virus (from 2 to 21 days). The first set of symptoms emerge suddenly and may include fever, headache, fatigue, muscle pain and sore throat. Afterwards, a more aggressive clinical condition is installed, with vomiting, diarrhea, rash, symptoms of impaired kidney and liver function, and in some cases internal and external bleeding. (WHO Website [2] February 2020) (CDC Website [3] November 2019)

2.1. Past Outbreaks

Ebola virus was discovered in 1976 in two nearly simultaneous outbreaks, in Central Africa. The first documented outbreak occurred in the Democratic Republic of Congo (DRC, former Zaire), in a village near the Ebola river, after which the virus received its name. A total of 318 cases were identified, leading to 280 reported deaths (which corresponds to a case fatality of 88%). (CDC Website [4] October 2019) The second outbreak occurred approximately 850 km away, in South Sudan. A total of 284 cases were identified in this outbreak, with the reported number of deaths amounting to 151 (which corresponds to a case fatality of 53%). (CDC Website [4] October 2019) Despite the geographical proximity, these two initial outbreaks were caused by two different strains of the virus, later identified as Ebola and Sudan strains, respectively. (CDC Website [5] September 2018)

Since Ebola was first identified in 1976, several outbreaks or case reports have occurred sporadically over rural areas in several Central African countries, such as Sudan, Democratic Republic of Congo, Uganda and Gabon. Most of these outbreaks had a small number of confirmed cases, with just a handful having more than 100. (CDC Website [4] October 2019) The largest outbreak recorded before the 2014-2016 outbreak in West Africa took place in Uganda in 2000, with 425 reported cases and a total of 224 deaths. (CDC Website [4] October 2019) (Coltart, et al. 2017)

2.2. 2014-2016 West African Outbreak

The 2014-2016 West African Outbreak was the largest and deadliest Ebola outbreak in history so far. According to the World Health Organization (WHO), 28.646 confirmed, probable and suspected cases of EVD were reported worldwide, of which 11.323 were fatal, as of the end of March 2016. (World Health Organization [1] March 2016) Three West African countries were heavily affected by this outbreak - Guinea, Sierra Leone and Liberia – that also moved across these borders to seven other countries – Italy, Mali, Nigeria, Senegal, the United Kingdom, Spain and the United States of America (USA). (CDC Website [4] October 2019) (World Health Organization [1] March 2016)

Outbreak Timeline

Retrospective investigations suggest that the outbreak started in the forest rural region of southeastern Guinea on December 2013, when an 18-month-old child became infected with the Ebola virus following a spillover event (index patient). Within a few weeks, the virus emerged within Gueckedou, a local urban center, and spread later on to the country's capital Conakry. On the 23rd of March 2014, and after 49 confirmed cases and 29 deaths in Guinea, the WHO officially declared an outbreak of EVD in the region. (CDC Website [6] March 2019) The Ebola virus quickly spread over Guinea's borders to Liberia and Sierra Leone, taking advantage of the poor surveillance systems and weak public health infrastructures available. The first EVD cases were confirmed in Liberia in March 2014, and in Sierra Leone in May 2014. Two months later, in July, the outbreak had already reached Monrovia and Freetown, the capital cities of Liberia and Sierra Leone, respectively. Figure 2 shows the geographical spread of the EVD in these three countries during the full outbreak period. (Coltart, et al. 2017) (CDC Website [6] March 2019) (Lo, et al. 2017) (Kaner and Schaack 2016)

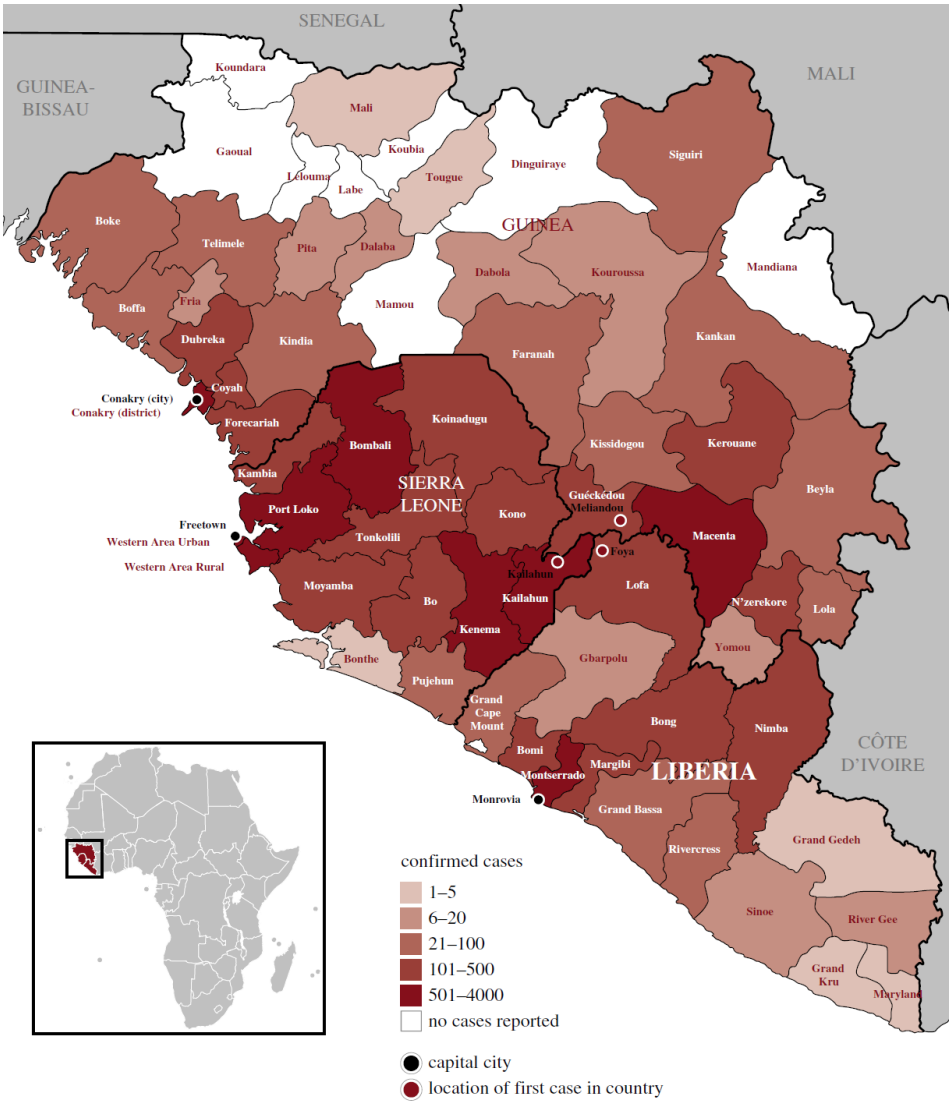


Figure 2: Geographical map of Guinea, Sierra Leone and Liberia showing the total number of confirmed cases by district (Coltart, et al. 2017)

In light of the severe and increasingly recognized epidemic in West Africa, on the 8th of August 2014, the WHO declared the Ebola outbreak a Public Health Emergency of International Concern (PHEIC), which is determined for serious public health events that have a high risk of potential international spread and that may require a coordinated international response. (WHO Website [3] August 2014) (WHO Website [4] July 2019)

Despite the above and the precautionary measures that followed, the Ebola virus linked with the West African outbreak was imported into countries outside Africa, by repatriated infected healthcare workers and travelers incubating the virus. Confirmed cases were diagnosed between September 2014 and May 2015 in the United States and several European countries. Additionally, isolated local human-to-human transmission to healthcare workers occurred in the United States and Spain. (Coltart, et al. 2017) (CDC Website [6] March 2019) (Kaner and Schaack 2016)

Each of the three West African countries was declared Ebola-free after fully meeting the WHO criteria for declaring the end of the EVD outbreak. Sierra Leone, the country with the largest number of EVD cases (confirmed, probable and suspected) in the aftermath of the outbreak, was declared Ebola-free on the 7th of March 2016. (Coltart, et al. 2017) Guinea was declared Ebola-free on the 1st of June 2016, immediately followed by Libera, which was declared Ebola-free just eight days after, on the 9th of June 2016. (Coltart, et al. 2017)

The end of the PHEIC status for the EVD outbreak in West Africa was declared by the WHO Director-General on the 29th of March 2016. (World Health Organization [1] March 2016) The timeline presented in Figure 3 depicts the key events that unfolded during the 2014-2016 West African Outbreak.

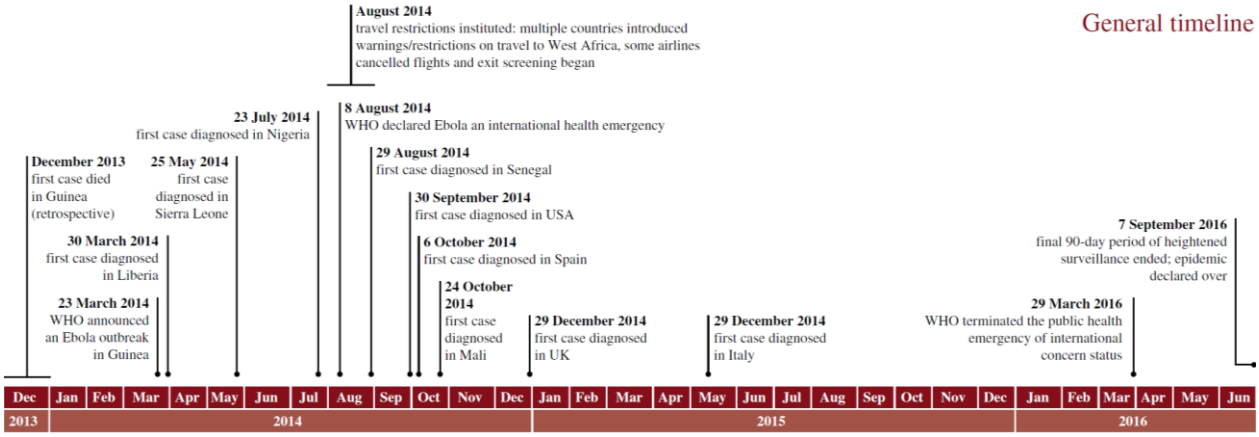


Figure 3: Timeline of key events (Coltart, et al. 2017)

Factors Leading to the Deadliest Ebola Outbreak

The 2014-2016 West African outbreak was unprecedent in its geographical scale, duration and impact. It also marked the first time that Ebola virus spread from isolated rural areas to highly populated urban centers, simultaneously affecting several countries. This provided easier mechanisms and opportunities for Ebola transmission and made its control efforts increasingly difficult, contributing to the outbreak progression. (Alexander, et al. 2015) Figure 4 demonstrates diversified transmission pathways, since the spillover event from the wildlife reservoir to human-to-human transmission in different contexts: rural villages, densely populated urban centers and medical facilities. (Alexander, et al. 2015)

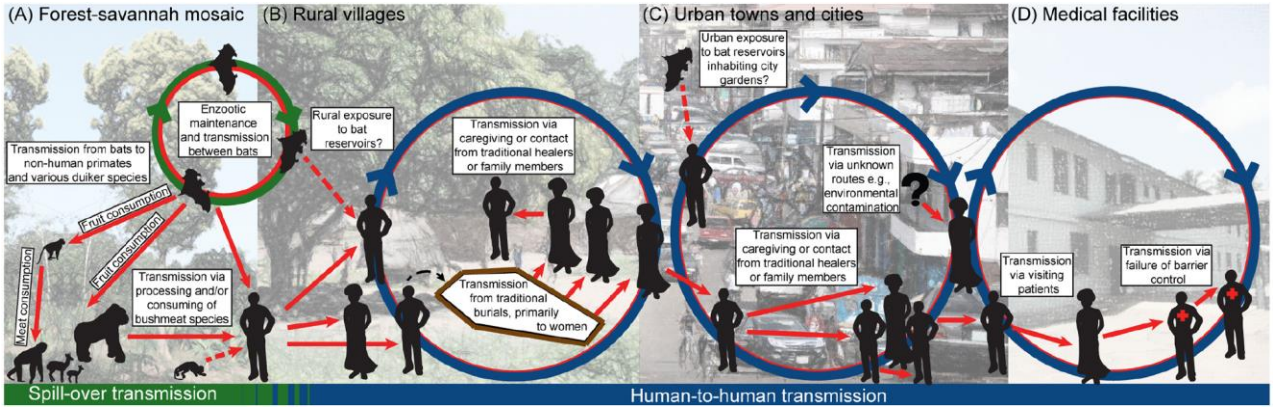


Figure 4: Schematic of spillover event and human-to-human transmission (Alexander, et al. 2015)

The network of possibilities that might explain the spillover of Ebola virus from the wildlife reservoir to human populations, and in particular to the index patient, is very complex. Meteorological factors and human-mediated changes in the environment may have had an impact on contact probabilities between susceptible and infected hosts, and on disease transmission pathways, especially when wildlife reservoirs are involved. However, the overwhelming consequences of this outbreak are intimately related with its human-to-human transmission and the political, social and structural factors that enhanced it. (Alexander, et al. 2015) These factors, that contributed to and influenced the progression and duration of this outbreak, as well as the difficulty to contain it, are described hereafter:

- Population size and mobility – several social and economic factors influence population movement across the country and between countries, critically impacting outbreak dynamics and its spread. Population growth and large scale rural to urban migration in the affected West African countries, driven by poverty, conflict and political instability, has increased the proportion of people living in urban areas and contributed to the urbanization of the outbreak. (Coltart, et al. 2017) (Alexander, et al. 2015) The location of the spillover event, in near proximity with the borders of Sierra Leone and Liberia and major road networks, as well as the failure to control the transmission in the early

phases of the outbreak, contributed to the rapid dissemination of the Ebola virus to densely populated urban centers, such as Conakry, Monrovia and Freetown. These major urban centers ultimately provided diversified means for local transmission as well as international spread. (Coltart, et al. 2017) (Alexander, et al. 2015)

- Lack of infrastructure – in face of the poor economic status of the West African countries and after decades of civil wars, the public health infrastructures were weak and inadequate to deal with an outbreak of this magnitude. (Coltart, et al. 2017) (Alexander, et al. 2015) Both laboratory and qualified human resources were lacking in capacity and were unable to identify suspected EVD cases in a fast and accurate way (this was aggravated by the fact that the symptoms of EVD resemble other endemic diseases in the area and by the uneven distribution of available health services, penalizing rural areas). This hindered surveillance, response activities and critical decision-making, highly contributing to the lack of infection prevention and control and to the spread of the epidemic. (Coltart, et al. 2017) Moreover, the insufficient infection control procedures increased the risk of contamination to healthcare workers, especially in the early stages of the outbreak. Lastly, transportation and telecommunication networks were limited, particularly in rural areas, which delayed the transportation of patients, diagnostic samples and the diffusion of public health campaigns and accurate information about EVD. (Coltart, et al. 2017) (Alexander, et al. 2015)

- Cultural practices – transmission dynamics, particularly in the case of Ebola virus (due to its transmission pathways), are vastly influenced by cultural practices and behaviors, social cohesion and communication. (Alexander, et al. 2015) West Africa is well known for its cultural diversity, both within and between countries, consequently shaping different transmission dynamics in communities and affecting local disease prevention and public health response plans:

    - Bushmeat consumption is an important mechanism for Ebola virus transmission from wildlife reservoirs to humans. Bushmeat was a significant protein source in the region, especially in Liberia, being more consumed as a consequence of population growth and migration to densely populated urban centers. It was also trafficked illegally within as well as outside the region, potentially spreading the outbreak. (Alexander, et al. 2015)

    - Traditional burial practices were an important and effective way of transmission, as they involved highly risky behaviors (such as washing and touching the deceased) and people travelling from long distances to prepare and attend the ceremony, potentially beginning chains of human-to-human transmission that facilitated the spread of Ebola to new geographical areas. In fact, these practices were responsible for more than half on new EVD infections in Guinea and Sierra Leone in August and November 2014, respectively. (Coltart, et al. 2017) (Alexander, et al. 2015)

- Traditional medicine is still heavily relied on by a great part of the West African population, as traditional healers and family members are often sought for care and health advice. However, they potentially posed a high risk for Ebola dissemination and duration, due to their lack of experience and possible transmission of false information within communities. (Alexander, et al. 2015)

- Local leaders, alongside traditional healers, may influence the community, their (mis)trust in foreign healthcare workers and (un)acceptance of public health campaigns and infection control efforts. The mistrust and fear towards foreign healthcare workers often verified during the outbreak led many individuals to stop seeking assistance from health officials, and rather turning to traditional healers and family members for care. (Alexander, et al. 2015) This directly impacted the effectiveness of surveillance and infection control practices (e.g.: contact tracing and safe burial activities), influencing the spread and duration of the outbreak. Additionally, lack of trust in government further obstructed cooperation and communities' engagement against the epidemic. (Coltart, et al. 2017) (Alexander, et al. 2015)

2.3. Response to the 2014-2016 West African Outbreak

This chapter focus on the public health measures developed and applied by the national and international communities to control and end the 2014-2016 West African Ebola Outbreak. It is mainly focused on the description and assessment of the regulatory system performance during this outbreak, while also briefly presenting the main fundamental public health strategies and interventions used to prevent further dissemination of EVD and fight the Ebola outbreak.

The international response to the outbreak involved a high number of entities and Governmental and Non-Governmental Organizations, that worked in close collaboration under the leadership of WHO and the United Nations (UN – within the UN Mission for Ebola Emergency Response, UNMEER). These partners included, but were not limited to: African Union, US Centers for Disease Control and Prevention (CDC), Médecins Sans Frontières (MSF), the International Federation of the Red Cross (IFRC), partners of the Global Outbreak Alert and Response Network (GOARN) and UN agency partners (in particular, UNICEF, WFP, OCHA, UNFPA and UNDP). (World Health Organization [2] April 2015)

2.3.1. Public Health Response

The outbreak of EVD in West Africa was officially declared by WHO on the 23rd of March 2014. (CDC Website [6] March 2019) However, the awareness and concerns related with the

magnitude, duration and impact of the outbreak by the international community only truly came during the summer. The international community surveillance and health response strategies were led by WHO (which coordinated the response efforts through the GOARN) throughout the duration of this Ebola outbreak. (World Health Organization [2] April 2015)

The Emergency Response Framework (ERF) has been developed in light of WHO's role on the International Health Regulations (2005) (IHR 2005), which define the procedures that WHO must follow to guarantee public health security, as well as the responsibilities of countries to assess, report and respond to public health events. (World Health Organization [3] July 2016) The purpose of the ERF is to provide crucial guidance to WHO and its staff on how the Organization should assess, grade and manage the response to any public health event or emergency with health consequences. In this framework, it is defined that WHO's emergency procedures and level of operational response are deployed based on the internal grading assigned to the public health event. This grading is composed of four levels, from Ungraded (for which no WHO operational response is required) to Level 3 (which requires a major WHO response). (World Health Organization [4] June 2017)

The Ebola outbreak was initially graded as Level 2 under the ERF, meaning that WHO would provide moderate support to the affected countries in West Africa. However, on the 24th of July 2014, and based on the severity and complexity of the outbreak, the WHO Director-General up-scaled the grading to Level 3, making WHO's response more significant and with greater mobilization of resources. (World Health Organization [5] July 2014) The WHO, together with the Governments of the three most affected countries, launched on the 31st of July 2014 a strategic action plan to tackle the outbreak in these countries, named *Ebola Virus Disease Outbreak Response Plan*, which was developed based on WHO's previous experiences in different epidemics and on the ERF grading system. (World Health Organization [5] July 2014)

The WHO Director-General, in alignment with the IHR Emergency Committee, has the responsibility to convene an Emergency Committee to advise on the need to determine if a health event falls under the category of a Public Health Emergency of International Concern, and define the emergency temporary recommendations that accompany it. The IHR (2005) defines a PHEIC as "an extraordinary event which is determined, as provided in these Regulations: (i) to constitute a public health risk to other States through the international spread of disease; and (ii) to potentially require a coordinated international response". (World Health Organization [3] July 2016) (WHO Website [4] July 2019) The accompanying temporary recommendations are health measures that are applied to the country where the public health event is occurring or to other countries in order to reduce or prevent its international spread. (WHO Website [4] July 2019) (World Health Organization [3] July 2016)

The first meeting of the IHR Emergency Committee on the Ebola outbreak in West Africa, convened by the WHO Director-General, occurred in August 2014. Considering the gravity of the epidemic, the risk of international spreading and need to deploy a coordinated international response, it was unanimously agreed that the outbreak fulfilled the criteria of a PHEIC, which

was declared, by the WHO Director-General, on the 8th of August. Several temporary recommendations to reduce the risk of international spread were defined and put in place from that day onwards. (WHO Website [3] August 2014)

The implementation of WHO's temporary recommendations under the IHR (2005) is contemplated on the *Ebola Response Roadmap*, an updated document issued by WHO on the 28th of August 2014 to guide and coordinate the international response, as well as to provide the core strategies for scaling up the response. (World Health Organization [6] August 2014) The roadmap had the ultimate goal of stopping Ebola transmission within 6 to 9 months in the affected countries (by giving attention to laboratory, human resources and response capacity, together with public health infrastructures) and strengthen the preparedness of all countries in case of any international spread. (WHO Website [5] August 2014) (World Health Organization [6] August 2014)

Following the inability to contain EVD and its international dissemination to countries outside West Africa, in particular the United States and European Countries, on the 19th September 2014, the UN Secretary General established the United Nations Mission for Ebola Emergency Response (the first UN emergency health mission), as a temporary measure to increase the outbreak response even further and deploy additional financial, logistical and technical support along with human resources to Guinea, Liberia and Sierra Leone. (Lo, et al. 2017) This mission was aligned with the key strategies described in UN's STEPP plan (STOP the outbreak, TREAT the infected, ENSURE essential services, PRESERVE stability and PREVENT outbreaks in countries currently unaffected), which integrated WHO's *Ebola Response Roadmap.* Having achieved its goal of scaling up the response on the ground, the Mission was closed on the 31st of July 2015, with the oversight of the UN Ebola emergency response system passing to WHO. (Lo, et al. 2017) (UN Website [1] March 2020)

Building on the achievements of the initial phases of response strategies (namely, reversing the uncontrolled spread of EVD in both densely populated urban centers and remote rural areas, and the increase in case numbers) and on the lessons learned with them, WHO launched the *2015 WHO Strategic Response Plan* for the West Africa Ebola Outbreak. This response plan was part of the last phase of the outbreak response and had the following objectives: stop transmission in the affected countries and reach zero Ebola cases; prevent new outbreaks in new regions or countries; reactivate indispensable health services; expedite Ebola research and development; and coordinate both national and international response. (World Health Organization [2] April 2015) One particular activity of great relevance was the development of an Ebola preparedness checklist to all countries, to ensure that were ready to detect, manage and report potential EVD cases, as well as rapidly and effectively respond to them. (World Health Organization [7] January 2015)

Major Public Health Strategies

Supportive treatment and containment measures have proved in the past to be reliable infection control procedures. All the high level initiatives mentioned in the previous subsection worked, to a lesser or greater extent, towards those routine public health and infection control strategies, that are identified below: (World Health Organization [2] April 2015) (World Health Organization [6] August 2014) (WHO Webiste [6] January 2016) (WHO Website [7] January 2016)

- Isolation of patients and suspected cases. The construction of dozens of Ebola Treatment Units (ETUs) and the increase of patient beds to isolate and treat them were key measures.

- Early and accurate diagnosis, and fast confirmation in reference laboratories (especially through RT-PCR tests).

- Trace people that had been in contact with an infected person and place them under active surveillance (contact tracing), consequently disrupting transmission chains.

- Safe burial practices, avoiding rituals that require washing or handling of the body potentially infected with Ebola virus.

- Community engagement in preventing transmission, by enabling the implementation of culturally acceptable public health strategies and trust between all parties. This was pivotal to control the Ebola outbreak, as mistrust and lack of community engagement in some of the affected areas impacted the effectiveness of infection control strategies.

- Infection control measures in healthcare settings, including education and training of healthcare workers, risk assessment and communication, and use of personal protective equipment while working with patients or suspected cases.

