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# Ebola virus disease: An emerging and re-emerging viral threat

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ABSTRACT

The genus *Ebolavirus* from the family *Filoviridae* is composed of five species including *Sudan ebolavirus*, *Reston ebolavirus*, *Bundibugyo ebolavirus, Taï Forest ebolavirus*, and *Ebola virus (previously known as Zaire ebolavirus)*. These viruses have a large non-segmented, negative-strand RNA of approximately 19 kb that encodes for glycoproteins (i.e., GP, sGP, ssGP), nucleoproteins, virion proteins (i.e., VP 24, 30,40) and an RNA dependent RNA polymerase. These viruses have become a global health concern because of mortality, their rapid dissemination, new outbreaks in West-Africa, and the emergence of a new condition known as *"Post-Ebola virus disease syndrome"* that resembles inflammatory and autoimmune conditions such as rheumatoid arthritis, systemic lupus erythematosus and spondyloarthritis with uveitis. However, there are many gaps in the understanding of the mechanisms that may induce the development of such autoimmune-like syndromes. Some of these mechanisms may include a high formation of neutrophil extracellular traps, an uncontrolled "cytokine storm", and the possible formation of auto-antibodies. The likely appearance of autoimmune phenomena in Ebola survivors suppose a new challenge in the management and control of this disease and opens a new field of research in a special subgroup of patients. Herein, the molecular biology, pathogenesis, clinical manifestations, and treatment of Ebola virus disease are reviewed and some strategies for control of disease are discussed.

## 1. Introduction

Ebola viruses (EBOVs) belong to the Filoviridae family and are characterized by a negative stranded RNA structure [1]. It should be noted that the nomenclature and disease classification of the *filoviruses* has been a subject of intense discussion as summarized elsewhere [2]. Of the various filoviruses, EBOV has garnered worldwide attention due to the rapidity of acute hemorrhagic disease and the highly infectious nature of the virus. Discovered during the first documented outbreak of EBOV disease in the town of Yambuku in the Democratic Republic of Congo (DRC) in 1976, these viruses have caused outbreaks of variable magnitude in several west and equatorial African countries. In the most recent outbreak in West Africa between 2013 and 2016, about 28,000 cases were confirmed and up to 11,000 deaths were reported, thus demonstrating the high mortality of this condition [3].

These viruses present human-to-human transmission secondary to contact with contaminated fluids which enables their spread in poverty-stricken areas. The African fruit bat (i.e., *Rousettus aegyptiacus)* is considered the natural reservoir for Ebolavirus and these bats can transmit the virus to Apes, monkeys and species such as antelopes that are resident in the forested areas. Humans living in the forested areas, eating such infected animals, and the handling of Ebolavirus infected dead bodies are considered risk factors associated with cultural and religious behaviors that hinder the control of outbreaks in these regions [4].

EBOV disease is characterized by the development of a severe acute symptomatology including fever, severe fatigue, arthralgia, and hemorrhagic manifestations that result in life threatening conditions such as shock, organ dysfunction, and death [4]. Young age, sex, and pregnancy are considered deleterious prognostic factors associated with mortality in early phases of the infection [5–8]. Thus, it is a viral threat with major repercussions in the field of public health including surveillance and management of suspected and confirmed cases.

Recently, it was demonstrated that despite the high rate of mortality associated with EBOV disease, some patients could survive and, in some cases, develop chronic manifestations that may resemble inflammatory or autoimmune conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) or spondyloarthritis and uveitis. It is important to note that the virus remains in select body fluids such as

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**Abbreviations**

| | |
|---|---|
| Ad5 | Adenovirus serotype 5 vaccine |
| BDBV | Bundibugyo ebolavirus |
| BSL | Biosafety level |
| ChAd3 | Chimpanzee adenovirus serotype 3 |
| DCs | Dendritic cells |
| DIC | Disseminated intravascular coagulation |
| DRC | Democratic Republic of Congo |
| dsRNA | Double-stranded RNA |
| EBOLA AgK-SeT | Ebola Virus Antigen Detection K-SeT |
| EBOV | Zaire ebolavirus - Ebola virus |
| EBOVs | Ebolaviruses |
| ELISA | Enzyme-linked immunosorbent assay |
| ESCRT | Endosomal sorting complex required for trafficking |
| ETC | Ebola treatment centers |
| FRC | Fibroblastic reticular cells |
| GP | Glycoprotein |
| HPIV3 | Human parainfluenza virus type 3 |
| HRR | Heptad repeat region |
| IFN | Interferon |
| IFNR | Interferon receptor |
| IL | Interleukin |
| IRF3 | Interferon regulator factor 3 |
| JAK | Janus kinase |
| KPNA | Karyopherin α |
| MAV5 | Mitochondrial antiviral-signaling protein 5 |
| MBL | Mannose-binding lectin |
| MIP-1α | Macrophage inflammatory protein 1α |
| MVA | Modified vaccinia Ankara |
| NETs | Neutrophil extracellular traps |
| NHP | Non-human primates |
| NK | Natural killer |
| NP | Nucleoprotein |
| NPC1 | Niemann-Pick C1 |
| PAHO | Pan American Health Organization |
| PM | Plasma membrane |
| PMOs | Phosphorodiamidate morpholino oligomers |
| PRISMA | Preferred reporting items for systematic reviews and meta-analyses |
| qRT-PCR | Real-time reverse transcriptase polymerase chain reaction |
| RA | Rheumatoid arthritis |
| rAd5 | Recombinant adenovirus serotype 5 vaccine |
| RBD | Receptor binding domain |
| RESTV | Reston ebolavirus |
| RIG | Retinoic acid-inducible gene |
| ROS | Reactive oxygen species |
| rVSV | Recombinant vesicular stomatitis viruses |
| sGP | Soluble GP |
| siRNAs | Small-interfering RNAs |
| SLE | Systemic lupus erythematosus |
| ssGP | Small soluble GP |
| STAT1 | Signal transducer and activator of transcription 1 |
| SUDV | Sudan ebolavirus |
| TAFV | Taï Forest ebolavirus |
| TAM | Tyro3, Axl, and Mer receptors |
| TIM-1 | T-cell immunoglobulin and mucin 1 |
| TLR | Toll-Like receptor |
| TNF | Tumor necrosis factor |
| Tsg101 | Tumor susceptibility gene 101 |
| UTRs | Untranslated regions |
| VEE | Venezuelan equine encephalitis |
| VLPs | Virus-like particles |
| VP | Virion protein |
| Vps | Vacuolar protein-sorting-associated proteins |
| VRP | Venezuelan equine encephalitis replicon particles |
| WHO | World Health Organization |
| YMH | Yambuku Mission Hospital |

semen for prolonged periods of time in survivors of Ebola virus infection retaining risks of transmission [9]. The clinical features of Ebola virus infection puts a high burden on the quality of life, and may cause social stigma and discrimination [10]. Currently, there is limited data about the prevalence of this syndrome in survivors, and few reports have shown that about one year after the recovery from the acute disease, signs and symptoms may disappear but virus still remains [11]. Thus, the chronic state of EBOV disease is a new concern in this subset of patients.

Historically, management of Ebola infection has consisted of the administration of plasma. However, there is a high risk of transmitting blood-borne infections with this therapy, especially in those rural areas in Africa with limited medical facilities [12]. Management with antivirals such as Favipiravir, have been effective in prolonging survival and reducing the viral load in this condition [13,14]. Recently, chimeric and humanized monoclonal antibodies have emerged as options for managing EBOV disease. Some treatments such as mAb114, REGN-EB3, and BCX4430 showed tolerability and safety in phase 1 studies, but their role in the treatment of the acute phase of the disease remains to be fully elucidated [15–17].

Prevention of EBOV disease includes the early identification of cases through active surveillance and preventing its spread and transmission. Other procedures such as burial ceremonies with safety precautions, and the use of a barrier of protection from contaminated body fluids are critical strategies in the early management of the disease [18,19]. Although candidate vaccines such as the rVSVdeltaG-ZEBOV-GP vaccine have been shown to be safe and highly immunogenic [20,21], further studies are warranted to validate this primary strategy to stop the propagation and appearance of new outbreaks. Herein, we present the current state of EBOVs including biology, management strategies, prevention, and new challenges associated with this infectious disease.

## 2. Ebola virus biology

### 2.1. Classification

According to the Baltimore V classification system, these viruses belong to the family *Filoviridae* from the order *Mononegavirales*, which includes three genera, *Cuevavirus, Marburgvirus*, and *Ebolavirus* [1]. The genus *Ebolavirus* is composed of five species and each species is represented by a single virus: *Sudan ebolavirus* (SUDV), *Reston ebolavirus* (RESTV), *Bundibugyo ebolavirus* (BDBV), *Taï Forest ebolavirus* (TAFV) also called *Cote d'Ivoire ebolavirus*, and *Ebola virus* (EBOV - previously known as *Zaire ebola virus*) [22]. In the last few years, *Filovirus* taxonomy has been adjusted and updated. In 2011, the International Committee on Taxonomy of Viruses *Filoviridae* Study Group proposed several changes to *Filovirus* taxonomy in order to address problems observed with the 2005–2011 classification. They emphasized that similar terms have different meanings: *Ebolavirus* and *Zaire ebolavirus* are taxonomic terms whereas EBOV is a virus belonging to the genus *Ebolavirus* and species *Zaire ebolavirus* [23].

Due to the confusion surrounding classification and nomenclature, experts in the field recently assembled and reached a consensus that resulted in a recent publication [2]. These topics have great importance in the identification of species that cause outbreaks worldwide since a correct identification of these viruses may allow for a better public health response, and as discussed below, help to identify different clinical manifestations of EBOV disease.

### 2.2. Genome and structure

The size of EBOVs is extremely variable with diameters of 50–80 nm and lengths between 10,000 and 14,000 nm. The general shape of virions varies from cylinders to branches and loops. However, the characteristic thread-like filamentous structure is maintained in all filoviruses [24]. EBOVs have a large non-segmented, negative-strand RNA of approximately 19 kb. This RNA genome contains seven sequentially arranged genes. The genes include the 3′ leader – nucleoprotein (NP) - virion protein (VP) 35, the matrix protein VP40, the glycoprotein (GP), the VP30, the VP24 and the RNA dependent RNA polymerase (L) – 5' trailer. Each one of these genes encode a single protein product except for GP, which encodes for three glycoproteins (Fig. 1) [25,26]. These genes are delineated by conserved leader and trailer regions, which have replication promoters and RNA packaging signals.

Each gene is flanked by 3′ and 5′ untranslated regions (UTRs). These are delimited by conserved transcriptional signals that begin close to the 3′ end of the genomic sequence with a start site and end with a stop site. Moreover, intergenic regions with different lengths separate most of the genes. However, an unusual feature of all EBOVs is the presence of gene overlaps in fragments of their UTRs (i.e., the stop site of an upstream 3' gene overlaps with the start of another downstream gene) [27].

The genetic diversity among EBOVs species ranges between 25 and 35% [28]. Gire et al. [29] found several mutations that produce genetically distinct sequences, showing that the source of new lineages during outbreaks are from a common ancestor. NP encodes for a structural nucleoprotein, GP for envelope glycoproteins and VP40 and VP24 for matrix proteins.

Apart from these structural proteins, polymerase matrix proteins encoded by VP30, VP35, and RNA polymerase L are the major non-structural proteins [28]. All of these proteins play different roles; NP, VP35, VP30, and L (i.e., ribonucleoprotein-RNP complex) are essential for the processes of viral transcription and replication. Whereas GP, VP40, and VP24 are membrane proteins that support the development of the filamentous virions. Herein, we summarize the most critical aspects of these proteins for EBOVs pathogenesis.

