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Rift Valley fever: biology and epidemiology

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Abstract

Rift Valley fever (RVF) is a mosquito-borne viral zoonosis that was first discovered in Kenya in 1930 and is now endemic throughout multiple African countries and the Arabian Peninsula. RVF virus primarily infects domestic livestock (sheep, goats, cattle) causing high rates of neonatal mortality and abortion, with human infection resulting in a wide variety of clinical outcomes, ranging from self-limiting febrile illness to life-threatening haemorrhagic diatheses, and miscarriage in pregnant women. Since its discovery, RVF has caused many outbreaks in Africa and the Arabian Peninsula with major impacts on human and animal health. However, options for the control of RVF outbreaks are limited by the lack of licensed human vaccines or therapeutics. For this reason, RVF is prioritized by the World Health Organization for urgent research and development of countermeasures for the prevention and control of future outbreaks. In this review, we highlight the current understanding of RVF, including its epidemiology, pathogenesis, clinical manifestations and status of vaccine development.

Keywords

Rift Valley fever; epidemiology; pathogenesis; transmission; vaccine; one health

Discovery and Historical Background

Rift Valley fever virus (RVFV) was originally discovered as the causative agent of an outbreak of 'enzootic hepatitis' in 1930 near Lake Naivasha in the Rift Valley of Kenya [1]. The outbreak manifested with numerous mortalities among newborn lambs, together with increased instances of mortality and abortions among adult sheep [1]. Within a few

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Conflicts of interest

The authors declare that there are no conflicts of interest.

weeks, thousands of sheep had died on the farm. To investigate if the disease was caused by a bacterium or a virus, blood from a diseased lamb was passed through a Chamberland porcelain filter and injected into an unaffected lamb, which reproduced the disease. The outbreak occurred in a period of heavy mosquito activity, leading the investigators to suggest the involvement of mosquitoes in disease transmission. In an attempt to limit the outbreak, healthy sheep were moved to a higher altitude, where mosquitoes were absent or were placed under mosquito netting. Both countermeasures were effective, and together with the apparent lack of direct animal-to-animal transmission, corroborated the suggestive involvement of mosquitoes in disease transmission [1, 2]. The involvement of mosquitoes as vectors was later confirmed when RVFV was isolated from several naturally infected species of *Aedes* and *Culex* mosquitoes [3, 4].

Enquiries during and after the outbreak revealed that almost all herders had experienced fever and severe pains [1]. Hundreds of human cases were thought to have occurred with no incidence of mortality. Risk of death from infection was therefore considered low and human susceptibility was confirmed by transfusing filtered blood from an infected lamb into a human volunteer [1]. Soon after the outbreak and in the subsequent years, numerous animal infection studies were carried out, documenting the susceptibility of a wide range of animal species [1, 2, 5–7] to inform most of what we know regarding the natural course of RVF in humans and animals. In this review, we highlight recent developments in the understanding of RVF, including its epidemiology, pathogenesis, clinical features and status of vaccine development.

Epidemiology

Transmission

Our understanding of the epidemiology of RVF is incomplete, particularly with regards to viral maintenance during interepizootic periods (IEPs). A single species of *Aedes* that was misidentified before 1985 as *Aedes lineatopennis*, later identified as *Aedes (Neomelanicolonia) mcintoshi* [8], has shown the ability to pass the virus to its progeny [9]. It is plausible to assume that RVFV can remain viable in the eggs of this species during the dry season before hatching once the rains return [9, 10]. Whether this is the only species capable of vertical transmission and the extent it allows RVFV to circulate during IEPs requires further investigation. Evidence of seropositivity in sheep and goats that have not lived through an RVF outbreak suggests low-level circulation of the virus can occur in livestock [11, 12]. Mosquitoes can also transmit RVFV to wild ungulates. Indeed, neutralizing antibodies targeting RVFV have been detected in a diverse range of species, such as African buffalo, giraffe, black rhino, impala and African elephants among many others [13, 14]. Some of these species, such as buffalo and giraffe, are susceptible to RVF disease [15], while others such as elephants appear not to be. There is, however, no evidence to suggest these animals develop sufficiently high viraemia to allow transmission to mosquitoes. Low-level viral maintenance in sylvatic cycles during IEPs is plausible, although it is likely that only ruminants and pseudoruminants function as amplifying hosts (Fig. 1).

During periods of exceptionally heavy rains, subsequent flooding results in large increases in mosquito populations, which can lead to RVF epizootics, whereby large numbers of livestock become infected. Because of the correlative link between RVFV infection and the weather, rainfall data and changes in vegetation have been used to predict RVF outbreaks [16]. However, accurate data on the variables, which feed into models predicting RVF outbreaks, often do not exist. For this reason, the predictive value of these models is variable [16, 17]. Syndromic surveillance of livestock herds during periods when conditions appear to be favourable for RVF outbreaks have also been used as an early warning system in Kenya [18]. These systems may lead to better awareness among farmers towards RVF and increases in vaccination uptake [18].

Numerous mosquito species are capable of transmitting RVFV [10]. Other arthropods, such as mites, ticks and sandflies can become infected with the virus and could potentially act as mechanical vectors [10]. A study of mosquitoes trapped during an epizootic found more than 53 species caught in the field were positive for RVFV [19], while more than 65 species are described as potential vectors, the vast majority from *Aedes* and *Culex* spp. [20]. The degree to which some of these potential RVFV vectors can successfully transmit virus varies between species [21].

Unlike animals, most human infections are attributed to contact with infected tissues or fluids, rather than mosquito bite [1, 22]. Numerous cases of human transmission during the 1930–1950s occurred by way of accidental laboratory infection [5]. Indeed, much of our early knowledge of the disease in humans came from these case reports. To date, direct human-to-human transmission has not been documented. Even during epidemics in hospital settings with sub-optimal personal protective equipment, there is no evidence of nosocomial transmission [23]. In one case, viral RNA was isolated from urine and semen in an immunosuppressed patient 4 months after initial onset of symptoms [24]. Whether RVFV can be transmitted sexually, however, is unknown. Vertical transmission, from mothers to foetus, has been documented in human cases [25, 26] and *ex vivo* experiments have demonstrated that RVFV can directly infect human placental tissue [27].