2.3.2. Regulatory System Response

No fully developed or licensed therapeutic medicinal products or vaccines existed for prevention, post-exposure prophylaxis and treatment of EVD in the awakening of the 2014-2016 West African Outbreak. Experimental products were under investigation but haven't been tested in humans and no scientific data from clinical trials existed to support their effectiveness and safety. There was only suggestive preclinical evidence of efficacy, as several experimental products had been tested on animals, including nonhuman primates. (Largent September 2016) (Keusch, et al. 2017) The valuable determination of experimental products' effectiveness and safety can only be accomplished by performing research in humans exposed to or infected with Ebola virus, which can just occur during an Ebola outbreak. (Keusch, et al. 2017)

The lack of licensed or fully tested treatments and vaccines available for EVD in 2014, despite decades of sporadic Ebola outbreaks, may have been due to the rarity of Ebola and the unpredictability of its outbreaks (in what concerns their location, size and duration), the absence of a clear development pathway for testing during an outbreak or challenges to material deployment. (Keusch, et al. 2017) Additionally, their remote location in low-income countries in Africa, probably made research and development financially unattractive to pharmaceutical companies. In fact, some public health officials, including the nominated WHO's Director General at the time (Dr. Margaret Chan), "have criticized the pharmaceutical companies' lack of investment in investigational treatments for EVD, stating that many companies had likely determined the return on investment for a treatment was not worth its development cost". (Largent September 2016) (TIME November 2014)

As a result of the absence of licensed or fully tested treatments and vaccines, the regulatory system worked mainly towards accelerated development processes and clinical trials for vaccines and candidate medicinal products to supplement the standard of care at that time. (Largent September 2016) (Keusch, et al. 2017) Initiatives that were promoted by WHO in alignment with Government representatives, Research Organizations, scientists, pharmaceutical companies, Regulatory Authorities, Ethics Committees, Public Health Organizations and Funding Agencies. Under its leadership, agreements and consensus were achieved in relation to clinical trials designs, ethics, data requirements, monitoring, capacity requirements and regulatory pathways. As part of the Ebola Response Roadmap, WHO called for the fast-track development of medicinal products and vaccines to address EVD. Simultaneously, given the magnitude of the outbreak, a call for the use of unregistered medical interventions in the field was significant. (World Health Organization [6] August 2014) (Largent September 2016)

Shortly after the declaration of the Ebola outbreak as a PHEIC, several consultation meetings were triggered by WHO. On the 11th of August 2014, an ethical consultation occurred to consider and assess the ethical implications for clinical decision-making of the potential use of unregistered experimental interventions that had shown promising results in laboratory and in animal models but that had not been evaluated for safety and efficacy in humans at the time. (World Health Organization [8] August 2014) The advisory ethics panel agreed unanimously that, under the circumstances of this particular outbreak and provided that certain conditions were met, the use of unapproved experimental medicinal products and vaccines for potential treatment or prevention of EVD was ethically acceptable. The conditions determined by the panel included, but were not limited to, the collection of all scientific data generated in the use of these unregistered interventions, including from compassionate use, and sharing them with the scientific community in a transparent and timely way, so that their effectiveness and safety could be assessed. (WHO Website [8] August 2014) (World Health Organization [8] August 2014)

On the 4th and 5th of September 2014, an international consultation meeting took place with the main objectives of reviewing the pipeline of potential Ebola therapies and vaccine options under development, prioritizing promising candidates and discussing the possible accelerated pathways for the development, evaluation and regulatory approval of therapeutic medicinal products and vaccines to fight Ebola. The participants focused on addressing three main questions: “do the identified products work and are they safe?; can they be developed more rapidly in order that they might be moved from the laboratory to the field?; and can they be scaled up to serve the necessary demand?”. (World Health Organization [9] September 2014) (World Health Organization [10] September 2014)

On the same line, in September 2014, the International Coalition of Medicines Regulatory Authorities (ICMRA) issued a statement promising that regulators worldwide would work together internationally, in enhanced cooperation with the WHO and between each other, to find innovative regulatory solutions to facilitate and speed up the evaluation and access to potential new medicines to counter Ebola outbreaks, and solve potential issues (e.g.: appropriate clinical trial design; emergency access to treatments; or the assembly of efficacy and safety data when investigational treatments are used in individual patients). (ICMRA September 2014) As such, several collaborative arrangements were established between international Regulatory Authorities, of which the following stands out:

- Confidentiality commitments between the United States Food and Drug Administration (US FDA) and the Ministry of Public Health and Hygiene of Guinea, the Pharmacy Board of Sierra Leone and the Liberian Medicines and Health Products Regulatory Authority in order to share confidential information between them. (Largent September 2016)

- Encouragement to researchers and stakeholders to submit their applications for orphan designations simultaneously to the US FDA and the European Medicines Agency (EMA), so that these Regulatory Authorities could work collaboratively and accelerate the development process. (Largent September 2016)

- Bilateral discussions and close collaboration between US FDA / EMA and pharmaceutical companies developing Ebola candidate vaccines. (Largent September 2016) (World Health Organization [11] October 2014)

- Extensive work from regional regulatory forums and networks, with the participation of the West African National Regulatory Authorities, to build capacity and promote harmonized practices. (World Health Organization [11] October 2014)

Vaccine specific consultation meetings and teleconferences were also triggered by WHO to discuss regulatory approaches and financing for expediting the development and availability of leading candidate vaccines. These took place between October 2014 and January 2015,

with the participation of representatives from Regulatory Authorities, pharmaceutical companies developing potential candidate vaccines, Ministries of Health and Foreign Affairs, among other stakeholders. (World Health Organization [11] October 2014) (World Health Organization [12] January 2015) (World Health Organization [13] October 2014) (World Health Organization [14] January 2015) The debates were centered on the identification of critical regulatory pathways for the lead candidate vaccines, the main regulatory and manufacturing challenges that could arise and the main avenues to address them (e.g.: bridging immunogenicity studies from animals to humans as a justification for initiating efficacy studies; single harmonized set of release tests to further reduce timelines; alternative sterile filing capacity). The timelines for availability of these vaccines for clinical trials and potential future deployment, and the financing of vaccine development, clinical trials and vaccination campaigns were also debated. (World Health Organization [11] October 2014) (World Health Organization [12] January 2015) (World Health Organization [13] October 2014) (World Health Organization [14] January 2015)

During these vaccine specific WHO consultation meetings, it was decided that WHO would develop Ebola vaccine target product profiles (TPP) to guide the preferences for vaccines on two distinct categories: for reactive/emergency use and for prophylactic use. (World Health Organization [14] January 2015) (World Health Organization [15] January 2016) The following characteristics were assessed for both categories: “indication for use, target population, safety/reactogenicity, efficacy, dose regimen, durability of protection, route of administration, species coverage, product stability and storage, co-administration with other vaccines, presentation, production, and registration and prequalification”. These Ebola vaccine TPPs came early in 2016 and assisted manufacturers in improving the characteristics of candidate vaccines already tested in clinical trials or under clinical development, and guided developers of new Ebola vaccines yet to reach clinical trials. (World Health Organization [15] January 2016)

In response to the 2014-2016 West African Outbreak, WHO also developed an Emergency Use Assessment and Listing (EUAL) procedure in September 2014, to expedite the availability of candidate medicinal products, vaccines and *in vitro* diagnostic tests that are needed in public health emergencies such as this, providing that the eligibility criteria are met (e.g.: the disease for which the product is intended had been declared as a PHEIC). (World Health Organization [16] January 2020) (WHO Website [9] March 2020) This extraordinary procedure intended to assess a minimum set of available quality, safety and efficacy/performance data of the three product categories and, if deemed acceptable, accelerate their use during the epidemic, by providing guidance to interested United Nations procurement agencies and National Regulatory Authorities of WHO Member States. However, WHO clarified that this procedure was not a WHO prequalification and that the inclusion of a product in a EUAL list could not compromise the implementation and completion of clinical trials. (World Health Organization [16] January 2020) (World Health Organization [17] July 2015) (WHO Website [10] April 2020)

During the outbreak, 2 EUAL applications for candidate vaccines against EVD (rVSV-ZEBOV and Ad26.ZEBOV/MVA-BN-Filo, as a rolling submission) and 25 EAUL applications for *in vitro* Ebola diagnostic tests were submitted. Of these, 7 *in vitro* Ebola diagnostic tests were listed until the end of the PHEIC status, declared on the 29th of March 2016. No EUAL applications for Ebola candidate medicinal products were submitted. (World Health Organization [16] January 2020) (WHO Website [9] March 2020)

EMA has been working together with other Regulatory Authorities to support WHO and advise on potential pathways for the development, design of clinical trials to gather robust evidence, assessment and approval of candidate medicinal products and vaccines. To contribute to the global Ebola response on the 2014-2016 West African Outbreak, EMA established an ad-hoc group of experts on vaccines, infectious diseases and clinical trials. (EMA Website [1] May 2020) The Regulatory Authority also put in place a rapid scientific advice procedure that allowed Ebola medicines and vaccines' developers to request accelerated advice on important issues, such as clinical trial designs, scaled-up production or post-authorization safety monitoring. (EMA Website [1] May 2020) This was accompanied by a form of rolling review, that allowed a continuous assessment of incoming data and development of robust and updated scientific opinions. These scientific opinions were subsequently shared with healthcare decision-makers in the most affected countries, for better informed decisions on the use of medicinal products and vaccines. This rapid scientific advice procedure was used for the first time in this outbreak for the advice on GlaxoSmithKline's ChAd3-EBOZ vaccine development plan. (European Medicines Agency [1] October 2014)

Additionally, the EMA performed a review of all quality, pre-clinical and clinical data available on several experimental Ebola treatments under development (for which a presumed direct antiviral activity against the Ebola virus existed), in order to support decisions on potential emergency use for individual patients and decision-making by Regulatory Authorities. This review was requested by EMA to the Committee for Medicinal Products for Human Use (CHMP) on the 23rd of September 2014, in accordance with Article 5(3) of Regulation (EC) No. 726/2014. An interim report was published by EMA on November 2014, while the final report on experimental treatments review was published on March 2016. (EMA Website [1] May 2020) (European Medicines Agency [2] February 2016)

A schematic timeline of the EMA activities performed during the outbreak period is presented in Figure 5.

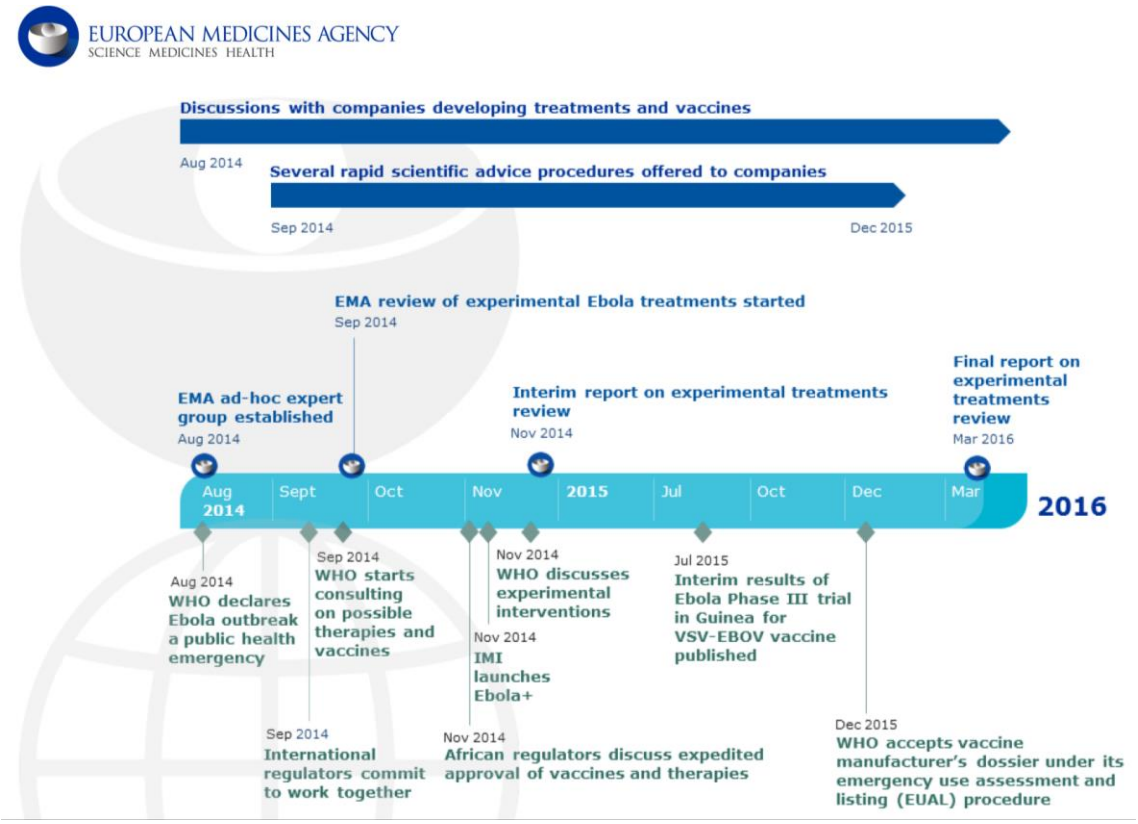


Figure 5: Timeline of the EMA activities performed during the 2014-2016 Ebola outbreak (EMA Website [1] May 2020)

EMA also made use of other regulatory pathways, to promote development of medicinal products against the Ebola virus, such as:

- Orphan Designation, that offers a variety of incentives to pharmaceutical companies, including protocol assistance, reduced fees or market exclusivity. (EMA Website [2] May 2020) Orphan Designation was granted by the European Commission to the investigational medicinal product ZMapp on October 2015. (European Medicines Agency [3] November 2015)

- Priority Medicines (PRIME) scheme, a regulatory mechanism that enhances the support to the development of medicines that target an unmet medical need. It fosters early interaction with the Regulatory Authority and allows additional advice in order to expedite the regulatory submission and assessment. (EMA Website [3] May 2020) The PRIME status was granted by EMA to the candidate vaccine rVSV-ZEBOV on June 2016 for active immunization against Ebola. (Business Wire July 2016) (European Medicines Agency [4] October 2019)

The US FDA also worked towards expediting the development and availability of medicinal products, vaccines and diagnostic test to help bring the Ebola outbreak under control,

establishing an Ebola Task Force to work in the most fast and flexible manner. (Largent September 2016) To accomplish this, the US FDA utilized existing drug development programs and expedited regulatory pathways to encourage companies to invest in this disease, such as:

- Orphan Drug Act, that offers pharmaceutical companies financial and regulatory incentives, such as market exclusivity, tax credits and research grants. Orphan designations were granted by US FDA to investigational medicinal products for EVD, including ZMapp in August 2014 and Remdesivir in September 2015; (Largent September 2016) (FDA Website [1] May 2020)

- Priority Review and the Priority Review Voucher Program, both of which entitle the applicant to a 6-month priority review period by US FDA, rather than the standard 10-month review period. (Largent September 2016) The Ebola virus was not part of the initial Priority Review Voucher Program, created in 2007 by the *Food and Drug Administration Amendments Act* (FDAAA), since it was not considered a Neglected Tropical Disease (NTD) by its historically low morbidity and mortality. This scenario changed on the 16th of December 2014, when President Barack Obama signed into law the *Adding Ebola to the FDA Priority Review Voucher Program Act*, an amendment to the FDAAA that introduced five strains of the genus *Ebolavirus* in the program; (Largent September 2016) (RAPS Website [1] February 2020) (United States Congress December 2014)

- Fast Track status, a process that facilitates the development and accelerates the review of medicinal products to treat serious conditions and fulfill an unmet medical need, by allowing more frequent meetings and written communication with the US FDA during the development phase, eligibility for accelerated approval and priority review, if certain criteria are met, and rolling review. Fast track status was granted by the US FDA to several investigational medicinal products for EVD, including TKM-Ebola in March 2014 and ZMapp in September 2015. (Largent September 2016)

- Breakthrough Therapy Designation, a process that expedites the development and review of medicinal products that fulfill certain requirements, by allowing eligibility to all fast track program features, more intensive guidance from the US FDA and priority review. (FDA Website [2] January 2018) Breakthrough Therapy Designation was granted by the US FDA to the candidate vaccine rVSV-ZEBOV on June 2016. (Business Wire July 2016)

- Emergency Use Authorization (EUA), that allows the US FDA to facilitate the availability and unapproved uses of medical countermeasures (MCMs) needed to prepare for and respond to chemical, biological, radiological and nuclear emergencies (CBRN). (FDA Website [3] May 2020) Following the declaration that circumstances existed justifying the emergency use of *in vitro* diagnostic tests for the detection of the Ebola virus by the Secretary of the US Health and Human Services (HHS) on the 4th of August 2014,

several EUAs were issued for Ebola virus *in vitro* diagnostic tests between August 2014 and May 2016. Of the EUAs issued in this period, nine are still active for emergency use, as of May 2020. (Department of Health and Human Services August 2014) (FDA Website [3] May 2020)

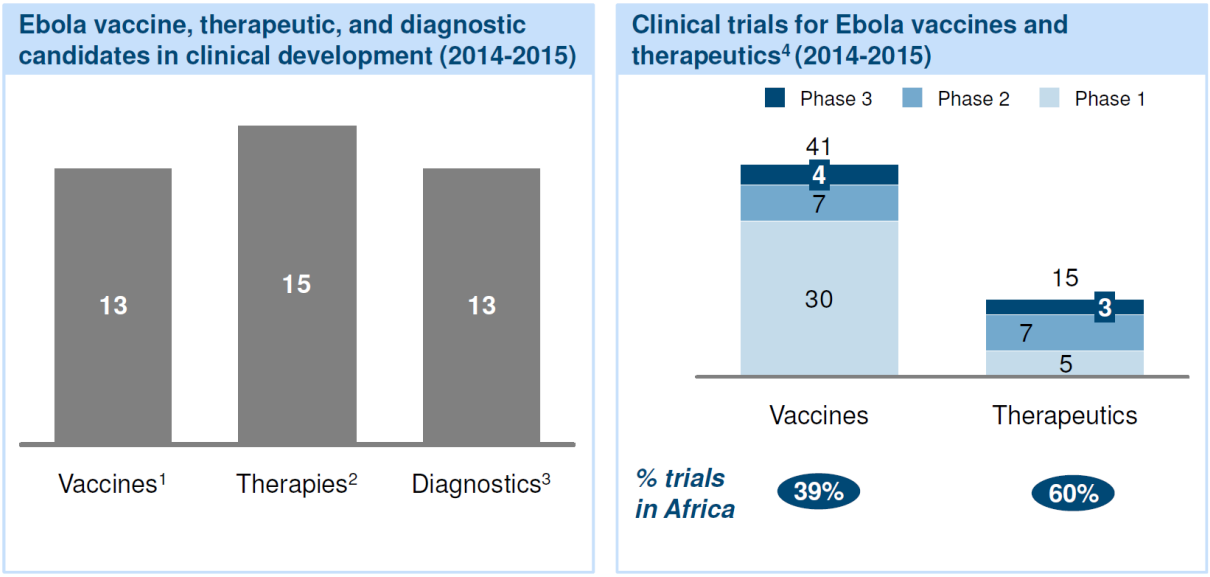
- Expanded Access Program (otherwise known as compassionate use), which is further discussed below.

In Africa, regional regulatory forums and networks, alongside West African National Regulatory Authorities, also took leading roles in addressing regulatory issues during the Ebola outbreak. Of importance, they assisted on the design and implementation of clinical trials, oversight, pooling of results, testing and access to investigational medicinal products. Moreover, they also debated and facilitated possible regulatory pathways for vaccines and potential therapeutic medicinal products to be used in affected countries. The most relevant regional regulatory programs and networks were the African Medicines Regulatory Harmonization (AMRH) and the African Vaccine Regulatory Forum (AVAREF). (World Health Organization [10] September 2014)

The AVAREF, created by WHO in 2006 as a network of African National Regulatory Authorities and Ethics Committees to build capacity and promote harmonized practices, was used to support the ethical and regulatory reviews and oversight for the clinical trials applications (CTAs) of candidate vaccines against Ebola. (Akanmori, et al. August 2018) This network made use of external expertise from other Regulatory Authorities with experience in pre-licensure vaccine trials (such as the US FDA, EMA and Health Canada), allowed for assisted and joint reviews of CTAs and established harmonized standards and common grounds of understanding between local National Regulatory Authorities regarding the revision procedures and minimum data required. This ultimately contributed to expedite revisions and decision-making regarding CTAs, reducing the normal clinical trials' timelines for candidate vaccines from years to only months. (World Health Organization [10] September 2014) (Akanmori, et al. August 2018)

On the funding perspective, several funding agencies stepped forward and provided financial support to research and development projects against EVD. Of notice, the IMI (a public-private partnership funded jointly by the European Commission and the European Federation of Pharmaceutical Industries and Associations, EFPIA), under the IMI 2 Joint Undertaking, launched the Ebola + program. This program had the objective to help tackle hurdles in vaccines development, clinical trials, storage, transport and diagnostics. It currently includes 12 projects, the majority launched during the 2014-2016 West African Outbreak. (Innovative Medicines Initiative March 2020)

Researchers and stakeholders thoroughly discussed the feasibility and best approaches on how to conduct clinical trials on the potential Ebola therapeutic medicinal products and vaccines, resulting in several clinical trials being formally conducted both outside and inside the Ebola affected countries during the outbreak. Figure 6 below depicts the number of vaccines, therapeutic medicinal products and diagnostic candidates in clinical development, as of October 2015, as well as the amount of clinical trials (phase 1 to phase 3) performed in the same period.



1 Considering different vaccine combinations/variants as distinct
2 Including therapies only given under compassionate use
3 Products that have received FDA or WHO emergency use listing; up to 80 are in some stage of development
4 Based on triangulation from public sources and stakeholder interviews. If a trial spans multiple phases or is unclassified, classification here is based on the highest phase or the trial's primary outcomes

Figure 6: High-level summary of Ebola clinical candidates during the 2014-2016 West African outbreak (World Health Organization [18] October 2015)

The next two subsections grasp the research and development efforts performed during this outbreak period, for both therapeutic medicinal products and vaccines, showcasing summarized lists of tested candidates.

Medicinal products

The international efforts on the research and development of potential therapeutic medicinal products to fight Ebola were heavily supported in different areas: researchers working in the affected areas; innovative measures from regulators; and investment from Governments, foundations and private sector. The efforts led to the use of some experimental medicinal products specifically developed for Ebola during the outbreak, either through clinical trials and/or compassionate use. These included:

- ZMapp, a cocktail of three mouse/human monoclonal antibodies (c13C6, c2G4 and c4G7), directed against three distinct epitopes in the Ebola virus glycoprotein; these monoclonal antibodies were selected from two other cocktails, ZMab and MB-003, and are produced in genetically modified tobacco plants. (European Medicines Agency [2] February 2016) (WHO Website [11] October 2015)

- MIL-77, a cocktail of monoclonal antibodies with the same sequence in the binding domain as ZMapp; the monoclonal antibodies are produced in CHO cells, allowing for a larger production quantity when compared to tobacco plants. (WHO Website [11] October 2015)

- TKM-130802, a lipid nanoparticle formulation containing three small interfering RNAs (siRNAs) directed against the RNA polymerase L and structural proteins VP24 and VP35; (European Medicines Agency [2] February 2016) (WHO Website [11] October 2015)

- TKM-130803, a new formulation of TKM-100802, with adapted small interfering RNAs that are specific for the outbreak variant of the Ebola virus. (European Medicines Agency [2] February 2016) (Keusch, et al. 2017)

- BCX4430, a nucleoside analogue acting as an inhibitor of RNA polymerase. (European Medicines Agency [2] February 2016) (WHO Website [11] October 2015)

- AVI-7537, an antisense oligonucleotide aiming at repressing the virus replication by binding to the VP24 gene. (European Medicines Agency [2] February 2016)

- Remdesivir (GS-5734), a prodrug of a modified adenine nucleoside analogue, that induces the inhibition of RNA synthesis. (European Medicines Agency [2] February 2016)

Convalescent whole blood and convalescent plasma obtained from EVD survivors were used as an alternative, as they had been in previous outbreaks. They were considered a therapy easy to obtain, inexpensive, potentially specific for the variant of the Ebola virus and with the additional benefit of restoring blood volume and refiling serum components, being therefore prioritized for use by WHO during the outbreak. (World Health Organization [10] September 2014) (Mendoza, Qiu and Kobinger February 2016) Platforms for the production of polyclonal sera were also developed: Anti-Ebola $F(ab')_2$ (specific polyclonal anti-Ebola immunoglobulin F(ab')2 fragments from immunized horses, targeting the Ebola virus), and EBOTAb (a purified polyclonal antibody of ovine origin raised against soluble recombinant Ebola glycoprotein ectodomain). (European Medicines Agency [2] February 2016)

Several existing medicinal products, already approved for different therapeutic uses other than treating EVD, were also considered early in the outbreak response for re-purposing to fight Ebola, since they had shown some level of potential efficacy *in vitro*. These included Favipiravir (approved by the Pharmaceuticals and Medical Devices Agency – PMDA, to treat Influenza A in Japan), Brincidofovir (approved to treat *Cytomegalovirus*), Interferons (approved for treatment of Hepatis B and C and multiple sclerosis), Amiodarone (approved to treat cardiac dysrhythmia), FX06 (peptide approved to treat vascular leakage), Amodiaquine (approved to treat Malaria), Lamivudine (antiretroviral) and Atorvastatin + Irbesartan +/- Clomiphene (approved for cholesterol control, hypertension and infertility, respectively). (World Health Organization [18] October 2015) (World Health Organization [19] July 2015) (WHO Website [11] October 2015)

The main advantages of considering re-purposed medicinal products include their known safety profiles (obtained from previous clinical trials) and their availability, which could ultimately provide the timely use of a safe and potentially effective medicinal product for EVD patients. (Largent September 2016) Some of these repurposed medicinal products were used in the regime of compassionate use and/or in formal clinical trials, as described hereafter.

