



# AGENDA ITEM

# West African Ebola Virus Epidemic 2014

<u>Under Secretary General</u> Nur Mürsel

# STUDY GUIDE Overarching Diplomacy

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## Agenda Item: West African Ebola Virus Epidemic 2014: Creating an Immediate Global Response and Combating The Spread of The Virus

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#### 1. Welcome Letters

#### a. Letter from the Secretary General

Esteemed Participants,

I proudly welcome you all to the third edition of MUNAAL as the Secretary General of the conference. I am Taha Ersoy and I am an 11th-grader at the Ankara Atatürk High School. It is a great honor for me to serve as the Secretary General of such a conference with an amazing organization and academic team. It has been a period of relentless efforts and sleepless nights for our team to finalize the preparations of MUNAAL'25 and make THE conference of the year possible.

The amount of trouble I personally have been through during the preparation phases of MUNAAL is unutterable and I would not be able to overcome the tough challenges we faced if not for our executive team and specifically our Director General, Eylül Koçak. She has been my greatest supporter through my best and worst, yet I can't imagine ever making MUNAAL'25 possible without her. She has been the backbone of the MUNAAL organization and with the joint efforts of our Directory General, Eylül, and her Deputy, Ecem, we managed to arrange a conference of the highest quality. I want to also thank my Deputy-Secretary General, Abrek, for being the best Deputy I could ever wish for.

We have selected a capable academic team and prepared eye-catching committees in order to exceed the conference to its limit. I would like thank our academic team; Dervişan Mehmet Savaş, Nur Mürsel, Ekin Dal, Edanur Altun, Ceylin Musalı, İpeksu Kaya, Ahmet Ozan Yılmaz, Mirata Deva, Atakan Duman, Çınar Mehmet Erduran and our Head of Crisis Görkem Can Coşkun. We have worked relentlessly to give you the best experience possible. Sincerely,

Taha Ersoy Secretary General of MUNAAL'25

#### b. Letter from the Under-Secretary General

Dear Delegates,

My name is Nur Mürsel, and I am more than honored to welcome you all to the committee WHO in MUNAAL'25. It is my 3rd year on this path and I hope you enjoy yours truly.

The committee WHO has a very special place in my heart, as it is the first historical committee I have prepared - As someone burning with desire for medicine for years, being a USG for this committee is a milestone for me and thankfully, it is happening. My Academic Assistant Ekin and I have worked tirelessly to present a wonderful experience to you. I deeply hope that this guide will help you during your preparation for the conference. I strongly believe that all the efforts we have given will be worth it, as we begin the sessions.

I would like to thank our Secretary-General Taha Ersoy, for giving me the opportunity to participate in MUNAAL'25 as an academy member. Furthermore, I would like to thank Ekin Dal, for not only helping me with the study guide, but also for being my partner in crime, deputy, little brother, and for being there whenever I needed him. I cannot thank him enough for what he has done to my life, and without him, this committee would not be possible to make.

We have worked so hard, day and night, to prepare you a guide that will -hopefullyinstruct you through your experience in MUNAAL. Please keep in mind that the committee will be taking place in 2014 and you will be the diplomats managing the newly arising Ebola virus epidemic. I know that there will be many first-timers among you, but please do not hesitate to speak up in the sessions, because this will be your one and only time in MUNAAL 2025. If you have any questions, please do not hesitate to contact me: <u>nur.mrsl.7@gmail.com</u> Best regards,

Nur Mürsel

#### c. Letter from the Academic Assistant

Dear Esteemed Delegates,

As your Academic Assistant in the World Health Organization Committee, it is my distinct pleasure to extend a warm welcome to you all. My name is Ekin Dal and I am a 10th Grader. As your Academic Assistant, I am thrilled to be a part of this esteemed conference gathering of passionate individuals dedicated to addressing the problems in our current time.

I would like to start by thanking my Tzar, President and our Secretary General Taha Ersoy. Since the first day of Dengemun'24, he became one of my best MUN friends. Even though I assassinated him 2 times and tried to throw him from his rank as the President of the United States of America, he is an individual that I can not thank enough. He is one of the key individuals that I owe my Crisis knowledge. I would like to also thank him again for not letting me kill his whole parliament in Tedmun'24. Secondly, I would like to thank Eylul Kocak for this opportunity in this prestigious conference. Thirdly, I would like to thank my Under-Secretary-General, Nur Mursel, my Partner in Crime, Final Boss of Anvumin, Queen of General Assemblies and Press team member in NAMUN'25. She is the one and only individual that I owe my General Assembly knowledge (After Deniz Ozturk of course) and without her, I wouldn't be in this position as your Academic Assistant in MUNAAL'25. Even though I will not be participating actively in the committee as I'm a Crisis Team member at the same time, I would still like to remind every delegate to read this Study guide until the conference day as it contains every knowledge that you must know to become an important figure within the committee.

Please do not hesitate to reach out to me or any member of the secretariat if you have any questions or concerns. My Email is: <u>ekinaviation@gmail.com</u> and it is always open for any emails. We are here to support you every step of the way and ensure that your MUNAAL'25 experience is both rewarding and memorable. Once again, welcome to MUNAAL'25. Best regards,

Ekin Dal

#### 2. Introduction to the Committee

#### a. Scope

Being the authority for global public health, the World Health Organization (also known as WHO) plays a vital role in the UN. WHO unites governments, partners, and people to promote health, keep the world safe, and protect those who are in need, ensuring that everyone, everywhere, has access to the best possible health (1).

To succeed in its role of uniting to promote health, WHO uses a six-point agenda system, covering two health goals, two tactical requirements, and two practical techniques. These involve ensuring development, encouraging health security, expanding healthcare systems, utilizing research, information, and evidence, augmenting collaborations, and enhancing output. Additionally, WHO is dedicated to the notion of responsibility, which is a basic value for an organization trusted by nations and other contributors to safeguard and enhance global health using limited resources effectively (2).

As a result, all of its efforts have made incredible impacts on the structure and frame of the committee. Some of the current roles of WHO are promoting medical and scientific research to enlighten the unknown aspects of diseases and illnesses, providing support and courage for the healthcare workers and researchers all around the world, and leading and uniting people in emergencies like pandemics and epidemics, which will be our main focus throughout the committee (3).