For livestock, direct transfer between animals may be rare or non-existent as evidenced by early experiments demonstrating that viraemic sheep fail to transfer the virus to naïve animals [1]. More recently, sheep with acute RVFV infections cohoused with highly susceptible immunocompromised naïve lambs failed to transmit any virus [28]. Vertical transmission occurs in all susceptible livestock species; this has been demonstrated even in pregnant sheep with no detectable viremia [29]. In a rodent model of pregnant rats, vertical transmission occurred in both sick and asymptomatic rats, with pregnant animals being more prone to death than their non-pregnant counterparts. The placenta of these animals was shown to be a major site of viral replication [27]. While outbreaks have so far been confined to Africa and the Arabian Peninsula, a wide range of mosquitoes can transmit RVFV and these can be found outside these two geographical settings [19].

Disease burden and impact

After the discovery of RVFV in the 1930s, outbreaks appeared regularly from the 1950s onwards [30]. This began with large outbreaks in Kenya and South Africa in 1950–1951

[14]. In 1974–1975, another outbreak in South Africa resulted in the country’s first human fatalities; 110 human cases were recorded resulting in seven deaths [31]. The largest RVF outbreak on record occurred in Egypt from 1977 to 1979, where 598 deaths were documented from an estimated 200 000 human cases [32]. Considerable human cases were reported in Mauritania in 1987, with 220 deaths [33]. In 1997–1998, after exceptionally heavy rainfall, a large outbreak in East Africa resulted in 478 deaths from an estimated 89 000 human cases [34].

The first outbreak of RVF outside the African continent occurred in the year 2000, where 880 laboratory-confirmed human cases and 123 deaths were recorded in Saudi Arabia over a six-month period [30, 35]. During this time, an additional 1328 cases and 166 deaths were recorded in Yemen. Evidence suggests the strain of RVFV that emerged on the Arabian Peninsula originated from the 1997–1998 East-African outbreak [36]. More recently in 2008, 747 human cases and 230 deaths were reported in Sudan and since 2016, smaller outbreaks in Niger and East Africa have resulted in numerous human deaths [37].

Estimating total animal losses during outbreaks is difficult as these numbers are generally poorly documented. The first recorded outbreak in Kenya resulted in an estimated 5000 animal deaths [1], while the much larger outbreaks in Kenya and South Africa in 1950–1951 resulted in over 100 000 sheep dying and approximately half a million abortions [14]. Even more were estimated to have died in the South African 1975 outbreak [31]. In Saudi Arabia, the outbreak resulted in wide-spread livestock deaths and up to 10 000 abortions in cattle, sheep, goats and camels [38]. In the 2006–2007 outbreak in Tanzania, livestock mortality was estimated at 50 000 [30].

RVF outbreaks can have dire socio-economic consequences at both local and national levels [39, 40]. In addition to the direct cost of human morbidity and death, livestock deaths and subsequent reduction in production has cost producers millions of dollars. These animal losses can have knock-on effects altering herd dynamics. For example, when significant proportions of young animals are killed, there are fewer to breed the following generation resulting in further, potentially long-term, production losses [39]. In addition to the direct losses of livestock, embargoes are placed on the exportation of livestock during outbreaks, which can have crippling impacts on economies heavily dependent on animal trade. In Somalia, for example, livestock exporters lost approximately US\$330M between 1998–2003 as a result of the ban on livestock imports, with further losses from producers and the subsequent reduction in tax intake for the government [41]. Overall, losses in Somalia due to the 2006–2007 outbreak have been estimated at US\$471M, representing 5 % of the total GDP. The same outbreak caused US\$66M losses in Kenya [39]. Saudi Arabia and Yemen suffered economic losses of US\$10M and US\$107M, respectively.

Risk factors

Numerous seroprevalence studies in human populations have been carried out, which shed light onto those most at risk of infection [42]. The most significant risk factor is having contact with susceptible animals and being involved in slaughter [43, 44]. Adults are more likely to be seropositive than children, either as a function of their age providing them more time to come into contact with RVFV, or due to the increased occupational risk [45]. Heavy

rainfall often precedes RVF outbreaks, where an increase in vector population may increase transmission potential. While it is not considered the primary cause of human infection, any behavioural factors that increase the frequency of mosquito bites, such as sleeping outdoors in RVFV-endemic areas, may also increase the chance of becoming infected [46]. Larger outbreaks, however, such as the Egyptian outbreak of 1977, are unlikely to have all resulted from direct animal contact. Here, *Culex pipiens* was implicated for the first time [47]. There are documented cases of human infections with no direct link to livestock, which were consequently attributed to mosquito bites [48].

It is currently poorly understood why some people remain asymptomatic or have only mild symptoms before recovering while others develop more severe disease with lasting problems. There is some evidence that coinfection with other pathogens may increase susceptibility. For example, HIV-1 coinfection was found to increase the likelihood of severe disease and death due to RVF, with case fatality estimated at 75 % [49]. Other studies have shown a role of host genetic factors on susceptibility, identifying an association between single nucleotide polymorphisms in genes involved in immunological pathways and severe disease [50].

Risk factors for livestock infections are less well understood and often contradictory [42]. For instance, numerous studies have associated either males or females with increased chance of seropositivity [42]. The relationship between animal type (sheep or goats) and risk of infection is also not always clear. While no association was found in certain herds, in others sheep seemed significantly more at risk [11, 12, 51]. Differences in host-genetic factors, environmental factors such as feeding preferences of vectors or differences in animal husbandry may explain why sheep could have a higher chance of infection. Proximity to water has also been identified as a risk factor, most likely linked to the number of mosquitoes present [52]. As with humans, older animals are more likely to be seropositive [42].

Disease Manifestations

Humans

Human infections can result in a wide spectrum of clinical outcomes [32]. While most cases induce a self-limiting febrile illness, an estimated 1–2 % of infections result in much more severe disease, often with high levels of mortality (Fig. 2). Following an incubation period of 2–6 days, clinical symptoms of RVF include fever, headache, backache, vertigo, anorexia and photophobia [53, 54]. The fever may last several days with a convalescent period ranging from a few days to a month. Some patients experience a biphasic febrile illness, where a reduction of symptoms occurs around the third day before recrudescence 1–3 days later [53]. Severe RVF disease can encompass a wide range of manifestations, summarized below.