The most promising therapeutic medicinal products were categorized and prioritized for testing or use in patients with EVD in a list, updated on a continuous base by WHO, as follows:

- “drugs under evaluation in formal clinical trials in West Africa”, as of 2015. (World Health Organization [19] July 2015)
- “drugs that had been prioritized for testing in human efficacy trials, but for which such trials were not yet underway”, as of 2015. (World Health Organization [19] July 2015)
- “drugs that had already been given to patients for compassionate reasons or in ad hoc trials”. (World Health Organization [19] July 2015)
- “drugs that demonstrated promising anti-Ebola activity *in vitro* or in mouse models, but for which additional data should be generated prior to proceeding to clinical trials”. (World Health Organization [19] July 2015)
- “drugs that had been prioritized or considered for prioritization and had been deprioritized based on new data or more detailed analysis of old data”. (World Health Organization [19] July 2015)

The categorization and prioritization were performed by the WHO Science and Technical Advisory Committee on Emergency Ebola Interventions (STAC-EE), taking into account the available evidence on safety and efficacy, as well as the feasibility (e.g. logistics and manufacturing capabilities) and utility to conduct formal clinical trials. (World Health Organization [19] July 2015)

Compassionate Use

Compassionate use (or expanded access) corresponds to the emergency use of unapproved, experimental medicinal products, outside of clinical trials to treat patients with serious or life-threatening diseases when no other comparably beneficial alternative treatment is available. During the 2014-2016 Ebola outbreak, as no approved treatments or vaccines were available, experimental medicinal products (new and re-purposed) were used under compassionate use grounds with the hope to reduce the morbidity and mortality associated with EVD and contain the outbreak spreading. This was justified by the ethical consultation panel, convened by WHO on August 2014, as an exceptional emergency measure. (WHO Website [8] August 2014) (Largent September 2016)

WHO also developed an ethical framework know as *Monitored Emergency Use of Unregistered and Experimental Interventions* (MEURI), which defined the criteria to be met for the use of experimental medicinal products for individual patients outside of clinical trials, including: inexistence of a proven effective treatment; impossibility to immediately start clinical trials; existence of preliminary data supporting the safety and efficacy of the experimental medicinal product (at least from laboratory or nonclinical studies); approval by the countries' Ethical Committees and Regulatory Authorities; availability of resources to minimize risks; informed consent; and intervention monitoring with the results being shared with the scientific community in a timely manner. (World Health Organization [20] 2016) Later, the WHO Ebola Ethics Working Group proposed to use the term MEURI instead of compassionate use. (WHO Ethics Working Group October 2014)

In this context, several Emergency Investigational New Drug (EIND) applications were submitted to and granted by US FDA for the emergency use of some investigational medicinal products in individual Ebola patients. European Regulatory Authorities (e.g.: from United Kingdom, France, Spain or Italy) also approved investigational medicinal products to be used under compassionate use grounds. Experimental medicinal products used under these provisions during this outbreak included ZMapp, ZMab, MIL-77, TKM-100802, Brincidofovir, Favipiravir, Remdesivir, FX06, Amiodarone, Amodiaquine, Lamivudine, and combinations of Atorvastatin, Irbesartan and/or Clomiphene. (Largent September 2016) (World Health Organization [18] October 2015) (Mendoza, Qiu and Kobinger February 2016) (World Health Organization [19] July 2015) (WHO Website [11] October 2015) (Uyeki, et al. February 2016)

The widespread demand for access and use of early-stage experimental medicinal products originated on the compassionate use of ZMapp in early August 2014. Among other interventions and despite the uncertainty about its effectiveness and safety, ZMapp was used on two American healthcare workers who became infected with the Ebola virus in West Africa and were evacuated to the USA for medical care. Their survival sparked this demand and triggered the ethical consultation meeting, convened by WHO on August 2014, previously discussed. Despite their survival, no clear evidence on ZMapp's efficacy and safety could be obtained. (Largent September 2016) (Borio, Cox and Lurie September 2015) The same

inconclusive results on safety and efficacy, and associated criticism, were imputed to the vast majority of the experimental medicinal products utilized under compassionate use circumstances during this outbreak, as they were often administrated in conjunction with other interventions (either with other experimental medicinal products or standard of care). (Largent September 2016) (Keusch, et al. 2017)

The broad administration of experimental medicinal products under compassionate use grounds was not consensual within the international community, leading to diversified viewpoints in different topics. Firstly, ethical questions on healthcare fairness were raised as the first administrations under compassionate use were made to healthcare workers, treated in high income countries. Secondly, the allocation of scarce resources was debated, as the quantities of experimental medicinal products were limited and their administration under compassionate use could jeopardize the collection of high-quality evidence on efficacy and safety in humans through clinical trials, ultimately potentially affecting future patients in subsequent outbreaks. (Largent September 2016) (Borio, Cox and Lurie September 2015) (Joffe October 2014) (Rojek and Horby November 2016)

Clinical Trials

During the course of the 2014-2016 Ebola outbreak in West Africa, several clinical trials were formally conducted on experimental medicinal products, both outside and within the Ebola affected countries. These trials represented an important opportunity to, ethically, gather the best possible evidence and knowledge on the candidates' efficacy and safety in humans, hopefully contributing for their approval and availability in future Ebola outbreaks. Before their launch, important issues were identified and debated during the meetings held by WHO on August and September 2014 and by the WHO Ebola Ethics Working Group on October 2014: location and capabilities of the clinical trials' sites; design of the clinical trials (taking into consideration the ethics, population acceptability and prior knowledge on effectiveness/safety of experimental medicinal products in animals and humans); inclusion and exclusion criteria; availability of the experimental medicinal products under evaluation; endpoints and how to collect the generated data; follow-up plans if the experimental medicinal products were deemed efficacious and safe. (World Health Organization [8] August 2014) (World Health Organization [10] September 2014) (WHO Ethics Working Group October 2014)

The choice of the most appropriate clinical trial design to rapidly and ethically assess candidate therapeutic medicinal products in the midst of an emergency situation was highly divisive and substantially debated. (Largent September 2016) (Lanini, et al. June 2015) Some investigators and methodologists advocated for the traditional randomized controlled trials (RCTs), based on the following reasons: they doubted that alternative designs would be methodologically rigorous to yield valid and unbiased results, which could lead to a misleading interpretation of efficacy and/or safety results, possibly jeopardizing the clinical research and its evidence-based use for future outbreaks; by opposition RCTs would be the optimal design to correctly

and confidently identify effective and safe interventions for EVD; additionally, it was also argued that randomization would be the best way to fairly allocate scarce resources (as it was the case for several experimental medicinal products) among the participants of a clinical trial, instead of alternative unethical ways, such as first-come-first-serve or sickest first. (Largent September 2016) (Joffe October 2014) (Borio, Cox and Lurie September 2015) (Cox, Borio and Temple December 2014) (Adebamowo, et al. October 2014) (Lanini, et al. June 2015) (Keusch, et al. 2017)

A different group of investigators and methodologists defended alternative clinical trial designs by questioning whether it was ethical to randomize individuals with a life-threating condition to a control arm and possibly deny them the opportunity to benefit from an experimental medicinal product, and therefore, supported that potentially beneficial interventions should be provided as widely as possible, even in the presence of a limited supply; moreover, they also stated that alternative trial designs had the potential to generate efficacy and safety data more quickly and with greater social acceptability. (Largent September 2016) (Joffe October 2014) (Borio, Cox and Lurie September 2015) (Cox, Borio and Temple December 2014) (Adebamowo, et al. October 2014) (Lanini, et al. June 2015) (Keusch, et al. 2017)

WHO, within the previously mentioned meetings to assess the research priorities for the outbreak and the ethical issues related with clinical trial designs, raised concerns on the use of classical randomized, placebo-controlled trials, as these would probably not be ethically appropriate and acceptable within the already mistrusted community. Therefore, encouragement was placed on alternative trial designs. (World Health Organization [10] September 2014) (WHO Ethics Working Group October 2014)

A total of 15 experimental medicinal products (new and re-purposed) entered formal clinical trials while the outbreak was occurring, with some only being studied under phase 1 human trials, while others went through to phase 2 and phase 3, as depicted in Figure 6. (World Health Organization [18] October 2015) Despite the urgency in fighting the outbreak, the collaborative work between Regulatory Authorities and stakeholders, and the diversified investment from Governments, foundations and private sector, the first registered clinical trial only began on December 2014 with the JIKI clinical trial for Favipiravir. The results of the trial were ambiguous, falling short on showing effectiveness in patients with high viral load. (Sissoko, et al. March 2016) (Mirza, et al. November 2018) (Keusch, et al. 2017)

Much like Favipiravir in the JIKI clinical trial, several other therapeutic candidates failed to continue pass phase 2 trials for efficacy, safety and tolerability. The most common reasons appointed for failure included the lack of proper controls, the low statistical power of the trials and the poor enrollment, mostly associated with the low amounts of medicinal products available and/or the rapid decline in the incidence of new EVD cases from early 2015 onwards. Safety reasons were also appointed, as was the case for TKM-100802, whose Investigational New Drug Application (IND) was put on clinical partial hold in healthy individuals by the US

FDA, due to concerns about the risk of cytokine release syndrome triggered by the action of siRNA. (World Health Organization [18] October 2015) (Mirza, et al. November 2018) (Dunning, et al. April 2016) (Keusch, et al. 2017) The summary of the main phase 2 and phase 2/3 clinical trials performed is presented in Table 1.

Regarding the clinical trial design, most trials were non-randomized trials, open-label with a single arm and making use of historical controls, that is, making the experimental medicinal product available as widely as possible and then comparing the study outcomes with the outcomes of a historical external group that was considered to be similar to the participants in the study. (Keusch, et al. 2017) (World Health Organization [18] October 2015)

On a different perspective, ZMapp was included in an adaptive randomized, open-label clinical trial (PREVAIL II). This was the first medicinal product included in and evaluated under the adaptive clinical trial common protocol developed by the National Institutes of Health, in collaboration with the US FDA and West African Regulatory Authorities and Institutions in early 2015. (Borio, Cox and Lurie September 2015) This adaptive trial design allowed for the study of more than one experimental medicinal product using a shared control group, to which the best available supportive care was given. If an experimental medicinal product subsequently showed to be effective against EVD, it could then be incorporated into the evolving standard of care, against which additional experimental medicinal products would be tested. (World Health Organization [18] October 2015) (The PREVAIL II Writing Group October 2016) The multicenter PREVAIL II trial was launched in four countries, with ZMapp plus optimized standard of care being compared with optimized standard of care alone. Additionally, based on the JIKI trial results, the Ministry of Health of Guinea opted to include Favipiravir as part of the optimized standard of care for the patients enrolled in that country. The main results of the trial are described in Table 1. (World Health Organization [18] October 2015) (Borio, Cox and Lurie September 2015) (Cox, Borio and Temple December 2014) (The PREVAIL II Writing Group October 2016)

Table 1: Summary of EVD Therapeutic Candidates Evaluated During the 2014–2016 Ebola Outbreak in Formal Phase 2 or 2/3 Clinical Trials

Therapeutic Candidate	Drug Type	Highest Pre-Clinical Evidence	Latest Formal Clinical Trial		
			Description & Design	Trial Information	Main Results
ZMapp	Cocktail of three monoclonal antibodies, optimized from two previous antibody cocktails (ZMab and MB-003), which specifically bind to the Ebola virus surface glycoprotein.	NHP: 100% survival when administered 5 days after virus challenge.	PREVAIL II (Phase 1/2 - safety and efficacy) - Multicenter; - Randomized, open-label; - 2 arms: ZMapp + oSOC vs. oSOC only - oSOC included Favipiravir in Guinea.	Location: Guinea, Liberia, Sierra Leone, USA Enrollment: 72 patients (adults and children) Timeline: March 2015 to November 2015 Sponsor: National Institute of Allergy and Infectious Diseases (NIAID)	ZMapp showed promise as a possible effective treatment agent for EVD, but there were insufficient data to determine definitively whether it is a better treatment for EVD than supportive care alone (results did not meet the prespecified statistical threshold for efficacy). Mortality proportion: ZMapp – 22% Control – 37%
Favipiravir	Small molecule antiviral with activity against many RNA viruses. Functions through inhibiting viral RNA-dependent RNA polymerase. Approved in Japan since March 2014 for treating novel / pandemic influenza virus.	Mice: 100% survival (if administered within 6 days post-infection).	JIKI (Phase 2 - safety and efficacy in reducing mortality) - Proof-of-concept noncomparative trial; - Multicenter; - Non-randomized, open-label; - Single arm, historical controls (preceding 3 months, same treatment and care, favipiravir excluded).	Location: Guinea Enrollment: 126 patients (adults and children) Timeline: December 2014 to June 2015 Sponsor: Institut National de la Santé Et de la Recherche Médicale (France)	Efficacy and tolerance inconclusive. Efficacy may be dependent on viral load (results suggest that monotherapy with Favipiravir on the studied dose is unlikely to decrease mortality in patients with very high viral load).

Table 1: Summary of EVD Therapeutic Candidates Evaluated During the 2014–2016 Ebola Outbreak in Formal Phase 2 or 2/3 Clinical Trials

Therapeutic Candidate	Drug Type	Highest Pre-Clinical Evidence	Latest Formal Clinical Trial		
			Description & Design	Trial Information	Main Results
TKM-130803	Small interfering RNA (siRNA) which catalytically cleaves Ebola RNA once inside the cell, repressing the virus replication and pathogenesis. Sequence-specific to this strain of Ebola.	NHP: 67 or 100% survival (survival differed by study groups).	RAPIDE-TKM (Phase 2 - safety and efficacy) - Part of a multistage trial design with boundaries based on historical/contemporary controls with results guiding subsequent trial design; - Non-randomized, open-label; - Single arm, historical controls.	Location: Sierra Leone Enrollment: 14 patients (adults) Timeline: March 2015 to June 2015 Sponsor: University of Oxford	Early results from the study, demonstrated that TKM-130803 was not effective in increasing the survival fraction above 50%. Did not demonstrate an overall therapeutic benefit to patients when compared with historical controls. The sponsor suspended further clinical development of TKM-130803 for Ebola virus.
Brincidofovir	Small molecule antiviral with activity against dsDNA viruses. Developed and used for treatment and prophylaxis of *cytomegalovirus* (CMV).	Company publicized *in vitro* activity against Ebola. Preliminary data from studies in mouse EBOV model did not show any indication of activity.	RAPIDE-BCV (Phase 2 - safety and efficacy) - Part of a multistage trial design with boundaries based on historical/contemporary controls with results guiding subsequent trial design; - Non-randomized, open-label; - Single arm, historical controls.	Location: Liberia Enrollment: 4 patients (adults and children) Timeline: January 2015 Sponsor: Chimerix	Efficacy and tolerance inconclusive due to small sample size. Clinical trial halted in late January 2015 due to lack of patients being enrolled. Company withdraw the drug for investigational use in Ebola patients.

Table 1: Summary of EVD Therapeutic Candidates Evaluated During the 2014–2016 Ebola Outbreak in Formal Phase 2 or 2/3 Clinical Trials

Therapeutic Candidate	Drug Type	Highest Pre-Clinical Evidence	Latest Formal Clinical Trial		
			Description & Design	Trial Information	Main Results
Convalescent plasma (CP)[a]	Convalescent plasma transfusions from EVD survivors, containing antibodies.	NHP: although human plasma hasn't been studied, related studies show: - 100% survival, using IgG purified from the blood of NHP EVD survivors; - 0% survival using whole blood transfusion	Ebola-Tx (Phase 2/3 - safety and efficacy) - Non-randomized, open-label; - Single arm, historical controls (SOC was initially considered as control).	Location: Guinea Enrollment: 99 patients (adults, including pregnant women, and children) Timeline: February 2015 to July 2015 Sponsor: Institute of Tropical Medicine (Belgium)	The transfusion of up to 500 ml of convalescent plasma with unknown levels of neutralizing antibodies in 84 patients with confirmed EVD was not associated with a significant improvement in survival, compared to historical controls.
Interferon beta 1a[b]	Immune modulator with antiviral activity.	NHP: significantly delayed death but no survival benefit (0%).	Phase 1/2 - safety and efficacy - Non-randomized, open-label; - Single arm, historical controls.	Location: Guinea Enrollment: 9 patients (adults) Timeline: March 2015 to April 2016 Sponsor: FOSAD & CEFORPAG	The treatment seemed to be associated with clearance of virus from blood, better clinical features and, potentially, improved survival.

Notes: NHP – nonhuman primates; oSOC – optimized Standard of Care; a – only the clinical trial with a higher number of patients enrolled and a primary completion date within the outbreak period was considered. Other clinical trials occurred in Liberia, Sierra Leone and the USA; b – trial registration was delayed, occurring only in 2016.
Source: (World Health Organization [18] October 2015) (World Health Organization [19] July 2015) (Sissoko, et al. March 2016) (Dunning, et al. April 2016) (The PREVAIL II Writing Group October 2016) (Dunning, Kennedy, et al. September 2016) (Griensven, et al. January 2016) (Edwards, et al. February 2016) (Konde, et al. February 2017) (Keusch, et al. 2017) (ClinicalTrials.gov [1] July 2019) (ISRCTN March 2019)

Vaccines

The international efforts on the research and development of therapeutic medicinal products to fight Ebola was also applied to the development of effective vaccines that could potentially prevent EVD, by inducing Ebola-specific immune responses. The ideal vaccine would provide rapid and durable protection, provide protective immunity against multiple *Ebolavirus* species (four species cause disease in humans), be safe in special populations (e.g.: pregnant women, children and immunocompromised individuals), easy to administer, thermostable, and quickly available when needed. (World Health Organization [15] January 2016) Those efforts resulted in the inclusion of several candidate vaccines in clinical trials during the outbreak. These included:

- rVSV-ZEBOV (also referred to as V920), a live attenuated, replication-competent, recombinant vaccine, consisting of a single vesicular stomatitis virus (rVSV) expressing the Ebola virus surface glycoprotein. The vesicular stomatitis virus works as a vector, where the gene encoding the VSV G envelope glycoprotein is replaced with the gene encoding the *Zaire ebolavirus* (ZEBOV) surface glycoprotein, significantly attenuating the virus. Developed by the Public Health Agency of Canada and NewLink Genetics and then licensed to Merck Sharp & Dohme (Merck) in 2014 for further development. (Higgs, et al. September 2017) (Martins, et al. September 2016)

- ChAd3-EBOZ, a recombinant chimpanzee adenovirus serotype 3 (ChAd3) expressing the Ebola virus surface glycoprotein. The ChAd3 works as a vector with a DNA fragment insert that encodes the Ebola virus surface glycoprotein, which is expressed on the surface and is critical for attachment to host cells and catalysis of membrane fusion. This vaccine was evaluated as an alternative to human adenovirus vectors to avoid the challenges of pre-existing immunity while simultaneously inducing a robust immune response with a single dose. Developed by GlaxoSmithKline in collaboration with NIAID. (Higgs, et al. September 2017) (Martins, et al. September 2016) (World Health Organization [21] October 2018)

- Ad26.ZEBOV/MVA-BN-Filo, a two-dose heterologous prime-boost vaccine regimen comprised of the replication-incompetent monovalent vaccine Ad26.ZEBOV (as the prime vaccine component, to induce an immune response) and the replication-incompetent multivalent vaccine MVA-BN-Filo (as the boost vaccine component, to enhance the immune response and increase its duration). Ad26.ZEBOV is based on human adenovirus type 26 vector expressing Ebola virus surface glycoprotein, while MVA-BN-Filo is a Modified Vaccinia Virus Ankara (MVA) strain containing Sudan virus, Ebola virus and Marburg virus glycoproteins, and Tai Forest nucleoprotein inserts. Developed by Crucell Holland N.V. (now called Janssen Vaccines & Prevention, B.V., one of the

Janssen Pharmaceutical Companies of Johnson & Johnson, and Bavarian Nordic. (Shukarev, et al. January 2017) (Martins, et al. September 2016) (World Health Organization [21] October 2018)

- A recombinant nanoparticle vaccine using the Ebola virus surface glycoprotein sequence from the 2014-2016 West African Outbreak strain, developed by Novavax. (World Health Organization [18] October 2015) (World Health Organization [21] October 2018)

- Ad5.EBOV, a replication-incompetent vaccine based on human adenovirus type 5 (Ad5) vector expressing the Ebola virus surface glycoprotein. This was the first vaccine to demonstrate efficacy in non-human primates; however, subsequent studies highlighted the presence of pre-existing immunity to Ad5 vector, reducing the efficacy of the vaccine alone in humans and non-human primates. Developed by the Beijing Institute of Biotechnology and Tianjin CanSino Biotech. (Higgs, et al. September 2017)

- GamEvac-Combi, a heterologous VSV- and Ad5-vectored prime boost vaccine, expressing the Ebola virus surface glycoprotein. Developed in Russia. (World Health Organization [21] October 2018)

- rVSVN4CT1-EBOV, a live, replication-incompetent, oral vaccine, consisting of a VSV vector backbone. Developed by Profectus BioSciences. (World Health Organization [18] October 2015)

- INO-4212, a DNA vaccine comprised of a 1:1 mixture of INO-4201 (contains the DNA sequence that codes the surface glycoprotein of past Ebola virus outbreak strains) and INO-4202 (contains the DNA sequence that codes the surface glycoprotein of the Ebola virus 2014-2016 West African Outbreak strain). Developed by Inovio. (Martins, et al. September 2016) (World Health Organization [21] October 2018)

A total of 13 candidate vaccines, considering different vaccine combinations/variants as distinct, entered formal clinical trials in Africa (including the three most affected countries in the 2014-2016 West African Outbreak), USA and Europe while the outbreak was occurring. Some were only studied under phase 1 human trials, while others went through to phase 2 and phase 3 (sometimes concurrently), as depicted in Figure 6. (World Health Organization [18] October 2015) WHO used a set of criteria and data analysis to determine the leading candidate vaccines that would be fast-tracked for clinical evaluation. rVSV-ZEBOV and ChAd3-EBOZ met those criteria in August 2014, while Ad26.ZEBOV/MVA-BN-Filo and the recombinant nanoparticle vaccine from Novavax met the same criteria later in the epidemic. (Henao-Restrepo, et al. April 2016)

rVSV-ZEBOV

One of the leading candidate vaccines in August 2014, rVSV-ZEBOV, was heavily studied during the outbreak, because of the efficacy and immunogenicity demonstrated in pre-clinical animal models and its general safety, tolerability and capability to induce an immunogenic response in humans in phase 1 clinical trials. (Higgs, et al. September 2017) These trials were in part supported by the African and European VSV-Ebola Consortium (VEBCON), a consortium created by WHO on September 2014 to help initiate phase 1 trials and expedite decisions on dose and safety. (Henao-Restrepo, Preziosi, et al. April 2016) A total of 8 phase 1 clinical trials were performed in healthy volunteers (nearly 800 adults and 40 pediatric subjects), starting from October 2014 in EVD non-endemic countries in Africa, North America and Europe. (Higgs, et al. September 2017) (Henao-Restrepo, et al. April 2016) (Keusch, et al. 2017)

Building on top of this and given the urgent outbreak situation, some large phase 2 and 3 clinical trials began in early 2015, mainly within West African countries, using different study designs and target participants to increase the likelihood of collecting robust safety, immunogenicity and possibly efficacy data. (World Health Organization [18] October 2015) Two of the most important trials included:

- STRIVE (Sierra Leone Trial to Introduce a Vaccine against Ebola), that used a stepped wedge design to accelerate the availability of the vaccine and the full vaccination of a high-risk population - healthcare and frontline response workers who could come in contact with EVD cases professionally (their status crossed over from unvaccinated to vaccinated during their randomly assigned vaccination week); (Higgs, et al. September 2017) (Martins, et al. September 2016) (Samai, et al. May 2018) (Gupta, Coller and Feinberg September 2018)