#### b. History

After the 2nd World War, to diminish the catastrophic consequences, diplomats came together in a conference to form an international organization, United Nations, in 1945. In this conference held in San Francisco, one of the key aspects that was considered was to bring all nations together to achieve the best possible quality of health for all. With this idea being the main foundation of WHO, on 7 April 1948, the World Health Organization was officially established as a part of the United Nations. Moreover, 7 April is now annually celebrated as World Health Day (4) (5) (6).

#### 3. Introduction to the Agenda Item

The Ebola virus is deadly, and without treatment, up to 90% of cases are fatal. It triggered the 2014-2016 Ebola disease outbreak in West Africa, the greatest to date, with over 28,600 cases confirmed. It was also linked to an epidemic in the Democratic Republic of the Congo from 2018 to 2020, with a minor number of patients recorded across the border in Uganda. Other big outbreaks of the Ebola virus have resulted in hundreds of cases in the DRC and Gabon. Smaller outbreaks have also been reported in the Democratic Republic of the Congo, Gabon, the Republic of the Congo, and South Africa (7).

Ebola is caused by a group of viruses called as orthoebolaviruses. These viruses can cause significant sickness that, if not treated, can lead to death. Orthoebolaviruses were identified in 1976 in the Democratic Republic of the Congo and are mostly prevalent in Sub-Saharan Africa (8). Ebola virus sickness is a dangerous viral disease that spreads from person to person. Infection is spread by direct or indirect contact with infected people's blood, bodily fluids, or secretions (stool, urine, saliva, semen), but only if they exhibit symptoms. Ebola cannot be transferred by air. The illness typically has a high fatality rate, but with the current Ebola outbreak, the rate is between 55% and 60%.

Ebola made its initial appearance in 1976 in a community along the Ebola River in the Democratic Republic of Congo (formerly Zaire). Since its identification, multiple Ebola outbreaks have occurred in various parts of Africa (9).

#### 4. Key Terms

- Virus: The term virus is a type of pathogen which stands for the small sized genetic information (DNA or RNA) stored inside of a Protective Shell which is located inside an Microscopic Organism. A virus organism is capable of infecting host organisms like humans, plants or animals.
- **Pathogen:** Pathogens can be defined as the Organisms that are capable of causing a disease to its host organism such as human, plant or animal. Pathogens are widely diverse and include viruses and bacteria. At the same time, they can be divided into unicellular and multicellular eukaryotes. During the living periods of all organisms, they are affected by pathogens.

- Eukaryotes: The definition of Eukaryote stands for the group of complex singular or multiple cellular organisms. This includes humans, pathogens or plants, whose genetic information is secreted into a membrane-bound nuclei.
- Fatal: A situation that is able to cause death.
- Vaccine: A harmless preparation of dead or inactivated pathogens that is injected into the body of an individual to induce an immune response.
- Active Immunity: Active immunity is an type of defence mechanism to a specific type of a disease if their body has made its own antibodies and memory cells that protect against the disease. These memory cells can last in the body for many years. A individual can develop active immunity by:
  - Having the specific type of a disease and recovering from it,
  - Being Vaccinated.
- Antigen: It is a type of a chemical which is recognized by the body as being "foreign". Its purpose is to stimulate the production of antibodies of the body.
- Antibodies: An antibody of a protein molecule with a particular shape. This shape is complementary to the shape of another molecule, which is called an antigen. Each pathogen has its own antigens, which have specific shapes. To destroy a particular pathogen, antibody molecules must be made which are a perfect complementary shape to the antigens on the pathogen. In some cases, once the antibody molecules bind with the antigen, this combination directly kills the pathogen, however, the antigens stick the pathogens together. This stops the pathogens dividing or moving, making it easier for phagocytes to destroy them.

- **Transmissible Disease:** A type of a disease which is able to be passed from one host to another; these diseases are caused by pathogens. Transmissible Disease can be divided to two groups:
  - Direct Contact
  - Indirect Transmission
- **Memory Cell:** Memory Cells are the cells that have long-term lives produced by the division of lymphocytes that have contracted their antigen; memory cells are able to respond quickly to subsequent with the same antigen
- Viral Hemorrhagic Fevers (VHFs): These are the group of illnesses caused by pathogens which cause damage to the blood vessels in an individual's body which can result in severe bleeding and lower chance of blood clotting in the damaged blood vessels.
- **Filovirus:** The 'Filovirus' is the name of the pathogen family which Ebola Hemorrhagic Fever belongs to. This specific type of pathogen family is highly dangerous and fatal.
- Endemic Region: An Endemic Region is a particular geographical area where a specific type of disease is spread out. On most occasions, the area would be not allowed for further travel until the pathogenic danger is solved.
- **Biosafety Level 4 (BSL-4):** Biosafety Level was created by Centers for Disease Control and Prevention (CDC). A level 4 Laboratory is highly dangerous and exotic, posing a high risk of aerosol-transmitted infections. Two examples of microbes worked within a BSL-4 laboratory include Ebola and Marburg viruses.

#### 5. Ebola Virus

#### a. Signs and Symptoms

Ebola's signs and symptoms are classified in groups, as early and late symptoms, which is an important stage in diagnosing the virus. Early symptoms can occur in 2 to 21 days following an encounter with the virus. Initially, symptoms are nonspecific and referred to as "dry" symptoms. These include fever, aches and pains in the muscles and joints, intense headaches, weakness and exhaustion, and sore throat.

After 4-5 days of exposition to the virus, patients develop other symptoms, called "wet" symptoms. Wet symptoms for the Ebola virus are loss of appetite, unexplained bleeding, gastrointestinal symptoms like nausea, abdominal pain, diarrhea and vomiting. These are the most common wet symptoms, although there are other symptoms that are minorly developed by some patients, which are chest pain, shortness of breath, red eyes, skin rash, hiccups and seizures (10).

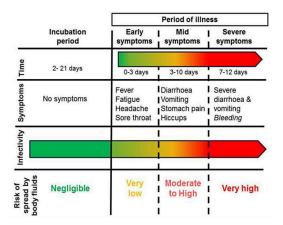


Figure 1.1: An image showcasing early, mid and late symptoms of Ebola Virus throughout the incubation period (11).

Apart from early and late symptoms, there are also long-term complications that patients suffer from throughout the 21 days. The most common ones include tiredness, headache, muscle and joint pain, eye and vision problems (consisting of blurred vision, pain, redness, and sensitivity to light), weight gain, stomach pain or loss of appetite. Memory loss, neck swelling, dry mouth, chest tightness, hair loss, hearing problems, pain or tingling in the hands and feet, inflammation of the tissues around the heart, inflammation of one or both testicles, changes in menstruation, impotence, decreased or lost interest in sex, difficulty falling or staying asleep, depression, anxiety, and post-traumatic stress disorders, are all possible health issues.