Hepatitis, jaundice and haemorrhagic disease

As the major site of RVFV replication, the liver becomes damaged, which can lead to jaundice and haemorrhagic disease. Elevation of liver enzymes aspartate transaminase

(AST) and alanine transaminase (ALT) occurs, with highest levels occurring in fatal cases [56]. Haemoglobin and platelet counts are reduced with clotting time increased. Other manifestations may include thrombosis [54]. Patients with haemorrhagic fever have a very high fatality rate and usually succumb within a week or two after the onset of symptoms [54, 57].

Ocular disease

Ocular disease is estimated to occur in 2–5 % of RVFV infections, while prevalence among those experiencing severe disease can be >10 % [58, 59]. It usually develops 1–3 weeks after initial onset of symptoms and most commonly involves macular and paramacular oedema [58–60]. Other symptoms may include photophobia, reduced vision, blind spots, uveitis, retinitis and retinal haemorrhage [30, 54]. Disease duration varies from being permanent to resolving in a matter of weeks [30].

Encephalitis and neurological disease

In addition to the symptoms of mild disease, severe and lasting problems can occur shortly after initial symptoms subside, including reduced consciousness, hallucinations, confusion, vertigo, excessive salivation, weakness, paralysis, decerebrate posturing, hemiparesis and pleocytosis [30, 54].

Abortions/miscarriage

The link between RVFV infection and human abortion is less clear than in ruminants. A study looking into the incidence of abortion during the 1977 outbreak in Egypt found no increase above the normal frequency of abortions [61]. However, a study in 2016 showed for the first time a significantly increased risk of miscarriage after laboratory-confirmed RVFV infection during pregnancy [62]. The risk of abortion in humans, however, appears to be lower than that in livestock. Further studies on the mechanisms underlying pregnancy loss due to RVF are warranted.

Animals

RVFV affects a wide range of animals in an age-dependent manner, where young animals are significantly more likely to succumb than adults. However, the various species are not equally susceptible to disease [54]. As in human disease, the major site of RVFV replication is the liver and it is this organ which bears the brunt of disease in all species. Liver lesions generally result in elevated expression of liver enzymes. Animals with severe RVF disease exhibit leukopenia [21] and while tropism is mostly limited to hepatocytes and monocytes, virus is disseminated to other tissues through circulation in blood [63]. Severe disease can also occur suddenly, causing death in the absence of any other symptoms [64].

Sheep are the most susceptible of livestock species. The incubation period of the disease is 24–36 h with signs including fever, listlessness, loss of appetite, disinclination to move, abdominal pain and bloody diarrhea [54]. Post-mortem analysis reveals multi-focal liver necrosis and occasional mild splenomegaly [65]. The breed of sheep can influence the severity of clinical manifestations [65] Adult sheep mortality after experimental infection is

between 20–30 % [5]. Mortality in newborn lambs is much greater at 95–100 % [5] and acutely infected pregnant ewes have almost 100 % chance of abortion [54].

Goats are also highly susceptible with similar symptoms to sheep. However, the course of disease can be somewhat more variable, with viremia and symptoms inconsistent after infection [5]. Peak viremia in the blood of goats is also significantly lower than in lambs of identical age after experimental infection [5]. Also, unlike lambs, goats do not always experience febrile illness [5]. When disease does occur, the formation of hepatic lesions is followed by necrotic hepatitis. In adults, hepatic lesions are more focal.

Cattle are less susceptible to disease than sheep and goats. RVFV infections in adults are usually asymptomatic but can also manifest as acute disease with mortality between 0–5 % [54]. As with the other livestock species, younger animals are more susceptible and calves usually develop acute disease with mortality of approximately 10 % [54, 66], although experimental infections have resulted in significantly higher rates [5]. A more recent study has demonstrated that the onset and duration of fever, in addition to other aspects of disease, including viraemia and liver pathology, are less consistent when compared with sheep [66].

There are few examples describing clinical disease in camels suggesting that these pseudoruminants are less susceptible than cattle, with the vast majority experiencing asymptomatic infection. However, acute RVFV infection may still result in severe disease and death. Symptoms can include ocular discharge, haemorrhages and foot lesions [67]. The first human deaths from RVF in an outbreak in Mauritania, 2010, were associated with contact with an infected dromedary camel [67]. Abortions of pregnant camels during outbreaks have also been documented [67].

Virology

Structure and host cell entry

RVFV is a *Phlebovirus* in the *Phenuiviridae* family (formerly *Bunyaviridae*). The *Phenuiviridae* family includes other viruses of biomedical significance (e.g. Severe fever with thrombocytopenia syndrome virus [SFTSV] and Sandfly fever virus [SFV], which encompasses sandfly Naples virus, sandfly Sicilian virus and Toscana virus). RVFV contains a predominantly negative-sense tripartite RNA genome consisting of a small (S), medium (M) and large (L) segment [20] (Fig. 3). The S segment encodes the nucleoprotein (N) and a non-structural protein (NSs), and is the only segment that employs an ambi-sense strategy (Fig. 3). The L segment encodes the viral polymerase. The M segment encodes another non-structural protein (NSm) and a 78 kDa glycoprotein in addition to the two structural glycoproteins, Gn and Gc. The function of the 78 kDa protein is not fully understood but appears to play a structural role in mosquito-cell-derived virions but not those expressed in mammalian cells [68, 69].

RVFV Gn and Gc form heterodimers, which further assemble as pentamers and hexamers with $T=12$ icosahedral symmetry on the envelope surface of the mature virus, and work in concert to facilitate host-cell entry [70–73]. RVFV Gc facilitates the pH-dependent merger of the host and virion membrane and adopts a class-II fusion protein fold, resembling fusion

proteins of other phleboviruses, hantaviruses, alphaviruses and flaviviruses [74–79]. The N-terminal ectodomain region of RVFV Gn shares the same fold architecture with the Gn of another *Phlebovirus*, SFTSV, and has been shown to shield hydrophobic fusion loops on the cognate Gc protein [70, 80]. Prior to endocytosis of the virus, virions can attach to cells via the interaction between Gn- and Gc-displayed oligomannose-type glycans and the C-type lectins, DC-SIGN and L-SIGN [81–83]. DC-SIGN is highly expressed on dermal dendritic cells, where RVFV can replicate productively [84]. Heparan sulfate proteoglycans have also been identified as an important host-cell attachment factor (Fig. 4) [85, 86].