- PREVAIL I (Partnership for Research on Ebola Vaccines in Liberia), that allowed for the simultaneous assessment of two vaccine candidates, rVSV-ZEBOV and ChAd3-EBOZ, against placebo. Initially designed as a phase 3 clinical trial for approximately 28.000 individuals with a phase 2 sub-study to assess safety and immunogenicity, the PREVAIL I study protocol was subsequently modified due to the decrease in the incidence of EVD cases in Liberia (cancellation of the phase 3 component of the study and expansion of the phase 2 sub-study to a total of 1500 individuals), as graphically shown in Figure 8. (Higgs, et al. September 2017) (Martins, et al. September 2016) (Kennedy, et al. October 2017) (Gupta, Coller and Feinberg September 2018)

Additionally, Merck also started a phase 3 clinical trial in North America and Europe to gather safety and manufacturing batch consistency data that would be essential in the regulatory package for the vaccine’s registration and approval. The main results of the trials are described in Table 2. (Higgs, et al. September 2017) (Martins, et al. September 2016) (Halperin, et al. May 2017) (Gupta, Coller and Feinberg September 2018)

But perhaps the most impactful rVSV-ZEBOV clinical trial was Ebola Ca Suffit!, commonly known as the Guinea Ring Vaccination Trial, operated under the leadership and regulatory sponsorship of the WHO. This was the only trial of an Ebola candidate vaccine that had the capacity to draw conclusions and demonstrate efficacy in humans, by using an innovative ring vaccination design, with a high probability of generating robust evidence despite the decrease in the incidence of EVD cases. This design was developed by the Guinea Vaccine Consortium, created by WHO on October 2014, and was based on the WHO vaccination campaign strategy responsible for the eradication of smallpox. (Higgs, et al. September 2017) (Henao-Restrepo, Preziosi, et al. April 2016) (Gupta, Coller and Feinberg September 2018)

It consisted on the vaccination of an epidemiologically defined ring of people (contacts and contacts of contacts) around a newly identified EVD patient (designated as index case), as illustrated in Figure 7. The ring would then be randomized to either receive the rVSV-ZEBOV vaccine immediately or after 21 days, in a 1:1 ratio. However, due to the positive results observed in the interim analysis, the delayed arm of the study was discontinued on July 2015 and all subsequent rings received the vaccine immediately. Additionally, following the publications of the interim results, the trial was expanded to Sierra Leone in August 2015 through an amendment to the clinical trial protocol under the Expanded Access Program. (Higgs, et al. September 2017) (Henao-Restrepo, Preziosi, et al. April 2016) (Ebola ça suffit ring vaccination trial consortium July 2015) (Gupta, Coller and Feinberg September 2018)

The main results are presented in Table 2 and suggest that the vaccine is efficacious in the context of a reactive ring vaccination strategy and that it could help contain an active outbreak if used in such a setting. Still, uncertainties remained as to the actual level of protection, its duration (participants were only followed until day 84) and the best type of protection (pre- or post-exposure prophylaxis). (Higgs, et al. September 2017) (Henao-Restrepo, Preziosi, et al. April 2016) (Ebola ça suffit ring vaccination trial consortium July 2015) (Gupta, Coller and Feinberg September 2018)

A parallel open-label study was also performed in healthcare workers in Guinea to assess safety and immunogenicity data in this high-risk population, adding valuable information to the one obtained in the STRIVE and PREVAIL I trials in Sierra Leone and Liberia, respectively. (Higgs, et al. September 2017) (Gupta, Coller and Feinberg September 2018) (Juan-Giner, et al. September 2018)

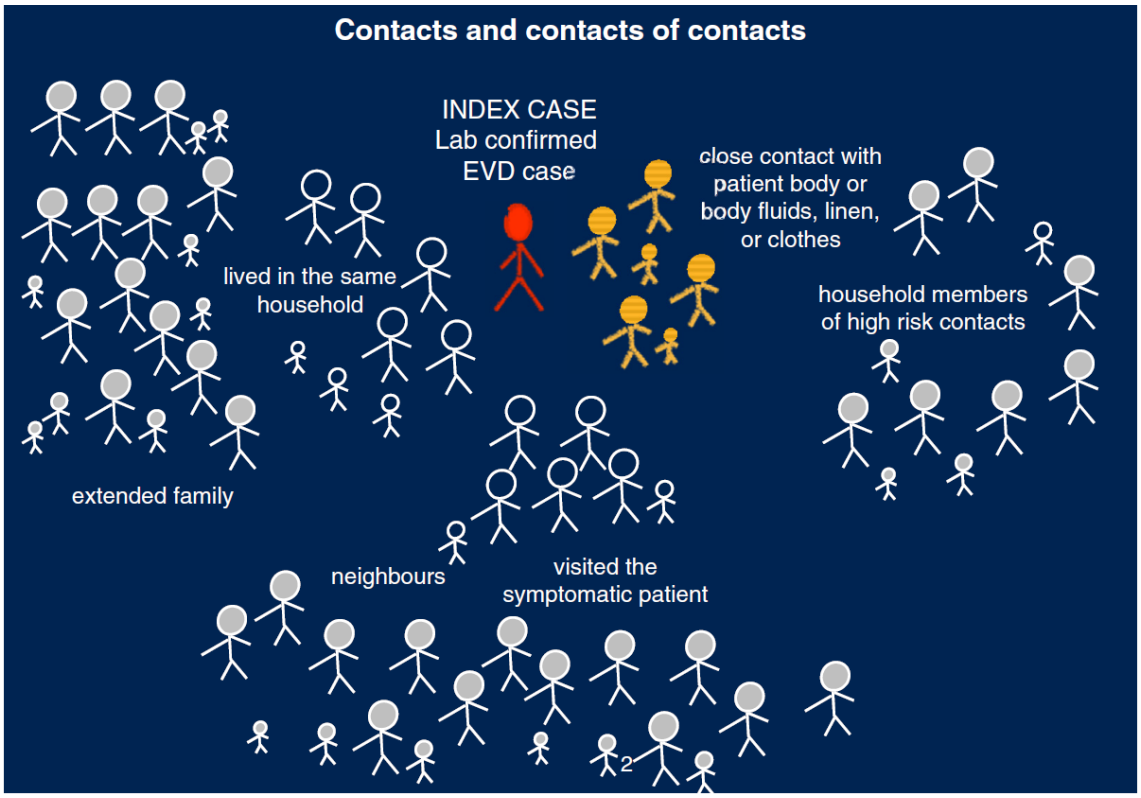


Figure 7: Illustration of a ring vaccination design (Henao-Restrepo, et al. April 2016)

Between the 17th of March and the 21st of April 2016, more than 1500 individuals in Guinea (including individuals aged between 6 and 17 years of age and healthcare workers) were vaccinated under compassionate use grounds with the rVSV-ZEBOV vaccine in response to a small flare-up of cases of EVD in the country. This corresponded to the first time that a candidate Ebola vaccine was used in an outbreak setting outside clinical trials, with the vaccine being deployed under a ring vaccination strategy, as used in the phase 3 clinical trial in Guinea. (Gsell, et al. December 2017) Approval for an Expanded Access protocol was rapidly sought and obtained within 48 hours from relevant authorities (WHO Ethics Review Committee, Guinea Ethics Review Committee and Guinea Regulatory Authority). No EVD cases were observed among the vaccinees for 10 days or more after vaccination, which was consistent with the analysis of the phase 3 clinical trial results, showcasing that the ring vaccination was a viable option and that it could be rapidly and effectively implemented as part of a response to future Ebola outbreaks. (World Health Organization [21] October 2018) (Gsell, et al. December 2017)

The cumulative data from the 12 phase 1, 2 and 3 clinical trials performed during the outbreak period suggested that rVSV-ZEBOV vaccine has an acceptable safety profile, is immunogenic and effective against the circulating Ebola virus in the adult population after a single dose administration, owning a positive benefit-risk ratio. These data, combined with the results of pre-clinical studies and manufacturing process validation

and controls, was part of the regulatory package submitted later to the Regulatory Authorities. (Higgs, et al. September 2017)

Merck received rapid Scientific Advice from CHMP on April and September 2015, to discuss important quality, non-clinical and clinical aspects, as well as the regulatory pathways for licensure and timely availability of the vaccine, possibility of data submission on a rolling basis during review, and submission of trials data as post-marketing commitments. (European Medicines Agency [4] October 2019) Additionally, to further expedite and enhance the vaccine's scientific and regulatory support, assessment and potential approval, Merck applied for and received the Breakthrough Therapy Designation from the US FDA and the PRIME status from the EMA in June 2016. (Business Wire July 2016)

In parallel to seeking formal product licensure, Merck also filed an EUAL application with the WHO in December 2015. Had it been approved, it would have allowed the expedited deployment of rVSV-ZEBOV prior to licensure and outside clinical trials, in the context of a public health emergency. (Gupta, Coller and Feinberg September 2018)

In addition, in April 2017 the WHO Strategic Advisory Group of Experts (SAGE) recommended that the rVSV-ZEBOV vaccine should be promptly deployed under the Expanded Access Program (with an appropriate protocol approved by the manufacturer, National Regulatory Authorities and Ethics Committees, individual informed consent and in compliance with the Good Clinical Practice) in case a new EVD outbreak from the species *Zaire ebolavirus* occurs before a candidate vaccine is licensed. It also recommended the delivery strategy to be the ring vaccination, as used in the phase 3 clinical trial in Guinea, adapted to the social and geographic conditions of the outbreak and affected areas and including people at risk (healthcare and frontline workers in affected areas and areas at risk of expansion of the outbreak). (Walldorf, et al. November 2019) (SAGE [1] April 2017) (World Health Organization [21] October 2018)

ChAd3-EBOZ

Similarly to rVSV-ZEBOV, the other leading experimental candidate vaccine in August 2014, ChAd3-EBOZ, was thoroughly studied during the outbreak, based on the promising data obtained in pre-clinical animal models and human phase 1 clinical trials. This vector had also been tested in human clinical trials for other indications, including malaria, human immunodeficiency virus 1 infection (HIV) and hepatitis C, demonstrating high immunogenicity and tolerability. (Higgs, et al. September 2017) (World Health Organization [21] October 2018) However, some results in pre-clinical studies showed that the generated immunity faded after a single administration, which consequently led to the inclusion of an MVA-vectored vaccine as a booster vaccination. Heterologous prime-boost schemes with ChAd3-EBOZ and MVA-based vaccines (MVA-BN-Filo and

MVA-EBOZ) were, therefore, also studied in phase 1 clinical trials during the outbreak, starting from November 2014. (Martins, et al. September 2016)

ChAd3-EBOZ alone was studied in 3 phase 2 clinical trials in African, including PREVAIL I, and was considered safe and generally immunogenic, including in children and adolescents aged 1 to 17 years old. The main results are presented in Table 2. (Higgs, et al. September 2017) (Martins, et al. September 2016) (Tapia, et al. March 2020)

As an example of international cooperation and as part of the AVAREF's role to support the ethical and regulatory reviews of the clinical trials applications of candidate Ebola vaccines, one of the phase 2 ChAd3-EBOZ clinical trials (conducted in Cameroon, Mali, Nigeria and Senegal) was part of a joint review by the National Regulatory Authorities and Ethics Committees of the concerned countries, with support from the US FDA, EMA, Health Canada and Swissmedic. This joint review contributed positively to reduce the timeline for review and expedite the study's approval and start. (Akanmori, et al. August 2018) (World Health Organization [22] December 2014)

Ad26.ZEBOV/MVA-BN-Filo

The two-dose heterologous prime-boost vaccine combination Ad26.ZEBOV/MVA-BN-Filo, was also heavily studied during the outbreak, initially to assess the dose and vaccination schedule and later on phase 2/3 clinical trials in Africa, US and Europe to gather safety, tolerability and immunogenicity data. The published results indicated that the prime immunization was readily induced by Ad26.ZEBOV and further enhanced by the MVA-BN-Filo boosting, and that the heterologous prime-boost regimen confers durable immunity with a good safety and tolerability profile. (Martins, et al. September 2016) (World Health Organization [21] October 2018) Additionally, phase 3 clinical trials were conducted in the US to gather safety and immunogenicity data on different doses and different Ad26.ZEBOV batches, which would be essential in the regulatory package for the vaccine's registration and approval. (Martins, et al. September 2016) (Shukarev, et al. January 2017) (ClinicalTrials.gov [2] November 2016) (ClinicalTrials.gov [3] June 2017)

Johnson & Johnson created the Ebola Vaccine Development Consortia alongside Research Institutions and Non-Government Organizations and the EBOVAC project, to speed up clinical development, collate and present the data generated on the several Ad26.ZEBOV/MVA-BN-Filo clinical trials and to promote manufacturing capability and deployment. The associated projects were designated as: EBOVAC1, EBOVAC2 and EBOVAC3 to assess safety and tolerability through clinical trials (including the EBOVAC-Salone trial); EBODAC to promote the acceptance and uptake of the new Ebola vaccine, through community engagement and communication; and EBOMAN to accelerate its development and manufacture. (Martins, et al. September 2016) (Mooney, et al. October

2018) (EBOVAC Projects March 2020) In December 2014, the IMI awarded funding from the Ebola + program to the consortia to further support the development of the Ad26.ZEBOV/MVA-BN-Filo candidate vaccine. All projects were included in the Ebola + funding program. (EBOVAC Projects March 2020) (Innovative Medicines Initiative March 2020)

Additionally, AVAREF also supported the ethical and regulatory reviews of the two phase 2 Ad26.ZEBOV/MVA-BN-Filo clinical trials conducted in Africa. The trials were part of a joint review by the National Regulatory Authorities and Ethics Committees of the concerned countries, with support from the US FDA, EMA, Health Canada, Medicines and Healthcare Products Regulatory Agency (MHRA) and Ghana FDA. (World Health Organization [23] May 2019)

Ad5.EBOV

Phase 1 clinical trials conducted in China reported a good safety and immunogenic profile for Ad5.EBOV. (World Health Organization [21] October 2018) The Beijing Institute of Biotechnology also sponsored a phase 2 trial in Sierra Leone, comparing a high dose and a low dose of the vaccine. The published results demonstrated that Ad5.EBOV was safe and highly immunogenic, regardless of the presence of pre-existing immunity against the vaccine vector. The low-dose vaccine was considered the optimal dose, even in participants with pre-existing immunity to the vector, as it presented a similar humoral response to the high-dose vaccine. However, the humoral immunity was not robust and long-lasting, with a lower antibody titre being observed on day 168 for both vaccine doses. This short durability of vaccine-elicited antibodies indicated a need for a study of a prime-booster regimen to prolong immunity. (Zhu, et al. February 2017) The clinical trial is described in Table 2.

Additional studies conducted after the 2014-2016 West African Ebola Outbreak

A new clinical trial named PREVAC (Partnership for Research on Ebola Vaccination) was launched on March 2017, after the 2014-2016 West African Ebola Outbreak had ended, and is ongoing as of May 2020. This phase 2 clinical trial intends to address some of the unanswered questions from previous trials, namely assess the speed, intensity and durability of the immune response, as well as the long-term safety and tolerability of two candidate vaccines (rVSV-ZEBOV and Ad26.ZEBOV/MVA-BN-Filo), in both children and adults. (ClinicalTrials.gov [4] February 2020) (NIH Website [1] April 2017) The 2-stage study design includes three vaccination strategies that may trigger a durable immune response and prevent EVD: Ad26.ZEBOV vaccination followed 8 weeks later by MVA-BN-Filo boost; and the rVSV-ZEBOV vaccination with and without homologous

boosting after 8 weeks. Each of these vaccination strategies is being compared to an identical regimen of placebos. (ClinicalTrials.gov [4] February 2020) (NIH Website [1] April 2017)

This clinical trial has been supported by the PREVAC research consortium, established in 2017, that includes the National Institute of Health and Medical Research (Inserm), NIAID, the London School of Hygiene & Tropical Medicine (LSHTM) and the National Regulatory Authorities of Guinea, Liberia and Sierra Leone. (NIH Website [1] April 2017) The clinical trials details are presented in Table 3.

The two vaccines being assessed under the PREVAC clinical trial were also included in additional trials, ongoing as of May 2020. Merck launched a new phase 2 clinical for rVSV-ZEBOV, on August 2017, with the aim to assess the safety and immunogenicity of the vaccine in HIV infected adults and adolescents. (World Health Organization [21] October 2018) On the other hand, Johnson & Johnson launched a prospective study on May 2016 to assess the long-term safety profile of Ad26.ZEBOV/MVA-BN-Filo in adults that were previously enrolled in phase 1, 2 or 3 clinical trials with this vaccine. This study is also assessing the outcome of the vaccine on female participants who became pregnant during previous trials and children born of female participants exposed to Ad26.ZEBOV/MVA-BN-Filo. (World Health Organization [21] October 2018) The results of both trials were not published as of May 2020.

Another trial launched on August 2017 saw the candidate vaccine GamEvac-Combi being studied outside Russia for the first time. (World Health Organization [21] October 2018) The results of this phase 3 trial have also not been published as of May 2020.

Table 2: Summary of EVD Vaccine Candidates Evaluated During the 2014–2016 Ebola Outbreak in Formal Phase 2 or 3 Clinical Trials

Vaccine Candidate	Vaccine Type	Highest Pre-Clinical Evidence	Latest Formal Clinical Trial		
			Description & Design	**Trial Information**	**Main Results**
rVSV-ZEBOV	Live attenuated recombinant vaccine, consisting of a vesicular stomatitis virus (rVSV) expressing the Ebola virus surface glycoprotein.	100% effective in four published NHP challenge studies (total n=37).	Ebola ça Suffit! – Part A (Phase 3 - efficacy and safety; ring vaccination) - Cluster-randomized, open-label; - Vaccinees are “rings” (contacts and contacts of contacts) of confirmed Ebola cases; - Immediate vs. delayed (21 days) vaccination. Delayed vaccination was discontinued in July 2015 (no randomization from this point onwards).	Location: Guinea (extended to Sierra Leone in August 2015) Enrollment: 11 841 adults and children (from 6 years old), divided in 117 clusters/rings Timeline: March 2015 to February 2016 Sponsor: World Health Organization	Interim analysis suggested that rVSV-ZEBOV offered very high protection, leading to the delayed vaccination arm being discontinued. Final data from all trial clusters showed that rVSV-ZEBOV offers substantial protection against EVD, with no cases among immediately vaccinated individuals (contacts and contacts of contacts) from day 10 after vaccination. Adverse events data indicated no safety concerns.
			Part B (Phase 2 – safety and immunogenicity; part of the previous trial) - Non-randomized, open-label; - Single arm receiving vaccine (a small number of participants did not wish to receive the vaccine but agreed to participate as a control group).	Location: Guinea Enrollment: 2115 adults - frontline workers (2016 vaccinated and 99 as control group). Timeline: March 2015 to July 2016 Sponsor: World Health Organization	Adverse events 3 days after vaccination were common. The most frequently reported symptoms were headache, fatigue, arthralgia, subjective fever and myalgia.

Table 2: Summary of EVD Vaccine Candidates Evaluated During the 2014–2016 Ebola Outbreak in Formal Phase 2 or 3 Clinical Trials

Vaccine Candidate	Vaccine Type	Highest Pre-Clinical Evidence	Latest Formal Clinical Trial		
			Description & Design	**Trial Information**	**Main Results**
rVSV-ZEBOV	Live attenuated recombinant vaccine, consisting of a vesicular stomatitis virus (rVSV) expressing the Ebola virus surface glycoprotein.	100% effective in four published NHP challenge studies (total n=37).	STRIVE (Phase 2/3 – efficacy, safety and immunogenicity) - Randomized, open-label; - Immediate vs. delayed (18-24 weeks) vaccination; - One sub-study included for safety (in 453 individuals); - One sub-study included for immunogenicity (in 539 individuals).	Location: Sierra Leone Enrollment: 8651 adults (healthcare and frontline response workers) Timeline: April 2015 to December 2016 Sponsor: Centers for Disease Control and Prevention (CDC)	rVSV-ZEBOV was generally well tolerated with no vaccine related serious adverse events.
			Phase 3 – safety and immunogenicity of 3 consistency batches and a high-dose batch - Randomized, double-blind, placebo-controlled trial; - Five arms: 1 for each of the three consistency batches, 1 for the high-dose batch, 1 for placebo	Location: USA, Canada and Spain Enrollment: 1197 adults Timeline: August 2015 to June 2016 Sponsor: Merck Sharp & Dohme Corp.	rVSV-ZEBOV was generally well tolerated with increased rates of injection-site and systemic adverse events compared to placebo. There were no vaccine-related adverse events or deaths.

Table 2: Summary of EVD Vaccine Candidates Evaluated During the 2014–2016 Ebola Outbreak in Formal Phase 2 or 3 Clinical Trials

Vaccine Candidate	Vaccine Type	Highest Pre-Clinical Evidence	Latest Formal Clinical Trial		
			Description & Design	**Trial Information**	**Main Results**
ChAd3-EBOZ	Recombinant chimpanzee adenovirus serotype 3 (ChAd3) expressing the Ebola virus surface glycoprotein	100% effective in one published NHP challenge study (n=8).	Phase 2 – safety and immunogenicity in adults - Randomized, double-blind; - Immediate vs. placebo + delayed (6 months) vaccination.	Location: Cameroon, Mali, Nigeria and Senegal Enrollment: 3024 adults Timeline: July 2015 to December 2016 Sponsor: GlaxoSmithKline	ChAd3-EBOZ was generally well tolerated with no vaccine related serious adverse events. By 1 month after vaccination, the vaccine had elicited immune responses that were largely maintained through 12 months.
			Phase 2 – safety and immunogenicity in pediatrics - Randomized, observer blind; - Immediate ChAd3-EBOZ + Nimenrix vaccine at 6 months vs. Immediate Nimenrix vaccine + ChAd3-EBOZ at 6 months	Location: Mali and Senegal Enrollment: 600 children Timeline: October 2015 to May 2017 Sponsor: GlaxoSmithKline	ChAd3-EBO-Z was immunogenic and well tolerated in children aged 1–17 years. It was associated with transient and non-severe local pain, fever, headache and fatigue. No serious adverse events related to the vaccination were reported. The antibody concentrations were highest at 30 days post-vaccination and declined by 6 months post-vaccination, remaining relatively stable thereafter.

Table 2: Summary of EVD Vaccine Candidates Evaluated During the 2014–2016 Ebola Outbreak in Formal Phase 2 or 3 Clinical Trials

Vaccine Candidate	Vaccine Type	Highest Pre-Clinical Evidence	Latest Formal Clinical Trial		
			Description & Design	Trial Information	Main Results
rVSV-ZEBOV **+** **ChAd3-EBOZ**	---	---	PREVAIL I (Phase 2 – efficacy, safety and immunogenicity) - Randomized, double-blind, placebo-controlled trial; - Three arms: 2 treatment arms (rVSV-ZEBOV or ChAd3-EBOZ), 1 placebo arm.	Location: Liberia Enrollment: 1500 adults Timeline: February 2015 to June 2016 Sponsor: National Institute of Allergy and Infectious Diseases (NIAID)	By 1 month after vaccination, the vaccines had elicited immune responses (94% for rVSV-ZEBOV and 87% for ChAd3-EBOZ) that were largely maintained through 12 months. No safety concerns were identified (in the two vaccine arms, side effects were generally not severe, were time-limited and similar to reports from phase 1 studies that used various doses of the two vaccines).
Ad26.ZEBOV / MVA-BN-Filo	Adenovirus 26 vectored glycoprotein and MVA-BN-Filo	100% effective in a company publicized NHP challenge study (n=8)	Phase 2 – safety, tolerability and immunogenicity - Randomized, observer blind, placebo-controlled trial; - Receive Ad26.ZEBOV or placebo, followed by MVA-BN-Filo or placebo; - Three arms: different times for the second vaccination.	Location: France and UK Enrollment: 423 adults Timeline: July 2015 to January 2018 Sponsor: Janssen Vaccines & Prevention B.V.	Interim results: the 2-dose Ad26.ZEBOV/MVA-BN-Filo vaccination was immunogenic (antibody responses persisted at least up to one year post-dose 1) and well tolerated, with no safety signals identified.

