Variola Virus, Variolation, Cowpox Virus, and Vaccination

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Cowpox viruses (CPXVs) exhibit the broadest known host range among the *Poxviridae* family and have caused lethal outbreaks in various zoo animals and pets across 12 Eurasian countries, as well as an increasing number of human cases. Modern CPXV isolates can not be equated to historical isolates of "cow-pox", which have been instrumental to the eradication of smallpox, which is caused by the closely related variola virus.

Keywords: poxviruses ; cowpox virus ; vaccinia virus

1. Introduction

Members of the *Orthopoxvirus* genus are large double-stranded DNA (dsDNA) viruses that replicate exclusively in the host cell's cytoplasm [1]. They are well known and studied due to their roles in shaping human history and health. Perhaps the most notorious orthopoxvirus is the variola virus (VARV), the causative agent of smallpox, which is thought to have caused epidemics in humans for thousands of years and is estimated to have caused 300 million deaths in the 20th century alone [2]. VARV was the first eradicated human disease by vaccination with vaccinia virus (VACV), which causes much milder infections in humans and confers immune cross-protection against other orthopoxvirus infections [3][4][5]. Recent outbreaks of feral VACV in Brazil [6][7] and India [8], among other countries, as well as the current global mpox (formerly known as monkeypox) outbreak, which is caused by the monkeypox virus and has infected more than over 80,000 people, illustrates that orthopoxviruses still pose major threats to human health [9]. The triumph of VACV vaccination over VARV has historically overshadowed an orthopoxvirus that played a major role in the development of the process: the cowpox virus (CPXV) (species designation: *Cowpox virus*). The CPXV name is derived from "cow-pox", a viral disease famous for its role in the popular narrative of the discovery of vaccination. Material from cow-pox patients contained the first known disease agent that was used to induce immunity against a distinct, yet related, infectious agent leading to the development of vaccination as popularized by Edward Jenner. Afterwards, the cow-pox agent was also called vaccinia and the process of vaccination spread across the world [10][11]. This discovery has saved countless human lives and revolutionized biology, giving rise to the scientific disciplines of immunology and virology. While cow-pox is acknowledged as a precursor to VACV, popular accounts often lack discussions of modern understandings of the distinction between ancient cow-pox, both ancient and modern VACV, and modern CPXV [12][13]. This misunderstanding is not helped by modern research that demonstrates that the CPXV name encompasses genetically distinct dsDNA viruses which have traditionally been thought of as a single species of the *Orthopoxvirus* genus [14]. This monophyletic convention has endured in the most current International Committee on Taxonomy of Viruses (ICTV) official report. ICTV nomenclature changes for CPXV are awaiting proposals and pending "results of a wide-scale genome sequence study" [15] despite research supporting CPXV species distinctions since 2004 [16].

A lack of viral distinction due to the absence of concepts such as viruses and genomics has historically plagued the designation "cowpox virus", once ascribed to any pox-forming disease derived from cows (*Bos taurus*). Attempts starting in the late 1930s to bring order to the designation [17] have inadvertently expanded the name to include poxviruses, which people now believe to be members of at least five unique clades, likely representative of different viral species. Unifying characteristics of these genetically distinct CPXVs are a Eurasian distribution, suspected rodent reservoirs, large genomes, and broad host ranges. This broad host range is of increasing concern as cases of fatal and nonfatal CPXV infections in non-endemic zoo animals, farm animals, and humans are on the rise [18][19][20], with ~40% of documented human cases occurring in a single modern outbreak between 2008–2011 [21]. While human cases are still relatively rare and only appear fatal in immunocompromised individuals, the need to better understand and define these viruses is apparent.

2. Variola Virus, Variolation, Cowpox Virus, and Vaccination

The complete historical account of CPXV begins with another virus: VARV, the causative agent of smallpox [22]. For millennia, humans have been afflicted by VARV with evolutionary analyses putting its origin around 2000–1000 BCE in the eastern part of Africa [22]. Although it has not been confirmed with molecular techniques due to a lack of preserved samples, it is assumed that VARV most likely caused many of humanity's early plagues, with past contemporary texts highlighting overlapping symptoms with more recent VARV outbreaks, such as the Roman Empire's "Great Pestilence" or Antonine Plague in 165 CE [23] and descriptions of smallpox-like symptoms in China 340 CE [24]. Increased trade and contact between civilizations led to smallpox-like outbreaks spreading throughout large parts of the world, with epidemics in early civilizations in Europe, Africa, and Asia [24][25]. Outbreaks devastated civilizations, such as the Japanese smallpox outbreak of 735–737 CE which killed a third of the island's population [26]. Later in the 15th and 16th centuries, VARV outbreaks aided western colonizers in their invasion of North and South America, as the disease they brought from Europe had never been encountered by the native people who were immunologically naïve, causing over 3 million native people's deaths [27]. Due to its long-term association with humanity, worldwide spread throughout the ages, and the high mortality rate of VARV major strains of between 10 and 30% [28], many estimates have placed smallpox as one of the deadliest human pathogens ever, with some claiming a death toll higher than all other infectious disease combined [29].