Phylogeny

It is estimated that RVFV diverged from a recent common ancestor during the 1880–90s [88, 89]. The virus circulates throughout East Africa, with outbreaks in other regions often the result of a single introduction [36]. Several studies conducting sequence analysis of RVFV isolates throughout Africa and Saudi Arabia have shown limited genetic diversity of ~5 % at the nucleotide level and ~2 % at the amino-acid level [88–90]. A large study of 198 isolates obtained over a 67 year period from numerous countries categorized sequences into 15 lineages (A–O) [88]. These individual RVFV strains are not unique to specific regions and many have been isolated from multiple geographical settings [91]. Sequence analysis has demonstrated that numerous strains can circulate concurrently during outbreaks [91] and there is evidence of previous genetic reassortment between them [88, 90]. Data regarding the virulence of different RVFV strains is limited. While all isolates belong to a single serotype [92], importantly, and despite the limited diversity, individual strains of RVFV can cause differential disease severity in natural host species [65, 66].

Domain-specific analysis of the glycoproteins demonstrated that the most membrane distal region of Gn undergoes the greatest level of non-synonymous mutations, suggestive that this region of the molecule is under comparatively strong selection pressure and is subject to fewer structural constraints [93]. The relatively conserved nature of the antigenic RVFV Gn-Gc surface bodes well for efforts to develop broadly efficacious vaccines capable of protecting against any strain.

Immunology

Naturally acquired immunity

Protection against RVFV in all species is conferred by long-lived neutralizing antibodies (nAbs), which can be detected within the first week post-infection [21, 94]. Sheep and cattle exposed to RVFV have been shown to be completely resistant to disease upon re-infection [1]. Passive serum transfer experiments in non-human primate and rodent models have confirmed the role of antibodies in protection against RVFV infection [95, 96]. Neutralizing antibodies were detected in two persons 12 and 25 years post-infection, respectively, in the absence of subsequent exposure [53, 97].

The N protein is the immunodominant protein of many bunyaviruses, where IgG and IgM specific to N are abundant after natural infection in all species evaluated [21, 98, 99]. However, there is no evidence that anti-N antibodies exhibit virus neutralizing activity.

Instead, the only identified targets of nAbs appear to be the surface glycoproteins, Gn and Gc [100–105]. Experimental challenge in animals has revealed measurable IgM levels in the first few days after infection. This drops to <10 % prevalence in animals after 50 days. Positivity for RVFV-specific IgG begins to appear shortly after IgM with animals generally becoming IgG positive within 3 weeks [21].

The production of anti-RVFV neutralizing antibodies is likely the primary mechanism of protection in all species. It is possible that the diversity of known IgG structures amongst species, such as the ultralong loop in the third heavy-chain complementarity-determining-region (CDR H3) of cattle antibodies and the heavy-chain only antibodies of camels may allow the recognition of species-specific epitopes [106, 107]. The single domain antibodies of camelids, for example, are only ~90 kDa in size, significantly smaller than conventional IgG and may have access to epitopes that larger antibodies do not. A more detailed understanding of the humoral immune response to RVFV could help to guide future vaccine strategies. Identification of neutralizing epitopes may allow the omission of parts of the RVFV proteins, which do not contribute to protection, leaving the immune response to focus on those that do [108]. The possibility of reducing the antigen size while maintaining or increasing immunity could potentially be exploited by allowing the combination of additional antigens in vaccines. Furthermore, vaccine development can be guided by a detailed characterization of naturally acquired immunity, known to provide long-lived protection. This may also highlight immunological differences within or between species which affect susceptibility. The degree to which virus–host interactions differ between species is an area in need of future research.

In comparison to antibodies, relatively little is known about T-cell responses against RVFV, particularly after natural exposure. Dendritic cells and macrophages are among the first immune cells encountered after infection and replication of RVFV has been demonstrated in both [84, 109]. African green monkeys exposed to RVFV via aerosolized droplets develop neurological disease similar to that seen in humans [110]. In these animals challenged with RVFV, early proliferation of CD4+ and CD8+ T cells and expression of Th1 cytokines was associated with non-lethal outcomes [110]. This is in line with findings that higher concentrations of IL-10, a cytokine that suppresses Th1 response, is associated with fatal cases compared to non-fatal cases in humans [56]. The same study also found that B cell and neutrophil activators were elevated in non-fatal compared to fatal cases [56].

Innate immunity plays a critical role in RVF disease progression [56]. The NSs protein, an IFN antagonist, is the major virulence determinant of RVFV. RVFV lacking NSs induces strong type-I IFN responses, which explains its attenuation in livestock and humans [111–114]. Counteracting the innate immune response by RVFV is achieved through various mechanisms [115]. YY1, a host protein involved in modifying IFN- β transcription, is bound by NSs and another host protein, SAP30. Together this complex serves to suppress IFN- β at the transcriptional level, occurring very early on in the first few hours post-infection [21, 116]. After this, NSs interacts with components of the transcription factor TFIID, preventing their assembly and thereby causing a rapid general decrease in host cellular RNA synthesis [117]. Alongside transcriptional shutoff, NSs promotes viral replication via degradation of

Protein Kinase R (PKR) [115, 118, 119]. PKR plays a key function in antiviral defense by inhibiting protein synthesis and thus its degradation blocks host translational shutoff.

Vaccine-induced immunity

As with natural exposure, protection through vaccination is primarily conferred via induction of nAbs towards the viral glycoproteins. Hence, the aim of RVF vaccine programmes is to elicit high titre RVFV nAbs. Vaccination with attenuated RVFV in humans, depending on the particular vaccine and schedule, can induce nAbs which are long-lived [120, 121].

In livestock, immunization can induce detectable nAbs in as early as 4–5 days in some animals and in all animals by 2–4 weeks [104, 122, 123]; nAb titres can be further boosted following challenge [104, 122]. In some areas there have been questions about the efficacy of live-attenuated livestock vaccines. In Egypt, for example, despite 70 % of cattle being vaccinated some studies have found significantly lower seropositivity [124, 125]. Whether this is directly related to the vaccine rather than issues with implementing the vaccination programme requires further investigation. Some widely used livestock vaccines, such as the inactivated RVF ZH501 and RVF Menya require multiple doses in order to generate protective immunity [126], increasing the costs and logistics involved in vaccination.

