by fever and occasionally secondary mastitis. Dairy workers become infected during milking, leading to the appearance of localized lesions at the site of contact, usually on the hands and arms, lymphadenopathy, fever and prostration.[11] Cowpox virus, which is endemic in certain regions of Europe, causes a disease similar to Cantagalo virus, with low mortality rates, fever and localized lesions on the skin.[12] All three OPVs are maintained in the environment through a rodent reservoir and are transmitted to humans by contact with infected animals or through an intermediate species such as cattle or domestic pets.[9,12,13] Exposure rates vary and one study, conducted in Ghana, showed that OPV antibodies could be detected in 53% of the people living in proximity to forest-dwelling rodent populations.[14] Interestingly, variola virus is thought to have evolved from a rodent virus between 16 000 and 68 000 years ago.[15,16]

Other species of OPVs that are genetically related to variola virus, such as camelpox and ectromelia viruses, can cause severe systemic disease in their natural hosts (camels and mice, respectively), but have not been found to infect humans. The genetic susceptibility of OPVs to a particular host has been attributed to the acquisition and adaptive evolution of host response modifier genes.[17,18] These genes are often found to be virulence factors that down-regulate the host immune response and facilitate systemic virus spread.[19] Phylogenic analyses have shown that many of these genes are undergoing positive selection, suggesting that OPVs are continuing to evolve and increasing the likelihood of zoonotic transmission and appearance of variants with altered virulence.[17] Although smallpox is no longer a disease found in humans, the possibility exists that new variants of circulating OPVs may emerge to cause more frequent human disease.

4.2 Natural History of Human OPV Infections

The life cycle of variola virus, like other OPVs, begins with virus replication at the site of entry followed by systemic spread to distal sites.[20] Disease severity is related to the ability of a particular OPV to spread in the host and can be influenced by many factors that include the amount of virus entering the host, route of entry and host response to infection.[20] Clinical observations made during smallpox epidemics have defined four major types of disease associated with variola virus infection characterized by the morphology of the virus-specific lesion and severity of disease symptoms. Ordinary smallpox is characterized by raised pustular skin lesions that can be confluent or discrete, with a mortality rate of $\sim$30%. Variola sine eruptione is characterized by fever without rash, requiring serological analysis to confirm diagnosis. Flat-type and hemorrhagic smallpox are the most severe, with mortality rates of 97%, and are characterized by confluent flat pustules and widespread hemorrhages in the skin and mucous membranes, respectively.[2]

Orthopoxviruses are large, double-stranded DNA viruses whose genomes vary in size from 145 to 290 kb.[17] Unlike most DNA viruses that replicate in the nucleus, OPVs replicate exclusively in the cytoplasm of infected cells. Vaccinia virus is the prototype OPV and has been used to study many aspects of the virus