Table 2: Summary of EVD Vaccine Candidates Evaluated During the 2014–2016 Ebola Outbreak in Formal Phase 2 or 3 Clinical Trials

Vaccine Candidate	Vaccine Type	Highest Pre-Clinical Evidence	Latest Formal Clinical Trial		
			Description & Design	Trial Information	Main Results
Ad26.ZEBOV / MVA-BN-Filo	Adenovirus 26 vectored glycoprotein and MVA-BN-Filo	100% effective in a company publicized NHP challenge study (n=8)	Phase 2 – safety, tolerability and immunogenicity - Randomized, observer blind, placebo-controlled trial; - Receive Ad26.ZEBOV or placebo, followed by MVA-BN-Filo or placebo; - Three arms for healthy adults and elderly and two arms for children and HIV infected adults: different times for the second vaccination.	Location: Ivory Coast, Burkina Faso, Kenya and Uganda Enrollment: 1075 participants (children, healthy and HIV infected adults) Timeline: November 2015 to February 2019 Sponsor: Janssen Vaccines & Prevention B.V.	Results not published as of May 2020.
			Phase 2 – safety, tolerability and immunogenicity - Randomized, observer blind, placebo-controlled trial; - Part 1 (USA participants): receive MVA-BN-Filo or placebo, followed by Ad26.ZEBOV or placebo; - Part 2 (African participants): two arms; one receives Ad26.ZEBOV or placebo, followed by MVA-BN-Filo or placebo, the other receives in the opposite order.	Location: USA, Kenya, Mozambique, Nigeria, Tanzania and Uganda Enrollment: 578 participants (healthy and HIV infected adults) Timeline: December 2015 to December 2018 Sponsor: Janssen Vaccines & Prevention B.V.	Results not published as of May 2020.

Table 2: Summary of EVD Vaccine Candidates Evaluated During the 2014–2016 Ebola Outbreak in Formal Phase 2 or 3 Clinical Trials

Vaccine Candidate	Vaccine Type	Highest Pre-Clinical Evidence	Latest Formal Clinical Trial		
			Description & Design	**Trial Information**	**Main Results**
Ad26.ZEBOV / MVA-BN-Filo	Adenovirus 26 vectored glycoprotein and MVA-BN-Filo	100% effective in a company publicized NHP challenge study (n=8)	EBOVAC-Salone (Phase 3 – safety and immunogenicity) Part of the EBOVAC1 project. Stage 1 - Non-randomized, open-label; - One arm: Ad26.ZEBOV + MVA-BN-Filo Stage 2 - Randomized, double-blind, controlled trial; - Two arms: Ad26.ZEBOV + MVA-BN-Filo vs. MenACWY + Placebo (as control)	Location: Liberia Enrollment: 1023 participants (adults in stage 1 and adults and children in stage 2) Timeline: September 2015 to June 2019 Sponsor: Janssen Vaccines & Prevention B.V.	Interim results: the Ad26.ZEBOV/MVA-BN-Filo vaccine regimen was well tolerated in adults, with no significant safety signals and no vaccine related serious adverse events. Robust and persistent immune responses to the vaccine regimen were observed.
			Phase 3 – safety and immunogenicity to evaluate a range of dose levels - Randomized, double-blind, placebo-controlled trial; - Four arms: 1 for each of the three dose levels, 1 for placebo	Location: USA Enrollment: 525 participants (adults) Timeline: September 2015 to November 2016 Sponsor: Janssen Vaccines & Prevention B.V.	Results not published as of May 2020.

Table 2: Summary of EVD Vaccine Candidates Evaluated During the 2014–2016 Ebola Outbreak in Formal Phase 2 or 3 Clinical Trials

Vaccine Candidate	Vaccine Type	Highest Pre-Clinical Evidence	Latest Formal Clinical Trial		
			Description & Design	Trial Information	Main Results
Ad26.ZEBOV / MVA-BN-Filo	Adenovirus 26 vectored glycoprotein and MVA-BN-Filo	100% effective in a company publicized NHP challenge study (n=8)	Phase 3 – safety, tolerability and immunogenicity of 3 batches of Ad26.ZEBOV and 1 batch of MVA-BN-Filo - Randomized, double-blind, placebo-controlled trial; - Four arms: 1 for each of the three Ad26.ZEBOV batches, 1 for placebo	Location: USA Enrollment: 329 participants (adults) Timeline: September 2015 to July 2016 Sponsor: Janssen Vaccines & Prevention B.V.	Results not published.
Ad5.EBOV	Replication-incompetent, human adenovirus type 5 vector expressing the Ebola virus surface glycoprotein	100% effective in a guinea pig study. 100% protective in a NHP challenge study.	Phase 2 – safety and immunogenicity - Randomized, double-blind, placebo-controlled trial; - Three arms: 2 treatment arms (high dose and low dose), 1 placebo arm.	Location: Sierra Leone Enrollment: 500 participants (adults) Timeline: October 2015 to April 2016 Sponsor: Ministry of Health & Sanitation (Sierra Leone) and Beijing Institute of Biotechnology (China)	Ad5.EBOV was safe and highly immunogenic. The low-dose ($8{\cdot}0 \times 10^{10}$ viral particles) was considered the optimal dose, even in participants with pre-existing immunity to the vector (similar humoral response to the high-dose vaccine). The short durability of vaccine-elicited antibodies indicated a need for a prime-booster regimen to prolong immunity.

Notes: NHP – nonhuman primates

Source: (World Health Organization [18] October 2015) (Higgs, et al. September 2017) (Samai, et al. May 2018) (Kennedy, et al. October 2017) (Halperin, et al. May 2017) (Henao-Restrepo, Camacho, et al. February 2017) (Juan-Giner, et al. September 2018) (Thiebaut, et al. April 2019) (Leigh, et al. April 2019) (ClinicalTrials.gov [5] January 2018) (ClinicalTrials.gov [6] May 2018) (Mooney, et al. October 2018) (Zhu, et al. February 2017) (ClinicalTrials.gov [3] June 2017) (ClinicalTrials.gov [2] November 2016) (Tapia, et al. March 2020) (World Health Organization [21] October 2018)

Table 3: Summary of EVD Vaccine Candidates Evaluated After the 2014–2016 Ebola Outbreak in Formal Phase 2 or 3 Clinical Trials

Vaccine Candidate	Vaccine Type	Highest Pre-Clinical Evidence	Latest Formal Clinical Trial		
			Description & Design	**Trial Information**	**Main Results**
rVSV-ZEBOV **+** **Ad26.ZEBOV / MVA-BN-Filo**	---	---	PREVAC (Phase 2 – safety and immunogenicity) - Randomized, double-blind, placebo-controlled trial. Stage 1 - Two arms: 1 treatment arm (Ad26.ZEBOV + MVA-BN-Filo) and 1 placebo arm. - Treatment arm receives Ad26.ZEBOV followed by MVA-BN-Filo. Stage 2 - Three arms: 2 treatment arms (rVSV-ZEBOV with or without boosting) and 1 placebo arm. - Treatment arms receive rVSV-ZEBOV and rVSV-ZEBOV, followed by rVSV-ZEBOV (boost) and placebo (without boost).	Location: Guinea, Liberia, Sierra Leone and Mali Enrollment: 4789 participants (adults and children) Timeline: March 2017 to May 2020 Sponsor: National Institute of Allergy and Infectious Diseases (NIAID)	Results not published as of May 2020.

Table 3: Summary of EVD Vaccine Candidates Evaluated After the 2014–2016 Ebola Outbreak in Formal Phase 2 or 3 Clinical Trials

Vaccine Candidate	Vaccine Type	Highest Pre-Clinical Evidence	Latest Formal Clinical Trial		
			Description & Design	Trial Information	Main Results
rVSV-ZEBOV	Live attenuated recombinant vaccine, consisting of a vesicular stomatitis virus (rVSV) expressing the Ebola virus surface glycoprotein.	100% effective in four published NHP challenge studies (total n=37).	Phase 2 – safety and immunogenicity - Randomized, double-blind, placebo-controlled trial. - Four arms (different CD4 T-cell counts in each arm). - Each arm will receive treatment and placebo.	Location: Canada and Africa Enrollment: 200 participants (HIV infected adults and adolescents) Timeline: August 2017 to December 2019 Sponsor: Merck Sharp & Dohme Corp.	Results not published as of May 2020.
Ad26.ZEBOV / MVA-BN-Filo	Adenovirus 26 vectored glycoprotein and MVA-BN-Filo	100% effective in a company publicized NHP challenge study (n=8)	Phase 3 – long-term safety - Prospective	Location: USA, France, UK, Burkina Faso, Kenya, Uganda and Tanzania. Enrollment: 677 participants (children and adults who participated in phase 1, 2 or 3 clinical trials with Ad26.ZEBOV/MVA-BN-Filo) Timeline: May 2016 to January 2023 Sponsor: Janssen Vaccines & Prevention B.V.	Results not published as of May 2020.

Table 3: Summary of EVD Vaccine Candidates Evaluated After the 2014–2016 Ebola Outbreak in Formal Phase 2 or 3 Clinical Trials

Vaccine Candidate	Vaccine Type	Highest Pre-Clinical Evidence	Latest Formal Clinical Trial		
			Description & Design	Trial Information	Main Results
GamEvac-Combi	Heterologous VSV- and Ad5-vectored prime boost vaccine, expressing the Ebola virus surface glycoprotein	---	Phase 3 – safety, immunogenicity and epidemiological efficacy - Randomized, double-blind, placebo-controlled trial. - Two arms: 1 treatment arm and 1 placebo arm.	Location: Guinea and Russia Enrollment: 2000 participants (adults) Timeline: August 2017 to January 2020 Sponsor: Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation	Results not published as of May 2020.

Notes: NHP – nonhuman primates
Source: (ClinicalTrials.gov [4] February 2020) (NIH Website [1] April 2017) (World Health Organization [21] October 2018) (ClinicalTrials.gov [7] November 2019) (ClinicalTrials.gov [8] November 2017) (ClinicalTrials.gov [9] June 2019)

2.3.3. Response Assessment

The 2014-2016 West African Ebola Outbreak exposed some weaknesses in the national and international community's capacity to rapidly and effectively respond to an emerging infectious disease epidemic. Some criticized WHO's late raise of international attention and major response action, that only occurred some months after the official outbreak declaration on the 23rd of March 2014, and others the absence of fully developed medicinal products and/or vaccines available in the beginning of the epidemic, despite decades of previous Ebola outbreaks. (Coltart, et al. 2017) (Médecins Sans Frontières March 2015) (Moon, et al. November 2015) However, enormous efforts were made on the escalation of the outbreak response and on the medicinal products and vaccines research and development field, with successful pre-clinical and clinical studies being conducted, overcoming regulatory, ethical and operational challenges. (Coltart, et al. 2017) (Moon, et al. November 2015)

The local and worldwide regulatory systems performance in response to the 2014-2016 West African Ebola Outbreak had positive aspects, the major being:

- Global efforts to coordinate, collaborate and expedite development and clinical research. The accelerated development in the EVD outbreak setting benefited from the experience and close work of foreign Regulatory Authorities, pharmaceutical companies, International Health Organizations, among others. International consortia were established to pool resources and expertise, and regional regulatory networks, such as AVAREF, worked to harmonize practices and support ethical and regulatory reviews within the region, reducing duplication of work and expediting the review timelines of clinical trial applications of candidate vaccines. (Akanmori, et al. August 2018)

- Regulatory Authorities, such as the US FDA and EMA, established Ebola specific task forces in order to be more flexible and expedite the regulatory support during the outbreak. Drug development programs and alternative regulatory pathways (Orphan Designation, PRIME scheme, Fast Track status and Breakthrough Therapy Designation) were put in place to encourage companies to invest, develop and seek regulatory consultation, and to expedite the candidates' assessment and future approval. Other pathways, such as the Emergency Use Authorization and the Expanded Access Program, were also used to grant early access to *in vitro* diagnostic tests and experimental medicinal products. These programs and alternative regulatory pathways showcase both Regulatory Authorities' panoply of programs that encourage drug development and the flexibility of their regulatory framework.

- WHO developed a mechanism, designated Emergency Use Assessment and Listing, to assess, list and expedite the availability of candidate medicinal

products, vaccines and *in vitro* diagnostic tests in the context of public health emergencies. 7 *in vitro* Ebola diagnostic tests were approved and listed under this procedure during the outbreak. (World Health Organization [16] January 2020)

- Accelerated development of Ebola virus vaccines, including their assessment in humans, transforming a process that usually takes years to only months. The leading candidate vaccines progressed from phase 1 first-in-human clinical trials (which began in September 2014) to phase 2/3 clinical trials in just five months. (Higgs, et al. September 2017) This accelerated clinical development was largely due to the existence of pre-clinical data obtained in the years prior to the outbreak, the capacity to conduct phase 2/3 trials in parallel, the international engagement and the collaboration between key partners, prioritization of ethical and regulatory approvals for these trials and the timing of responses from regulators and ethics committees leading to rapid decision-making. Each of the three most affected countries (Guinea, Sierra Leone and Liberia) conducted phase 2/3 trials for Ebola candidate vaccines in the midst of the outbreak, ultimately increasing the countries' clinical research capacity for future epidemics. (Higgs, et al. September 2017)

- Development of different vaccine types, including monovalent, homologous and heterologous prime-boost schemes. If proven safe, efficacious and tolerable, these different vaccines will allow for diversified vaccination approaches in future Ebola outbreaks: from single-dose vaccines for ease of administration and immediate immunity in reactive vaccination strategies, to homologous / heterologous prime-boost schemes for durable immunity and use in more preventive or prophylactic vaccination strategies. (Shukarev, et al. January 2017)

However, some less positive aspects in the local and worldwide regulatory systems performance were identified, the most important being:

- Despite the accelerated clinical research, its initiation was delayed for a serious of reasons. Some of these reasons were associated with the economic status, lack of proper public health infrastructures and community resistance in the affected West African countries. Other reasons appointed were related with the absence of human clinical data of candidate medicinal products or vaccines from previous Ebola outbreaks, the absence of clinical research agenda for the outbreak response in early 2014, the absence of predefined clinical protocols that could expedite the clinical research, the duplication of efforts, the lack of clarity on the roles and responsibilities of regulators and ethics committees in the affected West African countries and the poor coordination and management of scarce resources (e.g.: administration of candidate medicinal products, such as

ZMapp, under compassionate use grounds). (Largent September 2016) (Akanmori, et al. August 2018) (Røttingen, et al. February 2017) (Moon, et al. November 2015)

- Delayed phase 2/3 clinical trial initiation relative to the epidemiological peak of the outbreak in the three affected countries, as shown in Figure 8. The decrease in the incidence of EVD cases due to the implementation of successful public health measures led to the modification of some clinical trials for candidate vaccines and the inability to collect enough data to assess their efficacy directly from clinical EVD endpoints. In fact, only one clinical trial was able to assess the efficacy of a candidate vaccine during the outbreak (rVSV-ZEBOV), by using an innovative ring vaccination design. (Higgs, et al. September 2017) (Keusch, et al. 2017) An opportunity to gather additional and more robust efficacy and safety data, including in special populations, was missed.

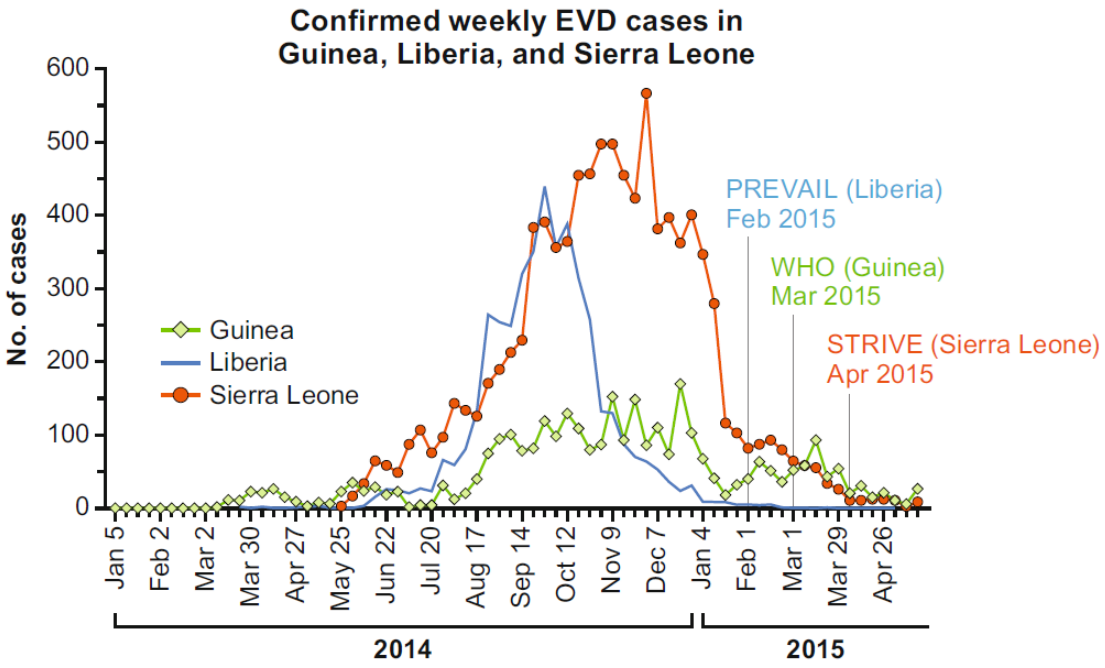


Figure 8: Start of phase 2/3 clinical trials on vaccines and incidence of EVD cases in Guinea, Liberia and Sierra Leone (Higgs, et al. September 2017)

- Despite the number of clinical trials performed, several unknowns regarding vaccination against the Ebola virus remained after the end of the epidemic, including: the safety, tolerability, immunogenicity and efficacy profile in special populations (few data was generated for children, pregnant women, immune-compromised and elderly individuals); the long-term safety profile in all populations and identification of the mechanisms leading to some of the observed adverse events; the rapidity and durability of immune responses; the identification

of correlates of protection (correlation of immune response and immediate and long-term clinical protection), which would be important to reassess all the vaccines' immunogenicity data obtained and conclude on their potential clinical benefit; cross-protection against other viruses within the genus *Ebolavirus* and other filoviruses. (Lévy, et al. September 2018)

- Similarly to the clinical research on vaccines, none of the clinical trials on candidate medicinal products ended with conclusive results on efficacy, with some being cancelled due to the lack of patients being enrolled. The reasons appointed were: delayed initiation relative to the epidemiological peak of the outbreak in the three affected countries, as shown in Figure 9; existence of too many clinical trials enrolling simultaneously, which led to inadequate sample sizes in each trial and an overwhelming pressure on the National Regulatory Authorities to deal with several clinical trial applications. (Keusch, et al. 2017)

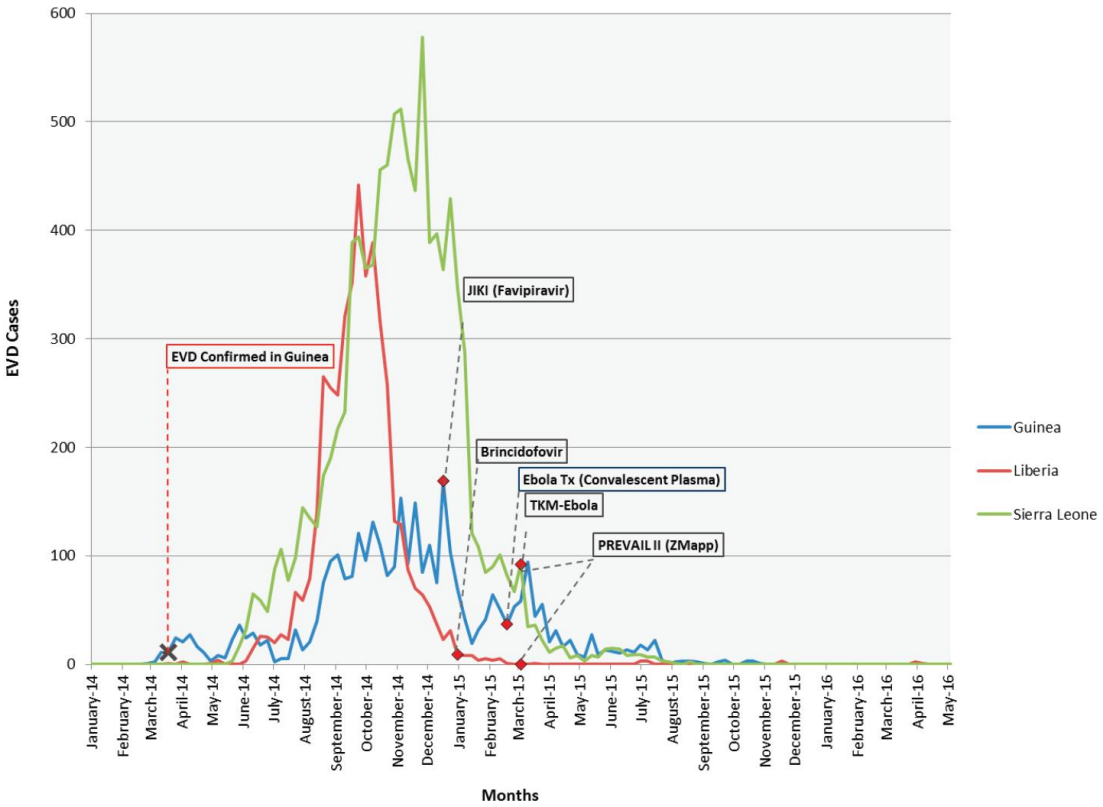


Figure 9: Start of phase 2/3 clinical trials on medicinal products and incidence of EVD cases in Guinea, Liberia and Sierra Leone (Keusch, et al. 2017)

- Additionally, multiple clinical trials of candidate medicinal products made use of historical controls, which may not be relied upon to make valid conclusions. Survival rates of historical controls may vary for several reasons, including the existence of evolved standards of care over time, different geographic locations,

or prognostic variables such as age. These could lead to wrong assumptions and conclusions regarding a medicinal product's safety and efficacy. (Russek-Cohen, et al. January 2016) (Keusch, et al. 2017) These single arm trials may have missed worthwhile effects, possibly discounting a potentially beneficial product for future studies. (Russek-Cohen, et al. January 2016) (Keusch, et al. 2017)

The regulatory system response in the 2014-2016 West African Ebola Outbreak was able to generate positive outcomes, particularly in the context of a catastrophic environment, with very limited resources, poor healthcare system and limited regulatory experience. It demonstrated that it is possible to conduct clinical trials during an epidemic, in a fast-passed way, through pragmatic solutions and alternatives to the conventional drug research and development models, and still meet internationally accepted standards. The importance of having expedite clinical research and accelerated development of medical countermeasures was widely recognized as critical to a global health response for future public health crisis.