#### 2.2.1. Nucleoprotein

NP has two critical functions: protection of the viral RNA against exogenous nucleases, and encapsidation of the genome during virus assembly. This protein is made up of three major domains: N-terminal, core (located in the center) and C-terminal domains. N and C, lobes of the core domain, recognize and clamp to RNA binding groove regions. In addition, a tetrameric structure is made by the prolongation of N- and C- terminal domains in order to bind the RNA binding groove. This contributes to the formation of the RNP complex, which is necessary for

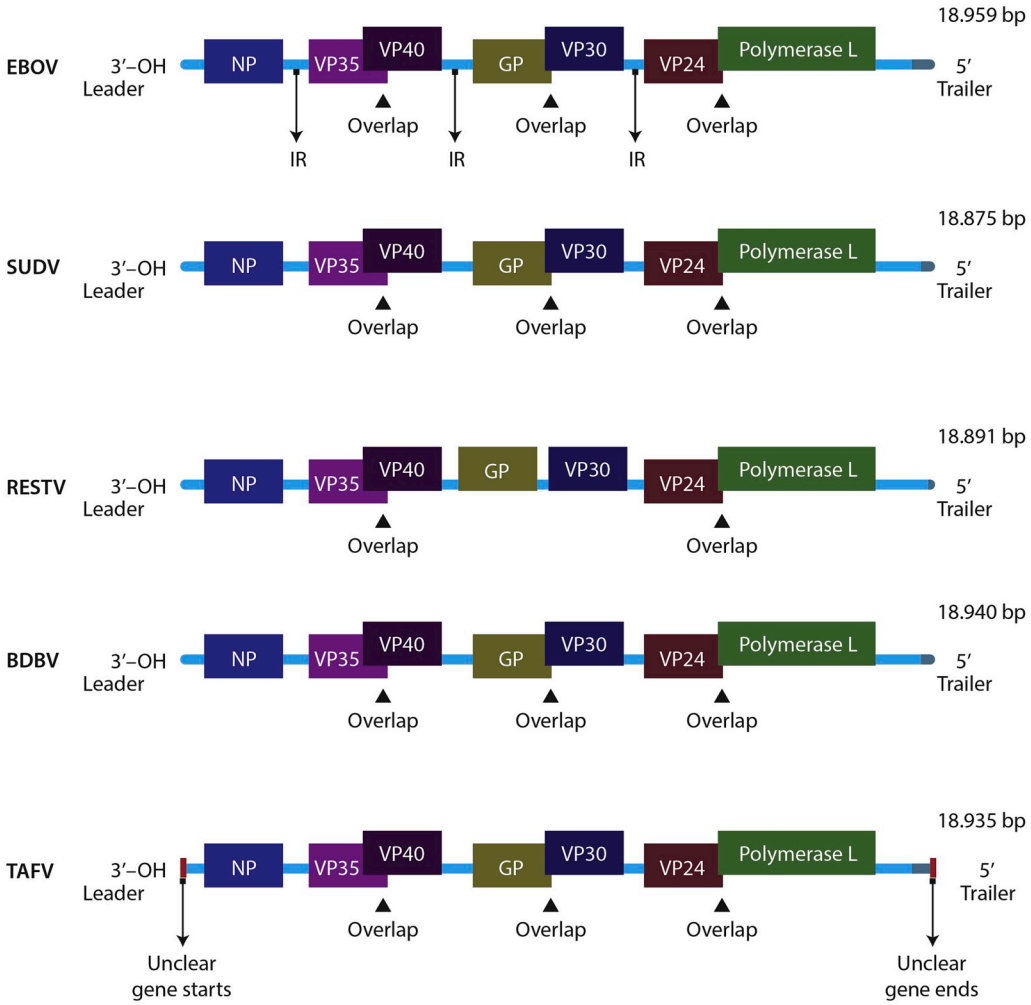


**Fig. 1.** Genome of Ebola viruses. Negative-strand RNA of EBOVs is of approximately 19 kb varying by species. RNA contains seven genes represented by colored boxes. Each gene encodes for a protein except for GP. RNA editing by polymerase L produces different GP transcripts (GP1/2, sGP and ssGP). EBOV: Ebola virus; SUDV: Sudan ebolavirus; RESTV: Reston ebolavirus; BDBV: Bundibugyo ebolavirus; TAFV: Taï Forest ebolavirus; IR: intergenic region; NP: nucleoprotein; VP: viral protein; GP: glycoprotein.

virus transcription, replication, and assembly [30]. The N-terminal region of this protein is vital for NP oligomerization and for NP tube structure formation. These structures are used as scaffolds for the assembly of viral nucleocapsid-like structures [31].

Furthermore, NP goes through post-translational modifications such as O glycosylation and sialylation in order to interact with VP35 [32]. *In vitro*, the NP C-terminal region has been shown to contain a hydrophobic site which interacts with VP35 N-terminal peptide by inhibiting NP oligomerization and releasing RNA from NP-RNA complexes for further replication [33]. Thus, VP35 recruits NP to form a VP35-NP complex that prevents premature NP oligomerization and confers changes to NP in the viral RNA synthesis machinery [34]. The C-terminal region of NP interacts with VP40 thus leading to its incorporation into virus-like particles (VLPs) [35]. Therefore, this region may be necessary for integrating VP40 into the assembly of new virions.

#### 2.2.2. Virion proteins

The VP24 is a minor matrix protein which plays different roles in nucleocapsid assembly, virus release, and immune response suppression. It was observed that VP24 silencing results in a decrease of released virions and an increase in viral proteins within the cell [32]. The N-terminal region of VP24 is necessary for protein-protein interactions that lead to capsid formation. Mutations in this region results in protein aggregation [36]. C-terminal deletion also inhibits nucleocapsid-like structure formation thus illustrating that both domains are important in nucleocapsid assembly [36]. Also, VP24 interacts with NP through its conserved loop. This interaction is dependent on VP24 amino acids V170 and N171 that help in the condensation of the viral nucleocapsid, thus triggering efficient packaging and the production of new virions [37].

VP24 is an antagonist of the IFN response and contributes to its high virulence. This protein can inhibit IFN-α/β/γ stimulation by sequestering proteins belonging to the karyopherin α (KPNA) family such as KPNA α1, α5, and α6 proteins thus inhibiting activated signal transducer and activator of transcription 1 (STAT1) [38]. Moreover, VP24 can also bind to STAT1 directly and inhibit its phosphorylation, nuclear transport, and IFN-associated gene activation [39]. Moreover, VP24 also inhibits IFN production via both IRF3 and early tumor necrosis factor (TNF)-induced NF-κB signaling [40].

As previously mentioned, VP35 plays a critical role in the formation of the viral nucleocapsid and dissociation of NP-RNA complexes. The VP35 N-terminal region has been described as interacting with RNA polymerase L, which may help in the transcription process through the RNA-dependent RNA polymerase complex (L + VP30) formation. The C-terminal region is pivotal in the interaction with NP since this interaction serves as a bridge for the binding of NP to RNA polymerase L during nucleocapsid assembly [41].

In addition to these functions, VP35 also has different abilities in the suppression of innate immune response [42]. This protein inhibits the RIG-I-like receptor pathway and prevents the activation of the interferon regulatory factor (IRF) 3 and 7 that triggers the anti-viral IFN-response. Specifically, VP35 blocks IRF-3 phosphorylation resulting in inhibiting protein dimerization and nuclear accumulation [43].

VP35 also blocks IFN production following TLR and RIG-I activation and increases SUMOylation of IRF-7 through interaction with SUMO E3 protein ligase PIAS1 and SUMO conjugating enzyme Ubc9 [44,45]. This type-I IFN signaling inhibition is due to the binding of VP35 C-terminal IFN inhibitory domain (which includes a hydrophobic pocket and a central basic region), and double-stranded RNA (dsRNA) while avoiding the activation of the RIG-I pathway [41]. Although this domain plays an important role in immune suppression, it does not interfere with viral RNA synthesis [46]. The importance of the role of VP35 in inducing immune suppression was highlighted by a study in which an Ebola virus construct with a mutation in VP35 not only lacked virulence in monkeys but when used to infect monkeys elicited highly protective immunity against challenge with a wild type Ebola virus [47].

In addition to NP and VP35, VP30 and the RNA polymerase L play a key role in the activation of viral RNA synthesis [48]. Specifically, VP30 is a transcription factor, and its main activity is dependent on its phosphorylation state. The N-terminal region contains a leucine-zipper motif that is important in its homo-oligomerization and a zinc finger domain, which plays a major role in transcription activity [49]. Moreover, a basic amino acid cluster in its C-terminal region interacts with NP; this interaction is critical for controlling VP30 activity [50]. Unlike transcription, this protein is not necessary for viral replication.

Biedenkopf et al. [51] showed that while phosphorylation of VP30 suppresses viral transcription, it increases viral replication. This phosphorylation modulates transition between transcription and replication, depending on the activity of the polymerase complex. Interestingly, this post-translational modification is dependent on the interaction between VP35 and VP30. The authors also mention that phosphorylation sites can overlap with the RNA binding site. The presence of phosphate groups in this region can alter the binding of VP30 to RNA due to electrostatic repulsion. Thus, VP30 is dissociated from RNA and released from the transcription complex. This study also showed that the interaction between NP and VP30 is influenced by phosphorylation, and it is important for the viral life cycle [51]. In addition to its role in transcription of this protein, VP30 also participates in cellular RNA silencing, thus blocking the effect of cellular RNA interference by interaction with Dicer, an RNase III-type enzyme that cleaves dsRNAs into small interfering RNAs [52].

L is an RNA-dependent RNA polymerase that participates with other proteins in the RNP complex (i.e., NP, VP30 and VP35) in viral genome transcription and replication [27]. This polymerase binds to genomic RNA at the 3′ leader promoter and changes EBOVs negative-sense RNA into positive-sense messenger RNA (i.e., production of the mono-cistronic capped viral mRNAs) to generate Ebola proteins for the production of new virions. The L protein also participates in mRNA polyadenylation and capping due to its catalytic activities [53]. This protein can also edit mRNA. For example, the editing activity of L protein can lead to the generation of a GP transcript instead of soluble GP (sGP), and can regulate the expression level of these proteins [54,55].

VP40 coordinates the virion assembly, maintains structural integrity, and directs budding of viral particles from the cell surface [56]. The expression of VP40 alone is enough to induce the formation of VLPs with the typical thread-like appearance of EBOVs virions [57]. VP40 has two major domains, N-terminal and C-terminal, linked by a flexible region. The N-terminal domain helps with VP40 dimerization and oligomerization in the cytoplasm through contact with cellular proteins such as tumor susceptibility gene 101 (Tsg101), vacuolar protein-sorting-associated proteins (Vps4), and Nedd4/Rsp5 thus leading to VP40 translocation to the plasma membrane. While the C-terminal domain mediates the interaction with the plasma membrane specifically, there are electrostatic interactions between a basic region in this domain with anionic lipids enriched in the plasma membrane inner leaflet [58]. VP40, which was shown to be a dimer, can oligomerize into both hexamers and octamers during the viral life cycle. Thus, VP40 can be found as a hexamer in the budding process or as an octamer in RNA binding and viral replication [59].

In budding, VP40 binds phosphatidylserine-containing membranes, which control oligomerization and placement of VP40 in the inner leaflet of the plasma membrane [60]. After that, the flexible hydrophobic loop of the C-terminal domain induces the insertion and docking of the plasma membrane-phosphatidylserine, thus allowing VP40 to remain in the plasma membrane [26]. In addition to these functions, VP40 can induce the formation of exosomes, which are involved in bystander cell death. This mechanism is the result of VP40 inducing the formation of the endosomal sorting complex which is required for trafficking (ESCRT) proteins such as Tsg101, VPS25, and VPS36 involved in exosome biogenesis [61].

#### 2.2.3. Glycoprotein

GP is essential in viral pathogenesis. It is the only protein visible on the viral surface. This protein induces EBOVs entry into host cells by receptor binding and fusion [62]. The GP gene encodes for three different proteins, which results from an editing process carried out by the L protein: GP with two subunits – GP1 as a participant in receptor binding and GP2 responsible for viral fusion. These are produced by the cleavage of their precursor P0. sGP does not contain the transmembrane domain and is formed from the unedited transcript. The third protein is a truncated form of sGP called small soluble GP (ssGP) but its biological activity is unknown [28,41,63]. A smaller fragment called Δ-peptide is also generated from the cleavage of sGP by Furin [64].

All of these proteins have different functions; GP1 mediates the binding between virus and target cell. This protein consists of three domains: the receptor binding domain-RBD (interacts with one or more receptors), the glycan cap (protects the RBD from antibody recognition and interacts with GP2 to prevent premature fusion), and the O-linked glycosylated mucin-like domain (a highly glycosylated site, which both protects RBD from immune recognition and has a cytotoxic effect through ERK and MAPK pathways) [26,65,66].

GP2 is responsible for membrane fusion and has five domains: the N-terminal heptad repeat region (HRR), C-terminal HRR, fusion loop, the transmembrane region and the cytoplasmic tail [67]. The fusion loop is essential in membrane fusion, since it contains a hydrophobic sequence that is introduced into host endosomal membranes in order to start membrane fusion. Subsequently, GP2 HRR forms a transmembrane six-helix bundle that serves as an opening in the membrane [68]. sGP is related to evasion of the immune system via antigenic subversion and by its ability to enhance viral immune evasion by acting as a decoy for antibodies against GP1 and GP2 thus redirecting GP-specific antibody responses [67]. Δ-peptide induces cellular toxicity through pore formation in the cellular membrane and enhancing ion permeability [69].

## 3. Pathogenesis

### 3.1. Ebolaviruses life cycle

#### 3.1.1. Cellular tropism and virus entry

EBOVs infection in humans occurs through the interaction of infected body fluids with mucous membranes or skin lesions that allow viruses entry by direct contact with targeted cells. Indeed, *in-vivo* studies in non-human primates (NHP) models have demonstrated that EBOVs effectively infect endothelial cells, adrenal cells, immature dendritic cells (DCs), monocytes, macrophages, and Kupffer cells in the liver [70,71]. Such diversity in target cells is mainly due to the ability of GP1 of the EBOV to interact with a variety of host-cell proteins. Even if no specific receptor has been identified, there are several attachment factors that have been found and may account for EBOVs binding (Fig. 2).