#### b. Diagnosis

Ebola symptoms appear after a varied duration of incubation period in which the infection multiplies. These symptoms can vary greatly from case to case, which has led to debate about whether the condition should be referred to as hemorrhagic fever. Feldmann found that by the time the virus is easily detected, the patient is usually on the edge of dying or recovering. "Often, particularly with less sensitive tests, you do not see a very strong or any immune response in people that surrender to infection very suddenly and early during disease progression." Thus, pathogen detection tests, rather than those that target the host immune response, are critical for diagnosing Ebola in outbreak conditions.

The number of readily accessible Ebola diagnostic tests has increased drastically during the epidemic and continues to grow, according to Feldmann; however, the majority of field laboratories continue to use their own assays, many of which lack positive controls due to the

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need for biosafety containment. "I think we have to do much, much more... to make sure that the laboratories... that are doing diagnostics in certain countries actually evaluate their tests," Feldmann says, better yet, to meet the World Health Organization's (WHO) demand for rapid, sensitive, safe, and simple Ebola diagnostics. Although it is thought that scientific research is on the way to achieving that, certain challenges remain (13).

However, because of very similar signs and symptoms, healthcare staff can often misinterpret signs and symptoms, by confusing other more common diseases such as malaria, influenza (flu), typhoid fever, meningococcal disease and other bacterial illnesses, including pneumonia (14). Furthermore, many pregnancy and Ebola symptoms are almost the same, making it even harder to diagnose Ebola. If Ebola is suspected, pregnant women should be examined as quickly as possible because of the risks to both the pregnancy and themselves. Ebola virus infection is confirmed by diagnostic procedures such as ELISA, antigen-capture detection, serum neutralization, RT-PCR, electron microscopy, and viral isolation by cell culture (15).

#### c. Transmission

Ebola virus disease is an uncommon but serious sickness in humans. It is usually lethal. According to the World Health Organization, people become infected with Ebola by getting in touch with contaminated animals while preparing, cooking, or eating them, contacting an infected person's body fluids such as saliva, urine, feces, or semen, or touching anything containing an infected person's body fluids such as clothes or sheets. Ebola enters the body through incisions in the skin or by contacting the eyes, nose, or mouth.

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Fruit bats from the Pteropodidae family are suspected to be natural hosts of the Ebola virus, which may be the zoonotic source for Ebola. The virus is transmitted to humans by direct contact with blood, secretions, organs, or other body fluids of infected animals such as fruit bats, chimps, gorillas, monkeys, forest antelopes or porcupines discovered ill or dead in the jungle.

Additionally, healthcare personnel have regularly become infected while treating Ebola patients. Close contact with patients happens when infection control protocols are not carefully followed, which poses great risk in the transmission of the Ebola virus disease. Burial procedures that entail intimate touch with the deceased's body can potentially help spread Ebola. People stay contagious for as long as the virus is present in their blood. Following recovery, there remains a risk of sexual transmission - as 21 days of incubation period is only an approximation - which can be decreased with care and information for survivors. Pregnant women who have acute Ebola but have recovered may still contain the virus in their breast milk or other pregnancy-related fluids and tissues (16).

#### d. Case Fatality Rate

Ebola disease (EBOD) is a viral infection with a high case fatality rate (CFR) of 25% to 90%. Overall statistics on the CFR of EBOD are required to offer an overview of the epidemic's worldwide situation, however the available data are not without limits. The most comprehensive estimate of the EBOD CFR came from a meta-analysis of 20 EBOD outbreaks between 1976 and 2014, which found a CFR of 65.4% for three strains of ebola virus: Zaire, Bundibugyo, and Sudan. The most current meta-analysis of EBOD data between 2010 and 2020 included 32,300 EBOD cases and 13,727 fatalities, yielding a pooled CFR of 60%. Nevertheless, drawbacks of prior meta-analyses included the removal of EBOD data for certain years. Indeed, the

meta-analysis done by Lefebvre et al. in 2014 did not include EBOD data after 2014, whilst Kawuki et al. in 2021 omitted EBOD data before 2010 and after 2021. As a result, there were no current CFR for all EBOD outbreaks and ebolavirus strains between 1976 and 2022, including the most recent EBOD outbreaks. Furthermore, it was uncertain if overall trends in EBOD case fatality rates are increasing or decreasing in an era of greater supportive treatment. However, a later study published in November 2023 presented a comprehensive summary for all the CFR of all outbreaks of the EBOD globally, between 1976-2022.

Jonathan Izudi and his team collected data from 16 nations across the world for their investigation. Between 1976 and 2022, there were 42 EBOD outbreaks, 35 of which (83.3%) occurred in SSA. In SSA, the DRC had 15 (35.7%) EBOD outbreaks, followed by Uganda with five (11.9%). Liberia, Sierra Leone, Ivory Coast, Senegal, and the Republic of South Africa had the fewest outbreaks, with one apiece. Outside of the SSA region, Russia and the United Kingdom each reported two EBOD outbreaks, while the United States and Spain each reported one epidemic. The results of the investigation are shown in the tables below (17).

