Health Organization (WHO) that used a live attenuated OPV (vaccinia virus) to vaccinate the general population and prevent new infections. The original smallpox vaccine was derived from the work of Edward Jenner in 1798, who discovered that scab material from cowpox lesions on dairy cows could be used to inoculate naive individuals who became immune to infection by variola virus.[3] Development of the smallpox vaccine was a major public health triumph, resulting in dramatic reductions in deaths caused by smallpox and ultimately its eradication.[2] The last known case of smallpox occurred in Somalia in 1977, and by 1980 the WHO declared that the virus had been eliminated from the environment.[2]

Although smallpox no longer exists in nature, variola virus isolates obtained during the eradication campaign have been retained and are stored in high-containment facilities located at the Centers for Disease Control and Prevention in Atlanta, GA, USA and at the State Research Center of Virology and Biotechnology in Koltsovo, Russia. The international community has lobbied hard to destroy the remaining virus stocks to safeguard the world from potential release of virus into the environment. However, some nations cite the threat of bioterrorism as a reason to continue research on this virus.[4] This threat has taken on new significance based upon recent allegations from a former deputy director of the Soviet Union's civilian bioweapons program reporting that since 1980, the Soviet government weaponized smallpox for use in bombs and intercontinental ballistic missiles. According to this source, the program was extensive and could produce tons of weaponized smallpox virus annually.[5] Moreover, it is feared that virus stocks produced during this period cannot be reliably accounted for, raising the possibility of their continued existence. Even if live virus stocks are not available, the sequence of the variola virus genome is publicly accessible, raising the possibility that the virus could be reconstructed from parts, as was demonstrated with poliovirus.[6] Based on this information, the US Institute of Medicine issued a report calling for the development of two antiviral compounds that act by different mechanisms for the treatment of OPV infections to complement our existing stocks of smallpox vaccine.[7]

Variola virus is not the only OPV that can infect humans. Three other OPV species (monkeypox, cowpox and vaccinia-like viruses) continue to circulate in the environment and cause sporadic human disease. The most virulent of these is monkeypox virus, which is endemic in some areas of the Democratic Republic of the Congo (DRC).[8] Infection with monkeypox virus causes a systemic disease that resembles a milder version of smallpox, with a mortality rate of 1–5%.[9] Unlike variola virus, monkeypox virus is less transmissible and outbreaks are short-lived and with limited human-to-human spread.[2,9] Cowpox virus and vaccinia-like viruses cause less severe disease, with fewer lesions and with little to no mortality. In certain parts of South America, a vaccinia-like virus termed Cantagalo virus, which shares phenotypic and genotypic features of the smallpox vaccine strain that was used in Brazil during the eradication campaign, causes localized outbreaks in dairy workers.[10] In cattle, the disease is characterized by pustular lesions on the teats and udders and is accompanied