One of the main receptors involved in virion attachment are lectins within the host membrane such as the C-type lectins DC-SIGN and L-SIGN that serve as co-receptors for EBOVs entry into DCs [72,73]. Moreover, increased infectivity of EBOV compared to RESTV may be due to an increase in the glycan extension on the viral GP from the EBOV, which has high affinity for the "macrophage galactose-type calcium-type lectin" that potentially contributes to its relative infectivity [74]. Other co-receptors such as β1-Integrin [75], folate receptor-α [76], glycosaminoglycans [77], Tyro3, Axl, Mer (TAM) receptor tyrosine kinases [78], and T-cell immunoglobulin and mucin 1 (TIM-1) [78], have all been proposed as EBOVs entry factors by their

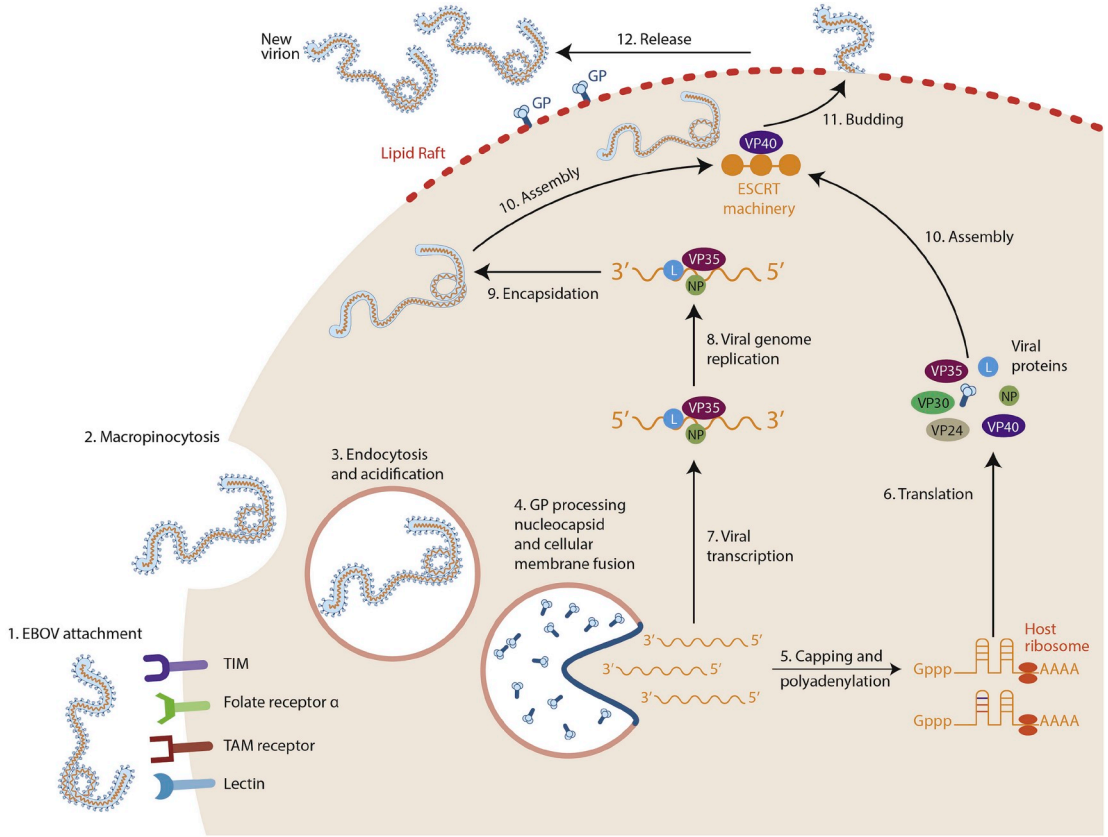


**Fig. 2.** Viral replication cycle. First, virus binds to the host cell through different co-receptors, followed by entry into the host cytoplasm where viral RNA is released. Then, viral RNA is transcripted into viral proteins and viral genome is replicated followed by encapsidation, assembly and budding of a new virion. EBOV: Ebola virus; ESCRT: Endosomal sorting complexes required for transport; GP: Glycoprotein; TIM-1: T-cell immunoglobulin and mucin domain 1; TAM: Tyro3, Axl, and Mer receptors; VP: Virion protein; NP: Nucleoprotein.

respective ability to interact with the GP1 viral protein. This wide array of receptors accounts for the diversity of permissive cells.

After binding, the virion is taken up into the target cells by a process called macro-pinocytosis, a non-specific endocytosis mechanism, which, in a physiological context allows the uptake and processing of apoptotic cells [79,80]. In the case of EBOVs, phosphatidylserine on the virion interacts with the host cell membrane and activates the re-organization of the cytoskeleton and triggers the ruffling of the plasma membrane and invagination of the virion with further internalization into the early endosome. Subsequently, EBOVs are trafficked to late endosomes where low pH allows GP processing and, consequently, virus and host-cell membrane fusion [81–83].

### 3.1.2. Transcription, translation, and genomic replication

After membrane fusion, the nucleocapsid is released into the cytoplasm where viral RNA is translated into mRNA by host cell machinery. The main hallmarks of EBOVs mRNA are the formation of stem-loops at the 5′ end and the synthesis of the long non-coding region at the 3′ and 5’ ends which contributes to their stability. Viral proteins such as GP, NP, VP24, VP35, VP40, and L are then translated from viral mRNA by the host machinery. Then, NP, VP35, and L proteins act as a viral polymerase complex and allow viral genome replication. The first step in replication is the generation of an anti-genomic RNA consisting of a positive strand RNA from which a complementary genome is synthesized by the viral polymerase complex followed by rapid encapsulation by NP, VP24, VP30, and VP35 [84].

### 3.1.3. Assembly and release

*De novo*-synthesized proteins undergo different post-translational modifications and accumulate within the lipid raft together with the encapsulated viral genome at the cellular membrane [26]. Interaction of viral VP40 with the host ESCRT machinery allows viral budding and release of a new virion [85].

## 3.2. Host cell pathology

Tissues from EBOVs infected corpses show massive number of virions with extensive necrosis in parenchymal cells of different organs such as the liver, kidney, spleen, and gonads [86]. As explained above, EBOVs have a broad cell tropism, which accounts for the wide variety of infected tissues. After transmission of the virus and in the absence of health care support, dysregulated immune response, multi-organ failure, vascular and coagulation impairment leads to death within 10 days after the onset of symptoms [27]. Levels of viremia in the blood from infected patients has been correlated with the lethality of the infection [87]. In some cases, excessively high viremia has been found in patient serum reaching levels as high as $10^6$ plaque forming units of EBOV [88]. In this case, the intensity and level of pathogenesis mediated by the infection is such that infected individuals are not able to mount any effective immune response.

### 3.2.1. Innate immune response

The innate immune response is the organism's first line of defense against microbial infection including viruses. Cells such as DCs,

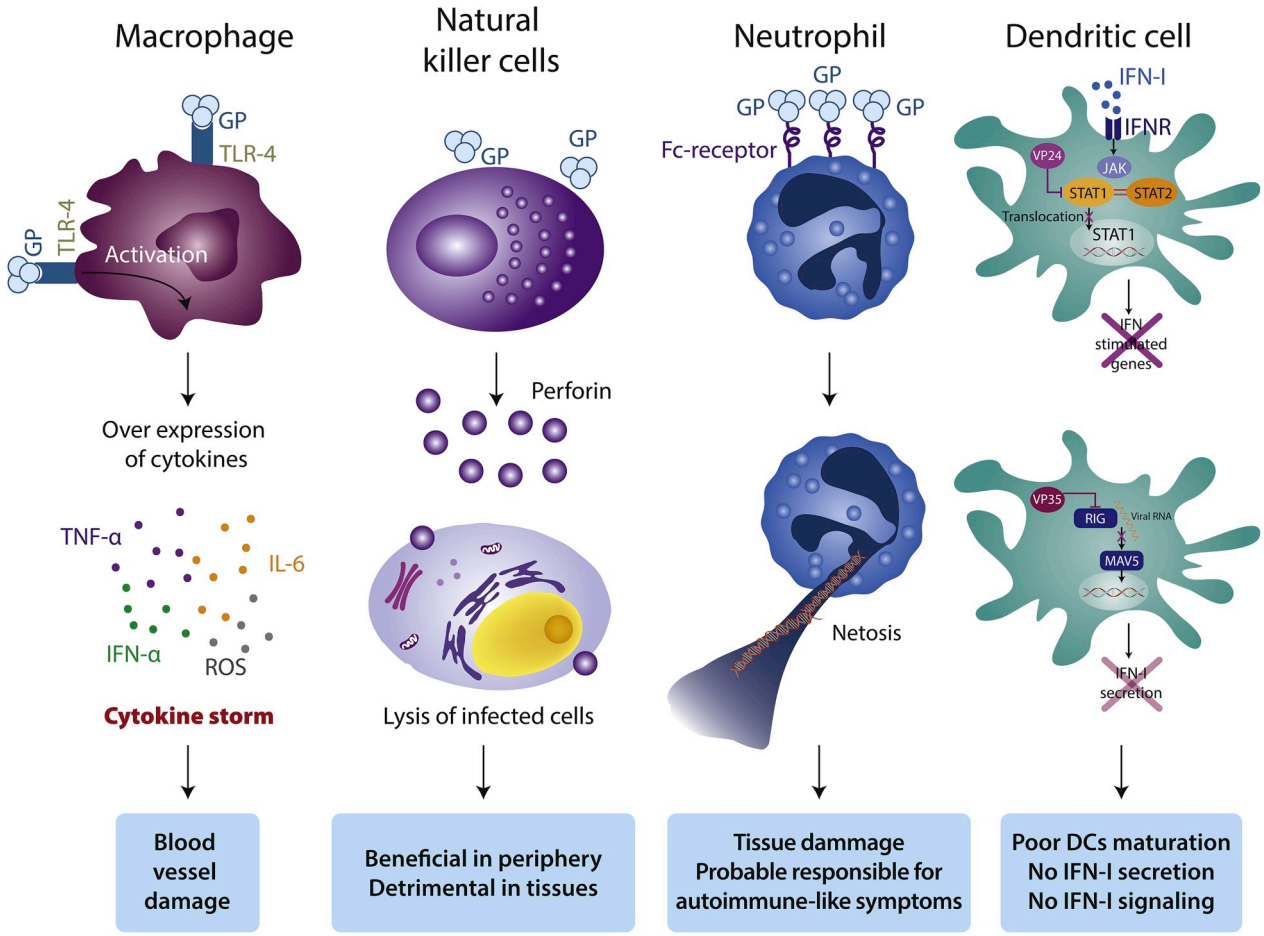


**Fig. 3.** Dysregulation of innate immune cells in Ebola infection. Consequences of this dysregulation in the pathology of the infection are pointed out in blue squares. DC: Dendritic cells; GP: Glycoprotein; IFN: Interferon; IFNR: Interferon receptor; IL: Interleukin; JAK: Janus kinase; RIG: Retinoic acid-inducible gene; ROS: Reactive oxygen species; STAT: Signal transducer and activator of transcription; TLR: Toll-Like receptor; TNF: Tumor necrosis factor; VP24: Viral protein 24; MAV5: Mitochondrial antiviral-signaling protein 5.

macrophages, monocytes, natural killers (NK), and neutrophils orchestrate this response (Fig. 3). In EBOV infection, the first cell lineage targeted are tissue-resident DCs and macrophages present at the site of infection that primarily account for the innate immune dysregulation [89], characteristic of acute EBOV infection [71].

Concerning macrophages, EBOVs infection leads to a profound increase in the secretion of pro-inflammatory cytokines such as IL-6, TNF, and IFN-β as well as the production of tissue factor and vasoactive peptides [89]. Activation of these macrophages is GP-dependent but could be triggered with the engagement of TLR-4 [90]. Murine models, support the fact that TLR-4 signaling induced by viral GP triggers hypersecretion of macrophage inflammatory protein 1α (MIP-1α), TNF, IL-1β, IL-6, IFN-γ, IL-2, IL-4, IL-12p70, IL-10, reactive oxygen species, and nitrogen radicals [91]. Interestingly, in the murine model, blockade of TLR-4 inhibits both macrophage migration to lymph nodes and hypersecretion of cytokines, thus decreasing the lethality of the infection [90]. In this regard, excessive TNF-α in the NHP model is associated with lymphocyte apoptosis contributing to the lymphopenia observed in EBOV disease.

In addition, infection by EBOVs causes defects in DC activation; EBOVs-infected cells are deficient in the production of type-I IFNs and do not undergo maturation [92]. Two viral proteins, VP35 and VP24, are the main drivers in the impairment of DC activation after viral infection. On the one hand, VP35 blocks the anti-viral sensing RIG-I-like receptors [43], thus obstructing the production of type I IFN by DCs. On the other hand, in a physiological context, IFN-I activates IFN receptor bearing cells through a pathway leading to STAT1 nuclear translocation. STAT1 acts as a transcriptional factor by activating the expression of multiple genes associated with the anti-viral immune response called the IFN signature genes. The viral protein VP24 is a competitor inhibitor of STAT1. It prevents STAT1 translocation and further IFN-I signaling [38,93]. Overall, EBOVs hijack IFN-I response on two fronts: first by inhibiting its production and second by preventing its signalization. This lack of INF–I signaling leads to defects in DCs maturation and, therefore, to an inability to mount an efficient adaptive immune response.

In regard to NK cells, their role in EBOVs infection is controversial and deserves further investigation. Reduction of peripheral NK cells has been observed in experimentally infected macaques and is most likely the result of apoptosis [94]. Warfield et al. [95] demonstrated, using a murine model, that NK cells stimulated by VLPs encoding GP were activated and were associated with protection against EBOVs infection. Note that this protection was dependent on perforin and not on IFN-α secretion by NKs. A more recent study using a murine model evaluated the function of NK cells located in the infected tissue. The authors concluded that a decrease in the NK cell count in the peripheral blood of the infected mice was concomitant with the accumulation of these cells in the tissues, more precisely in the liver. This view is supported by the finding that NK cell depletion delayed liver damage and decreased the viral load [96]. This indicates that NK cells could play a detrimental role in tissue damage during EBOV disease.