Along with the identified positive outcomes, several lessons were learned from the Ebola health crisis, and were considered afterwards in the global public health agenda and within the global research community, in order to implement clinical trials more rapidly and efficiently in the future. These lessons included:

- Incorporation of clinical research into the plans for future health crisis and further integration into an epidemic response, by defining research priorities, target product profiles and standardized clinical protocols prior to an outbreak onset. Figure 10 represents a model of an ideal clinical trial launch, and respective activities, in the midst of an epidemic. (Keusch, et al. 2017) It demonstrates the importance of performing research and development related activities and decision-making in the inter-epidemic periods, so that clinical trials of promising candidates can be conducted before the epidemic peak occurs. (Keusch, et al. 2017) (World Health Organization [24] May 2015) (Moon, et al. November 2015) (Largent September 2016) (Lang August 2015)

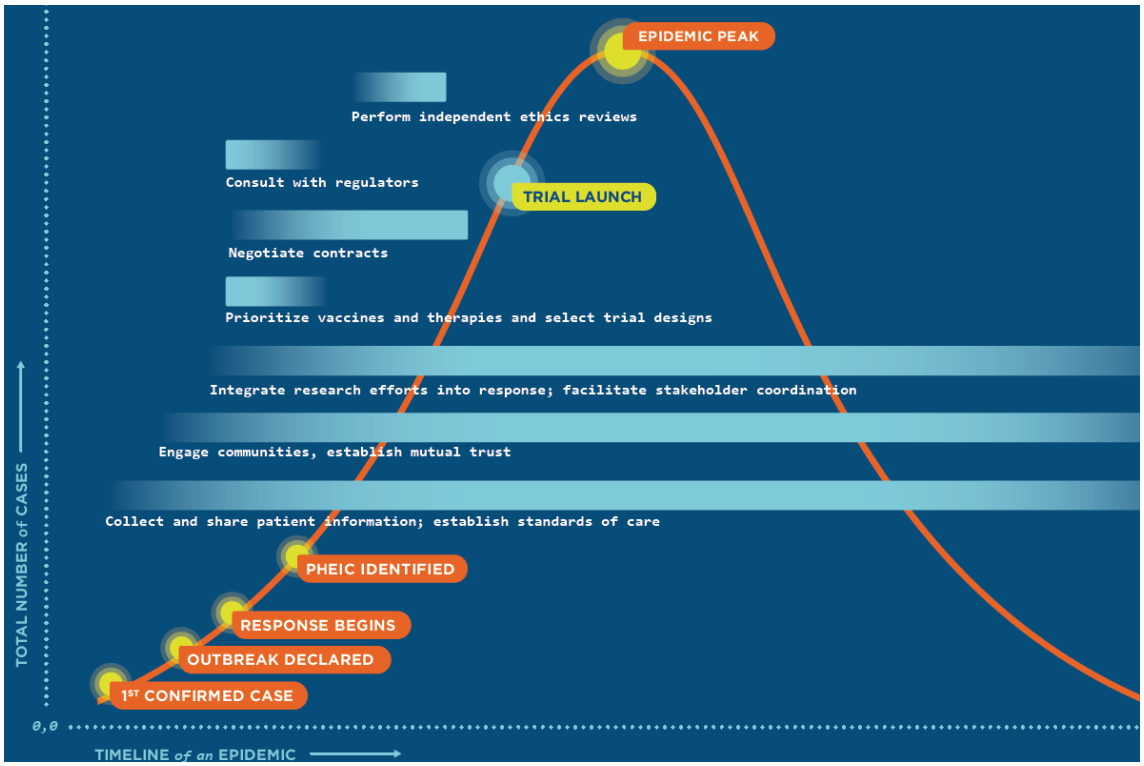


Figure 10: Representative model of an ideal clinical trial launch in an epidemic scenario (Keusch, et al. 2017)

- Development and/or clarification of the regulatory pathways for expedite approval of experimental medicinal products, vaccines and clinical trials in an epidemic scenario. Finding the appropriate balance between fast approval and patient protection is important, considering the limited data on safety and efficacy resultant from small sample sizes in clinical trials. (Keusch, et al. 2017) (Gates April 2015) (Largent September 2016)

- Planification on how research can be continued and concluded for promising candidate products that cannot be fully assessed (e.g.: use of surrogate endpoints that are reasonably likely to predict clinical benefit, such as immune response, if clinical endpoints cannot be reached due to the decline of incidence cases; flexible trial designs that can adapt to changing epidemics). (World Health Organization [24] May 2015)

- Share of research data in a timely and transparent manner to enable effective decision-making on use, funding and prioritization of candidate products. (Keusch, et al. 2017) (World Health Organization [24] May 2015) (Gates April 2015)

- Consideration for re-purposing of existing vaccines and medicinal products. (Keusch, et al. 2017) (World Health Organization [24] May 2015) (Gates April 2015) (Largent September 2016)

- Development of new funding strategies to encourage the research of medicinal products, vaccines and diagnostic test in advance, particularly for epidemic-prone diseases considered to be public health threats and that can strike poor populations in developing countries, where the market does not offer appropriate incentives. (World Health Organization [24] May 2015) (Gates April 2015) (Moon, et al. November 2015) (Largent September 2016) (Keusch, et al. 2017)

Other lessons on high level response to health crisis were also analyzed, and were largely associated with the need to improve healthcare systems (specially in low and middle-income countries and what concerns the obligations under the International Health Regulations), surveillance and laboratory testing capacity, research and development capacity, creation of mechanisms for the accountability of all stakeholders involved, and empowerment for organizations, in particular WHO, to be able to pool human and financial resources and act more swiftly and efficiently in the future. (Coltart, et al. 2017) (Gates April 2015) (Moon, et al. November 2015) (Keusch, et al. 2017) (World Health Organization [25] July 2015)

In the aftermath of the 2014-2016 West African Ebola Outbreak, there was a global realization on the importance of research as a vital part of the response to any epidemic and that a new alternative approach to conduct and finance research and development that prioritizes public health needs and improves global health security was needed. (Røttingen, et al. February 2017) (Kieny February 2018) (Higgs, et al. September 2017)

Following the recommendations of several panels that reviewed the global response to the Ebola outbreak (namely, the WHO Ebola Interim Assessment Panel and the Harvard University and the LSHTM's Independent Panel on the Global Response to Ebola), a platform for the global strategy, preparedness and rapid development of medicinal products, vaccines and diagnostic tests was developed by WHO and presented on May 2016 – the R&D Blueprint program. (World Health Organization [25] July 2015) (Moon, et al. November 2015) (Røttingen, et al. February 2017) (Kieny February 2018) Other programs were also established in the aftermath of the Ebola outbreak, one being the Coalition for Epidemic Preparedness and Innovations (CEPI). This program was launched to stimulate, finance, coordinate and guarantee that vaccines are developed for pathogens likely to cause epidemics and where the market incentive is insufficient. The R&D Blueprint is discussed in more detail in the following chapters. (Higgs, et al. September 2017) (Røttingen, et al. February 2017)

2.4. Subsequent Outbreaks

Following the end of the 2014-2016 West African Outbreak, two additional Ebola outbreaks from the species *Zaire ebolavirus* occurred in the Democratic Republic of Congo (DRC), the ninth and tenth in the country. The first of these new outbreaks occurred in the Bikoro region of the Equateur Province, in the northwestern part of the country. It was declared by the DRC government on the 8th of May 2018 and led to 54 probable or confirmed cases of EVD and 33 deaths. (CDC Website [7] August 2018) The WHO declared the end of the outbreak on the 25th of July 2018, after a period of 42 days since the second negative test of the last confirmed case. (CDC Website [7] August 2018) (World Health Organization [26] July 2018)

The second outbreak, the 2018-2020 Eastern DRC Outbreak, is still active as of May 2020 and is considered the second largest Ebola epidemic on record and the largest in DRC. (WHO Website [12] May 2020) According to the WHO, 3463 confirmed and probable EVD cases were reported, of which 2280 were fatal, as of the 24th of May 2020. These include 4 imported cases also reported in Uganda. (World Health Organization [27] May 2020) The outbreak was declared by the DRC Ministry of Health on the 1st of August 2018 in the North Kivu province, with cases also being reported in two other provinces: Ituri and South Kivu. (CDC Website [8] August 2019) This outbreak is occurring in regions characterized by intractable armed conflicts, violence against health officials, community reluctance, poverty, fragile social structures and high population movement, and in a time of political turmoil, all of which have contributed to the progression and duration of the outbreak. (CDC Website [8] August 2019) (WHO Website [12] May 2020) (Kalenga, et al. July 2019)

The decision of declaring the outbreak as a PHEIC was intensively debated, with opposite opinions within the public health community. In fact, even the IHR Emergency Committee had itself previously concluded in meetings convened by the WHO in October 2018, April 2019 and June 2019 that, while worrying, the epidemic was not a global health emergency. (Branswell May 2019) (WHO Website [13] June 2019) However, following the confirmed cases in Uganda, the WHO Director-General declared on the 17th of July 2019, the outbreak as a PHEIC, taking into consideration the very high public health risk at both national and regional levels, as the affected provinces in DRC are close to the borders of Uganda, Rwanda, Burundi and South Sudan. (WHO Website [14] July 2019) The last Emergency Committee meeting, held on the 12th of February 2020, unanimously decided that the epidemic still constitutes a PHEIC, but lowered the risk at both national and regional levels to high, and maintained the risk at global level as low. (WHO Website [15] February 2020)

2.5. Response to the 2018-2020 Eastern DRC Outbreak

Despite the hurdles of having an outbreak in conflict regions and with porous international borders, the public health response was able to mainly contain the outbreak within the previously mentioned DRC provinces, avoiding the Ebola virus spread to neighboring provinces and countries (only 4 EVD imported cases were reported in Uganda). (World Health Organization [27] May 2020) This response has been led by the DRC Ministry of Health in collaboration with WHO and other national and international partners. The applied public health and infection control strategies, similar in part to other outbreak responses, included: early identification of cases; real-time epidemiological surveillance; contact tracing, isolation and surveillance; safe burials; community engagement; vaccination of high-risk population; medical treatment with experimental medicinal products to all eligible people with laboratory confirmed EVD (either under compassionate use grounds or within clinical trials). (Kalenga, et al. July 2019) (Damon, et al. November 2018)

2.5.1. Regulatory System Response

As in previous outbreaks, no licensed medicinal products or vaccines existed for prevention, post-exposure prophylaxis and treatment of EVD in the awakening of the 2018-2020 Eastern DRC Outbreak. However, a lot of development and clinical work had been performed during the 2014-2016 West African Ebola Outbreak, and the knowledge gained in that period served as basis for the response in DRC. Additionally, the DRC outbreak has provided a new opportunity for further clinical development and generation of additional efficacy, safety and immunogenicity data that support regulatory submissions and licensing. (SAGE [2] February 2019)

Vaccines

As recommended by SAGE on April 2017, vaccination strategies were put in practice with the rVSV-ZEBOV vaccine for the two outbreaks in DRC, under the Expanded Access / Compassionate Use Program. (SAGE [1] April 2017) As part of the WHO response for the outbreak in the Bikoro region of the Equateur Province, more than 3400 individuals were vaccinated between the 21st of May and the 26th of June 2018, in accordance with a ring vaccination protocol (contacts and contacts of contacts of confirmed EVD cases, as well as frontline healthcare workers, were vaccinated). (World Health Organization [26] July 2018)

The response to the 2018-2020 Eastern DRC Outbreak marks the first in which an Ebola vaccine (rVSV-ZEBOV) was used from the start of the outbreak in order to try to contain it. The DRC Regulatory Authority and the Ethics Review Committee quickly approved

the Expanded Access protocol, allowing the vaccination to start only 7 days after the declaration of the outbreak. (World Health Organization [28] April 2019) (WHO Website [16] August 2018) Similarly to the previous outbreak in DRC and following SAGE's recent recommendations, rVSV-ZEBOV has been deployed using the ring vaccination strategy as well as vaccinating people at risk (healthcare workers and other frontline workers in affected areas or areas at risk). Geographic targeted vaccination, which comprises the vaccination of residents in the geographic area around an EVD case, has been recommended as an alternative strategy and was successfully used when the outbreak spread to Chowe in South Kivu. (World Health Organization [28] April 2019)

Vaccination eligibility in the Expanded Access protocol was expanded in February 2019 to include pregnant women, in April 2019 to include children over 6 months and lactating women, as authorized by the DRC Ethics Review Committee, and finally in May 2019 to add a third ring of immunized individuals who could potentially be involved in the tertiary generation of cases around an EVD index case, as recommended by SAGE and depicted in Figure 11. (SAGE [2] February 2019) (SAGE [3] May 2019) (SAGE [4] May 2019) As of the 24th of May 2020, more than 303.000 individuals have been vaccinated, including healthcare and frontline workers in the neighboring countries of Uganda, Rwanda, Burundi and South Sudan. (World Health Organization [27] May 2020)

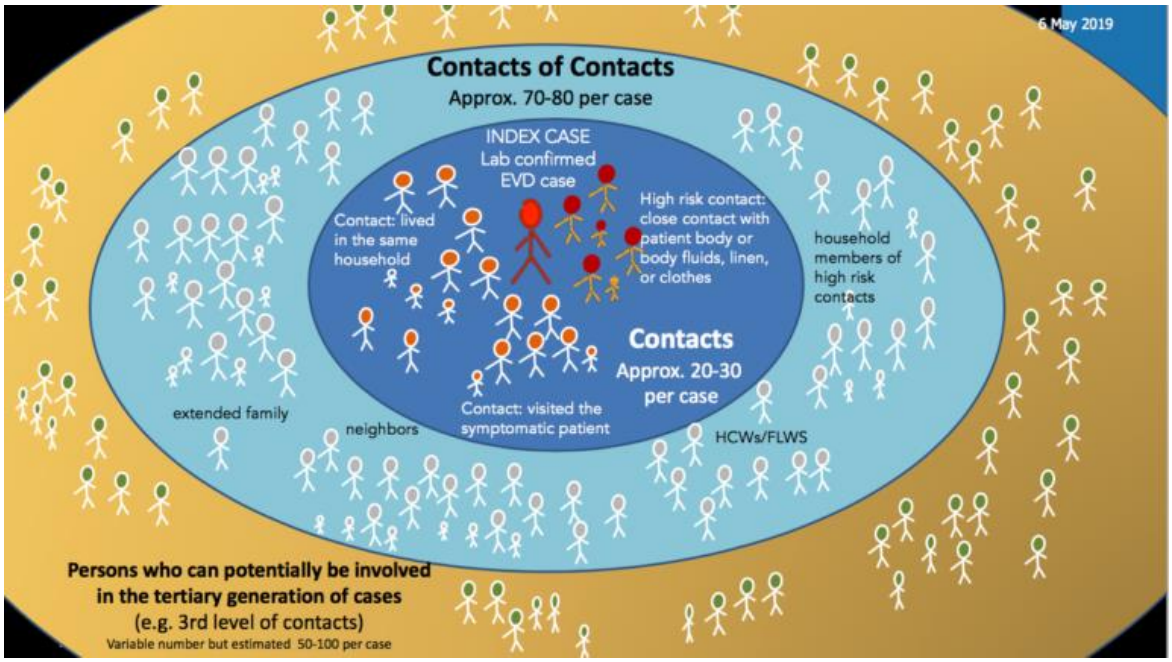


Figure 11: Addition of a third ring in the ring vaccination strategy for rVSV-ZEBOV (Branswell May 2019)

In April 2019, WHO published preliminary results from an observational study on the efficacy of rVSV-ZEBOV under compassionate use in the 2018-2020 Eastern DRC

Outbreak, showcasing the importance of integrating research into epidemic response (this integration has facilitated the further assessment of this vaccine, while contributing to the control of the outbreak). The data collected between the 1st of May 2018 and the 25th of March 2019 seems to confirm previous observations of high efficacy for this vaccine and the ring vaccination as an efficient delivery strategy during outbreaks. (World Health Organization [28] April 2019)

As a result of all the development, collaborative global efforts, pre-clinical and clinical data generated, Merck opted to obtain a regulatory approval from the US FDA and a centralized marketing authorization from EMA, as part of its regulatory strategy. Considering this, WHO published a roadmap to coordinate actions and collaboration with US FDA, EMA, Merck, AVAREF and African National Regulatory Authorities to speed up the licensing and roll-out of rVSV-ZEBOV in African countries. (World Health Organization [23] May 2019)

WHO's strategy encompassed the start of an expedited prequalification process (following the abbreviated procedure) after an approval was issued either by the US FDA or EMA, and support on the decision-making process and licensing of the vaccine in African countries at risk. This approach also included the participation of WHO prequalification representatives and African National Regulatory Authorities experts in the assessment process performed by EMA. (World Health Organization [23] May 2019) The major regulatory updates for rVSV-ZEBOV in this period included:

- On the 11th of March 2019, Merck submitted an application for a marketing authorization to EMA for rVSV-ZEBOV with the invented name Ervebo, through the centralized procedure (as per Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004). The application followed the legal basis of Article 8.3 of Directive 2001/83/EC, for a complete and independent application. (European Medicines Agency [4] October 2019) In addition, Merck requested an accelerated assessment, in accordance with Article 14 (9) of Regulation (EC) No 726/2004, which was accepted by CHMP based on the vaccine's high importance for public health (considering that EVD was a severe and mortal disease; an unmet medical need due to the lack of authorized medicinal products and vaccines; and the Ervebo's promising efficacy and safety data shown for the prevention of EVD). (European Medicines Agency [4] October 2019) (Council Regulation (EC) 726/2004)

- In light of the assessment performed, where some limitations in the pharmaceutical quality data were identified, the emergency situation and the nature of the target condition, CHMP issued on the 17th of October 2019 a positive opinion for granting a conditional marketing authorization for Ervebo in the European Union (as well as in the European Economic Area (EEA) countries Iceland, Liechtenstein and Norway), as per Article 14 (7) of Regulation (EC) No

726/2004 and Regulation (EC) No 507/2006. (European Medicines Agency [4] October 2019) (European Medicines Agency [5] October 2019) (Council Regulation (EC) 726/2004) (Commission Regulation (EC) 507/2006) In CHMP's opinion, the benefits of the immediate vaccine availability to public health outweighed the risks associated with the need for additional, more comprehensive, data. (European Medicines Agency [4] October 2019)

- The conditional marketing authorization, valid for 1 year, was officially granted by the European Commission on the 11th of November 2019, making Ervebo the first vaccine for active immunization of individuals aged 18 years and older at risk of infection with the Ebola virus, a landmark moment in public health. (EMA Website [4] December 2019) In order to have a complete marketing authorization, the marketing authorization holder will have to complete specific post-authorization obligations, as certain manufacturing process details were incomplete at the time of opinion (e.g.: confirmation of the validation status for both active substance and finished product manufacturing processes; comparability assessment between the commercial batches and the batches used in clinical trials). (European Medicines Agency [4] October 2019) The Ervebo's active substance (Recombinant Vesicular Stomatitis Virus strain Indiana with a deletion of the VSV envelope glycoprotein replaced with the Zaire Ebola Virus Kikwit 1995 strain surface glycoprotein) was considered by CHMP as a new active substance, since it was not part of any medicinal product previously authorized in the European Union. (European Medicines Agency [4] October 2019)

- Ervebo showcased EMA's regulatory flexibility, having been supported through the Agency's PRIME scheme and reviewed under the accelerated assessment program. Additionally, during the revision of Ervebo, EMA actively collaborated with WHO prequalification representatives and African National Regulatory Authorities experts through an innovative cooperative arrangement, in order to accelerate WHO prequalification and approval in African countries at risk. (WHO Website [17] October 2019) (European Medicines Agency [5] October 2019)

- Following CHMP's positive opinion for granting a conditional marketing authorization for Ervebo, WHO moved towards prequalification of the vaccine, which occurred on the 12th of November 2019. (WHO Website [18] November 2019) This meant that Ervebo met the WHO standards for quality, safety and efficacy, and that the United Nations agencies and Gavi, the Vaccine Alliance, could procure the vaccine for use in countries at risk, expediting its access and roll-out, as well as create an emergency stockpile. This was the first time WHO prequalified an Ebola vaccine, corresponding also to the fastest vaccine prequalification process ever conducted by WHO, which was possible due to an accelerated assessment and a rolling submission by Merck, with WHO revising

safety and efficacy data as they became available. (WHO Website [18] November 2019)

- On the 14th of February 2020, WHO announced that 4 African countries (DRC, Burundi, Ghana and Zambia) had licensed the Ebola vaccine rVSV-ZEBOV, just 90 days after the WHO prequalification, allowing for licensed doses to be stockpiled and used without requiring clinical trials or other research protocols or programs. (WHO Website [19] February 2020) This critical milestone was achieved quickly thanks to a different regulatory approach, where the national licensing procedures were done in parallel and based on a single scientific review process. This process was led by WHO with the collaborative support of AVAREF, EMA and Merck. (WHO Website [19] February 2020)

- Finally, on the 15th of July 2019, Merck completed the submission of the Biologics License Application (BLA) to US FDA for rVSV-ZEBOV, with the tradename name Ervebo (the initial submission of the non-clinical data occurred in October 2018, as part of a rolling BLA submission, in agreement with the US FDA). The US FDA accepted the application and granted priority review and a tropical disease priority review voucher in September 2019. (Food and Drug Administration [1] January 2020) (Food and Drug Administration [2] December 2019) The US FDA approved Ervebo on the 19th of December 2019, completing the assessment in less than 6 months (PDUFA goal date was set to March 2020). (Food and Drug Administration [1] January 2020) (Food and Drug Administration [2] December 2019)

- Like in Europe, Ervebo became the first US FDA-approved vaccine for the prevention of EVD in individuals 18 years of age and older, marking another important milestone in public health preparedness and response. (FDA Website [4] December 2019) Merck has committed to further present a post-marketing pediatric study to assess the safety and immunogenicity of Ervebo in children 12 months to 16 years of age. Following Ervebo's approval, one tropical disease priority review voucher (PRV) was granted to Merck, under section 524 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act). (Food and Drug Administration [2] December 2019) (FDA Website [4] December 2019) The US FDA highly supported the development and assessment of this vaccine, by granting a Breakthrough Therapy Designation and Priority Review, as well as PRV to further encourage the development of new medicinal products and biologics for the prevention and/or treatment of specific tropical diseases. (Food and Drug Administration [1] January 2020) (Food and Drug Administration [2] December 2019) (FDA Website [4] December 2019)

After some debate within the scientific community and global health entities, a second candidate Ebola vaccine was introduced in the response to the 2018-2020 Eastern DRC Outbreak – the two-dose heterologous prime-boost vaccine Ad26.ZEBOV/MVA-BN-Filo, manufactured by Johnson & Johnson. (WHO Website [20] April 2019) The choice of this vaccine over others (namely Ad5.EBOV) was based on an assessment performed with a framework developed by the WHO STAC-EE in 2015, in which criteria such as preclinical data, safety profile, immunogenicity, antibody persistence, vaccine stability or availability are compared. (WHO Website [20] April 2019)

Two main objectives were on the base of the decision to introduce a new vaccine: to complement the rVSV-ZEBOV vaccination strategy in course and help to speed up the end of the epidemic in DRC; to take the outbreak opportunity to test and assess the efficacy of another candidate vaccine against EVD (no previous clinical trials had been able to study the efficacy of Ad26.ZEBOV/MVA-BN-Filo). (WHO Website [21] September 2019) (SAGE [5] December 2018) (SAGE [4] May 2019) The vaccine was deployed to DRC on the 14th of November 2019, following the SAGE recommendations: vaccination of healthcare and frontline workers in areas that are not at high risk and do not have active Ebola transmission, thus not being eligible to receive the rVSV-ZEBOV vaccine as per the approved protocols. As of the 29th of February 2020, more than 20.000 individuals have been vaccinated with Ad26.ZEBOV/MVA-BN-Filo. (World Health Organization [29] March 2020)

In addition, a phase 2 clinical trial was launched in August 2019, in Uganda, in order to gather additional safety and immunogenicity data on healthcare and frontline workers (Table 4). (World Health Organization [30] August 2019) This trial is ongoing as of May 2020.

On the 6th of November 2019, Johnson & Johnson submitted two marketing authorization applications to EMA in parallel (one for each vaccine in the two-dose regimen), through the centralized procedure. In September 2019, CHMP had granted accelerated assessment for these applications. (EMA Website [1] May 2020) (Johnson & Johnson Website November 2019) (World Health Organization [30] August 2019) Johnson & Johnson also announced that discussions were occurring with the US FDA to define the necessary data to submit the vaccine regimen under the FDA's Animal Rule regulatory pathway (as no clinical efficacy data exists for this vaccine, the likelihood of protection should be assessed by comparing the human immunogenicity data against an animal model that describes the relationship between immunogenicity and survival). Discussions were also occurring with WHO for prequalification and to enable the registration in African countries. (Johnson & Johnson Website November 2019) (World Health Organization [30] August 2019)

Regarding other candidate vaccines, ChAd3-EBOZ has not been licensed and GlaxoSmithKline decided not to submit any regulatory dossier for the time being. Two additional Ebola vaccines based on adenovirus constructs were approved in their countries of origin for emergency use in the event of an Ebola outbreak: Ad5.EBOV in China (approval based on the Animal Rule pathway) and GamEvac-Combi in Russia, even though the available data on both vaccines is limited. (European Medicines Agency [4] October 2019) An EUAL application was also submitted to WHO for the Ad5.EBOV vaccine, on July 2018. (World Health Organization [21] October 2018)

Table 4: Summary of the 2/3 Clinical Trial for EVD Vaccine Candidates During the 2018–2020 Ebola Outbreak

Vaccine Candidate	Vaccine Type	Highest Pre-Clinical Evidence	Latest Formal Clinical Trial		
			Description & Design	Trial Information	Main Results
Ad26.ZEBOV / MVA-BN-Filo	Adenovirus 26 vectored glycoprotein and MVA-BN-Filo	100% effective in a company publicized NHP challenge study (n=8)	Phase 2 – safety and immunogenicity - Non-randomized, open-label. - Single arm.	Location: Uganda Enrollment: Estimated 800 participants (healthcare and frontline workers) Timeline: August 2019 to December 2021 Sponsor: MRC/UVRI Uganda Research Unit on Aids Janssen Pharmaceutical N.V Coalition for Epidemic Preparedness Innovations	Results not published as of May 2020

Notes: NHP – nonhuman primates
Source: (ClinicalTrials.gov [10] August 2019) (World Health Organization [30] August 2019)

Medicinal products

As an initial response to the 2018-2020 Eastern DRC Outbreak, investigational medicinal products were administered to individual EVD patients on an emergency basis outside clinical trials and as part of compassionate use protocols, in accordance with the dispositions of the WHO ethical framework (MEURI). (Damon, et al. November 2018) The assessment to determine whether the available information on investigational medicinal products supported their use under compassionate use grounds occurred in a WHO convened meeting of scientific experts (that included representatives from EMA, US FDA, among others) in the beginning of the outbreak in the Bikoro region of the Equateur Province, on the 17th of May 2018. (World Health Organization [31] May 2018)

On the 4th of June 2018, an Ethics Committee in DRC approved the use of 5 investigational medicinal products under compassionate use: ZMapp, Remdesivir, REGN-EB3 (a cocktail of three human monoclonal antibodies that target the Ebola virus glycoprotein), mAb114 (a recombinant human IgG1 antibody against the Ebola virus glycoprotein) and Favipiravir (only considered when the use of the other investigational medicinal products was not possible). (WHO Website [22] June 2018) (Damon, et al. November 2018) The information on these investigational medicinal products was updated under the context of the 2018-2020 Eastern DRC Outbreak, during a new WHO convened meeting on the 27th of August 2018. (World Health Organization [32] August 2018)

Under the R&D Blueprint platform, an ad-hoc expert consultation on clinical trials for Ebola therapeutics occurred on the 11th of October 2018 to plan ahead and determine how to make better evidence-based decisions on the investigational medicinal products for clinical trials, define a robust study design and a framework for an efficient collaboration across countries and outbreaks, by means of a common master clinical trial protocol to be used in future EVD outbreaks. A multi-outbreak, multi-country study was agreed upon by the partners attending the consultation, including representatives from EMA, US FDA, Ghana FDA and Institutions from countries at risk of Ebola. (World Health Organization [33] November 2018)

Following the ad-hoc expert consultation, a randomized, open-label, controlled clinical trial (PALM - “Together Save Lives”) of the 4 leading investigational medicinal products was launched in DRC, the first-ever multi-drug trial for an Ebola treatment and part of the multi-outbreak, multi-country study. (WHO Website [23] November 2018) (NIH Website [2] August 2019) According to the trial design, EVD patients were enrolled in a 1:1:1:1 ratio to receive one of the four investigational medicinal products under study - ZMapp, Remdesivir, REGN-EB3 and mAb114. ZMapp was selected as the active control

based on the previous results obtained in the PREVAIL II clinical trial. (Mulangu, et al. December 2019)

An interim analysis on data from 499 patients was performed on the 9th of August 2019 and the independent Data and Safety Monitoring Board recommended terminating the random assignment to both ZMapp and Remdesivir. This decision was based on two observations: the results for the REGN-EB3 met an early stopping criterion for efficacy defined in the study protocol; and the analysis of the mortality results showed a clear separation between groups, with the participants receiving REGN-EB3 or mAb114 having a greater chance of survival compared to the participants in the other two arms. (Mulangu, et al. December 2019) (NIH Website [2] August 2019)

The main results of the trial are described in Table 5. The study is ongoing as of May 2020 and formal conclusions on the efficacy and safety of the two investigational medicinal products still under assessment are expected in the future.