There are examples of challenge studies carried out in mice showing partial protection in the absence of detectable nAbs [105, 127]. This is the case when vaccinating mice with the N protein [105, 127]. The mechanism of this protection is poorly understood but cellular immunity has been implicated [105]. Indeed, there is evidence that the N protein is a potent human CD8+ T-cell antigen [128]. This protection may also come from non-neutralizing antibodies via cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) [127].

Immune epitopes

Wang *et al.* recently isolated RVFV monoclonal antibodies (mAbs) from a convalescent human returning from Angola [129], and found that Gn-specific mAbs were protective and function by blocking virus binding to cells. Another study in which rabbits were vaccinated with the ectodomain of the Gn identified a class of mAbs, which protects against RVFV infection in a mouse model by targeting the membrane-distal domain of Gn [93]. This class of antibodies recognizes a region that is spatially distinct from that targeted by the characterized human-derived mAbs, supportive of the possibility of a potent mAb cocktail targeting multiple epitopes for therapeutic use. No epitopes have yet been characterized in target livestock species.

In mice, both B- and T-cell epitopes have been identified in the viral glycoproteins Gn and Gc. A widely used commercially available mouse mAb recognizes a linear B-cell epitope on Gn [130], while CD8+ T-cell epitopes have been identified on both Gn and Gc [105]. More broadly, a study in the 1990s investigated mAbs raised in vaccinated mice and found examples targeting either Gn or Gc that were capable of neutralizing RVFV [101]. A later study in mice vaccinated with cDNA containing Gn or Gc, showed only Gn-vaccinated mice developed neutralizing antibodies, while Gc-vaccinated mice did not

[102]. A limitation of identifying epitopes using individual glycoproteins, however, is that the conformation of Gc or Gn alone will be different than they appear when presented as pentamers and hexamers of Gn/Gc heterodimers on the mature virion surface. Important epitopes may therefore be missed, particularly at the interface between Gn and Gc. While a low-resolution reconstruction of the RVFV envelope has allowed the positions of the Gn and Gc glycoproteins to be revealed [70], higher resolution structural information of the Gn/Gc assembly is needed to guide our understanding of the mature, antigenic surface of the virus.

Disease Control and Treatment

Diagnosis

As most human infections are asymptomatic or cause flu-like illness, often the first sign of an RVF outbreak is the near simultaneous abortions in herds of pregnant sheep termed 'abortion storms'. There are several methods to diagnose acute RVFV infection in livestock and humans, but all must be carried out in laboratory settings [20]. One method of diagnosing acute or very recent infection is to use ELISA detecting IgM towards RVFV antigens [131]. Molecular methods using real-time reverse transcriptase (RT)-PCR to detect viral RNA can also be used and are highly sensitive and specific. Virus can also be isolated by cell culture from blood samples taken during the febrile stage (or from organ samples collected post-mortem). Lastly, histopathological methods can be used; i.e. post-mortem examination of liver for hepatic lesions.

Viral neutralization assays are the gold standard in detecting previous exposure to RVFV due to their high sensitivity and specificity. However, these require specialist laboratory facilities capable of working safely with live RVFV. Commercial ELISA kits that detect antibody against the N protein are also available (ID-VET, Montpellier, France).

Treatment

Most human cases of RVF do not require treatment. For those with severe RVF disease there is no specific treatment other than general supportive therapy. Several groups are investigating potential RVF therapeutics, and some, such as Ribavirin and Favipiravir have shown efficacy in rodent models (reviewed in [132]). During the 2000 outbreak in Saudi Arabia, intravenous administration of Ribavirin to RVF patients was stopped due to the apparent increase of neurological disease in these patients [64]. The development of an effective treatment for RVF disease is of considerable importance and continued research is warranted.

Vaccines

At present, vaccination is regarded as the only method to prevent RVFV infections in livestock. However, there is significant room for improvement of existing livestock vaccines. In addition, tools to limit spillover into humans are hampered by the absence of any licensed human vaccines [133]. Replicating the long-lived protection resulting from natural exposure is an attractive goal. For humans, there are two vaccines currently defined as Investigational New Drugs in the USA; MP-12 and TSI-GSD-200 [134]. MP-12 was created in the 1980s, the strain contains 23 nucleotide mutations distributed over all three genome segments [135].

It has been conditionally licensed for animal vaccination [134] and is safe and immunogenic in both animals and humans although some teratogenic effects have occurred in pregnant ruminants [20, 120]. TSI-GSD-200 is a formalin-inactivated vaccine created by the US army to protect those whose work may put them at risk of infection. It has an excellent safety profile but requires multiple boosters to achieve efficacy, and even then almost 10 % of vaccinees tend to have low nAb titres or fail to seroconvert [121].

For livestock, RVF vaccine use is inconsistent across Africa and the Arabian Peninsula with most countries having no implementation due to the sporadic nature of outbreaks or lack of reported cases [134]. The frequency of vaccination in countries that do vaccinate, such as Kenya, South Africa and Egypt among others, using a handful of licensed vaccines, varies based on the ecological setting [134]. For livestock, the most widely used commercial vaccine, named after its developer Smithburn, is a live-attenuated RVFV that induces long-lasting protection after a single dose [133]. However, the Smithburn vaccine cannot be administered to pregnant animals as residual virulence results in a high risk of abortion [136]. In addition, there is a possibility of reversion to virulence as may have occurred previously with this vaccine [137]. There is also the prospect of genetic reassortment with wild-type RVFV, however, this is unlikely to result in an increase in pathogenicity beyond that of the wild-type virus. A bonus of a novel RVFV vaccine would be the ability to differentiate between infected and vaccinated animals (DIVA). When using live-attenuated RVFV as a vaccine, such as Smithburn, the antibody profile generated is similar to natural infection, rendering the mapping of outbreaks difficult in the face of vaccination. Subunit vaccines have the advantage of not including all the RVFV antigens. By measuring responses to the N protein, if not present in the vaccine, it is possible to differentiate animals that have been naturally exposed from those that have been vaccinated.

Another livestock vaccine, clone 13, was one of a number of viral clones isolated from a human patient infected with the 74HB59 strain in the Central African Republic. It was found to be naturally attenuated due to a large deletion in the NSs gene, the primary virulence factor, with subsequent infection in mice showing it did not cause disease [138]. Clone 13 has proven safe and immunogenic after a single dose in cattle, sheep and goats [111, 112, 114]. Overdose studies in pregnant ewes, however, have found clone 13 able to cross the placental barrier and cause teratogenic effects [139]. A thermostabilized version, selected from viable clones after incubation at 56 °C, has been used to vaccinate livestock in Senegal and Mali [134].