Finally, neutrophils are a population of immune cells that deserve attention. An “omic analysis” of EBOV disease in survivors versus non-survivors showed an aberrant neutrophil signature. In lethally infected individuals, genes implicated in production, differentiation, and activation of neutrophils were highly expressed in EBOVs fatalities as compared to survivors. Moreover, proteins associated with the formation of neutrophil extracellular traps (NETs) have been found in EBOVs infected donors in comparison to healthy ones, and the plasma from fatal cases of EBOV disease was enriched for these proteins. It has been hypothesized that in EBOVs infection, excessive NETs formation could lead to tissue damage as has already been observed in other diseases [97]. Note that the formation of NETs has been implicated in the generation of autoimmune responses such as anti-DNA antibodies [98]. These types of auto-antibodies have been found in EBOVs survivors [99]. In addition, autoimmune-like processes have been described in survivors from EBOVs infection (described below). It is possible to hypothesize that an aberrant neutrophil activation could be the origin of such autoimmune phenomenon.

### 3.2.2. Adaptive immune response

Poor and/or defective antigen presentation by DCs secondary to defective maturation leads to the inability to generate an effective adaptive immune response in EBOVs infected patients. In addition, besides the role of EBOV proteins that induce immune suppression, the lymphopenia caused by excessive apoptosis of lymphocytes, mediated in part by the cytokine storm and dysregulation of the apoptosis pathway triggered by the EBOVs, accounts for the impairment of such response [100].

It is nonetheless important to identify surrogates of an effective adaptive immune response against EBOV in order to develop an effective vaccine strategy. Whether it is EBOV specific cellular response or humoral response that controls infection has been a matter of discussion but likely to include both as outlined below. In murine models, $CD8^+$ T cells appear to be indispensable to control EBOVs infection. For instance, the passive transfer of EBOV-specific $CD8^+$ T cells recovered from moribund mice illustrates the importance of $CD8^+$ T cells. Thus, naïve mice recipients of such passively transferred $CD8^+$ T cells when challenged with EBOV were protected from death [101]. Furthermore, in a murine model, Gupta et al. [102] demonstrated that $CD8^+$ T cells were indispensable to control EBOVs during the acute phase of disease. However, both B and $CD4^+$ T cells were needed to control viremia during the chronic phase of the infection.

In humans, the use of polychromatic flow cytometric techniques has provided some clues as to the effect of EBOV infection on the subset distribution of lymphoid cells and the expression of cell surface markers that identify immune function. One of the major findings has been the identification of a high frequency of activated T lymphocytes; however, these lymphocytes appear to have an exhausted phenotype exemplified by high levels of PD-1 and CTLA-4 expression [103,104]. Such immune exhausted phenotype supports the view that the immune system is unable to mount an effective immune response against EBOV, thus accounting for the lack of control of the infection in the majority of the cases.

Whereas the above studies underscore an important role for virus specific $CD8^+$ T cells in inducing protective immunity against EBOV infection, a series of other studies make a strong case for a prominent role for virus specific humoral immunity. Thus, in humans and NHP models, an increasing amount of evidence defines humoral response as the key factor for EBOVs control in survivors. Indeed, Marzi et al. [105] established a cocktail of human-mouse chimeric neutralizing antibodies that upon passive transfer confers partial protection from EBOV disease in a group of macaques. Moreover, the same group found that in the NHP model of vaccinated macaques, depletion of $CD8^+$ T cells resulted in the survival of the animals, whereas depletion of $CD4^+$ T cells, completely nullified the antibody response and resulted in the death of the animals. While these findings demonstrate a pivotal role of humoral antibodies in controlling EBOVs infection at least in this model [106], it appears that there is also a role for $CD8^+$ T cells in conferring protection and perhaps the differences could be attributed to the models being utilized to study protective immunity.

Further support for the role antibodies against EBOV was obtained by the finding that therapy of rhesus macaques with monoclonal neutralizing antibodies against viral GP were protected from death following challenge with a lethal dose of EBOV [107]. In humans, comparison between EBOV disease survivals and fatalities showed that levels of EBOV specific IgG and IgM predicted viral control. Furthermore, this humoral response was necessary to support a good cellular response. In fatal cases, the levels of IgM were low and EBOV-specific IgG were undetectable [108]. The fact that high levels of antibodies have been detected in survivors from different outbreaks is consistent with this data. These antibodies persist over time and can confer

protection [109–112]. Moreover, a recent study on sera from survivors of the EBOVs outbreak in Sierra Leona showed increased levels of EBOV specific IgG1 and IgA isotype antibodies that mediated their anti-viral effect via innate immune effector functions [113].

The consensus opinion appears to be that a strong humoral response against EBOVs is pivotal for additional activation of EBOV specific cellular immune response as well as the activation of innate functions to confer protection. Thus, an effective vaccine should minimally elicit an appropriate antibody response (i.e., IgG1 or IgA isotype, neutralizing function) in order to be protective.

#### 3.2.3. Hematological compromise

The lymphoid organs are a mayor target of EBOV. Indeed, DCs and macrophages being mayor targets for the virus, these immune cells are able to spread the virus toward the proximal lymph nodes. Once in the lymphoid tissues, fibroblastic reticular cells (FRC) located at the T cells zone of the cortex are, at their turn, infected. Infection of FRC correlates with lymphocyte apoptosis [120]. Moreover, histological analyses of EBOV infection in NHP models have shown within lymph nodes a massive destruction of lymphocytes, loss of follicular structure and destruction of parenchyma [121]. Robust destruction of lymphoid organ structure may account for the immunosuppression observed during EBOV disease.

#### 3.2.4. Vascular system damage

Another feature of lethal EBOV disease is the disruption of the vascular endothelium causing permeability in the blood-tissue barrier [70]. This disruption induces vascular permeability, leakage of blood, incomplete blood circulation, and intravascular coagulation that contributes to the severity of the disease [114]. Even if endothelial cells are permissive to EBOVs infection, Geisbert et al. [70] showed, in a NHP model, that disruption of the endothelial barrier was not due to the cytopathogenic effects of EBOVs on infected cells but rather secondary to indirect immune signals secreted by macrophages. An important finding from this study is the lack of apoptosis in the EBOVs-infected endothelial cells which suggests that the disruption of vascular endothelium observed in infected macaques is a functional impairment rather than structural damage. Indeed, *in-vitro* stimulation of endothelial cells disrupts endothelial junctions and induces barrier permeability [115]. Wahl-Jensen et al. [116] demonstrated that VLPs encoding for viral GP induce activation of endothelial cells and a dysfunctional endothelial barrier. This impairment of barrier permeability was accentuated in the presence of TNF-α and suggests that the pro-inflammatory milieu induced by EBOVs would lead to the impairment of the vascular system. Further studies are warranted in order to assess the precise mechanisms that lead to deficiencies in blood circulation observed during EBOVs infection.

#### 3.2.5. Coagulopathy

Hemorrhagic episodes are common as noted during the various EBOV outbreaks [117]. Hemorrhagic events can be provoked by platelet deficiency observed during the infection. Nevertheless, a real association between the platelet count and the bleeding episodes has not been confirmed [118]. Another irregularity in the coagulation pathway observed throughout EBOV disease is the disseminated intravascular coagulation (DIC) syndrome, characterized by the activation of the coagulation system that triggers the development of thrombosis. DIC has been observed in approximately 25% of the cases of EBOVs infection from 2006 to 2008, and it correlates with the disease severity [119].

Geisbert et al. [122] using the NHP model of EBOV infection demonstrated that a tissue factor secreted by infected macrophages triggers the activation of the coagulation system and induces the fibrin coating of the infected cells. In this study, the authors also described a deficiency in protein C, a potent anti-coagulant which may account for the abnormalities in coagulation. Inflammation, low platelet count, and a decrease in the anti-coagulant factors seem to play a pivotal role in the coagulation defects observed in EBOVs disease. Nevertheless, the detailed mechanisms involved in EBOV induced coagulopathy need to be clarified in efforts to identify effective treatments in a timely manner.

### 3.3. Virus persistence

Since EBOVs-infection is highly lethal, data on the persistence of the virus in survivors is scarce. A systematic review starting from 2015 evaluated the persistence of EBOVs in body fluids from survivors and concluded that the infectious virus can be found in semen, breast milk, urine, and in the ocular aqueous humor [122]. The seminal fluid reservoir is considered one of the most problematic since it may account for sexual transmission observed during subsequent outbreaks [123]. Indeed, the infectious virus can be isolated from the semen up to 82 days after the onset of symptoms, and genomic RNA have been found up to 284 days after the onset of the disease [122]. Due to the difficulty of establishing biosafety level (BSL) 4 laboratories in the field, the mechanism for persistence is still unknown. Caviness et al. [124] hypothesized that such persistence may be due to the existence of defective viral particles, which are unable to replicate in the presence of wild-type virus but can persist in the cells without viral replication. In the *in-vitro*-model, these defective virus particles can be effectively reactivated by stimulation with phorbol-12-myristate-13-acetate which suggests that persistence can lead to new viral replication during the convalescence period. The reactivation and active replication mechanisms of the virus in human EBOVs survivors and/or NHP models of EBOV infection need to be established in order to clarify both the time frame in which EBOVs survivors are still contagious and the contingency measures that need to be taken in order to avoid human-to-human transmission.

## 4. Epidemiology and demographics

EBOVs are emerging and re-emerging zoonotic pathogens, which cause acute hemorrhagic fever and have an elevated case-fatality ratio in humans [125]. The first series of cases of hemorrhagic fever were reported in commercial laboratory facilities located in Marburg and Frankfurt, Germany and in Belgrade, Yugoslavia in August 1967. A total of 37 laboratory workers and their associates became ill after handling monkeys coming from Uganda resulting in 25% fatalities [126]. In June 1976, nine years after the cases reported in Marburg, there was a case in the Democratic Republic of Sudan near the border with the DRC (previously named Zaire). This patient had bleeding, vomiting, and diarrhea. The epidemic persisted from June to November 1976, leaving 284 people infected with 53% mortality. The infection was attributed to *Zaire ebolavirus* (Ebola virus - EBOV) [127]. On September 1, 1976, a man attended the Yambuku Mission Hospital (YMH) in northeastern Zaire with malarial symptoms. After treating the malaria with an intramuscular injection of chloroquine, the symptoms disappeared, but after five days, EBOV disease developed [128]. Mortality in this epidemic was 88%, resulted in 280 deaths and lasted one month [88].

After this second epidemic, based on the evidence, the World Health Organization (WHO) hypothesized that someone ill from Sudan traveled to Zaire spreading the disease. However, Pattyn and colleagues revealed that the epidemic that occurred in Sudan (by SUDV) was caused by a different EBOV isolate than the one that was the etiological agent of the outbreak in Zaire [129].

The second epidemic was apparently due to non-sterilized needles used on patients in the YMH [88]. In 1989, the RESTV species was isolated from cynomolgus monkeys imported from the Philippines that were housed in a laboratory facility in Reston, Virginia, USA that were dying of a hemorrhagic fever. Four out of nine animal handlers were found to have antibodies against RESTV, but none were associated with EBOV disease [130]. Up to now, RESTV has not resulted in symptoms in

humans. The presence of RESTV has been recently discovered in swine on farms in the Philippines. Although many workers had positive antibody titers to RESTV, which confirmed the potential transmission, none of them developed EBOV disease. Moreover, since infection was concurrent with porcine reproductive and respiratory syndrome virus, there is no evidence that EBOV can cause disease in swine [131].

The fourth EBOV discovered was the TAFV, reported in 1994. This virus was previously known as Cote d'Ivoire virus since it had been isolated from an ethnologist doing an autopsy on a chimpanzee found dead in Taï National Park [132,133]. Between 1994 and 1996 four outbreaks of EBOV occurred, three in Gabon and one in DRC [134,135]. Four years later, there was a period in which seven outbreaks in a row occurred from 2000 to 2005. SUDV caused two of these EBOV disease outbreaks, the first one in Uganda with 425 reported cases and a mortality rate of 53% was the largest outbreak ever reported in this country [136]. In contrast, in 2004, the second outbreak which occurred in Sudan only reported 17 cases. The remaining outbreaks were caused by EBOV, four in the Republic of Congo and one in Gabon [137,138].

The last and newly identified EBOV species, BDBV was discovered in 2007 in Bundibugyo, Uganda. This virus species caused an epidemic resulting in 131 infected people with a 32% mortality rate. However, the index case for this epidemic could not be identified [139]. Since the discovery of EBOV in 1976, there have been 23 outbreaks in Africa, 16 caused by EBOV, five by SUDV and two by BDBV. This is in addition to four isolated cases (Table 1) [88,127,131,132,134–136,138–152]. To date, the largest Ebola outbreak is the one associated with EBOV between 2014 and 2016 in West Africa, which infected more than 28,600 individuals [143]. The index case was an 18-month-old boy who was presumably infected by insectivorous bats in a small village in the southern Guinea forests [153]. Because of the poor surveillance systems, the outbreak spread to Conakry, the capital city of Guinea and to the neighboring countries, Liberia and Sierra Leone. This was not the first time an outbreak reached an urban area, since in 2000 a similar situation occurred in Uganda, but the transmission during the outbreak in West Africa was more transmissible and largely contributed to widespread infection [154].