Table 5: Summary of the 2/3 Clinical Trial for EVD Therapeutic Candidates During the 2018–2020 Ebola Outbreak

Therapeutic Candidate	Drug Type	Highest Pre-Clinical Evidence	Latest Formal Clinical Trial		
			Description & Design	Trial Information	Main Results
ZMapp + Remdesivir + REGN-EB3 + mAb114	---	---	PALM (Phase 2/3 - safety and efficacy) - Multicenter; - Randomized, open-label; - 4 arms: ZMapp + oSOC vs. Remdesivir + oSOC vs. REGN-EB3 + oSOC vs. mAb114 + oSOC - ZMapp + oSOC is the control arm	Location: DRC Enrollment: 1500 patients (expected) 681 patients (as of 9th of August 2019) Timeline: November 2018 to November 2023 Sponsor: National Institute of Allergy and Infectious Diseases (NIAID)	Interim analysis showed that the combination of standard care plus either MAb114 or REGN-EB3 was superior to standard care plus ZMapp. Incidence of death, overall: ZMapp – 49.7% Remdesivir – 53.1% REGN-EB3 – 33.5% mAb114 – 35.1% Based on this interim analysis, ZMapp and Remdesivir were removed from the trial. The reason for a higher mortality among patients who received ZMapp in this trial (50%) vs. the PREVAIL II study in West Africa (22%) is still unclear.

Notes: oSOC – optimized Standard of Care
Source: (ClinicalTrials.gov [11] October 2019)

3. Regulatory System

As previously described, the global regulatory system has a critical role in managing health crisis and improve global health security. It must be fully prepared, flexible and responsive in order to act quickly and efficiently to public health threats and crisis. The major Regulatory Authorities have regulatory mechanisms that foster the development of medicinal products, vaccines and diagnostic tests to attack the health threat and control its spreading, expedite their assessment, approval, roll-out and access, whilst maintaining their quality, safety and efficacy standards. The next subsections describe those mechanisms for the major Regulatory Authorities, who act both domestically and in a global context.

3.1. European Medicines Agency

The European regulatory system is a unique model in the global regulatory environment, being comprised of a network of National Regulatory Authorities (for both human and veterinary medicines) from EU and EEA member states, united in the Head of Medicines Agencies (HMA), the European Medicines Agency, the European Commission and with the support of other European organizations such as the European Directorate for the Quality of Medicines & HealthCare (EDQM) of the Council of Europe. (European Medicines Agency and Heads of Medicines Agencies December 2015) The main goal of this network is to promote and protect the health of the population it serves through medicines regulation. Pivotal to EMA's role in promoting and protecting health is its capacity to effectively address and tackle emerging public health threats, by providing regulatory support to public health decisions, stimulating medicines development in areas of unmet medical need or neglected diseases, as well as enabling innovative, expedite and flexible pathways for their timely assessment and authorization. (European Medicines Agency and Heads of Medicines Agencies December 2015)

EMA has developed a plan for emerging health threats, setting out the roles, responsibilities and general guidance within the Agency during a public health threat. The plan was published in December 2018 and was based on EMA's Pandemic Plan of 2006 and on the experience gained from the 2009 Influenza H1N1 pandemic and the 2014-2016 West African Ebola outbreak. (European Medicines Agency [6] December 2018) The main objectives are to:

- "Initiate and coordinate scientific and regulatory activities, involving all interested parties within the European regulatory framework". (European Medicines Agency [6] December 2018)

- “Manage discussions on the development, authorization and surveillance of medicines to be used in the health threat context”. (European Medicines Agency [6] December 2018)
- “Provide the reviews outcome to EU partners”. (European Medicines Agency [6] December 2018)
- “Provide support to international partners (including interaction with international Regulatory Authorities, such as the US FDA or Health Canada), stakeholders involved in the research and development of medicines and public health authorities outside Europe (e.g.: WHO)”. (European Medicines Agency [6] December 2018)

The plan also encompasses operational regulatory aspects, such as facilitating regulatory input into clinical trials, providing rapid scientific advice, fast-track approval through the centralized procedure and post-approval follow-ups. (European Medicines Agency [6] December 2018) Planning for and addressing emerging public health threats was foreseen in the EU Medicines Agency Network Strategy to 2020 and is a key part of the current EMA’s Regulatory Science strategic reflection for 2025. (European Medicines Agency and Heads of Medicines Agencies December 2015) (European Medicines Agency [7] March 2020)

EMA has a wide range of mechanisms within its regulatory framework, apart from the traditional regulatory approach, to support medicines development and/or early access, including Scientific Advice, PRIME scheme, Orphan Designation, Compassionate Use, Accelerated Assessment and conditional approval by means of a Conditional Marketing Authorization. EMA also has a procedure specific for medicines for use outside the EU, introduced in Article 58 of Regulation (EC) No 726/2004 to facilitate access to essential medicines in low- and middle-income countries. These tools, that are not mutually exclusive, are briefly described hereafter, with more details being available at the EMA website.

Scientific Advice

The Scientific Advice allows EMA to provide early regulatory and scientific support and advice on the most appropriate ways to test and develop a quality, safe and effective medicinal product and generate robust evidence on its benefits and risks. It focuses on development strategies and not on pre-evaluation of data. This is intended to ease the preparation for the submission of a marketing authorization application that meets

European regulatory requirements and enable a timely assessment procedure, contributing to an earlier availability of a medicinal product for patients. (EMA Website [5] May 2020) (European Medicines Agency [8] June 2017) (EMA Website [6] May 2020) A special form of Scientific Advice, designated Protocol Assistance, exists for developers of orphan medicinal products and follows the same dispositions as the general Scientific Advice. (EMA Website [5] May 2020) (European Medicines Agency [8] June 2017) (EMA Website [6] May 2020)

Scientific Advice is foreseen in Article 57-1 (n) of Regulation (EC) No 726/2004 (protocol assistance is foreseen in Article 6 of Regulation (EC) No 141/2000) and can be requested for all medicinal products for human use, regardless of their eligibility for the centralized procedure. (Council Regulation (EC) 726/2004) (Council Regulation (EC) 141/2000)

The pharmaceutical or developing company can ask for this advice at any stage of the development or during the post-authorization phase, by presenting specific questions on quality, non-clinical, clinical aspects or overall development strategies, and propose responses or solutions, which are then assessed by the EMA's Scientific Advice Working Party (SAWP), discussed and adopted by the CHMP. Other Working Parties, Committees or ad-hoc groups can provide their input when relevant. The evaluation phase of the procedure takes 40 or 70 days (the later if SAWP decides that there is a need for a discussion meeting). (EMA Website [5] May 2020) (European Medicines Agency [8] June 2017) (EMA Website [6] May 2020)

However, any Scientific Advice given is not legally binding on EMA or on the pharmaceutical company with regards to a marketing authorization application of the concerned medicinal product. While it can facilitate and expedite the assessment procedure (because the information submitted is likely to be more robust, appropriate and complete), Scientific Advice does not guarantee a marketing authorization approval nor it pre-assesses the benefits and risks of a medicinal product. (EMA Website [5] May 2020) (EMA Website [6] May 2020)

EMA and the US FDA have a program to provide Scientific Advice and protocol assistance in parallel, with the main purpose of allowing assessors from both Regulatory Authorities and applicants to exchange their opinions on scientific issues during the development phase of new medicinal products. (European Medicines Agency and Food and Drug Administration April 2017) (European Medicines Agency [8] June 2017) This mechanism provides several potential advantages: increased dialogue between the two Regulatory Authorities and applicants from the start of the new medicinal product's lifecycle; greater understanding of the bases that underline scientific and regulatory decisions and requirements; optimized research and development, avoiding unnecessary replication or diverse testing methodologies. Each Regulatory Authority will provide their independent advice on the questions posed, which may not be similar after

the joint discussion. However, both will strive to provide convergent Scientific Advice responses. (European Medicines Agency and Food and Drug Administration April 2017) (European Medicines Agency [8] June 2017)

Scientific Advice has been made available and often used by EMA to help address and contribute to the global response of some public health crisis and health threats, including pandemic Influenza (H1N1 strain), Ebola and Zika. Moreover, for the 2014-2016 West African Ebola Outbreak, EMA put in place a rapid scientific advice procedure, which reduces the evaluation time to a maximum of 20 days, with no pre-specified submission deadlines. (EMA Website [5] May 2020) (EMA Website [1] May 2020)

PRIME scheme

The PRIME scheme, launched by EMA in March 2016, is a pre-authorization regulatory tool that promotes an early dialogue with the Regulatory Authority and further supports a medicinal product development plan and regulatory strategy, from a clinical development stage up to the submission of a marketing authorization application. It is eligible for innovative medicinal products, not authorized in the EU, that target unmet medical needs and with the potential to provide major therapeutic advantages over available treatments or benefit patients without any treatment alternatives, based on pre-clinical and preliminary clinical evidence. (EMA Website [3] May 2020) (European Medicines Agency [9] May 2018) (European Medicines Agency [10] May 2018)

PRIME makes use of the existing regulatory framework and mechanisms, namely the Scientific Advice (at key development milestones or for major issues) and the Accelerated Assessment (at the time of submission of a marketing authorization application, with the potential eligibility being determined in an earlier stage). Besides these two regulatory tools, additional PRIME features for enhanced support are available, including: early rapporteur appointment from CHMP (or from the Committee for Advanced Therapies, CAT, in the case of advanced therapy medicinal products) that provides continuous scientific and regulatory guidance and support; organization of a kick-off meeting with the rapporteur and a multidisciplinary team of experts from the EU network, in which guidance on development plans and regulatory pathways and requirements is provided; and a dedicated single contact point within EMA. (EMA Website [3] May 2020) (European Medicines Agency [9] May 2018) (European Medicines Agency [10] May 2018) This scheme can, therefore, optimize a medicinal products' development and expedite its submission, evaluation and access to patients. (EMA Website [3] May 2020)

As of May 2020, EMA has used this tool to help address two critical health threats: the Ebola and Zika viruses. Eligibility to the PRIME scheme has been granted for the vaccines rVSV-ZEBOV (in June 2016) and TAK-426 (in March 2019), used for the active

immunization of individuals against the Ebola and Zika viruses, respectively. rVSV-ZEBOV was removed from the PRIME scheme following the submission of the marketing authorization application to EMA, whereas the vaccine TAK-426 is within the scheme as of May 2020, since its development is still ongoing. (European Medicines Agency [11] May 2020)

Orphan Designation

The European legislative framework on orphan medicinal products intends to promote the research and development of medicinal products for rare, life-threatening diseases by providing incentives to the pharmaceutical companies developing such medicinal products. (EMA Website [2] May 2020) A medicinal product can be designated an orphan medicinal product if it meets the criteria established in Article 3(1) of Regulation (EC) 141/2000: “it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10.000 persons in the EU or that without incentives it is unlikely that the marketing of the medicinal product in the EU would generate sufficient return to justify the necessary investment; and that there exists no satisfactory method of diagnosis, prevention or treatment of the condition that has been authorized in the Community or, if such method exists, the medicinal product will be of significant benefit to those affected by that condition”. (Council Regulation (EC) 141/2000)

The applications for an Orphan Designation are submitted to EMA and assessed by the Committee for Orphan Medicinal Products (COMP), within 90 days from a valid submission. The final decision is made by the European Commission within 30 days, taking into consideration COMP’s opinion. (Council Regulation (EC) 141/2000)

If the Orphan Designation is granted, a range of incentives to encourage the development of the orphan medicinal product is made available. These include Protocol Assistance, access to the centralized marketing authorization procedure, market exclusivity in the EU for a period of 10 years after the marketing authorization is granted and if the Orphan Designation is maintained throughout (this period can be extended by 2 additional years if a pediatric investigation plan is agreed upon and fully performed), reduced fees for regulatory activities (e.g.: Protocol Assistance, inspections, marketing authorization applications, variation applications) and eligibility to receive research grants. Orphan medicinal products are also qualified for a conditional marketing authorization. (EMA Website [7] May 2020)

Orphan designation has been used to help address some major health threats, including the Ebola virus: it was granted to several medicinal products for the treatment of EVD, ZMapp and Remdesivir amongst them. (European Medicines Agency [3] November 2015) (European Medicines Agency [12] March 2016)

Compassionate Use

Compassionate Use is one of the regulatory tools focused on providing early access and is commonly requested to manage health crisis. This program intends to ease the availability of an unauthorized treatment option to seriously ill patients that are suffering from a disease for which no comparably beneficial and authorized alternative treatment is available and that cannot be enrolled in ongoing clinical trials. (EMA Website [8] May 2020)

Article 83 of Regulation (EC) No 726/2004 introduces and lays down the provisions for Compassionate Use in the EU. The eligibility criteria for an unauthorized medicinal product to be used under Compassionate Use grounds include: use in chronically, seriously debilitating or life-threatening diseases, for which no satisfactory medicinal product is authorized in the EU; targets a group of patients (and not an individual patient); is subject of a marketing authorization application through the centralized procedure or is undergoing clinical trials; falls under the scope of a centralized marketing authorization procedure. (Council Regulation (EC) 726/2004) (European Medicines Agency [13] July 2007)

Compassionate Use implementation and coordination is a competence of each National Regulatory Authority within the EU, each having their own set of procedures and rules. Following a notification or if requested by an EU Regulatory Authority, CHMP can provide non-binding recommendations on subjects related with the administration, distribution and use of medicinal products under this program. (EMA Website [8] May 2020) (European Medicines Agency [13] July 2007) Article 83 of Regulation (EC) No 726/2004 is, therefore, complementary to national legislations and seeks to harmonize the Compassionate Use program, increase transparency, and ease the access to patients in need within the EU. (European Medicines Agency [13] July 2007)

The first Compassionate Use recommendations provided by CHMP occurred in early 2010 for the use of oseltamivir phosphate and zanamivir against the pandemic Influenza (H1N1 strain) infection. (EMA Website [8] May 2020)

Accelerated Assessment

Another regulatory tool that is focused on providing early approval and access to medicinal products is Accelerated Assessment, which reduces the CHMP's review timeframe of a marketing authorization application to 150 days or less (compared to the standard 210 days, excluding clock stops). (EMA Website [9] May 2020) This procedure, illustrated in Figure 12, is available for medicinal products of major interest for public health, particularly from a therapeutic innovation perspective (by addressing an unmet

medical need), as dictated in Recital 33 and Article 14(9) of Regulation (EC) No 726/2004. (EMA Website [9] May 2020) (Council Regulation (EC) 726/2004)

Figure 12: Accelerated Assessment general procedure (LoQ – List of Questions; LoOI – List of Outstanding Issues) (European Medicines Agency [14] July 2017)

Applicants can request Accelerated Assessment 2 to 3 months before the submission of the marketing authorization application. Before this request is made, EMA strongly recommends that a pre-submission meeting takes place, 6 to 7 months before the submission, between the applicant and rapporteurs from CHMP and any other concerned Committee, to discuss the proposal for Accelerated Assessment. (EMA Website [9] May 2020) (European Medicines Agency [15] February 2016) If the PRIME scheme has been granted previously, the applicant can receive feedback on the medicinal products' potential eligibility for Accelerated Assessment earlier, during the clinical development phase. (EMA Website [9] May 2020) (European Medicines Agency [15] February 2016)

The decision on whether a medicinal product is eligible for an Accelerated Assessment is made by CHMP, based on the request submitted, the justification presented by the applicant and the rapporteurs' recommendations. (EMA Website [9] May 2020) (European Medicines Agency [15] February 2016)

Conditional Marketing Authorization

A third regulatory tool that could provide early approval and access to medicinal products in the interest of public health is the Conditional Marketing Authorization, in which a marketing authorization can be granted to a specific medicinal product based on less comprehensive data than normally required and subject to post-authorization obligations (start or complete ongoing studies to confirm that the risk-benefit balance is favorable). This conditional marketing authorization is valid for 1 year and can be renewed annually. (EMA Website [10] May 2020) (Council Regulation (EC) 726/2004)

As per Regulation (EC) No 507/2006, a Conditional Marketing Authorization can be considered for medicinal products to be used for the diagnosis, prevention or treatment of seriously debilitating or life-threatening diseases, for emergency situations, in response to public health threats, and for orphan medicinal products. The following requirements must be fulfilled so that CHMP can grant a Conditional Marketing Authorization: positive risk-benefit balance; the applicant will likely be able to submit the comprehensive data after authorization; fulfills an unmet medical need; the benefits of an immediate availability to public health outweigh the risks related with additional data still being required. (Commission Regulation (EC) 507/2006) (European Medicines Agency [16] February 2016)

A Conditional Marketing Authorization can be considered when only the clinical data on safety and efficacy is less complete than normal. However, for emergency situations in response to public health threats, less comprehensive preclinical and quality data may also be accepted. Upon obtaining the full data and completing the previously agreed post-authorization obligations, the Conditional Marketing Authorization may be converted in a standard one, not subject to specific obligations. (EMA Website [10] May 2020) (Commission Regulation (EC) 507/2006) (European Medicines Agency [16] February 2016)

When the comprehensive clinical data cannot be generated, a different marketing authorization, named Marketing Authorization Under Exceptional Circumstances, can be granted. (EMA Website [10] May 2020) (European Medicines Agency [16] February 2016)

Applicants are encouraged to discuss the possibility of using this regulatory pathway as soon as possible with EMA, either through Scientific Advice / Protocol Assistance or PRIME scheme. This is particularly important when addressing public health threats, as it was the case for vaccines against the pandemic Influenza and the Ebola viruses. (EMA Website [10] May 2020) (European Medicines Agency [4] October 2019)

Article 58 Procedure

Article 58 of Regulation (EC) No 726/2004 introduced a procedure for medicinal products intended exclusively for use outside EU. (Council Regulation (EC) 726/2004) In it, EMA works in collaboration with experts from WHO and relevant National Regulatory Authorities outside EU to provide tailored scientific opinions and assess medicinal products of major public health interest or that address an unmet medical need. (EMA Website [11] May 2020) (World Health Organization [34] April 2010)

Medicinal products under Article 58 may benefit from the entire EMA regulatory tools, including Scientific Advice, PRIME scheme or Accelerated Assessment. This

collaborative regulatory pathway aims to facilitate prequalification of an essential medicinal product by WHO and further registration in a designated country, and has been used to ease the access of vaccines and other medicinal products, in low- and middle-income countries, to fight priority public health diseases and build stockpiles for emergency responses. (EMA Website [11] May 2020) (World Health Organization [34] April 2010)

3.2. US Food and Drug Administration

The US FDA has a very flexible regulatory system, capable of effectively regulate, stimulate the development and expedite the access of medical countermeasures to address public health threats in an emergency context, including chemical, biological, radiological, or nuclear agents (known as CBRNs), or emerging infectious diseases. In its role to protect public health and improve global health security, the US FDA works in close partnership with the scientific community, pharmaceutical companies, International Organizations (including WHO) and Regulatory Authorities, and with Federal Agencies as part of the US HHS Public Health Emergency Medical Countermeasures Enterprise (PHEMCE). (FDA Website [5] March 2020) Several laws and programs address FDA's role on the management of public health crisis, including:

- The Medical Countermeasure Initiative Program, launched by the US FDA in August 2010 to coordinate and foster the development of medicinal products and promote their timely access to address potential CBRNs and emerging infectious diseases. (FDA Website [6] March 2020) (FDA Website [7] March 2019) The work has been done by developing clear regulatory pathways and guaranteeing that laws, policies and regulations support the preparedness and response mechanisms in place. Additionally, this program, within its regulatory science arm, is also focused on bridging the gap between science and technology innovation and its translation to safe and effective medicinal products, by defining the most appropriate tools and approaches to correctly assess them. (FDA Website [6] March 2020) (FDA Website [7] March 2019)

- The Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA), signed into law on March 2013, recognized and empowered US FDA's role in managing and responding to public health emergencies, while also refining some regulatory tools. (FDA Website [8] November 2018) (FDA Website [9] December 2019)

- The 21st Century Cures Act, signed into law on December 2016, also fosters the development and assessment of medicinal products and welcomes the introduction of new innovations and modernization of mechanisms. It addresses the incorporation of patients' perspective into the development stages, the

inclusion of real-world data in clinical trials and provides more authority to US FDA. (FDA Website [10] January 2020)

Similarly to EMA, the US FDA has also developed a single, comprehensive plan for the management of a wide variety of national and international incidents, including emerging health threats. This plan is designated as *FDA Emergency Operations Plan*, and lays down the roles, responsibilities, general mechanisms, and coordination of resources within the Agency before, during and after public health crisis, among others. (Food and Drug Administration [3] July 2019)

The panoply of regulatory tools and mechanism at US FDA's disposal to support and stimulate medicinal products development and early access includes Fast Track Designation, Breakthrough Therapy Designation, Accelerated Approval, Priority Review, Orphan Drug Designation, Animal Rule, Emergency Use Authorization and Expanded Access. These tools, that are not mutually exclusive, are briefly described hereafter, with more details being available at the US FDA website.