There are several promising vaccine candidates currently under development, which aim to address the shortfalls of current vaccines, namely single dose-efficacy and safety concerns. A subunit vaccine using the GnGc glycoproteins has shown 100 % efficacy in sheep [140]. Another, RVFV-4s, where the M segment is split into two parts separately encoding Gn and Gc, has conferred sterile immunity in lambs after a single vaccination [141]. In addition, vaccinated pregnant sheep showed no teratogenic effects with no presence of RVFV-4s virus in the blood or organs of their foetuses [142]. Another candidate is ChAdOx1 RVF, a replication-deficient chimpanzee adenovirus vectored vaccine encoding the Gn and Gc glycoproteins. ChAdOx1 RVF has shown 100 % efficacy against RVF viral challenge in sheep, goats and cattle [104]. ChAdOx1 RVF is also planned for use in humans where

the ChAdOx1 vector expressing other antigens has demonstrated an excellent safety profile [143, 144]. A first-in-human trial of ChAdOx1 RVF is due in 2020.

Future Outlook and Research Priorities

In recent years, more research has focused on emerging pathogens with the aim of increasing our preparedness for future outbreaks [145, 146]. RVFV has a complicated ecological cycle involving a wide range of vectors, livestock and wildlife species. Due to the large geographic area potentially vulnerable to RVF outbreaks, adequate surveillance is key to coordinating efforts to limit its spread. In addition, as human outbreaks appear to occur only after initial amplification in livestock, by identifying livestock outbreaks early, human disease can be minimized by implementing appropriate control measures (e.g. vaccination) [147]. Unfortunately, current surveillance is sub-optimal in numerous at-risk countries with many outbreaks remaining unreported [148]. Ideally, proper surveillance measures will enable farmers to report unexplained disease in their livestock, which can be investigated and allow suitable measures to be implemented to reduce spread [18].

The development of specific therapeutics and vaccines is also of major importance. Disadvantages of current livestock vaccines and the absence of a licensed human vaccine have limited our ability to effectively respond to outbreaks. Further research is required for a better understanding of viral maintenance during IEPs; the role of vertical transmission in mosquitoes and circulation in wildlife in various ecological settings. Knowledge of how different routes of human exposure, such as through mosquito bite or contact with infected animal products (via percutaneous route or through aerosols), affect the immune response and disease outcomes is still lacking. Additionally, the role cellular immunity plays in livestock and humans is still unclear. Finally, a better understanding of the causes of the various manifestations of RVF disease may help to rationalize why an infection is asymptomatic or associated with clinical, sometimes fatal, illness. As a single serotype of RVFV causes disease in multiple species, opportunities exist to look more broadly at immunological differences between species and how they influence disease outcome.

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Abbreviations

ADCC	Antibody-dependant cell-mediated cytotoxicity
ALT	Alanine transaminase
AST	Aspartate transaminase
CDC	Complementdependent cytotoxicity
ELISA	Enzyme-linked immunosorbent assay

ER	Endoplasmic reticulum
GDP	Gross domestic product
HIV-1	Human immunodeficiency virus - 1
IEP	Inter-epizootic period
IFN	Interferon
mAbs	Monoclonal antibodies
N	Nucleoprotein
nAbs	Neutralizing antibodies
NSm	Non-structural protein (M segment)
NSs	Non-structural protein (S segment)
PKR	Protein Kinase R
RdRp	RNA-dependent RNA polymerase
RVF	Rift Valley fever
RVFV	Rift Valley fever virus
SAP30	Sin3A-Associated protein
SFV	Sandfly fever virus
SVTSV	Severe fever with thrombocytopenia syndrome virus
TFIIH	Transcription factor II Human.

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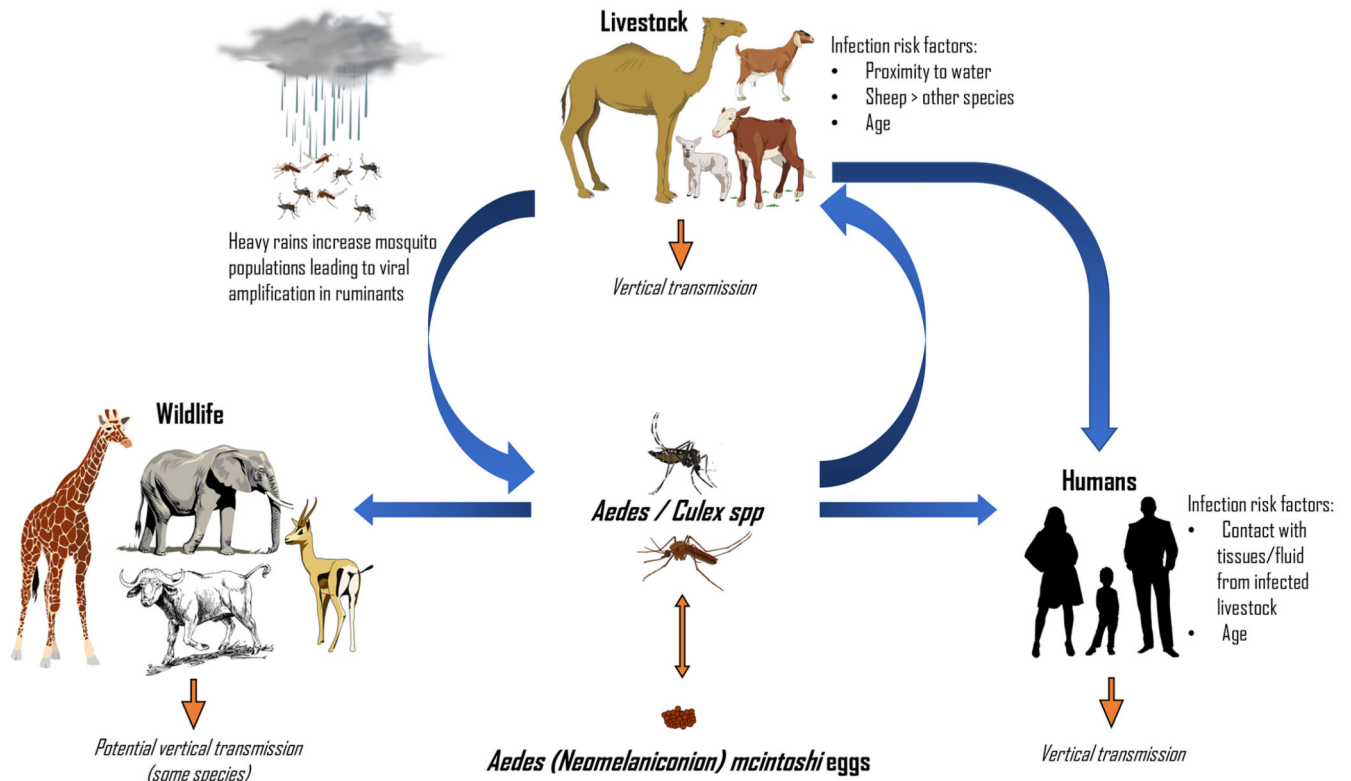