The ninth EBOV disease outbreak started on May 8, 2018 near the town of Bikoro in the Province of Équateur in the north-western part of the DRC. The outbreak was contained within the province and was the first time that therapeutic vaccination was used during the first stages of an outbreak in an attempt to control the infection [155]. The WHO declared the outbreak to have ended on 24 July 2018 [156]. One-week later on August 1, 2018 the second outbreak in DRC was declared in the eastern region of Kivu, which included Ituri Province. There is no evidence linking the two EBOV disease outbreaks in the DRC in 2018. In fact, the National Institute of Biomedical Research, DRC reported that although the two strains belonged to the same species, these outbreaks were completely different [154]. The index case of this outbreak seems to have been the burial of a 65-year-old man who presumably acquired EBOVs infection under non-sanitary conditions [154]. In June 2019, the virus reached Uganda through a 5-year old Congolese boy who traveled with his family seeking health care, but the local health authorities contained the case. A new case on July 17, 2019, 100 km from the eastern region of Kivu, in Goma, obligated the WHO to convene an emergency committee, and to announce a Public Health Emergency of International Concern [157].

The latest update by WHO reporting on the status of the outbreak in the last 21 days was on August 22, 2019. From July 31 to August 20, 2019, a total of 216 cases were reported mainly in Beni, Mandima, and Butembo. During the last few weeks, there has been a demographic expansion of cases, so the number of areas affected has reached 69 with 19 having new reported cases. By the time this review was written a total of 2927 EBOV disease cases had been reported, with 2822 confirmed and 105 probable cases associated with a 67% fatality ratio. Of the total cases, 58% (1697) were female, and 28% (830) were children under 18 years of age. To date, 154 health workers have been infected [157]. The average number of new cases per week is 70, which is extremely high after more than one year of attempts to contain the outbreak. This is partly due to the military conflict that this province has been experiencing since January 2015. The security risks together with resistance within the community hinders the prompt response of the health authorities. This outbreak is the largest EBOV disease outbreak in the DRC and the second-largest epidemic after the one in West Africa between 2014 and 2016 [157].

## 5. Transmission

Over the last 40 years, since the discovery of EBOV, there have been several EBOV disease outbreaks mainly focused in Central and West Africa. The outbreaks have affected human, NHP and duikers

**Table 1**
Cases and outbreaks of Ebola virus disease.

| Year | Country | Species of EBOV | Reported cases | Number of fatal cases (%) | References |
|---|---|---|---|---|---|
| 1976 | England | *Sudan* | 1 | 0 (0) | [147] |
| 1976 | Sudan | *Sudan* | 284 | 151 (53) | [127] |
| 1976 | DRC | *Zaire* | 318 | 280 (88) | [88] |
| 1977 | DRC | *Zaire* | 1 | 1 (100) | [148] |
| 1979 | Sudan | *Sudan* | 34 | 22 (65) | [150] |
| 1989 | Philippines | *Reston* | 3 (asymptomatic) | 0 (0) | [149] |
| 1990 | USA | *Reston* | 4 (asymptomatic) | 0 (0) | [151] |
| 1994 | Cote d'Ivoire | *Taï Forest* | 1 | 0 (0) | [132] |
| 1994 | Gabon | *Zaire* | 52 | 31 (60) | [134] |
| 1995 | DRC | *Zaire* | 315 | 250 (79) | [135] |
| 1996 | Russia | *Zaire* | 1 | 1 (100) | [a] |
| 1996 | South Africa | *Zaire* | 2 | 1 (50) | [a] |
| 1996 | Gabon | *Zaire* | 60 | 45 (75) | [134] |
| 1996 | Gabon | *Zaire* | 37 | 21 (57) | [134] |
| 2000 | Uganda | *Sudan* | 425 | 224 (53) | [136] |
| 2001 | RC | *Zaire* | 59 | 43 (73) | [a] |
| 2001 | Gabon | *Zaire* | 65 | 53 (81) | [a] |
| 2002 | RC | *Zaire* | 143 | 128 (89) | [138] |
| 2003 | RC | *Zaire* | 35 | 29 (83) | [142] |
| 2004 | Russia | *Zaire* | 1 | 1 (100) | [a] |
| 2004 | Sudan | *Sudan* | 17 | 7 (41) | [a] |
| 2005 | RC | *Zaire* | 12 | 10 (83) | [a] |
| 2007 | Uganda | *Bundibugyo* | 131 | 42 (32) | [139] |
| 2008 | DRC | *Zaire* | 32 | 15 (47) | [141] |
| 2008 | Philippines | *Reston* | 6 (asymptomatic) | 0 (0) | [131] |
| 2011 | Uganda | *Sudan* | 1 | 1 (100) | [144] |
| 2012 | Uganda | *Sudan* | 6* | 3* (50) | [145] |
| 2012 | DRC | *Bundibugyo* | 36* | 13* (36) | [145] |
| 2014 | DRC | *Zaire* | 69 | 49 (71) | [146] |
| 2014 | WAE[1] | *Zaire* | 28,610 | 11,308 (39) | [143] |
| 2014 | Italy | *Zaire* | 1 | 0 (0) | [140] |
| 2014 | Mali | *Zaire* | 8 | 6 (75) | [143] |
| 2014 | Nigeria | *Zaire* | 20 | 8 (40) | [143] |
| 2014 | Senegal | *Zaire* | 1 | 0 (0) | [143] |
| 2014 | Spain | *Zaire* | 1 | 0 (0) | [152] |
| 2014 | USA | *Zaire* | 4 | 1 (25) | [143] |
| 2017 | DRC | *Zaire* | 8 | 4 (50) | [a] |
| 2018 | DRC | *Zaire* | 54 | 33 (61) | [a] |
| 2019 | DRC | *Zaire* | 2,927[b] | 1,961[b] (67) | [c] |

This table was constructed based on information at: https://www.cdc.gov/vhf/ebola/history/chronology.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvhf%2Febola%2Foutbreaks%2Fhistory%2Fchronology.html.
DRC: Democratic Republic of the Congo; RC: Republic of the Congo; * Laboratory confirmed cases only; [1] West African Epidemic in Guinea, Liberia and Sierra Leone.

[a] https://www.cdc.gov/vhf/ebola/history/chronology.html.

[b] Situation as at August 20, 2019.

[c] Based on information at https://www.who.int/csr/don/22-august-2019-ebola-drc/en/.

(antelopes) (Fig. 4). The high mortality rate in these animals suggest that these are not natural hosts or reservoirs [158]. The increase in EBOV disease outbreaks since 2000, may be due to augmented contact between humans and wildlife, increased deforestation, as well as climate changes [159]. Although the index case in most of the outbreaks is unknown, there is always a spillover event, which is the transmission from an animal to a human. Even though up to date there is no conclusive reservoir for any EBOV, the most dominant hypothesis refers fruit bats as the most likely EBOVs reservoir [160–162]. However, to date there has been neither a live replication competent EBOV isolated from a fruit bat nor has been a case of a fruit bat hunter reported as an index-case in any outbreak [163].

Most of the studies have focused on EBOV, but differences on ecology, season of appearance, index case infection and incubation period may determine different reservoirs [164]. Of all EBOVs, RNA from EBOV has been detected in 3 species of African fruit bats, duikers (*Cephalophus species*), gorillas (*Gorilla gorilla*), chimpanzees (*Pan troglodytes*), and several rodents [160,165,166]. Besides bats, the other animal species mentioned might also serve as intermediate hosts infected by bats [167]. Antibodies against RESTV have been detected in Asian bats, whereas no serology or PCR identification of SUDV and BDBV has so far been reported [164].

EBOV disease is spread to humans because of handling bush meat and contact with infected fruit bats used as a source of protein in those regions [168]. The incubation period for onset of EBOV disease is 5.3–12.7 days for EBOV, 3.35–12 days for SUDV, and 6.3–7 days for BDBV [164]. The main mode of transmission in human outbreaks is human-to-human transmission through direct contact with broken skin or mucous membranes by bodily fluids such as urine, saliva, sweat, feces, vomit, breast milk and semen [169–171]. It is noteworthy to note that EBOV RNA was detected in semen up to 18 months after recovery from EBOV infection [169].

## 6. Clinical manifestations

One of the major barriers for the early identification of EBOV disease is the non-specificity of signs and symptoms as well as the proven variances in clinical manifestations among the different species of EBOVs. It is well known that a major threat in EBOVs control is the delay in case identification, mainly due to the lack of training and experience on the part of physicians that take care of patients on the front line of treatment and diagnosis in endemic areas [4]. The primary clinical approach includes a travel assessment to identify the country of contagion, timeframe, and other likely infectious conditions that may overlap with EBOV disease [172]. As discussed above, outbreaks have taken place at different times and in different countries, and some reports suggest different clinical patterns of presentation across epidemics (Table 2) [88,127,173–175]. These viruses differ in their characteristics and fatality exemplified by the asymptomatic human infections reported thus far for the RESTV and the acute hemorrhagic fever and death commonly associated with BDBV, SUDV, and EBOV infections that have been reported to have 25%, 50%, and 80% rate of fatality, respectively [4,170]. For example, in the Yambuku outbreak in 1976, hemorrhage was present in 96.5% of probable cases [88], whereas their prevalence was as low as 18% in the recent west Africa outbreak [174]. This information is pivotal in early clinical suspicion and may help in releasing timely alerts, especially in those countries outside Africa such as USA and Spain, which formerly reported imported cases [4].

The clinical presentation of EBOV disease ranges from asymptomatic/mild infection to severe disease characterized by hemorrhagic manifestations, accompanied by shock, organ dysfunction, and death [4]. The natural history of signs and symptoms of EBOV disease could be classified in three phases: 1. Contagious/prodromal phase, 2. Fatal disease, and 3. Chronic/convalescence phase [4]. After infection with EBOVs, between days 2 and 21, patients develop non-specific acute symptoms including malaise, high fever, fatigue, myalgia, and arthralgia. Interestingly, at this stage, a study done in Sierra Leone found that 14 (7.5%) patients with positive anti-EBOV GP antibodies did not develop symptoms compatible with EBOV disease neither at the beginning of the disease nor during the quarantine period [176]. This suggests that some patients do not develop clinical features at the contagious phase and some of them do not develop an overt EBOVs disease. Whether these patients were able to transmit the infection/disease remains unknown [177]. These individuals constitute a source of unique and important information to decipher new pathways of disease and treatment.

Following initial symptoms, between days 7 and 14, patients may present with nausea, vomiting, diarrhea, and melena [127]. At this phase, patients develop a rapid fluid loss of about 10 L per day and other less common symptoms such as dyspnea, cough, hiccups, chest and abdominal pain [178]. All these signs and symptoms are considered a prelude to the development of a more severe form of the disease.

**Fig. 4.** Ebola virus transmission. Fruit bats are considered natural reservoirs of EBOVs and these seem to infect NHP and duikers, which mostly constitute the spillover event (Lines in red). The virus disseminates from person to person, potentially affecting a large number of people (Lines in blue). The virus spreads through direct contact with broken skin or mucous membranes in the eyes, nose, or mouth and semen. However, EBOVs may spread through the handling and consumption of bushmeat (Lines in yellow).

**Table 2**
Clinical manifestations of Ebola virus disease in the acute phase in different outbreaks.

| Sign and symptoms (%) | Zaire 1976[a] [88] | Sudan 1976[a] [127] | Bundibugyo 2007[b] [173] | West Africa 2014[a] [174] | Congo 2018[a,b] [175] |
|---|---|---|---|---|---|
| Fever | 231/231 (100) | 183/183 (100) | 55/55 (100) | 1002/1151 (88) | 40/42 (95) |
| Diarrhea | 228/231 (99) | 148/183 (81) | 47/54 (87) | 72171099 (66) | 23/32 (72) |
| Nausea/vomiting | 225/231 (97) | 108/183 (59) | 48/54 (89) | 753/1114 (68) | 22/35 (63) |
| Bleeding | 223/231 (97) | 130/183 (71) | 30/56 (54) | 168/932 (18) | 14/43 (33) |
| Headache | 210 (91) | 183/183 (100) | 48/53 (91) | 553/1035 (53) | 19/33 (58) |
| Oral/throat lesions | 208/231 (90) | NA | NA | NA | NA |
| Conjunctivitis | 208/231 (90) | NA | NA | 137/658 (21) | 12/35 (34) |
| Cough | 208/231 (90) | 90/183 (49) | NA | 194/655 (30) | NA |
| Sore throat | 207/231 (90) | 115/183 (63) | NA | 102/467 (33) | NA |
| Myalgia | 206/231 (89) | NA | 44/50 (88) | 385/990 (39) | 19/34 (56) |
| Abdominal pain | 201/231 (87) | NA | 47/53 (89) | 439/992 (44) | 22/35 (63) |
| Arthritis/arthralgia | 193/231 (84) | NA | NA | 374/950 (39) | 18/37 (49) |
| Edema | 193/231 (84) | NA | NA | NA | NA |
| Jaundice | 191/231 (83) | NA | NA | 65/627 (10) | NA |
| Lymphadenitis | 141/231 (61) | NA | NA | NA | NA |
| Abortion | 73/231 (32) | NA | NA | NA | NA |
| Fatigue | NA | NA | 49/50 (98) | 866/1133 (77) | 37/41 (90) |
| Anorexia/weight loss | NA | NA | 43/51 (84) | 681/1055 (65) | 37/41 (90) |
| Dysphagia | NA | NA | 27/51 (53) | 169/514 (33) | 10/33 (30) |
| Chest pain | NA | 152/183 (83) | NA | 254/686 (37) | 15/34 (44) |
| Dyspnea | NA | NA | 23/50 (46) | 155/665 (23) | 11/32 (34) |
| Rash or desquamation | NA | 95/183 (52) | 25/54 (46) | 37/642 (6) | NA |
| Hiccups | NA | NA | 16/51 (31) | 108/947 (11) | NA |
| Eye pain | NA | NA | NA | 48/622 (8) | NA |

[a] Probable cases.
[b] Confirmed cases. NA: Not available.