Country	Deaths	Cases	Case Fatality Rate	%	95% CI
Species = Bundibugyo virus			1		
Uganda 2007	42	131		32.1	[24.2; 40.8]
Democratic Republic of Congo 2012		36			[20.8; 53.8]
Random effects model	10	00	-		[25.8; 40.2]
Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.63$				02.0	[20.0, 40.2]
interogeneigen					
Species = Sudan virus					
South Sudan 1976	151	284		53.2	[47.2; 59.1]
South Sudan 1979	22	34		64.7	[46.5; 80.3]
Uganda 2000	224	425		52.7	[47.8; 57.5]
South Sudan 2004	7	17		41.2	[18.4; 67.1]
Uganda 2011	1	1		0.00	[ 2.5; 100.0]
Uganda 2012	7	17		41.2	[18.4; 67.1]
Uganda 2022	55	164		33.5	[26.4; 41.3]
Random effects model			-	48.5	[38.6; 58.4]
Heterogeneity: $I^2$ = 76%, $\tau^2$ = 0.0076, $\rho$	< 0.01				
Canalan a Tai Farrat Juna					
Species = Tai Forest virus	0			0.0	100.0751
Ivory Coast 1994	0	1 •		0.0	[0.0; 97.5]
Species = Zaire virus					
Democratic Republic of Congo 1976	280	318		88.1	[84.0; 91.4]
United Kingdom 1976	0	1 .		0.0	[ 0.0; 97.5]
Democratic Republic of Congo 1977		1			[2.5; 100.0]
Gabon 1994	31	51			[46.1; 74.2]
Democratic Republic of Congo 1995	254	315			[75.8; 84.9]
Republic of South Africa 1996	1	2	•	50.0	[ 1.3; 98.7]
Gabon 1996	66	91	<b>_</b>	72.5	[62.2; 81.4]
Russia 1996	1	1		0.00	[ 2.5; 100.0]
Democratic Republic of Congo 2001	44	59		74.6	[61.6; 85.0]
Gabon 2001	53	65	<b>-</b>	81.5	[70.0; 90.1]
Democratic Republic of Congo 2003	157	178		88.2	[82.5; 92.5]
Russia 2004	1	1		0.00	[ 2.5; 100.0]
Democratic Republic of Congo 2005	10	12		83.3	[51.6; 97.9]
Democratic Republic of Congo 2007	187	264		70.8	[64.9; 76.2]
Democratic Republic of Congo 2008	15	32		46.9	[29.1; 65.3]
Democratic Republic of Congo 2014	49	69		71.0	[58.8; 81.3]
Italy 2014	0	1 •		0.0	[ 0.0; 97.5]
Senegal 2014	0	1 •		0.0	[0.0; 97.5]
Spain 2014	0	1 •		0.0	[0.0; 97.5]
United Kingdom 2014	0	1 .		0.0	[0.0; 97.5]
United States of America 2014	1	4		25.0	[0.6; 80.6]
Guinea 2014	2544	3814	•		[65.2; 68.2]
Liberia 2014	4810	10678			[44.1; 46.0]
Sierra Leone 2014	3956	14124	0		[27.3; 28.8]
Mali 2014	6	8			[34.9; 96.8]
Nigeria 2014	8	20			[19.1; 63.9]
Democratic Republic of Congo 2017		8			[15.7; 84.3]
Democratic Republic of Congo 2018		3524	_		[64.2; 67.4]
Democratic Republic of Congo 2020		130			[33.7; 51.3]
Guinea 2021	12	23			[30.6; 73.2]
Democratic Republic of Congo 2021 Democratic Republic of Congo 2022		23 6			[42.7; 83.6]
Random effects model	0	0			[54.1; 100.0] [55.9; 76.8]
Heterogeneity: $l^2 = 99\%$ , $\tau^2 = 0.0417$ , p	= 0			50.0	[99.9, 70.0]
Random effects model			<u> </u>	60 E	[51.6; 69.4]
Prediction interval				50.0	[12.9; 99.1]
Heterogeneity: $l^2 = 99\%$ , $\tau^2 = 0.0397$ , $p$	= 0	a			[12.5, 55.1]
Test for subgroup differences: $\chi_3^2 = 28.22$		< 0.01)	0 20 40 60 80 100		
		0.017			

Figure 1.2: An image portraying the case fatality rates (CFRs) of the Ebola virus in specific

regions throughout history (17).

Country	Deaths	Cases	Case Fatality I	Rate	%	95	5% Cl
Continent = Rest of the world			1				
United Kingdom 1976	0	1 .			0.0	[ 0.0;	97.5
Russia 1996	1	1			100.0	[ 2.5; 1	
Russia 2004	1	1			100.0	[ 2.5; 1	
Italy 2014	0	1 .			0.0	[ 0.0;	
Spain 2014	0	1 .			0.0	[ 0.0;	
United Kingdom 2014	0	1 .			0.0	[ 0.0;	1999 (19 <sup>8</sup>
United States of America 2014	1	4			25.0	[ 0.6;	S
Random effects model		7		<u></u> 1		[ 0.0;	
Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ , $\rho = 0.54$				_	24.5	[ 0.0,	07.9]
Heterogeneity: $I = 0\%$ , $\tau = 0$ , $p = 0.54$							
Continent = Sub-Saharan Africa							
South Sudan 1976	151	284			53.2	[47.2;	59.1]
Democratic Republic of Congo 1976	280	318		-	88.1	[84.0;	91.4]
Democratic Republic of Congo 1977	1	1		•	100.0	[ 2.5; 1	00.0]
South Sudan 1979	22	34			64.7	[46.5;	80.3]
Ivory Coast 1994	0	1 .	•		0.0	[ 0.0;	97.5]
Gabon 1994	31	51			60.8	[46.1;	74.2]
Democratic Republic of Congo 1995	254	315			80.6	[75.8;	84.9]
Republic of South Africa 1996	1	2			50.0	[ 1.3;	98.7]
Gabon 1996	66	91	-		72.5	[62.2;	81.4]
Uganda 2000	224	425			52.7	[47.8;	57.5]
Democratic Republic of Congo 2001	44	59	-		74.6	[61.6;	85.0]
Gabon 2001	53	65			81.5	[70.0;	90.1]
Democratic Republic of Congo 2003	157	178			88.2	[82.5;	92.5]
South Sudan 2004	7	17		_33	41.2	[18.4;	67.1]
Democratic Republic of Congo 2005	10	12			83.3	[51.6;	97.9]
Uganda 2007	42	131			32.1	[24.2;	40.8]
Democratic Republic of Congo 2007	187	264			70.8	[64.9;	76.2]
Democratic Republic of Congo 2008	15	32		_	46.9	[29.1;	65.3]
Uganda 2011	1	1		· · ·	100.0	[ 2.5; 1	00.0]
Uganda 2012	7	17		-01	41.2	[18.4;	67.1]
Democratic Republic of Congo 2012	13	36	<b>-</b>		36.1	[20.8;	53.8]
Democratic Republic of Congo 2014	49	69	+		71.0	[58.8;	81.3]
Senegal 2014	0	1 .	•		0.0	[ 0.0;	97.5]
Guinea 2014	2544	3814		•	66.7	[65.2;	68.2]
Liberia 2014	4810	10678	D		45.0	[44.1;	46.0]
Sierra Leone 2014	3956	14124	D		28.0	[27.3;	28.8]
Mali 2014	6	8		•	75.0	[34.9;	96.8]
Nigeria 2014	8	20			40.0	[19.1;	63.9]
Democratic Republic of Congo 2017	4	8			50.0	[15.7;	84.3]
Democratic Republic of Congo 2018	2320	3524		•	65.8	[64.2;	67.4]
Democratic Republic of Congo 2020	55	130	_ <b>_</b>		42.3	[33.7;	51.3]
Guinea 2021	12	23			52.2	[30.6;	73.2]
Democratic Republic of Congo 2021	15	23			65.2	[42.7;	83.6]
Uganda 2022	55	164			33.5	[26.4;	41.3]
Democratic Republic of Congo 2022	6	6		•	100.0	[54.1; 1	00.0]
Random effects model					61.3	[52.8;	69.6]
Heterogeneity: $l^2 = 99\%$ , $\tau^2 = 0.0397$ , $p =$	= 0						
Random effects model					60.6	[51.6;	69.4]
Prediction interval						[12.9;	99.1]
Heterogeneity: $I^2 = 99\%$ , $\tau^2 = 0.0397$ , $p = 0.0397$		1000000000000					
Test for subgroup differences: $\chi_1^2$ = 3.31,	df = 1 (p =	= 0.07) (	0 20 40 60	80 100	)		