Fig. 1. RVFV cycle. Between epidemics RVFV may be maintained through transovarial transmission in *Aedes (Neomelanicion) mcintoshi* eggs. Wild ungulates and livestock can also harbour low-level infection. During heavy rains, a surge in mosquito populations leads to increased infection of livestock and viral amplification between numerous vector species and ruminants occurs. As more livestock become infected, the chances of spillover into humans increases. Human infection can occur via mosquito bite, or more commonly, via contact with infected animal tissue and fluid.

Variable case fatality rates

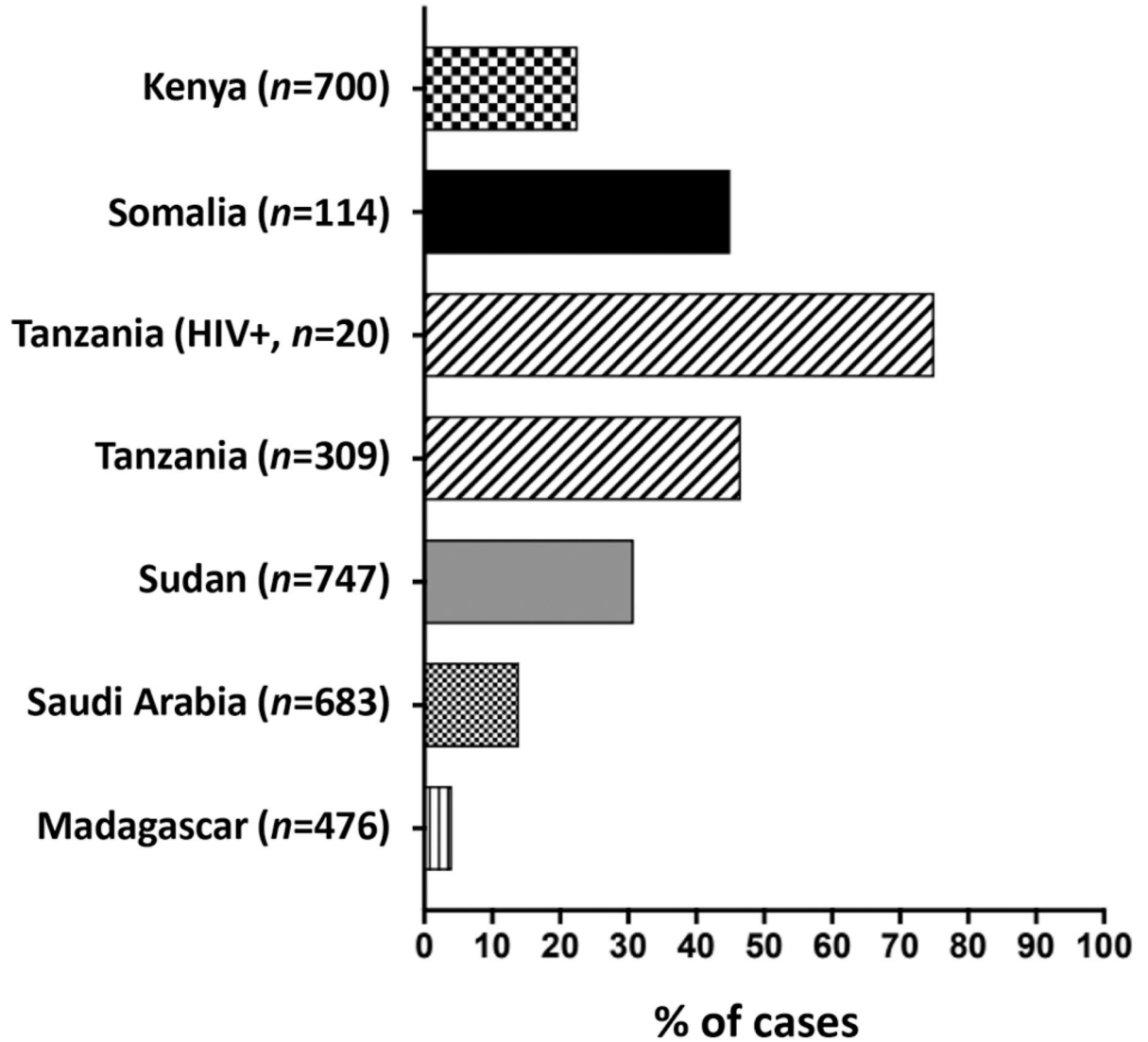


Fig. 2.
Case fatality rates among patients hospitalized with RVF disease. Data sourced from [35, 37, 49, 55].