Predictors of mortality at this stage might vary and could be age and sex dependent. It is well known that young age is a predictor of mortality, and children tend to suffer more severe disease [5,6]. Furthermore, rates of mortality are higher in men and in patients older than 40 years [7,8]. Pregnant women exhibit the highest rates of mortality which have been reported to be as high as 95.5% with hemorrhagic manifestations as the principal cause of death [179,180]. Physicians must be aware of these risk factors in the management of patients with EBOV disease.

Following the contagious/prodromal phase, approximately between days 22 and 35, patients develop life-threatening manifestations characterized by septic shock, metabolic acidosis and organ failure [4]. This is secondary to both fluid loss and hemorrhagic events, including hematemesis, blood in the stool, bleeding gums, bloody nose, bloody cough, and hematuria [174]. Hypoperfusion following septic shock in these patients causes renal failure and muscle break down which,

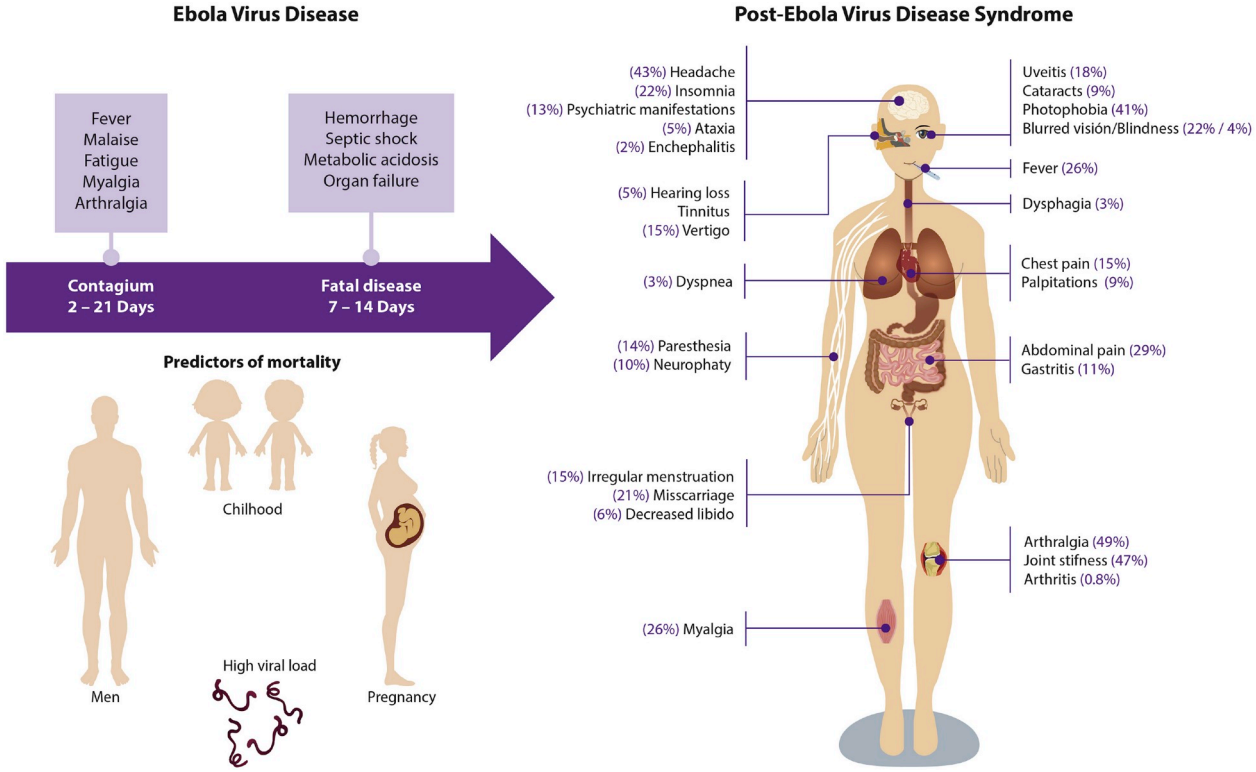


**Fig. 5.** Clinical manifestations of Ebola virus disease in acute and chronic stages.

together with a high viral load, are consistently considered predictive factors of mortality in EBOV disease [181,182]. In addition, EBOVs infection is commonly observed in poverty-stricken areas and under developed countries, which face a high burden of additional infectious diseases in their environment such as malaria that could increase the deleterious effects in this condition [4,181].

### 6.1. Post-Ebola virus disease syndrome

As noted above, the mortality rates of EBOV infection in these patients is high. However, some subjects survive and may develop chronic manifestations. It is well known that EBOVs may persist from weeks to months in immunologically privileged sites that allow the re-emergence of disease during the convalescent period [4]. For example, some reports showed the re-emergence of EBOV disease secondary to sexual transmission after 16 months of clinical improvement [183]. This is of interest from the public health perspective since counseling for safe sex after clinical recovery should be implemented, and the local facilities, if possible, should test for the presence of the virus in the seminal fluid [4].

Patients that survive the acute phase of EBOV disease may show chronic rheumatological, ophthalmological, and neurological manifestations that include arthralgia, arthritis, uveitis, and encephalitis [184–187]. This entity has been recently named "*post-EBOV disease syndrome*", and it includes all the clinical manifestations presented in EBOV survivors during the convalescent stage (Fig. 5) [188]. The *post-EBOV disease syndrome* has emerged as a novel viral threat given the high burden of this condition in populations with post-EBOVs outbreaks as well as the lack of strategies in diagnosis, management, and prevention of such sequelae.

Results of a study performed by Pers et al. [189] showed that 8.8 months after clinical discharge of EBOV disease patients, 45% of them showed both inflammatory and mechanical pain, and 77% exhibited low back pain. Articular compromise was more common in large joints (73%) than in small joints (41%) with symmetrical distribution in 90% of subjects. In addition, in the study done by Etard et al. [186] the authors found that a large percentage of patients, developed neurosensory disorders, musculoskeletal symptoms, and ophthalmological manifestations (i.e., uveitis) after 800 days of follow up and to a lesser degree, deafness. This suggests that survivors exhibit a heterogeneous clinical presentation with different chronic conditions that put a high burden on quality of life, that may also result in social stigma and discrimination [10].

Although some reports have shown several clinical sequelae in EBOVs survivors, little is known about their frequency of presentation nor the clinical domains impaired by this condition. Thus, we reviewed those clinical manifestations and their presentation rate in this subset of patients through a systematic review of literature (For methods see: Supplementary material 1). The Preferred Reporting Items for the Systematic Reviews and Meta-analyses (PRISMA) flow-chart is shown in supplementary material 2. General, musculoskeletal, cutaneous, cardiovascular, gastrointestinal, neurological, ocular, auditory, genitourinary, among other manifestations were observed in the different studies done on EBOVs survivors (Supplementary material 3).

The most common long term sequelae were arthralgia, joint stiffness, headache, and photophobia with a frequency of more than 40% (Table 3) [11,186,189–221]. It is well known that during the acute phases of the disease, patients show general manifestations that include fever, fatigue, weakness, anorexia, and chest pain. However, as shown in Table 3, these manifestations are still present in about 25% of patients with *post-EBOV disease syndrome*. This suggests that these clinical manifestations are still present even in those subjects during the convalescent phase and may contribute to the confusion in the identification of new cases in areas where EBOVs is endemic. We submit that further analysis intended to evaluate the role of these symptoms in the identification of either acute or convalescent cases is warranted.

Most of the patients with *post-EBOV disease syndrome* present musculoskeletal manifestations including arthralgia, joint stiffness, myalgia, and to a lesser extent, arthritis. In the study done by Clark et al. [190] they demonstrated chronic health issues in 49 survivors compared to 157 matched controls after two years of infection. Note that survivors were more likely to show arthralgia in large joints and myalgia. In another study, in Kikwit, DRC, the authors showed sequelae up to 21 months after infection. Arthralgia and myalgia were significantly more frequent in the EBOVs survivors compared to

**Table 3**
Clinical manifestations of patients with post-Ebola virus disease syndrome.

| Systemic Compromise | Clinical Manifestations | Frequency (%) |
|---|---|---|
| General Manifestations | Fever | 496/1877 (26) |
| | Fatigue | 612/2719 (23) |
| | Weakness | 29/135 (22) |
| | Parotid Pain | 24/135 (18) |
| | Anorexia | 415/2439 (17) |
| | Chest Pain | 225/1503 (15) |
| | Palpitations | 143/1575 (9) |
| | Dizziness | 68/1021 (7) |
| | Dyspnea | 3/113 (3) |
| Musculoskeletal Manifestations | Arthralgia | 1894/3845 (49) |
| | Joint Stiffness | 44/93 (47) |
| | Myalgia | 744/2894 (26) |
| | Pain with chewing | 32/137 (23) |
| | Jaw Pain | 30/137 (22) |
| | Back Pain | 250/1253 (20) |
| | Neck Pain | 46/951 (5) |
| | Arthritis | 7/904 (0.8) |
| Cutaneous Manifestations | Xerostomia | 68/180 (38) |
| | Hair loss | 153/512 (30) |
| | Rash | 166/1427 (12) |
| | Skin Pigmentation | 17/860 (2) |
| Gastrointestinal Manifestations | Abdominal or pelvic pain | 865/3031 (29) |
| | Gastritis | 137/1297 (11) |
| | Dysphagia | 29/909 (3) |
| Neurological Manifestations | Headache | 1340/3105 (43) |
| | Insomnia | 216/974 (22) |
| | Paresthesia | 4/28 (14) |
| | Psychiatric manifestations[a] | 304/2267 (13) |
| | Neuropathy | 4/38 (10) |
| | Ataxia | 1/20 (5) |
| | Encephalitis | 1/38 (3) |
| | Tremor | 2/880 (0.23) |
| Auditory Manifestations | Vertigo | 3/20 (15) |
| | Hearing Loss or tinnitus | 129/2805 (5) |
| Ocular Manifestations | Photophobia | 218/529 (41) |
| | Tearing | 195/573 (34) |
| | Ocular Motility Disorders | 7/23 (30) |
| | Xeroftalmia | 124/474 (26) |
| | Blurred Vision | 599/2670 (22) |
| | Eye redness | 190/914 (21) |
| | Uveitis | 947/5338 (18) |
| | Eye floaters | 46/277 (17) |
| | Ocular pain | 234/1424 (16) |
| | Flashes of light | 43/277 (16) |
| | Cataracts | 427/4900 (9) |
| | Keratoconjunctivitis | 13/189 (7) |
| | Conjunctivitis | 78/1253 (6) |
| | Blindness | 46/1076 (4) |
| | Iiridocyclitis | 12/822 (2) |
| | Episcleritis | 6/341 (2) |
| | Glaucoma | 12/968 (1) |
| | Interstitial keratitis | 3/341 (1) |
| Genitourinary and Gynecological Manifestations | Miscarriage | 42/196 (21) |
| | Irregular Menstruation | 197/1333 (15) |
| | Stillbirth | 6/48 (13) |
| | Testicular Pain | 16/154 (10) |
| | Erectile Dysfunction | 42/453 (9) |
| | Decreased libido[b] | 97/1539 (6) |
| | Testicular edema | 3/104 (3) |

[a] This includes: depression, memory loss, hallucinations, and anxiety disorders.
[b] Includes men and women.

uninfected household contacts [216]. Thus, arthralgia may be considered one of the most common manifestations in the *post-EBOV disease syndrome*.

Anatomical distribution of arthralgia in EBOV survivors varies across studies. Several reports suggest a symmetrical distribution of arthralgia affecting back, knees, small joints, hips, wrists, neck, shoulders, ankles, and elbows [222]. In the study done by Pers et al. [189] the authors found that up to 91% of patients showed symmetrical distribution of arthralgia, and 59% of survivors exhibited polyarticular compromise (i.e., > 4 joints involved). In that cohort, about 9% (n: 4/44) of patients presented synovitis. In our review, only seven out of 904 survivors (0.8%) exhibited arthritis during the convalescent period. Whether this low frequency is secondary to a lack of systematic physical examinations is unknown, and upcoming studies should evaluate the presence of synovitis in survivors as well as assess the likely development of autoimmune diseases such as RA.

Ocular compromise is another clinical domain that is commonly reported in the literature on EBOVs survivors. In select reviews, we found that tearing, ocular motility disorders, exophthalmia, blurred vision, and eye redness were the most common symptoms. Note that uveitis was presented in about 18% of patients, and 9% of survivors showed cataracts, which put a high burden on quality of life for these survivors. Some reports have shown an association between articular compromise and ocular manifestations such as uveitis [184,196] that resemble spondyloarthritis [222]. Other manifestations such as ocular pain, flashes of light, keratoconjunctivitis, blindness, episcleritis, and glaucoma are also found in patients with *post-EBOV disease syndrome*.

A lower proportion of patients with *post-EBOV disease syndrome* may also show cutaneous manifestations that include xerodermia, hair loss or alopecia, rash and skin pigmentation abnormalities. These manifestations have been closely related to hematological compromise such as prolonged anemia and leukopenia [147]. This may suggest an association with conditions such as SLE. Although this is interesting, little evidence exists about the likely role of EBOVs in the development of autoimmune conditions. A recent study by Fausther-Bovendo et al. [99] found that EBOVs induce the production of auto-antibodies against dsDNA and heat shock protein 60 secondary to polyclonal B-cell activation. In addition, they found that these auto-antibodies accumulate in fluids of eyes, brain, and joints of mice that survive the EBOVs challenge. Whether this could explain the chronic conditions observed in EBOV disease survivors deserves further study.