Figure 1.3: Figure 1.2: An image portraying the case fatality rates (CFRs) of the Ebola virus in specific regions throughout history (17).

#### e. Prevention and Control

People at high risk of contracting Ebola can get the Ervebo vaccination. This includes persons who work in laboratories with ebola viruses as well as healthcare personnel who treat Ebola patients. Public health agencies seek to control Ebola outbreaks by monitoring for new cases and taking safeguards to keep healthcare workers safe while caring for patients with the disease. When caring for someone with Ebola, protective equipment (a mask, goggles, apron, and gloves) should be worn. Even if the person is wearing gloves, contact with any of their bodily fluids should be avoided and hands should be washed afterward. Condoms should be used or any intercourse should be avoided until tests show that the ebola virus is not present in both parties in sex.

Even if the patient senses no adverse symptoms and signs, infection might remain in semen for a long period. There is little indication that it remains infectious in vaginal secretions for as long. Touching anything that may have come into contact with infectious bodily fluids should be avoided. Sperm should not be contacted unless testing shows that it no longer contains the virus. Handling the corpse of someone who died with Ebola must be avoided, and protective equipment should be worn if necessary. This contains funeral traditions. Any contact with the bodily fluids and tissues of animals (dead of living) that may contain Ebola should be avoided. Consuming bush meat should be avoided. If the patient has just returned from visiting an area where there is an Ebola outbreak, the symptoms must be observed over the next 21 days (18).

#### 6. Historical Context

#### a. Discovery & First Cases

On 22nd of August 1976, the 42-year-old headmaster of the Yambuku Mission School returned from a 2-week driving excursion to northern Zaire. Along the route, he purchased antelope and smoked monkey meat. In the day of 26th of August 1976, he presented himself to the outpatient clinic of the 120-bed Yambuku Mission Hospital (YMH) with chills and fever and was as his symptoms were matching with Malaria, he was assigned to Malaria treatment with Chloroquine injections of 2 sets and an antipyretic by the Chief Medical Assistant at Yambuku Mission Hospital. On the very first day after the treatments were completed, the patient stated to the Hospital that he was no longer suffering from fever and chills. However, after 1 week, he returned back to the hospital with severe headache, muscle pain, nausea, abdominal complaints, and intestinal bleeding. Sadly, he died on September 6 with a hemorrhagic syndrome of unknown cause. On the day of 28th of August 1976, an adult male was sent to Yambuku Mission Hospital (YMH) due to epistaxis, dysentery, and fever. This patient remained at the hospital for only 2 days and left without a follow-up and at the same time, due to his specific residence location being unknown, no medical personnel was able to reach the patient.

Several patients coming to Yambuku Mission Hospital (YMH) with a variety of conditions including pregnancy were given vitamins and other medicines by the usage of injectors for faster results and being a route favored by patients and medical personnel in the hospital. As every outpatient department, inpatient medicine wards, and prenatal and village outreach clinics had five glass syringes and metal needles, they had to be used repeatedly to cover the patient numbers. However, the needles and syringes were mostly being used repeatedly without sterilization and only occasionally were rinsed. In early September, 1976, several dozen patients who had received injections at Yambuku Mission Hospital (YMH) developed a similar febrile hemorrhagic syndrome and died in about 1 week. At the same time, most of the patients' contacts have died as well due to face-to-face contacts (19).

#### b. Initial Responses

#### i. National Response

As the mysterious disease of yambuku was spreading every single day, the first national response came from the chief medical officer of the Bumba zone, Ngoy Mushola, who arrived and stayed at Yambuku state between 15 to 19 September 1976. After his stay in the State of Yambuku, he established a report to Kinshasa which was the first report to describe the term "Mystery Disease of Yambuku" manifesting fever, headache, abdominal pain, and intestinal bleeding. At the same time, from 5th of September to 22 of September, Ngoy reported 30 cases of this Mysterious Disease and 22 deaths caused by it. In Ngoya's report, it was also stated that patients were fleeing the Yambuku Mission Hospital (YMH) to not be infected with the disease. However, later studies made by the Ministry of Health proved that more than 120 cases had occurred during Ngoya's stay. It was also proved that over half of the cases were caused by injections made by unsterilized injections.

When the dates showed 23rd of September 1976, a national scientific research team led by Jean-Jacques Murembe-Tamfun, a microbiologist, and Colonel Omombo, and epidemiologist was assigned to Yambuku by Nguete Kinkhela who was the times Minister of Health. On the day of 24th of September, 3 deceased nurses were used to collect postmortem liver tissue and blood

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specimens for typhoid diagnosis. At the same time, a 40-year-old Belgian midwife nun who had been delivering newborns from a sick woman was taken to the hospital by her parents after having heavy fever and headaches. Once arrived at the hospital, she reported that she was vaccinated against typhoid and yellow fever in the past. However, she and several other patients with the same symptoms were treated with an antimicrobial and other types of drugs which are many given by injection technique. On the day of 24th of September, the National Scientific Research Team returned to Kinshasa with the sick nun, her sister and a priest that was working at the same church as them; they were transported by a private medical jet from Bumba to Kinshasa via Kisangani. Once they landed at the city of Kinshasa, they were taken to the University of Kinshasa by the use of 3 private Ambulances escorted by 2 Police vehicles.