After centuries of global death, VARV outbreaks led to the discovery of basic immunological principles such as immunological memory, with the inciting observation that smallpox survivors were protected from subsequent infection [30]. This observation combined with attempts to transmit less virulent versions of VARV led to the invention of variolation or inoculation, with records claiming variolation techniques back to around 1000 CE in China [24][31]. The knowledge was later exported as it was first documented outside of China around 1549 and around 1581 in India, though variolation in India might have been practiced much earlier [24][32]. Variolation in China was carried out by blowing smallpox scabs, after ritualistic treatment of scabs with various herbs and salts, into the noses of patients [33], while in India the technique consisted of using a "fine sharp-pointed thorn" to pierce an infected patient's smallpox pustule then using the thorn to gently puncture the recipient's skin [34]. These techniques resulted in a less severe smallpox infection and generally robust protection against future infection but had risks including death and the potential to cause outbreaks, which was a concern of future adopters of these techniques [35]. Yet, the procedure spread across Asia and westward to the borders of the Ottoman Empire and into Africa. The Indian forms of variolation were advocated for in the west by Cotton Mather and Zabdiel Boylston in the 13 original British colonies in America and by Lady Mary Wortley Montague in Britain [36]. In Boston during the early 1720s, Mather, who was informed about smallpox variolation by literature, and his slave Onesimus, who was inoculated in Africa, tried to crusade for variolation but it failed to gain widespread acceptance in the early puritanical America of the 1720s. Mather's proposed inoculation from infected smallpox patients to healthy individuals was attempted by Zabdiel Boylston, who was initially skeptical but possibly convinced by the intensity of the 1721 smallpox epidemic in Boston. The procedure was successfully conducted on his own son and the children of his slaves. Boylston was then elected to the Royal Society of London in 1726 after the procedure gained some acceptance in the colonies [37]. Around the same time, Lady Mary Wortley Montague, a wife to a British diplomat stationed in the Ottoman Empire and mother of two young children, learned of the technique through a different source, a local Greek practitioner [32]. Caring for her children's safety, she had them inoculated against the disease in 1721 as at the time VARV was endemic to Europe where it overwhelmingly infected and killed children. Her advocacy after their return to the British Isles and the subsequent dissemination of the technique with Boylston's help led to its wide adoption amongst physicians and made it a great success, with a 10x lower case fatality rate of variolation versus natural infection [38].

Throughout Europe, an increasing demand for inoculation dispensaries caused the procedure to be well known in the West [39]. It is during this period that the first mention of recorded cow-pox emerged. Pre-1768, cow-pox was recorded as a relatively rare benign disease acquired by milkmaids while milking infected cows in western England and Europe [40]. This origin has been contested in the modern day with arguments that claim the first accurate record of cow-pox came from John Fewster, who was first informed of cow-pox by farmers in 1768 (discussed further below) [41].

The true origins of the first cases of cow-pox are lost to time, but Jenner claimed that dairy workers in the area at the time were frequently exposed to cow-pox as it was "known among the dairies time immemorial, and that a vague opinion prevailed that it was a preventative of the small pox" [10]. Named after one of its hosts, cows, cow-pox infection generally resulted in a few typical vesicular pox lesions, a mild fever, and led to the surprising observation from afflicted milkmaids and/or farmers of long-term protection from smallpox infection. From observations of this phenomenon, a few individuals, including Benjamin Jesty and Peter Plett, began working on inoculating children, the most susceptible group to smallpox, with cow-pox [30][42]. The most famous among them was Edward Jenner, the physician credited with the scientific documentation and dissemination of vaccination; though, his path to this discovery was built on the work of others, which even he acknowledged [30][41]. One such contributor was the British physician John Fewster, who claimed in 1768 to have

noticed a patient who had no response to VARV inoculation [43]. Upon questioning, the patient revealed that he had never had smallpox but had been infected with cow-pox. Fewster allegedly connected the two ideas and believed that cow-pox may be protective against smallpox infection, urging others to investigate for themselves at a medical society dinner that was attended by a young Edward Jenner [44]. Years later, Jenner experimentally tested this hypothesis by infecting a child, James Phipps, with a sample of cow-pox from a milkmaid named Sarah Nelmes, which resulted in a single pustule and mild fever. He then challenged the young boy six weeks later by infecting him with a sample of smallpox to which the boy had no reaction to [11]. These efforts led to the discovery of the cross-protective nature of orthopoxvirus infection, a rare viral/immunological phenomenon, wherein infection from one member of the genus generates immunological memory that protects from infection by other genus members [45]. From there, Jenner popularized vaccination with cow-pox as a safer alternative to variolation after a presentation to the British Royal Society, his self-publication of his experimental findings [11], and a subsequent world tour championing cow-pox vaccination [46]. These efforts paved the long road to the eradication of smallpox through surveillance, control initiatives, and worldwide vaccination campaigns with VACV in the 20th century, led by the World Health Organization (WHO) which on 8 May 1980 at the 33rd World Health Assembly declared natural VARV eradicated [3].

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