Other clinical manifestations in *post-EBOV disease syndrome* include neurological symptoms such as headache, insomnia, and paresthesia. Psychiatric conditions such as memory loss, depression, and anxiety are common in these patients. Together with these clinical features, vertigo, hearing loss and tinnitus are also found in about 15% of cases. In a recent meta-analysis, Xu et al. [223] found that survivors were more likely to develop hearing loss in comparison to controls (OR = 7.50, 95% CI, 3.91–14.39). Thus, clinicians must be aware of neurological compromise associated with EBOVs infection.

As discussed above, pregnant women have a high risk of mortality during the initial phases of the disease. During the convalescent phase, they may present with miscarriage and stillbirth with a frequency of 21.3% and 13%, respectively. Non-pregnant women may develop gynecological manifestations such as dysmenorrhea, oligomenorrhea, or menorrhagia with a 15% frequency. Current reports also support the persistence of EBOVs in seminal fluid of men [183]. Regarding this, it was reported that men can develop testicular pain, erectile dysfunction, testicular edema, and decreased libido which supports the notion that this virus can persist in the genitourinary tract and thus could be sexually transmitted.

The natural history of this syndrome is still unknown; however, some recent studies have shown the evolution of symptoms in survivors. In the study done by the PREVAIL III Study Group [11], the authors followed patients for intervals of six months to one year. At the end of the follow-up period, the authors found that the frequency of symptoms such as arthralgia, headache, fatigue, muscle pain, memory loss, neurological and abdominal findings had decreased in the cohort. In addition, the cases of uveitis increased at the end of the follow-up in comparison to the beginning of the study. This suggests that chronic manifestations in *post-EBOV disease syndrome* may decrease over time, and other sequelae such as uveitis may last longer. Further analyses and a longer follow-up studies are warranted to clarify the frequency of these manifestations.

## 7. Diagnosis

For several decades, diagnosis of EBOVs was made either by virus isolation in cell culture (i.e., Vero cells), use of enzyme-linked immunosorbent assay (ELISA) that detect antibodies, and/or electron microscopy [4]. IgG and IgM EBOVs-antigen specific antibodies were commonly detected by ELISA and immunofluorescence assay using previously infected cells with EBOVs as antigens [224]. Nevertheless, to do these tests, BSL4 facilities were required, and countries with the highest burden of EBOV did not have the infrastructure to carry out these procedures [4]. These basic facts suggested that other diagnostic tools were necessary to do molecular diagnosis, especially in poverty-stricken areas and remote areas to improve epidemiologic surveillance.

In recent years, the real-time reverse transcriptase polymerase chain reaction (qRT-PCR) has emerged as the “Gold-standard” in diagnosis of EBOVs. Rieger et al. [225] validated the analytical sensitivity of the Filovirus Screen kit and Zaire Ebolavirus kit for diagnosing EBOVs disease. The former detected EBOV, SUDV, TAFV, BDBV, and RESTV with a sensitivity of 95% and showed good discrimination between species. The latter, which only recognizes EBOV, showed a higher detection sensitivity at low RNA concentrations than the Filovirus Screen kit. Other commercial kits are available on the market, and they are more specific for a single species of the EBOVs. EBOV and SUDV are considered the most common pathogens affecting humans, thus their identification during the early stages of outbreaks is of great interest. In this respect, when a precise species is suspected, virus-specific assays are preferred since they are more sensitive than assays that may detect the family or genera of these viruses [226].

Technological platforms have been recently developed to improve field implementation of molecular diagnosis in remote areas. The Xpert® Ebola (Cepheid) system, integrates RNA extraction, amplification, and detection [227,228]. This platform detects GP and NP genes of EBOVs and gives results within 90 min with a sensitivity of 100% [227]. A recent study in Liberia showed that this technology was easily introduced in national protocols, and technicians trained in remote areas found it easy to use. As a result, we submit that this technology could help to strengthen outbreak preparation and response in future EBOV disease emergencies [229].

Other technologies have been developed to decrease cost, time, and assist bed-side diagnosis. The rapid diagnostic test based on lateral flow immunoassays that require minimal training to operate, give results in minutes, and are useable in bed-side settings. The ReEBOV Antigen Rapid Test kit that identifies the VP40 viral matrix protein was shown to have 100% sensitivity and 92% specificity in both point-of-care and reference laboratory testing on patients in Sierra Leone [230]. Another option among these types of tests is the EBOV Antigen Detection K-SeT (EBOLA AgK-SeT), which has a sensitivity of 88.6% and specificity of 98.1% [231]. Although the sensitivity and specificity of these tests varies, their utility in outbreak response and surveillance should not be under-estimated. In addition, clarifying their role in the management of EBOVs is aimed at encouraging the development of on-the-field studies [4]. As the outbreaks of EBOVs are most common in poverty-stricken areas, economic analysis of these tests is of interest for policy makers in those areas.

Patients frequently show a high viral load about 3–6 days after the onset of symptoms [232]. However, a negative qRT-PCR in the early stages of the disease, in select cases, could correspond to a false-

**Table 4**
Therapies used for EBOVs infection.

| Treatment | Description | Results | References |
|---|---|---|---|
| Convalescent plasma | Convalescent whole blood or plasma from patients who have survived from EBOVs disease. | Convalescent plasma with high levels of anti- EBOV antibodies had a great effect on viral load control. | [279] |
| | | Rhesus monkeys infected with EBOV-Makona were treated with heterologous convalescent plasma. Experimental results show that plasma is not sufficient to provide 100% protection when administered at the onset of viremia. | [280] |
| | | Ebola Tx trial (NCT02342171) evaluated the efficacy of convalescent plasma in Conakry-Guinea during 2014–2015. | [281] |
| | | Transfusion of convalescent plasma in 84 Guinean patients with confirmed EBOVs disease was not associated with a significant improvement in survival. In West Africa, two clinical studies were conducted during the 2014–2015 outbreak: Ebola-CP consortium in Sierra Leone and the EVD001 trial (NCT02333578) in Liberia. None of the ongoing clinical studies have informed their results. | [282] |
| MAb114 | MAb114 is a monoclonal antibody isolated from a survivor of the DRC. | Monotherapy with mAb114 protected macaques from lethal EBOV infection. | [283] |
| | | A phase I trial (NCT03478891) demonstrated tolerability, safety, and linear pharmacokinetics of mAb114 treatment. | [17] |
| MIL77E | MIL77E is a chimeric cocktail of mAb obtained from Chinese hamster ovarian cells. This cocktail uses two ZMapp antibodies (i.e., c2G4 and c13C6). | MIL77E exhibited 100% protection in NHP after a lethal dose of EBOV-Makona. | [252] |
| ZMapp | ZMapp is a mixture of three humanized monoclonal antibodies (i.e., c2G4, c4G7, and c13C6) against the EBOV GP epitopes. ZMapp is produced in genetically modified plants (e.g., *Nicotiana benthamiana*). | A randomized controlled trial in West African patients showed that ZMapp is beneficial. However, this antibody cocktail did not meet the statistical threshold of efficacy. | [253] |
| | | ZMapp applied on five post-challenge in NHP, reduced 100% of the infection in rhesus macaques. This treatment generated a complete recovery with decreased liver enzymes, hemorrhages of the mucosa and petechia. | [254] |
| | | ZMapp administered to mice through a viral vector conferred protection against systemic and airway-acquired EBOV infection. | [255,256] |
| | | In mice, ZMapp reduced the mobility of virions in the mucus of the respiratory tract and the reduced the access of EBOV to the epithelium of the respiratory tract. | [257] |
| REGN-EB3 | REGN-EB3 is a combination of three human monoclonal antibodies (i.e., REGN3470-3471-3479) targeting three non-overlapping epitopes on EBOV. | A phase I study (NCT002777151) demonstrated safety, pharmacokinetics and immunogenicity of treatment in humans. | [16] |
| | | A study showed a high-level of post-exposure protection against lethal EBOVs disease in NHP. | [258] |
| TKM-100802/TKM-130803 | siRNAs against the gene products encoding for viral antigens: VP24, VP35, and L polymerase. | Treatment with TKM-100802 in individuals with occupational exposure to EBOVs in West Africa prevented the spread of infection. | [259] |
| | | TKM-130803 administered by intravenous infusion did not improve the survival of adult patients with EBOVs disease. | [260] |
| | | African patients treated with TKM-100802 and convalescent plasma recovered without serious long-term sequelae. | [261] |
| Remdesivir (GS-5734) | Remdesivir is a 1′-cyano-substituted adenosine nucleotide analogue prodrug with antiviral activity against multiple variants of EBOVs and other filoviruses. | In rhesus monkeys infected with EBOVs, intravenous administration of Remdesivir significantly decreased virus replication and protected against lethal disease. | [262] |
| | | A newborn with congenital infection survived after treatment with ZMapp and Remdesivir. | [263] |
| | | Remdesivir decreased viremia and mortality in NHP infected with EBOVs. | [264] |
| BCX4430 | BCX4430 is a synthetic adenosine nucleoside analogue, its function is the inhibition of viral RNA polymerase activity. | Post-exposure intramuscular administration of BCX4430 protected against infection by EBOV and Marburg virus in rodents. | [15] |
| | | A first phase I study in healthy subjects (NCT02319772) demonstrated tolerability and safety. | [265] |
| Favipiravir (T-705) | Chemical agent derived from Pyrazinecarboxamide. Favipiravir inhibits virus replication through the RNA polymerase enzyme. | A retrospective study showed that Favipiravir increased survival in Guinean patients. | [13,14] |
| | | Treatment was associated with prolonged survival and reduced viral load in patients at Sierra Leone-China Friendship Hospital. | [266] |
| | | Efficacy in individuals with low to moderate levels of virus. | [267] |
| | | High doses prolonged survival in NHP infected with EBOVs. | [268] |
| | | Knockout mice for IFNR $\alpha/\beta/\gamma$ (IFNAGR KO) treated with Favipiravir reduced 83% of EBOVs infection. | [269] |
| | | IFNAGR KO mice treated with Favipiravir showed a rapid elimination of the virus, and a decrease in the biochemical parameters of the severity of disease. | [270] |
| | | Favipiravir reduced Marburg virus particles and RNA levels in a mouse model. | [271,272] |
| AVI-6002 | AVI-6002 is an experimental drug consisting of 2 PMO. AV-7537 (*VP24* gene) and AV-7539 (*VP35* gene) target viral mRNA encoding EBOV. | AVI-6002 suppressed the disease in NHP infected with EBOV. | [273] |
| | | Two single dose studies showed the pharmacokinetics and safety of AVI-6002. | [274] |
| Brincidofovir | Brincidofovir is the 3-hexadecyloxy-1-propanol lipid conjugate of the acyclic nucleoside phosphonate cidofovir. | Brincidofovir was necessary for *in vitro* antiviral activity against EBOV. | [275] |
| | | | [276,277] |

(*continued on next page*)

**Table 4** (*continued*)

| Treatment | Description | Results | References |
|---|---|---|---|
| FX06 | FX06 (MChE-F4Pharma) is an experimental fibrin-derived peptide. | Two studies did not show conclusive data about the role of Brincidofovir in survival rate due to the small sample size. A German patient treated with 3 doses of FX06 along with ventilatory support, antibiotic treatment and renal replacement therapy had virological remission. This showed that FX06 could be used in supportive therapy. | [278] |

DRC: Democratic Republic of Congo; NHP: Non-Human Primates; siRNAs: small interfering RNA; EBOV: Ebola virus.

negative result and a new test could be necessary 72 h after clinical admission [225]. Physicians must be aware of the possible species that could be the cause of an outbreak as well as the viral load that has been shown to be correlated with poorer outcomes during the early stages of the disease [232–235]. In this respect, it is well known that cycle threshold values obtained by qRT-PCR are negatively correlated with viral load. In the West African outbreak in 2014, the initial viremia in EBOV disease survivors was found to be lower than in non-survivor subjects, and these concentrations were associated with length of the outbreak [234]. Kinetic analyses of the levels of viremia showed that these differences appear on the second day of EBOV disease onset, and survivors generally exhibit lower mean peak viremia levels compared to non-surviving patients on the fifth and seventh days, respectively. Decay of viremia in these patients was faster in survivors than non-survivors and thus suggests that this likely due to a better immunological response in the former group [235].

As previously discussed, some patients do not develop symptomatology at the beginning or during the quarantine period. In these cases, viremia is low, and immunological tests directed at measurements of EBOV specific IgM and IgG are the tests of choice [236,237]. Patients that progress to the development of chronic disease show detectable EBOV-RNA by qRT-PCR after remission of symptoms [184,187,216,238–240]. In post-mortem cases, the diagnosis of EBOV disease is usually done by qRT-PCR from an oral swab sample [241,242].