#### ii. International Response

Caused by the increasing alarm of the unknown disease, Jean Francois Ruppol, Chief of the Belgian Fonds Medical Tropical (FOMETRO), Gerard Raffier, chief of the French Medical Mission; and Dr. Krubwa of the National University of Zaire visited Bumba and Yambuku by the use of Military Helicopters from the 4th of October to 9th of October. Once they arrived at Kinshasa, blood samples were taken from 2 separate individuals who were believed to have recovered from the unknown disease. The research team suggested the Commissaire du Zone, Ipoya Olonga, that Bumba Zone which includes 250,000 Individuals to be put under strict quarantine and Yambuku Mission Hospital (YMH) to be closed for operation until further order. The suggestion was accepted by the Ministry of Interior and Ministry of Health which ceased commercial airplane landings, movement in and out of villages, and prohibition of riverboats from entering nearby water sources of the villages located within the quarantine zone. During the

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quarantine and research, 13 out of 17 Yambuku Mission Hospital (YMH) personnel became ill with the disease while 11 of them died afterwards (19).

#### c. Virus Isolation and Identification

On 28th of September 1976, new set up blood specimens were taken from the sick nun from Yambuku before her death by Jacques Courteille, a Belgian physician working at Ngaliema Hospital in the city of Kinshasa. Before her death, Jacques stated that she had a 5 day lasting febrile, hemorrhagic illness which was possibly yellow fever. After the blood specimens were taken from the patient, they were sent to the Institute of Tropical Medicine located in Antwerp, Belgium in a broken vial by the usage of a Commercial Passenger flight. A specimen of a postmortem liver was taken from the same patient and sent to the Institute of Tropical Medicine the day after the blood specimens arrived at the city of Antwerp, Belgium. These specimens were inoculated into Vero cells and analyzed by Guido van der Groen, Rene Delgadillo, and Peter Piot in the microbiology department directed by Stefaan Pattyn; a cytopathic effect was observed from all of these specimens that were gathered from the patient.

After a research conducted by electron microscopist Wim Jacop who was working in the World Health Organization (WHO), it was seen that the virus was in a Marburg-like virus shape. After this research, the ITM team was told by Paul Bres of the World Health Organization to send all the specimens immediately to the Microbiological Research Establishment (MRE) which arrived there on 5th of October. At the same time, some of the materials in the specimens were sent to the Centers for Disease Control and Prevention (CDC) located in the city of Atlanta, USA which arrived on 11th of october and 13th of October due to being sent by 2 different commercial planes. It should be noted that both of these materials were sent to laboratories with maximum containment for highly pathogenic viruses. At the same time, both of these laboratories were licensed with Biosafety Level-4 (BSL-4). At the Microbiological Research Establishment, Ernest Bowen, Graham Lloyd, William Harris, Geoff Platt, Arthur Baskerville, and Ethelwald Vella carried out a series of analyses. During this time period, in the city of Kinshasa, Gerard Raffier continued on sending out blood samples to Pierre Sureau at the Institut Pasteur located in the city of Paris, France. However, after receiving the specimens, the Institut Pasteur was not equipped with the needed containment units for the virus. As a result, Sureau was urged by Bres to ship out all specimens to Centers for Disease Control and Prevention as soon as possible to reduce the spreading risk of the virus. Inoculation into animals and cell lines occurred in all 3 laboratories, and virus was grown. At the same time, Filovirus particles, resembling Marburg Virus, were also seen by negative contrast electron microscopy (EM) of Vero Cell culture supernatant of blood and by thin-section electron microscopy (EM).

Laboratory, Test/Culture Systems	Criterion for Positive Test Result	Time, d	Electron Microscopy or IF Tes Result for Filovirus (Date)
Institute of Tropical Medicine, Antwerp, Belgium			
Newborn mice	Dead	4–5	ND
Weaning mice	Dead	7	ND
Vero cells	CPE complete	11	Positive (11 October)
Porton Down, United Kingdom			
Newborn mice	Dead	5–9	ND
Guinea pigs (blood and liver)	Fever, dead	4-7, 12	Positive (5–13 October)
Vero cells	CPE partial	6–7	Positive (5-13 October)
CDC, Atlanta, GA			
Vero cells	CPE partial	3, 6–7	Positive (13 October)
Patient liver	Virus seen		Positive (13 October)
Immunofluorescence antibody testing	1:160 titer	1	Positive (14 October)

Figure 1.4: Testings for the Ebola Virus.

During this experiment, by the usage of the remaining drops of convalescent serum squeezed from a black cotton mass in a broken test tube received from Sureau, a new etiologic agent was identified in the Special Pathogens Branch, CDC, by Patricia Webb, James Lange, and Karl Johnson. It was shown by Patricia Webb that serum from 1 convalescent DRC patient did not cross-react with an archived Marburg virus in a 2-way immunofluorescence antibody (IFA) test; sera from the convalescent DRC patient and from Marburg patients were tested against viruses from a DRC patient and a Marburg virus, and a positive reaction occurred only between DRC sera and DRC virus and between Marburg sera and archived Marburg viruses, At the same time period, the iconic electron microscopy (EM) pictures of the new virus were taken by Alyne Harrison and Fred Murphy at the CDC. These pictures were taken by performing on thin-section EM examinations of fixed liver specimens from DRC patients.

However, after a series of inspections made by many Biosafety Organizations, it was seen that the biosafety precautions taken in Antwerp and Paris were those taken on an open bench, without a hood or laminar flow system. At the same time, it was seen that laboratory coats, gloves, absorbent covering on the bench, and hypochlorite solution for disinfection were being used. However, the main concern in Antwerp was avoiding contamination of cell cultures. On the other hand, in Paris, upon opening a subject container which arrived freshly from Kinshasa, due to personnel mistake, 1 test tube was reported as broken. To contaminate the subjects in the test tube, the contents were transferred to another vacutainer. After this mistake, the World Health Organization (WHO) ordered the Paris research team to send the Materials to CDC for further search. After this order, the materials were firstly packaged and sent to CDC for further research and complete isolation of the virus specimen (19).

