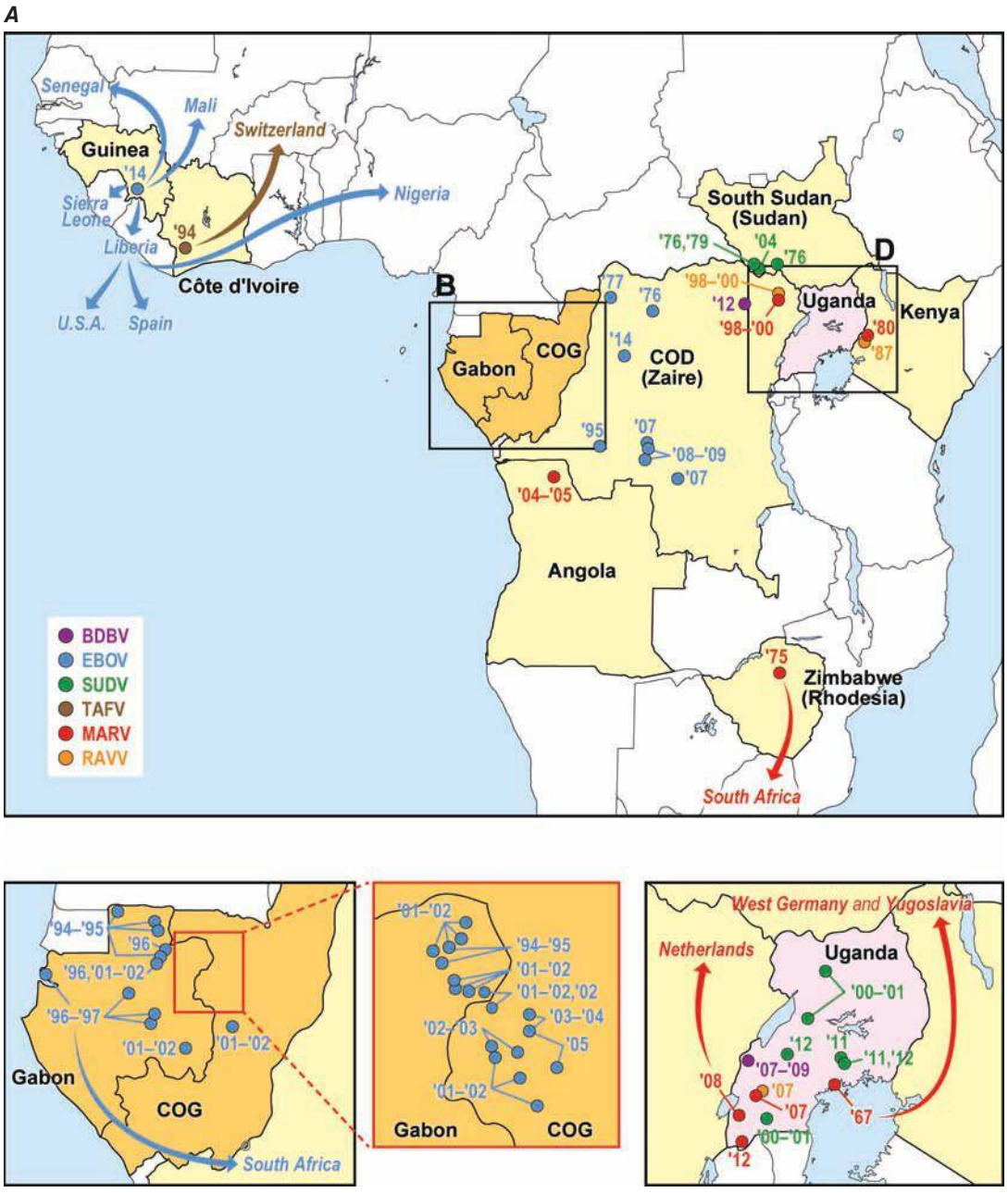

FIGURE 234-4 **Geographic distribution of human filovirus disease outbreaks and years of occurrence.** *Arrows* indicate international case exportation. BDBV, Bundibugyo virus; COD, Democratic Republic of the Congo (formerly Zaire); COG, Republic of the Congo; EBOV, Ebola virus; MARV, Marburg virus; RAVV, Ravn virus; SUDV, Sudan virus; TAFV, Taï Forest virus.

well, definitive proof is still lacking. In fact, thus far, only EBOV and RESTV have been loosely connected to frugivorous and insectivorous bats by means of antibody or genome fragment detection, whereas the hosts of BDBV, SUDV, and TAFV remain unclear.

PATHOGENESIS

Human infections typically occur through direct exposure of skin lesions or mucosal surfaces to contaminated bodily fluids or material or by parenteral inoculation (e.g., via accidental needlesticks or reuse of needles in poorly equipped hospitals). Numerous studies, both in vitro and in vivo (in several animal models of human disease), have shed light on key pathogenetic events that evolve subsequent to filovirion exposure. The $GP_{1,2}$ spikes on the surface of filovirions determine their cell and tissue tropism by engaging yet-unidentified cell-surface molecules and the intracellular receptor Niemann-Pick C1.

One of the pathogenetic hallmarks of filovirus infection is a pronounced suppression of the immune system. The first targets of filovirions are local macrophages, monocytes, and dendritic cells. Several structural proteins of filovirions, in particular VP35, VP40, and VP24, then suppress cellular innate immune responses by, for instance, inhibiting the interferon pathway and thereby enabling a productive filovirus infection. The result is the secretion of copious numbers of progeny virions, as evidenced by high titers in the bloodstream (>10^6 plaque-forming units [pfu]/mL of serum in humans) and the lymphatics, and dissemination to most tissues. Filovirions then infect additional phagocytic cells, such as other macrophages (alveolar, peritoneal, pleural), Kupffer cells in the liver, and microglia, as well as other targets, such as adrenal cortical cells, fibroblasts, hepatocytes, endothelial cells, and a variety of epithelial cells. Infection leads to the secretion of soluble signaling molecules (varying with the cell type) that most likely are crucial factors in immune response modulation and development of multiorgan dysfunction syndrome. For instance, infected macrophages react by secreting proinflammatory cytokines, a response that leads to further recruitment of macrophages to the site of infection. In contrast, infected dendritic cells are not activated to secrete cytokines, and expression of major histocompatibility class II