## 8. Therapeutic strategies for EBOV infection

Currently, a variety of treatments for EBOV disease have entered clinical trial phase. At present, there is only a FDA-approved vaccine for EBOVs prevention, the rVSV-vectored vaccine which provided 100% protection [243]. Supportive medical care should be provided to the patient based on clinical characteristics. Initially, broad spectrum antibiotics, opiates or anti-emetic medications, and non-steroidal anti-inflammatory drugs can be used [178]. The use of oral or parenteral fluids are very useful in early stages of the disease, and hemodynamic stabilization through the administration of crystalloid fluids is considered the standard of care in EBOV disease. Management of confirmed and suspected cases should include regular measurement of biochemical parameters that may accelerate electrolyte balance recovery and prevent renal failure [244]. In addition, timely treatment with oxygen supplementation, mechanical ventilation, or renal replacement therapy has been shown to prevent the death of critically ill patients with this condition [245]. Anti-coagulants such as recombinant nematode anticoagulant protein c2 (rNAPc2) and recombinant human activated protein C have been used to prevent hemorrhages with promising results in the late phases of the disease [246,247].

Prevention of EBOV disease at present consists of pre-exposure prophylaxis (i.e., protective vaccines) and treatment consists of post-exposure prophylaxis, or post-exposure treatment (i.e. therapeutic vaccines and antiviral agents). Anti-viral treatments should be administered to subjects with suspected or confirmed contact with primary cases of EBOV disease. Such therapeutic strategies have been shown to reduce severity of disease, transmission of the virus, and duration of clinical presentation with several methods of administration (e.g. oral, intramuscular or intravenous) depending on the clinical manifestations and progression of the disease [248].

In November 2014, the WHO published a brief list of treatments and vaccines that were under evaluation [249]. The EBOV disease public health emergency is a challenge for the evaluation of candidate vaccines or antivirals agents. Therefore, different therapeutic agents were used in the EBOVs West Africa outbreak during 2013–2016. Health regulatory authorities established a review committee of therapies based on the WHO ethical protocol (MEURI, Monitored Emergency Use of Unregistered and Experimental Interventions). The first agent approved was a monoclonal antibody MAb114 (with specificity for the receptor binding domain of the Ebola GP), followed by biological products such as REGN-EB3 (a cocktail of 3 monoclonal antibodies) and ZMapp (also a cocktail of 3 monoclonal antibodies but made in plants), and finally the anti-virals, Remdesivir and Favipiravir [250].

In recent years, researchers have used reverse genetics to identify new targets within the viral genome and produce recombinant viruses [251]. Anti-viral compounds also include antisense therapies and small immunotherapeutic molecules (Table 4) [13–17,252–283]. The most innovative therapies are small molecules targeting L (RNA dependent RNA polymerase and the large protein, L) involved in viral replication. These include nucleoside analogs that are transformed intracellularly into the active nucleoside triphosphates. The anti-sense treatments are small-interfering RNAs (siRNAs) and phosphorodiamidate morpholino oligomers (PMOs). siRNAs stimulate degradation of mRNA transcripts and PMOs interfere with translation [284]. The viral GP is the common target of immunotherapeutic agents. Monoclonal antibodies directed at GP exhibit neutralizing activity by binding GP and the glycan capsid [285]. Another immunotherapeutic agent that has shown efficiency in mice and *in vitro* assays is the mannose-binding lectin (MBL) [286].

EBOVs use host proteins for entry and replication. Cathepsins (e.g., CatB and CatL) are cysteine proteases that cleave the viral GP before viral entry. Expectedly, cathepsin inhibitors decrease viral entry and thus the replication of EBOVs in cultured cells [83]. Other host proteins involved are Niemann-Pick C1 (NPC1, a protein involved in intra-cellular cholesterol transport) and TIM-1 (T cell immunoglobulin and mucin domain known to play a role in T cell function). NCP1 binds the GP after cathepsin-mediated excision. MBX2254 and MBX2270 are novel therapies that inhibit GP from binding to NPC1, and thus hinder *in vitro* infection [287]. The benzylpiperazine adamantane diamide-derived compound reduces EBOVs infection by blocking the binding of NPC1 and GP [288]. In addition, TIM-1 binds to the receptor binding domain of EBOVs. The decrease in the cell surface expression of TIM-1 by RNA interference reduces EBOV infection in Vero cells *in vitro*. ARD5, a monoclonal antibody directed to the IgV domain of TIM-1 inhibits EBOVs binding [289].

Another strategy for the treatment of EBOV disease is the use of immunomodulators such as cytokines and chemokines. The role of immunomodulators is to improve the immune response, thus favoring viral elimination. Some researchers have described type I IFNs as possible treatments. The finding that therapy using ZMAb that protects 50% of the NHP from infection when combined with IFN-α increases protection to 100% exemplifies such additive therapies [290]. In addition, IFN-β therapy also prolongs the survival of rhesus macaque infected with EBOVs [291].

### 8.1. Vaccine development

The high lethality of the Ebola epidemic of 2014 prompted an acceleration in the development of different forms of vaccines that include both non-replicative vector-based vaccines and replicative vector-based vaccines. The former group uses non-replicative vectors that code for GP or another viral antigen with deletions in genes crucial for viral replication. These vaccines need high doses to produce a significant response and have high tolerability. The attenuated virus of Venezuelan equine encephalitis (VEE) is a candidate vector used for the preparation of candidate vaccines for EBOVs. The EBOV GP or NP genes are introduced into the VEE RNA. Recombinant replicons are packaged in VEE replicon particles (GP-VRP and NP-VRP). This vaccine has been tested in guinea pigs and BALB/c mice. GP-VRP alone or with NP-VRP protected guinea pigs and BALB/c mice from EBOVs infection. In contrast, vaccination with NP-VRP only protected mice [292]. Another study showed that 75–80% of C57BL/6 mice immunized with NP-VRP survived the lethal challenge of EBOVs [293]. *Cynomolgus macaques* immunized with a dose of GP-VRP were completely protected following lethal challenge of EBOVs [294].

In 2000, the vaccination strategy with adenoviral vectors demonstrated cellular and humoral immunity in *Cynomolgus macaques* [295,296]. The phase I trial (NCT00374309) of the recombinant adenovirus serotype 5 vaccine (rAd5) coding for EBOV GP demonstrated safety and immunogenicity [297]. After the 2014 outbreak, researchers developed a vaccine based on Ad5 vectors (Ad5-EBOV) with the new epidemic strain isolated from the Guinea outbreak. A phase I trial in China (NCT02326194) demonstrated its safety, tolerability, and immunogenicity [298].

In 2015, a phase II clinical trial of experimental Ad5-EBOV was initiated in Sierra Leone (NCT02575456). To avoid pre-existing immunity for human Ad5, other vaccines were developed with chimpanzee adenovirus serotype 3 (ChAd3) vector such as monovalent recombinant ChAd3-vectored vaccine expressing wild-type GP from EBOV (ChAd3-EBO-Z) and bivalent recombinant ChAd3-vectored vaccine expressing wild-type GP from EBOV or/and SUDV (cAd3-EBO). The monovalent and bivalent vaccine protects macaques from EBOV infection [299]. In humans, a phase I trial (NCT02231866) showed that the immunogenicity of experimental cAd3-EBO depends on the dose [300]. In addition, other phase I trials with ChAd3-EBO-Z indicated that antibody titers are dose dependent [301,302]. EBOV proteins expressed using other vectors such as Ad26 and Ad35 have also shown protection in NHP [303]. Currently, a phase I trial with Ad26.ZEBOV vaccine (VAC52150EBL1004) has demonstrated tolerability and immunogenicity in healthy human volunteers [304]. Multivalent vectored vaccines have been used in phase I/II clinical trials. One is the modified vaccinia Ankara (MVA)-BN multivalent Filo that encodes the GP from EBOV, TAFV, and SUDV. The other one is a monovalent MVA-vectored vaccine with EBOV GP [305].

The second group of vaccines have utilized replicative vectors that code for viral antigens. These vaccines are efficient with low doses but have lower tolerability. The rVSV-EBOV vaccine produced from recombinant vesicular stomatitis viruses (rVSV) encodes the GP of the Kikwit EBOV strain 1995. A pre-clinical study showed that rVSV-EBOV protects 100% of mice from lethal challenge [306]. Full protection has also been demonstrated in NHP [307]. Initial results of the rVSV-EBOV vaccine in phase I trials done in Lambaréné, Kilifi, and Hamburg demonstrated adequate immunogenicity but moderate reactions to vaccination [308]. Other clinical trials with this vaccine reported the appearance of arthritis, dermatitis, and cutaneous vasculitis [309]. In 2015, a phase III trial was performed in Guinea to evaluate the efficacy of rVSV-EBOV vaccine during the outbreak [243]. Only one serious adverse event causally related to vaccination was reported. rVSV-EBOV appears to increase the expression of genes that stimulate both the innate and humoral anti-viral immune responses [310]. Preliminary results show that rVSV-EBOV is the first vaccine to confer a high level of protection. Currently, it is the only vaccine approved by the FDA for prevention of EBOVs.

Modifications in the recombinant human parainfluenza virus type 3 (HPIV3) has been shown to generate the expression of EBOV-GP (HPIV3/EboGP) or EBOV-NP (HPIV3/EboGP-NP). Vaccinated guinea pigs were protected from lethal doses of EBOV [311]. Similar results were found in rhesus monkeys [312,313]. A phase I clinical trial (NCT02564575) including these recombinant formulations is now under study in USA.

Other strategies include the use of inactivated viruses, VLPs, DNA based vaccines and mutant virus formulations. Heat-inactivated viruses have demonstrated protection in guinea pigs [314] and in mice [315] infected with wild EBOV. Phase I studies (NCT00605514, NCT00997607) have shown that DNA vaccines induce immunogenicity as well as humoral and cellular response [316,317]. These DNA vaccines are safe and cost-effective. Currently, phase III studies are under development. Similarly, VLPs induce cellular and humoral immune responses in guinea pigs, mice, and NHP [318,319]. The results of a EBOV that has a mutated form of VP35 that is avirulent but induces immune responses that protect against challenge with wild type EBOV in monkeys also shows great promise [47]. Currently, a number of different clinical trials in progress are reasoned to lead to the use of combined vaccines directed at more efficient immunization.

## 9. Prevention and control of EBOV disease

Humanitarians and scientists are actively involved in the search for virus control mechanisms in vulnerable areas with violent conflicts, food insecurity, and lack of health infrastructure. Disease control is focused on preventing the transmission and spread of the virus through a multidisciplinary approach that includes factors such as early case identification, rapid isolation of suspected infected patients, adequate clinical management, safe burial practices, and health education [320].

Cases of EBOV disease should be identified early with surveillance systems in risk areas. Each area must have access to specialized laboratories for rapid detection of the virus and specialized centers for the isolation of cases. Ebola Treatment Centers (ETC) were established in Guinea, Liberia, and Sierra Leone during the 2013–2016 outbreak. ETCs are divided into two independent areas: 1. High-risk areas that shelter infected patients, contaminated materials, and dead bodies. 2. Low risk areas with offices, laboratory facilities, storage areas, and nursing stations. These centers offer high quality care for affected communities through visits to family members to inform them of medical activities and prevention measures [320].

In the DRC, individual treatment units were developed that facilitated adaptability and access for medical personnel in cases where the patient did not go to the ETCs. These isolation units are portable, individual rooms with a BSL4 level of containment and are located near the patient's home. The walls are transparent to allow direct communication with the family and facilitate patient monitoring by medical staff [4].

The contact and monitoring of families and neighbors of infected patients are an important tool for the control of outbreaks. In Liberia during 2014–2015, contact tracking allowed the detection of 3.6% of the new cases [321]. In addition, traditional burial ceremonies with safety precautions contributed to the effective control of the disease [18]. Health campaigns and educational activities help the community to recognize EBOV disease cases and act appropriately. In addition, these activities overcome cultural beliefs and practices that challenge disease control. It is highly recommended that traditional healers, religious leaders, or people exposed to the virus participate in the activities.

Humans acquire the infection through direct or indirect contact with body fluids of infected reservoir species, infected or deceased people, or surfaces and materials contaminated with these fluids. To prevent transmission, the Pan American Health Organization (PAHO)/

WHO develop health prevention programs which include protocols for environmental cleaning and disinfection, hand hygiene, use of disinfectants for surface and equipment decontamination, use of personal protective elements for health professionals and caregivers, and safe handling of potentially contaminated materials or biomedical wastes [19]. Other recommendations for the prevention and integral control of infection include safe processing of laboratory samples and setting up a committee to supervise activities in hospitals and communities.

Effective communication strategies are crucial in public health crises to establish relationships of trust with local communities. The credibility and evaluation of the information must be evaluated with biomedical and scientific tools and knowledge [322]. During the Ebola outbreak in West Africa, Claudia Evers, Ebola emergency coordinator at Medecins Sans Frontieres (MSF) in Guinea, said: *"MSF made a big mistake. We advocated for an increase in beds for too long, and everyone listened to MSF. Instead of asking for more beds we should have asked for more sensitization activities"* [323]. The result of this lack of communication was the population resistance towards the Ebola response teams. Effective communication strategies to combat Ebola at local and global levels should include traditional and innovative tools such as newspapers, radio, television, social networks. Thus, there are organizations such as *"Translators without Borders"* who are professionals and have a proven record on facilitating the communication of public health measures in local languages for the most efficient implementation of the proposed measures.

## 10. Conclusions

EBOV disease is a life-threatening condition with a high burden of global mortality and chronic sequelae. Poverty, cultural, and religious behaviors are associated with an increased risk for the development of EBOVs disease. Survivors exhibit chronic manifestations that resemble autoimmune and auto-inflammatory conditions. However, further analyses are warranted in order to clarify the immunological mechanisms associated with these clinical features. Control and prevention of EBOV disease should focus on control of human-to-human transmission, and new strategies such as prophylactic vaccines should be introduced in endemic areas to prevent the development of new outbreaks.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2019.102375.

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