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#### d. Vaccine Development

#### i. rVSV-ZEBOV

The rVSV-ZEBOV Vaccination is currently one of the two vaccinations which are licensed for usage. This specific type of vaccine is developed by the usage of a genetically engineered version of vesicular stomatitis virus also known as "VSV". The vesicular stomatitis virus is a type of animal virus that primarily affects cattle, to carry an Ebola Virus gene insert. These operations in developing this specific type of vaccine were made by the Public Health Agency of Canada and now licensed to MERCK. At the same time, during the first research for response to the Ebola outbreak in West Africa, various organizations including the U.S. Centers for Disease Control and Prevention (CDC) also assisted and conducted a series of additional studies for the production of rVSV-ZEBOV. This specific type of vaccination was and still being used to vaccinate contacts of individuals with ebola and their contacts by the help of World Health Organization (WHO) (20).

#### ii. cAd3-EBO

The National Institute of Allergy and Infectious Diseases and OKAIROS have conducted series of researches to create a candidate for the Ebola Virus, unlike the rVSV-ZEBOV Vaccines', cAd3-EBO Vaccine is produced by the usage of the Chimpanzee Adenovirus (cAd3) to deliver the needed Ebola Genetic Material. The collected Ebola genetic Material is turned into a protein designed to warn the human body to make an immune response by the usage of previously produced antibodies by lymphocytes. Secondly, unlike the vaccination produced by the Canadians, there are 2 Phases of this vaccination and at the end of all research, it was proven that the 2nd Phase of this specific type of vaccination was much more effective than Phase 1. Lastly,

it can be noted that this vaccination is still being improved by various Medical Research Companies (20).

#### iii. Ad26.ZEBOV and MVA-BN Filo

After the completion of the first phase of cAd3-EBO vaccination, The National Institute of Allergy and Infectious Diseases and other funding partners conducted a series of new experiments on creating a much more effective vaccination from any previous vaccinations that are in the market currently. These types of vaccinations were focused on protecting the individuals from the virus responsible for the 2014-2016 Ebola outbreak in West Africa and the ongoing outbreak in the DRC. When an individual is assigned to this vaccination set, he/she first gets the As26.ZEBOV vaccination for its vectors and a modified vaccinia virus known as Ankara (MVA) (20).

#### 7. Consequences

#### a. Economic Consequences

Till our current day, Ebola Virus Disease (EVD) is still a major public health threat in a global zone. This risk is higher in low-and-middle-income countries, mostly including African countries. As a result of this threat, there is a massive economic effect to keep public health safe. After the research conducted by many Governmental and Non-Governmental Organizations (NGOs), it can be seen that the economic evaluations are focused on the burden of illness, vaccine cost-effectiveness, willingness-to-pay for a vaccine shot, EVD Funding, and lastly, preparedness costs. Due to these costs, it is estimated that the economic impact of the 2014 EVD outbreak in Guinea, Liberia, and Sierra Leone ranged from 30 Billion United States Dollars

(USD) to 50 Billion United States Dollars. At the same time, facility construction and modification costs to block the virus from spreading has a very significant place in this economical effect. The EVD vaccine demonstrated cost-effectiveness in a dynamic transmission mode; resulting in an incremental cost-effectiveness ratio about 96 United States Dollars (USD) per additional disability adjusted life year averted. At the end of the day, it was seen that a minority group was able to pay about 1 United States Dollar (USD) per vaccination (21).

#### b. Social Consequences

As a result of the 2014 Ebola Virus Crisis, human development progress was reversed. This is caused by the issues that were formed in the Health, Education, Transport and Political industries that were majorly disturbed in the Ebola Virus Crisis. As a result of these issues, the standard of living for individuals that are living in the affected regions have negatively changed affecting their daily lives. At the same time, quarantines have had a disproportionate impact on the elderly, the poor, and people with chronic illness or disability. Individuals who were affected by the Ebola Virus Crisis also faced stigmatization. Due to a series of policies like "do not touch", social cohesion was heavily affected. On the other hand, as children from the affected regions were not allowed to go to school, cases of loss of education and risk of drop-out, teen pregnancy and child labour has increased since the Ebola Virus Crisis. As the Health system collapsed in the regions as well, many individuals had to lose their relatives to the virus due to insufficient medical personnel, funding and medicine (22).

#### c. Medical Consequences

One of the most significant and obvious medical consequences of the Ebola epidemic is the amount of deaths experienced by nations. Ebola has claimed the lives of approximately 15,266 individuals worldwide since 1976, which is a very dramatic number, in terms of human life (23). Ebola virus disease has heavy consequences, as the transmission possibility of the disease and the case fatality risk per patient is both too high, making the diseases spread faster and kill more people in less time. As a result, the virus becomes very deadly, in terms of medicine. Figure 1.5 represents the amount of cases seen in specific regions of Africa.

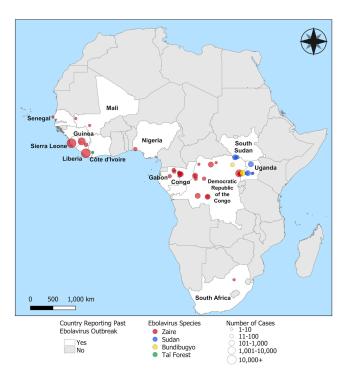


Figure 1.5: An image showing the number of cases of EBOD in Africa.

The Ebola Virus Disease (EVD) caused many deaths, as well as impacting the lives of survivors and others who have witnessed a death of a loved one, resulting in temporary or permanent damages in the mental health of the individuals. According to a study, 45.7% of EVD

survivors reported experiencing post-traumatic stress disorder (PTSD). Furthermore, 3.9% and 12.0% of EVD survivors reported major depression (MD) and drug use, respectively; all mental health outcomes above regional baseline estimates (PTSD: 6%-16%, MD: 1.1%, substance use: 2.2%). PTSD among EVD survivors was linked with acute EVD duration of  $\geq$ 21 days, age 35-44, and residence mobility. Additionally, the post-ebola-symptoms can have an effect on individuals' physical health as well. Major post-EVD symptoms are typical early in the recovery process and gradually fade as the severity of the disease decreases. However, even 5 years after an acute infection, the majority of people continue to have symptoms, which have a significant influence on their life. These findings highlight the need for more research into the processes behind post-EVD complications, as well as therapeutic strategies to aid the thousands of affected EVD survivors (24).

Another key aspect of these consequences that should be taken into consideration is that epidemics require immediate response by the national health systems and international organizations like the World Health Organizations. All of these efforts made by these institutions deters the overall health systems, by putting intense pressure on all healthcare workers and overwhelming them. However, this can also be thought of as an advantage, as the epidemic showcasted the gaps and weaknesses in the health systems that could be further developed in the future in order to not prevent but minimize the effect caused by epidemics and pandemics.