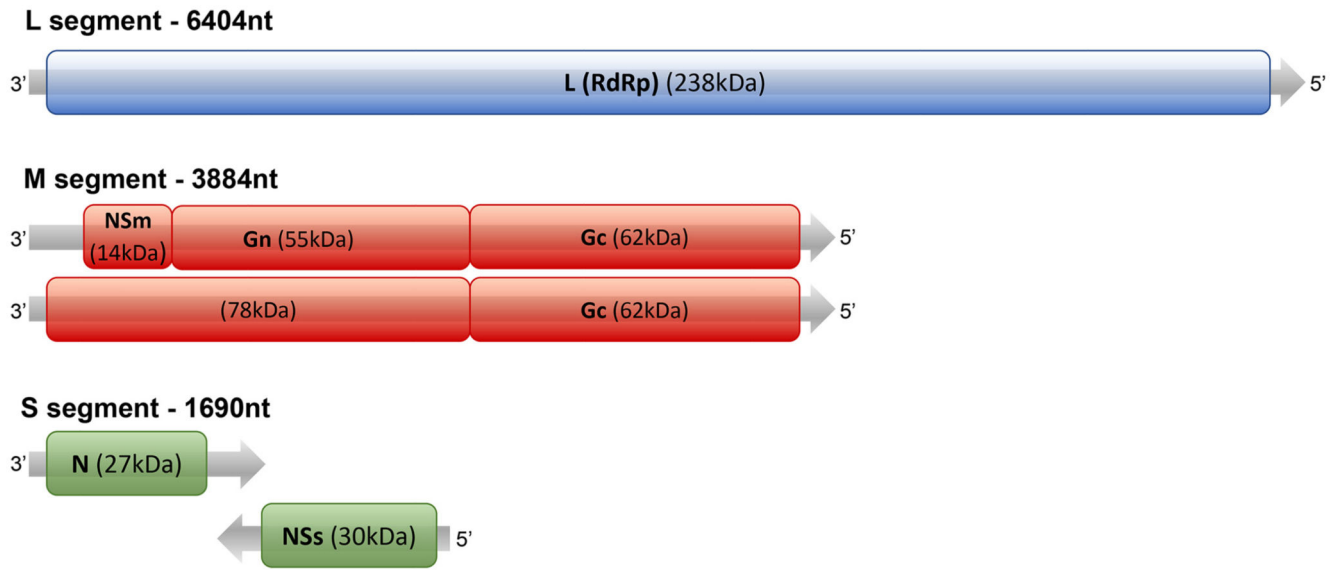


Fig. 3. Schematic of the RVFV genome. The L segment encodes the RNA-dependent RNA polymerase (RdRp) gene. The M segment encodes the precursor protein, which is cleaved into NSm, Gn and Gc. By using different AUG initiation sites, the M segment also codes for a precursor protein containing the 78 kD protein (which includes Gn) together with Gc. The S segment encodes for the N and NSs proteins in an ambisense manner.

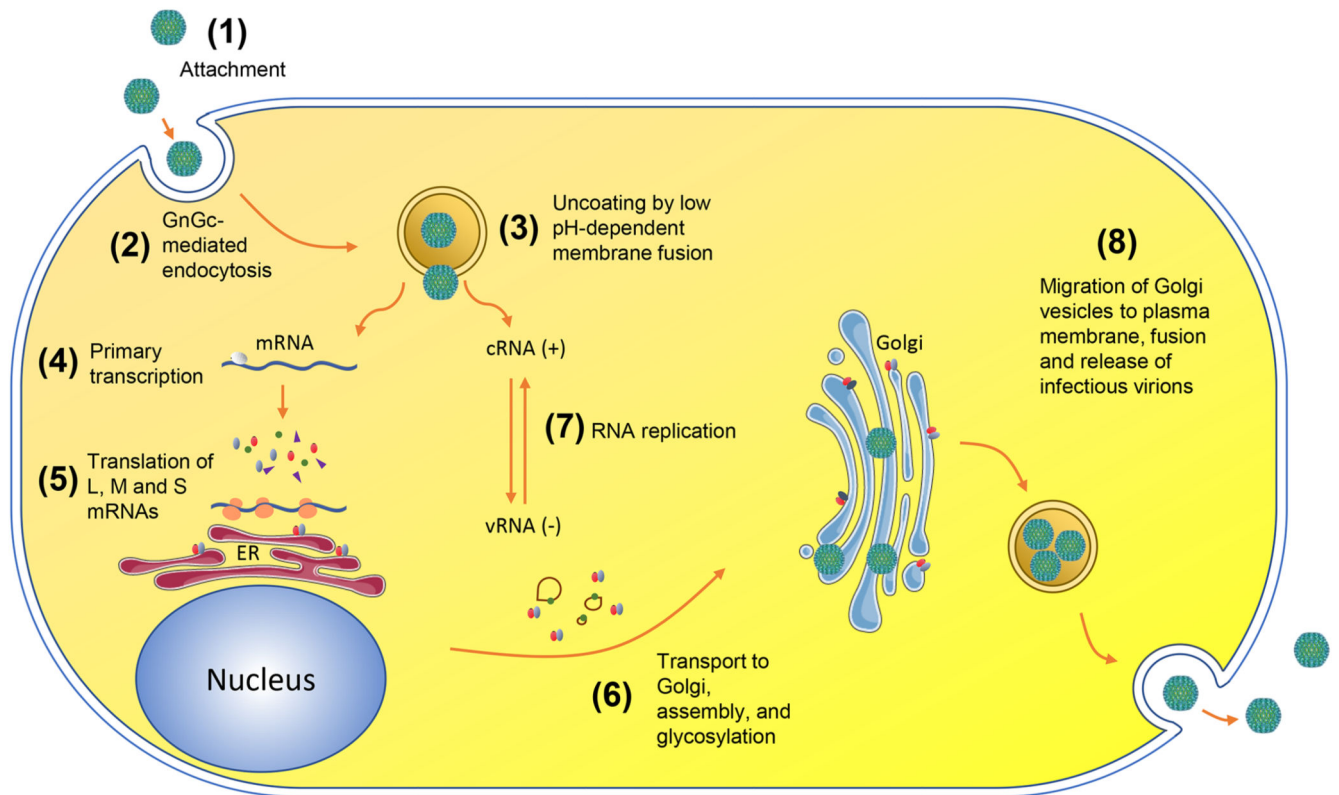


Fig. 4. Replication cycle of RVFV. (1) Viral attachment to host membrane. (2) GnGc-mediated endocytosis. (3) Uncoating by acidification of endocytic vesicles, fusion of viral and endosomal membranes. (4) Primary transcription of mRNA by viral RNA polymerase. (5) Translation of viral proteins, cleavage of M-segment polyprotein and dimerization of GnGc in the endoplasmic reticulum (ER). (6) Transportation of GnGc heterodimers to the Golgi, glycosylation of Gn and Gc and budding into the Golgi cisternae. (7) RNA replication into positive-sense complementary RNA (cRNA), which serves as a template for negative-sense viral RNA (or in the case of the ambisense S segment, templates for sub-genomic mRNA). (8) Migration of Golgi vesicles containing viruses to cell surface, fusion of vesicular membranes with plasma membrane, release of infectious virions. Adapted from [87]. Permission was obtained to adapt the figure from the authors and the copyright holder.