Fast Track Designation

Fast Track Designation is a regulatory tool, referenced in Section 506(b) of the FD&C Act as amended, that intends to speed up the development, assessment and availability of medicinal products that treat serious conditions and potentially fulfill an unmet medical need (either because there is no available treatment or they present advantages over existing therapeutic alternatives). (FDA Website [11] January 2018) (Food and Drug Administration [4] May 2014)

After a Fast Track Designation is granted, several features become available: frequent meetings and/or written communication with the US FDA regarding the development plan and generation of robust data necessary for the medicinal products approval; eligibility for other regulatory pathways, such as Accelerated Approval and Priority Review (if the applicable criteria are met); and rolling review, which allows the submission of sections for assessment as soon as they are complete, instead of submitting the entire application together later on. (FDA Website [11] January 2018) (Food and Drug Administration [4] May 2014)

Fast Track Designation can be requested at any stage of the development process after an Investigational New Drug (IND) application has been submitted, with the US FDA assessing the request within 60 days. (FDA Website [11] January 2018) (Food and Drug Administration [4] May 2014)

Fast Track Designation has been made available and often used by the US FDA to help address and contribute to the global response of some public health crisis and health threats, including Ebola, Zika, among others. (Largent September 2016) (Reuters [1] January 2018) (Reuters [2] May 2020)

Breakthrough Therapy Designation

Breakthrough Therapy Designation is another regulatory tool, foreseen in Section 506(a) of the FD&C Act as amended, that intends to accelerate the development, assessment and availability of medicinal products that treat serious conditions and that demonstrate, through preliminary clinical data, the possibility of a significant improvement over available alternative therapies on one or more relevant clinical endpoints. (FDA Website [2] January 2018) (Food and Drug Administration [4] May 2014)

When the Breakthrough Therapy Designation is granted, the same features described before for the Fast Track Designation become available. Additionally, intensive guidance on the medicinal products development program and commitment of US FDA senior managers is also accessible. (FDA Website [2] January 2018) (Food and Drug Administration [4] May 2014)

The request for a Breakthrough Therapy Designation should occur after an IND submission and, ideally, no later than the end of phase 2 clinical trials meeting, so that the available features can be used to support the generation of robust data necessary for the medicinal products approval. As before, US FDA will assess the request within 60 days. (FDA Website [2] January 2018) (Food and Drug Administration [4] May 2014)

Accelerated Approval

Accelerated Approval is a regulatory pathway that allows US FDA to approve a medicinal product faster than in a traditional regulatory procedure, based on the effect on an intermediate clinical endpoint or on a surrogate endpoint that is reasonably likely to predict its clinical benefit. (FDA Website [12] January 2018) (Food and Drug Administration [4] May 2014) This regulatory pathway is foreseen in Title 21 of the Code of Federal Regulations (21 CFR, Parts 314 and 601) and in Section 506(c) of the FD&C Act, as amended, and can be considered for medicinal products that treat serious conditions and fulfill an unmet medical need, expediting their availability to patients. Phase 4 confirmatory trials need to be conducted post-approval to confirm and describe the expected clinical benefit. If such trials fail to confirm the expected clinical benefit, the US FDA may withdraw the approval. (FDA Website [12] January 2018) (Food and Drug Administration [4] May 2014)

Priority Review

Priority Review is another regulatory pathway that allows US FDA to direct resources and expedite the assessment of a medicinal product application to a period of 6 months (compared to the 10-month standard review period). This regulatory pathway was introduced in the Prescription Drug User Fee Act of 1992 (PDUFA) and is eligible to medicinal products that meet the defined criteria: treatment of a serious condition and substantial improvement in effectiveness or safety, compared to available therapeutic alternatives. (FDA Website [13] January 2018) (Food and Drug Administration [4] May 2014)

Labelling change applications based on pediatric studies, medicinal products designated as “qualified infectious disease products” or applications submitted with a Priority Review Voucher are also eligible for Priority Review. It is important to state that this regulatory pathway does not change the development stages of the medicinal product nor the regulatory requirements for its approval. The request for a Priority Review can be made at the time of the application and the US FDA will assess that request within 60 days. (FDA Website [13] January 2018) (Food and Drug Administration [4] May 2014)

In order to stimulate the development of medicinal products for diseases that would normally not attract interest from pharmaceutical companies, the Priority Review Voucher (PRV) Program was launched by the FDAAA in 2007 and currently foreseen in the FD&C Act. Pharmaceutical companies can receive a transferable PRV from the US FDA (after approval of an eligible medicinal product) or purchase one from another company, which allows them to request an expedite review of one medicinal product to the US FDA under the Priority Review regulatory pathway. This request must be made at least 90 days before the submission of the application for which the voucher will be used. (RAPS Website [1] February 2020) (Food and Drug Administration [5] October 2016) (Food and Drug Administration [6] January 2018)

Currently, there are 3 types of PRVs: the Tropical Disease PRV, the Rare Pediatric Disease PRV and the Medical Countermeasure PRV, with the former addressing diseases that caused impactful outbreaks in the recent past, such as the Ebola and Zika viruses. (RAPS Website [1] February 2020) (Food and Drug Administration [5] October 2016) (Food and Drug Administration [6] January 2018)

Orphan Drug Designation

The US FDA, through the Orphan Drug Act, as amended, and implementing regulations (21 CFR Part 316), promotes the development of medicinal products for the treatment, prevention or diagnosis of rare diseases or conditions, either affecting less than 200.000 people in the United States or affecting more than 200.000 people but without expecting

to generate enough return to recover the investment on development and marketing. (FDA Website [14] March 2018) (FDA Website [15] May 2020) Additionally, a medicinal product seeking Orphan Drug Designation must justify its clinical superiority over an existing therapeutic alternative for the same rare disease or condition. If these criteria are met, an Orphan Drug Designation is granted by the US FDA. The request for an Orphan Drug Designation can occur at any stage of the development process. (FDA Website [14] March 2018) (FDA Website [15] May 2020)

A variety of financial and regulatory incentives is available to medicinal products with Orphan Drug Designation, including written recommendations regarding the preclinical and clinical development and generation of robust data necessary for the medicinal products approval, market exclusivity for a period of 7 years after the US FDA approval is granted, tax credits for qualified clinical testing and eligibility to receive research grants. (FDA Website [14] March 2018) (FDA Website [15] May 2020)

Orphan Drug Designation has been used by US FDA to help address some major health threats, including the Ebola virus: it was granted to several investigational medicinal products for the treatment of EVD, including ZMapp and Remdesivir. (Largent September 2016) (FDA Website [1] May 2020)

Animal Rule

The Animal Rule, originally launched in 2002 and foreseen in 21 CFR Parts 314 and 601, is a regulatory pathway that allows US FDA to approve a medicinal product for which conducting efficacy studies in humans is not feasible or ethical, and it can do so based on well-controlled and adequate efficacy studies in animals. The Animal Rule guidance lists the requirements that must be met to ensure that the efficacy studies in animals establish a reasonable likelihood of clinical benefit in humans, so that they can be considered in the application. (Food and Drug Administration [7] October 2015) The Animal Rule, however, does not replace the need for human safety data to be presented upon submission, as it normally would in a traditional application procedure. (Food and Drug Administration [7] October 2015) (FDA Website [16] March 2019)

The Animal Rule regulatory pathway is applicable to medicinal products that prevent serious or life-threatening conditions, possibly originated from CBRNs, emerging infectious pathogens, or others, and considering that efficacy studies in humans are not feasible or ethical. This eligibility is assessed on a case-by-case basis. Medicinal products developed under the Animal Rule are eligible for other regulatory tools and pathways, except the Breakthrough Therapy Designation, as it requires preliminary human clinical data. (Food and Drug Administration [7] October 2015)

This regulatory pathway has recently been discussed with the US FDA and considered for the development and regulatory submission of 2 EVD related products: Ad26.ZEBOV/MVA-BN-Filo and remdesivir. (Johnson & Johnson Website November 2019) (USAMRIID March 2019)

Emergency Use Authorization (EUA)

The EUA is one of the regulatory tools focused on facilitating early access to unauthorized medicinal products or unauthorized uses of already approved medicinal products during public health emergencies, to treat, prevent or diagnose serious or life-threatening conditions or diseases originated from CBRNs, emerging infectious pathogens, or others. (Food and Drug Administration [8] January 2017) (FDA Website [17] February 2020) This is, therefore, a commonly used tool by the US FDA to respond to public health crisis. Section 564 of the FD&C Act, as amended, allows the US FDA Commissioner to issue an EUA after the department of HHS Secretary determines a public health emergency (or a significant potential of that occurring) and makes a declaration justifying such EUA. This authorization remains valid until the declaration is terminated or if the below eligibility criteria ceases to be valid. (Food and Drug Administration [8] January 2017) (FDA Website [17] February 2020)

The eligibility criteria for an unauthorized medicinal product or its unauthorized use to be considered under a EUA includes: existence of a serious or life-threatening condition or disease; evidence of potential effectiveness to treat, prevent or diagnose the concerned serious or life-threatening condition or disease; positive risk-benefit balance; no approved and feasible alternatives exist. (Food and Drug Administration [8] January 2017)

It is important to state that an EUA can be requested to the US FDA by foreign countries, as it was the case during the 2014-2016 West African Ebola Outbreak. Besides Ebola, EUAs were also issued to address and contribute to the global response of other public health threats, such as Influenza (H1N1 and H7N9 strains), Zika and MERS-CoV. (FDA Website [3] May 2020) (Singh February 2015)

Expanded Access

The other regulatory pathway that allows the emergency use of unapproved, investigational medicinal products, outside of clinical trials, to treat patients with serious or life-threatening diseases, when no other comparably beneficial alternative treatment exists, is the Expanded Access Program (also referred to as Compassionate Use). However, not all patients are eligible for this program, as some cumulative criteria

(regarding the disease/condition, the absence of therapeutic alternatives, the risk-benefit balance, or no interference with planned or ongoing clinical trials) must be met to authorize an expanded access use. (FDA Website [18] April 2020) (Food and Drug Administration [9] October 2017)

Under the current regulations (21 CFR Part 312), there are 3 different categories of Expanded Access Programs: Expanded Access for individual patients (including for emergency use); Expanded Access for intermediate-size patient population; and Expanded Access for widespread treatment use. For each of these categories, the regulatory submission to obtain access to an investigational medicinal product can be made either through a new IND application (Expanded Access IND – only for treatment purposes) or through a protocol amendment to an existing IND (Expanded Access Protocol). (FDA Website [19] January 2018) (Food and Drug Administration [9] October 2017)

3.3. World Health Organization

WHO plays a critical and broad role in preventing, managing and responding to public health emergencies and safeguarding global health security, with particular importance in low- and middle-income countries. Part of the current WHO 2019-2023 Regulatory Action Plan is centered on the regulatory preparedness for public health emergencies, as well as strengthening regulatory systems, expansion of its prequalification program and its regulatory support activities. (WHO Website [24] May 2020) (World Health Organization [35] July 2019) Its role and general emergency procedures, briefly described in the previous chapter, are defined under the IHR 2005 and on the Emergency Response Framework. (World Health Organization [4] June 2017) (World Health Organization [3] July 2016)

There are 3 programs within WHO that stand out from a regulatory and pharmaceutical development perspective: Prequalification, Emergency Use Listing, and R&D Blueprint.

Prequalification

The WHO Prequalification program was created in 2001 and intends to ease and expedite the availability of essential medicinal products, for high burden diseases, that comply with international and WHO-recommended standards for quality, safety and efficacy, and also with the good manufacturing, clinical and laboratory practices. The medicinal products thus assessed and found compliant are included in the WHO List of Prequalified Medicinal Products Acceptable for Procurement by the UN Agencies. (World Health Organization [36] 2011) (WHO Website [25] May 2020)

WHO appointed experts perform a comprehensive assessment of the dossier submitted by the applicant and conduct inspections on the manufacturing and clinical site(s). This Prequalification assessment can be done with the collaboration of National Regulatory Authorities (e.g.: Article 58 procedure with EMA) and/or can also be based on a previous approval by a stringent Regulatory Authority that applies similar standards as those recommended by WHO. Provided any outstanding requests, a requalification procedure occurs every 5 years starting from the date of Prequalification. (World Health Organization [36] 2011) (WHO Website [26] May 2020)

To avoid delays in the approval and access of essential medicinal products in countries with restricted regulatory resources (where the assessment may take 2 to 3 years in some situations), WHO launched two collaborative initiatives to accelerate the assessment procedure and registration. (World Health Organization [37] 2016) (World Health Organization [38] 2018) These allow participating National Regulatory Authorities of WHO Member States to use the work already performed by WHO in the Prequalification assessment or by stringent Regulatory Authorities in their marketing authorization evaluations, save resources and harmonize their regulatory procedures and requirements with international practices. National Regulatory Authorities that agree to apply these initiatives commit to reach a regulatory decision within 90 days of receiving the assessment and inspection reports, and communicate it in 30 days. (World Health Organization [37] 2016) (World Health Organization [38] 2018)

The Prequalification program also offers the opportunity for National Regulatory Authorities of low- and middle-income countries to participate in the assessment and/or inspection stages and also receive adequate training from WHO, allowing them to build up knowledge in regulatory activities and optimize their regulatory procedures. (WHO Website [27] May 2020)

Emergency Use Listing (EUL)

The WHO EUL procedure was created based on the existing EAUL mechanism, which had been developed in response to the 2014-2016 West African Ebola Outbreak. Following the experience during the Ebola and Zika epidemics, where several *in vitro* diagnostic tests were listed, the WHO informal consultation on options to improve regulatory preparedness to address public health emergencies, held on May 2017, opted to introduce some changes and simplify the EUAL procedure, reframing it as EUL. (World Health Organization [39] May 2017)

The goal of the EUL remained unchanged: accelerate the access of unauthorized products (including diagnostic tests) in the context of a public health emergency and normally after the declaration of a PHEIC. (World Health Organization [16] January 2020) To accomplish this, eligible products are assessed on the available quality, safety and

efficacy/performance data, and, if deemed acceptable, are inserted in a time-limited list to assist UN procurement agencies and WHO Member States. This decision is reassessed annually. Additionally, it is expected that the applicant, as part of EUL eligibility criteria, completes the development of the concerned product and applies for WHO prequalification. (World Health Organization [16] January 2020)

The EUL procedure establishes the information required for the assessment and the necessary steps that must be followed during 3 different stages (pre-emergency stage, emergency stage and pro-listing stage) so that the decision-making process is not hindered and delayed. The EUL procedure and its assessment timelines are depicted in Figure 13. (World Health Organization [16] January 2020)

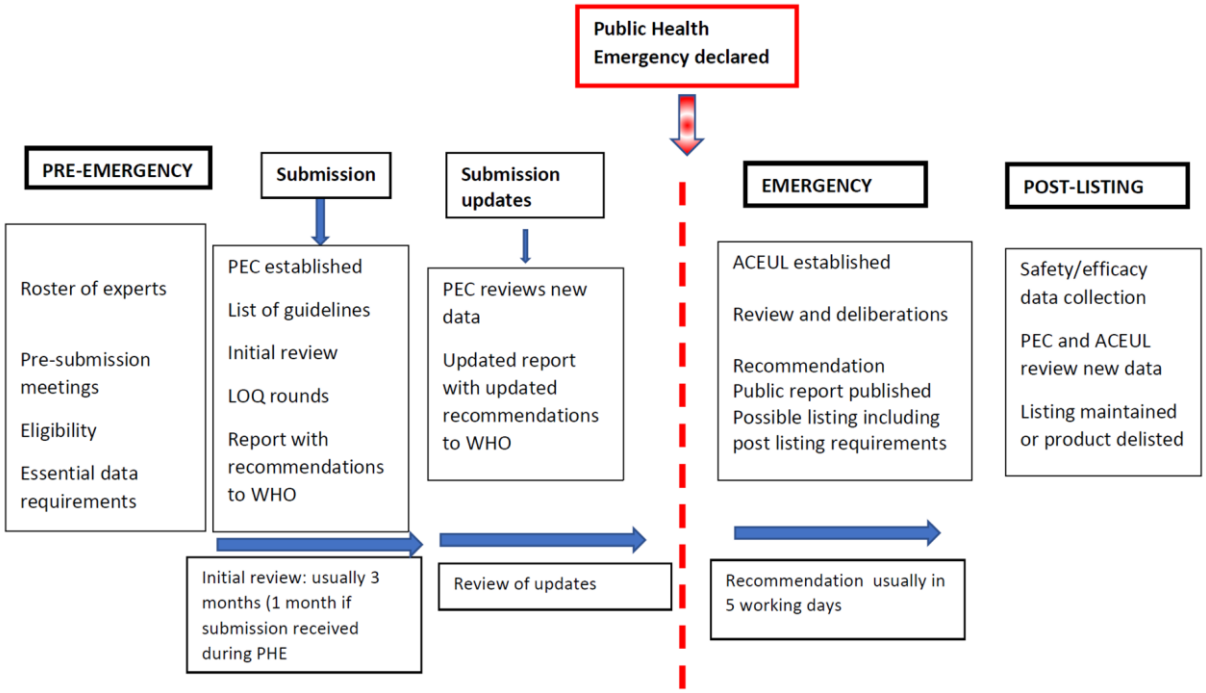


Figure 13: EUL procedure (ACEUL – Advisory Committee for Emergency Use Listing; PEC - Product Evaluation Committee; PHE - Public Health Emergency) (World Health Organization [16] January 2020)

R&D Blueprint

As discussed previously, the lessons learned from the 2014-2016 West African Ebola Outbreak highlighted the importance of research as part of an epidemic response and the existence of a global strategy and preparedness plan for its quick implementation. The WHO R&D Blueprint framework was launched on May 2016 based on these conclusions, and with the main purpose of accelerating the availability of medicinal products (including vaccines) and diagnostic tests than can effectively address a public health emergency, minimizing its impact and preventing it from becoming a large-scale

epidemic. (WHO Website [28] May 2020) (World Health Organization [40] January 2018) (World Health Organization [41] May 2016)

Under this global strategy and preparedness plan, different approaches have been put in place. The first one, “Improving coordination and fostering an enabling environment”, is engaged on having an effective coordination framework and governance, transparent and consensual processes for funding, and effective communication between stakeholders. (World Health Organization [41] May 2016)

A Global Coordination Mechanism was established in 2017, with the leadership of WHO, to promote faster, better coordinated, collaborative, transparent and more effective responses to global R&D challenges, before and during public health crisis. As an example, through this mechanism, WHO and CEPI signed a memorandum of understanding to join efforts on vaccine’s research for the identified priority diseases. (WHO Website [29] May 2020) (World Health Organization [40] January 2018)

On the second approach, “Accelerating R&D processes”, the broad plan of action involves several steps:

- Assessment of pathogens that pose a great threat to public health and development of a list of priority infectious diseases for priority research and development (diseases caused by pathogens such as Ebola, Zika, SARS or MERS- CoV are currently present in this list). (WHO Website [30] May 2020) (WHO Website [31] May 2020) (World Health Organization [41] May 2016)

- Creation and implementation of R&D roadmaps for each priority disease, and target product profiles, when relevant. (WHO Website [30] May 2020) (World Health Organization [41] May 2016)

- Outline adequate WHO guidance on regulatory and ethical pathways, in collaboration with Regulatory Authorities, and anticipate the data required for an effective regulatory review. (WHO Website [30] May 2020) (World Health Organization [41] May 2016)

All of these help to direct efforts into identified priority pathogens, detect R&D gaps, prioritize investments and expedite the availability of medicinal products and diagnostics, to better manage an outbreak response and/or improve the global response capacity before the next outbreak erupts. (WHO Website [30] May 2020)

The final approach, “Developing norms and standards in the epidemic context”, focuses on the development of innovative trial designs for the identified priority pathogens, prior

to an outbreak or epidemic, and support on the implementation of such trials in a local level. (WHO Website [32] May 2020) In fact, under the R&D Blueprint framework, experts from regulatory affairs, clinical trials and outbreaks management developed a general guidance on possible clinical trial designs, principles and methodologies for assessing vaccines in the context of public health emergencies. (WHO Website [33] May 2020) (World Health Organization [40] January 2018) This approach also promotes sample and data sharing between different stakeholders, in a collaborative way. (WHO Website [32] May 2020)

4. Conclusion

Public health threats can hit communities in devastating ways. When a crisis emerges, the public health system works towards mitigating their impact, reduce the death toll and any associated morbidity. A lot of pressure is put under the regulatory system to develop and/or provide access to medicinal products, vaccines and diagnostic tests as soon as possible, while keeping the standards of quality, safety and efficacy.

The global regulatory system has adapted itself over the years, so that it can be better prepared to address public health needs and manage health crisis. It often does so in the aftermath of severe emerging disease epidemics, as it was the case of the 2014-2016 West African Ebola Outbreak. During this outbreak, much of the regulatory focus and response strategy was placed on speeding up the development and providing earlier access to unproved medicinal products and vaccines. By the end of the outbreak, positive and less positive aspects of the local and worldwide regulatory systems performance were identified and discussed. The culmination was a variety of lessons to be considered, which marked a turning point in both regulatory and global health preparedness for managing health threats.

Part of those lessons were applied 2 years later, in the response to the 2018-2020 Eastern DRC Ebola Outbreak. As opposed to the previous outbreak in West Africa, the regulatory system action was swift, more organized, and better coordinated under WHO's umbrella. Specific roadmaps were set in motion early, to identify knowledge gaps and priority activities within research and development, and coordinate vaccine licensing. rVSV-ZEBOV and investigational medicinal products were quickly introduced in DRC, based on an expanded access protocol and the compassionate use program. Flexible regulatory pathways were used to expedite the assessment and approval of rVSV-ZEBOV, including accelerated assessment and a conditional marketing authorization by EMA, priority review by the US FDA, prequalification by WHO and a single, parallel scientific review for licensing in some African countries. Moreover, rolling submissions were accepted by the US FDA and WHO, and joint assessments (with data sharing) were performed by EMA, WHO and African National Regulatory Authorities, under an innovative collaborative arrangement.

The overall analysis of the response to both Ebola outbreaks showcased the flexibility and response capacity of the main Regulatory Authorities and International Health Organizations. They were able to apply alternative regulatory mechanisms that promote the development, the rapid assessment and availability of medicinal products, vaccines and diagnostic tests. Also important were the synergies created between them, other National Regulatory Authorities, Ethics Committees and international partners, particularly in the context of a catastrophic environment, with very limited resources, poor healthcare system and regulatory capacity.

The current regulatory framework is a direct result of the foundations built in previous health emergency situations and is better prepared to manage them than it was before. There is a global awareness of the need to plan, prioritize, finance and execute research and development programs for priority infectious diseases during inter-epidemic periods, and incorporate them in an epidemic response. A higher focus on re-purposing medicinal products already approved is also being placed, to reduce the time and costs of development. End-to-end platforms centered on global strategy and preparedness, such as the R&D Blueprint or CEPI, are important to accomplish this. Also relevant are the regulatory mechanisms that promote early discussions with Regulatory Authorities (e.g.: scientific advice and fast track designation), and that bridge the gap between the development stages and the regulatory requirements for approval. The current framework also has regulatory tools capable of expediting the access to unapproved medicinal products and vaccines, when necessary. From an approval perspective, several alternative regulatory pathways are available to either accelerate an application review (e.g.: accelerated assessment and priority review) or approve one based on less comprehensive data (e.g.: conditional marketing authorization and animal rule). Additionally, Regulatory Authorities, such as EMA and the US FDA, foresee the possibility of rolling reviews in an emergency context.

All these existing platforms and mechanisms seem positive and adequate to address public health crisis. However, they should be used in an organized and integrated way, to meet their intended purpose and allow for an effective response. Such coordination of research and regulatory efforts, prior to and during a public health emergency, should fall under the leadership of WHO (e.g.: under its R&D Blueprint framework). To do so, WHO should receive proper support, empowerment and resources. Another important improvement for an effective response, is to increase regulatory capacity and harmonization in low and middle-income countries, making their regulatory systems more responsive, robust, adaptable and prepared for public health crisis. Regional networks that promote assisted and joint reviews, such as AVAREF, are critical to achieve this end. Finally, all entities involved should strive for and stimulate innovation (e.g.: alternative clinical trial designs; use of real-world data), transparency, collaborative arrangements and partnerships, data sharing and clearer communication.

Some of these opportunities for improvement within the global regulatory system have been acknowledged by Regulatory Authorities, which embedded them in their long-term strategic plans of action. Examples include the *EMA Regulatory Science to 2025*, the *WHO's Five-year Plan to Help Build Effective and Efficient Regulatory Systems (2019-2023)* or the AVAREF's *New Plan to Accelerate Product development and Access in Africa (2018-2020)*, which also demonstrate the overall commitment for addressing and preparing for emerging public health threats. (European Medicines Agency [7] March 2020) (World Health Organization [35] July 2019) (AVAREF September 2017)

Unfortunately, the story does not end with Ebola. The onset and widespread of infectious diseases of international concern is inevitable in this highly populated and interconnected world. The COVID-19 pandemic is the most recent example of how unpredictable and impactful they can be. It is, therefore, imperative to have a proper global regulatory system in place, capable of both planning and reacting to these health threats. The current system, albeit its flaws, is more adaptative and responsive, and works more closely with other stakeholders to quickly address research and regulatory issues and foster development. Its role in recent public health emergencies showed how flexible and expedite it can be, and also how it can embrace innovative solutions, while keeping the standards of quality, safety and efficacy. This multivalent approach is key to face the current pandemic challenge and prepare for other health threats that might (re-)emerge. It will not stop them from occurring, but it can minimize their impact and protect our global health.

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