#### 8. Conclusion

As a result of a tenuous security dropout, new EVD vases continue to occur in the regions of North Kivu and Ituri provinces. While the confirmation of cases in a populous city like Goma is a notable achievement, countless efforts were made to achieve this goal and it was expected to be completed. At the same time, while the vaccination efforts are continuing and increasing every single day, it must be noted that the Ebola Virus is still evolving to survive against the vaccinations. To reduce the risk of another Crisis, more than 4000 medical personnel have been vaccinated for Ebola Virus and sent out assigned around the issued regions with high Ebola Cases. At the same time, many precautions have been taken since the first Ebola Virus outbreak including a series of technological advancements to many Medical Health Centers like Hospitals, Clinics and Field Hospitals. However, as stated before, this does not prove the claim that the Virus thread is fully resolved. The continuous transmission in major hotspots and involvement of new health areas remain a grave concern, and thus necessitates both the continuation of proven and the introduction of novel outbreak control inventions in all affected areas. It is imperative that resources, especially funding, be made available in order to maintain and potentially escalate the ongoing response operations over the wide geographical expanse of this EVD outbreak.

#### 9. Questions to be Considered

- What are the main reasons for the second Ebola Outbreak in the year of 2014?
- How did the disease spread to different regions in a short time period?
- What were the primary barriers and challenges faced by WHO and other Governmental and Non-Governmental Organization in controlling the Virus outbreak?
- What are the Economical and Political Effects of the Ebola Virus Outbreak?
- How did the insufficient and lowly-maintained Healthcare systems in the Affected Regions affected the Virus Crisis?
- What were the previous actions taken by Governmental and Non-Governmental Organizations?
- What were the previous Actions taken by the World Health Organization (WHO) to control this epidemic?
- What measurements can be taken to improve the Healthcare systems in the affected vulnerable regions to prevent future Ebola Virus Outbreaks?
- What actions can be taken by Governments to improve their disease control and warning systems?
- How can the medical personnel be trained to fight with the Ebola Virus?
- How can the funding for the decided projects be covered?
- How can WHO and its member states collaborate and develop a global system to reduce the chances of a third Ebola Virus outbreak?
- What role do the Governmental and Non-Governmental Organizations play in reducing the effects of the Ebola outbreak?

• How can international corporations be improved to ensure a fast response to a global health crisis in the future?

### **10. Further Reading**

- <u>https://cdn.who.int/media/docs/default-source/documents/communication-framework.pdf</u>
   <u>?sfvrsn=93aa6138\_0</u>
- <u>https://www.who.int/publications/i/item/9789240001381</u>
- <u>https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&cad=rja&uact=</u> <u>8&ved=2ahUKEwiIu8Dnn4KLAxVDAtsEHaS-J3YQFnoECBEQAQ&url=https%3A%2</u> <u>F%2Fwww.who.int%2Fnews-room%2Fquestions-and-answers%2Fitem%2Febola-vaccin</u> <u>es&usg=AOvVaw2Mv2\_grWGrlk7OCvWzalwG&opi=89978449</u>
- https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&cad=rja&uact= 8&ved=2ahUKEwiS4JP2n4KLAxWAnf0HHSOVJksQFnoECBgQAQ&url=https%3A%
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   <u>ldbank.org%2Fen%2Ftopic%2Fmacroeconomics%2Fpublication%2F2014-2015-west-afr</u> ica-ebola-crisis-impact-update&usg=AOvVaw1cAPYCDUzHzCnOch09YKRd&opi=899 78449
- <u>https://www.google.com/url?sa=t&source=web&cd=&cad=rja&uact=8&ved=2ahUKEwi</u>
   <u>744CKoIKLAxXuUMMIHVe8JfsQFnoECBUQAQ&url=https%3A%2F%2Fwww.cdc.g</u>

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- https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&cad=rja&uact= 8&ved=2ahUKEwi744CKoIKLAxXuUMMIHVe8JfsQFnoECBQQAQ&url=https%3A% 2F%2Fwww.gov.uk%2Fgovernment%2Fpublications%2Febola-origins-reservoirs-transm ission-and-guidelines%2Febola-overview-history-origins-and-transmission&usg=AOvVa w21aCAkzmKFYSih031mWlyJ&opi=89978449
- <u>https://onlinelibrary.wiley.com/doi/pdf/10.1111/tmi.13226#:~:text=Various%20forms%20</u>
   <u>of%20psychological%20distress%20were%20prevalent%20among%20EVD%20survivor</u>
   s,suicidal%20tendencies%20and%20self%2D%20stigmatisation.
- <u>https://pmc.ncbi.nlm.nih.gov/articles/PMC11116873/</u>
- <u>https://www.who.int/health-topics/ebola#tab=tab\_1</u>
- <u>https://www.who.int/emergencies/disease-outbreak-news</u>
- <u>https://www.ncbi.nlm.nih.gov/books/NBK544149/figure/ch5.fig4/</u>
- <u>https://www.gov.uk/government/publications/ebola-origins-reservoirs-transmission-and-g</u> uidelines/ebola-overview-history-origins-and-transmission
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- <u>https://www.sciencedirect.com/topics/computer-science/ebola-outbreak</u>
- <u>https://www.bcm.edu/departments/molecular-virology-and-microbiology/emerging-infect</u> <u>ions-and-biodefense/specific-agents/ebola-virus</u>
- <u>https://www.redcross.org/about-us/our-work/international-services/ebola.html?srsltid=Af</u> <u>mBOorsMvXpy-rkY6eUUdcGEaJW5tK9jpntCbjzigmG01eoE7uxlbmu</u>
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   exposure%2027.
- <u>https://www.who.int/activities/preparing-and-preventing-epidemics-and-pandemics</u>
- <u>https://pmc.ncbi.nlm.nih.gov/articles/PMC8999828/</u>
- <u>https://www.cdc.gov/orr/school-preparedness/infection-prevention/strategies.html</u>
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- <u>https://www.who.int/news-room/questions-and-answers/item/ebola-vaccines</u>
- https://www.cdc.gov/ebola/hcp/vaccines/index.html
- <u>https://www.cdc.gov/mmwr/volumes/73/wr/mm7316a1.htm</u>
- <u>https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/topics/ebola-vi</u> rus-vaccines
- <u>https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(24)00419-5/fulltext</u>
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