

Review

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Immunopathogenesis of Orthopoxviridae: Insights into Immunology from Smallpox to Monkeypox (Mpox)

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Review

Immunopathogenesis of Orthopoxviridae: Insights into Immunology from Smallpox to Monkeypox (Mpox)

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Abstract: Since 2019, notable global viral outbreaks have occurred necessitating further research and healthcare system investigations. Following the COVID—19 pandemic, an unexpected duality has occurred of SARS—CoV—2 and monkeypox virus (MPXV) infections. Monkeypox virus is of the *Orthopoxviridae* genus, belonging to the family *Poxviridae*. Zoonotic transmission (animal to human transmission) may occur. The *Orthopoxviridae* genus includes other Orthopoxviruses (OPXV) present in animal host reservoirs that include cowpox viruses (CPXV), vaccinia virus (VACV) and variola virus (VARV), with the latter being causal agent of smallpox and excessive mortality. The aim in this review is to present facts about MPXV specific pathogenesis, epidemiology, and immunology alongside historical perspectives. Monkeypox virus was rarely reported outside Africa before April 2000. Early research since 1796 contributed towards eradication of VARV leading to immunisation strategies. The World Health Organisation (WHO) announcement that VARV had been eradicated was confirmed in 1980. On the 23rd of July 2022, the WHO announced MPXV as a health emergency. Therefore, concern due to propagation of MPXV causing MPOX disease requires clarity. Infected hosts display symptoms like extensive cellular initiated rashes and lesions. Infection with MPXV makes it difficult to differentiate from other diseases or skin conditions. Anti—viral therapeutic drugs were typically prescribed for smallpox and MPOX disease; however, the molecular and immunological mechanisms with cellular changes remain of interest. Furthermore, no official authorised treatment exists for MPOX disease. Some humans across the globe may be considered at risk. Historically, presenting symptoms of MPOX resemble other viral diseases. Symptoms include rashes or lesions like *Streptococcus*, but also human herpes viruses (HHV) including *Varicella zoster* (VZV).

Keywords: orthopoxvirus; molecular; health; immunology; monkeypox; smallpox; innate; adaptive; cells

Introduction

Monkeypox virus (MPXV), the causal virion of MPOX disease, affects living animal populations by causing systemic disease, but in specific tissues and cells through host cell receptors and intracellular propagation. Historically, research into variola virus (VARV) occurs under WHO rules due to such virulence seen by the original VARV eradicated pathogen. Recently research development utilises lesser virulent orthopoxviruses (OPXVs), like those derived from vaccinia virus (VACV), as well as cowpox virus (CPXV), although horsepox virus (HPXV) was examined recently. Considerably less was known in 1980, when VARV (major/minor) was eradicated of the molecular and cellular interactions involved in OPXV propagation [1]. In 2017, reports appeared analyzing a 1902 VARV vaccine suggestive of high (99.7%) levels of similarity with HPXV, although the origins of *Poxviridae* remain unknown [2,3]. Below is shown some historical perspectives of *Orthopoxviridae* (see Figure 1).

The MPXV particle size is 200–450 nm in length with approximate width 160–260nm and a genome size of approximately 197kb [4,5]. Viral components are a linear double—stranded deoxyribonucleic acid (dsDNA) genome, a nucleoprotein core containing transcription factors (TFs), surface tubules and two lateral bodies [6]. Monkeypox virus encodes structural proteins with virions that are ovoid/brick—shaped, together with a lipoprotein outer membrane. Within the OPXV family there are an estimated 22 species across 83 genera. The MPXV genome is composed of approximately

190 open reading frames (ORFs). Approximately 90 ORFs are considered to encode MPXV proteins required for replication. Some of these may undergo gene mutations affecting biological function [7,8]. There are an additional two conserved non-repeating (NR1 and NR2) gene sequences that are known to flank inverted terminal repeat (ITR) sequences in OPXV genomes. Therefore NR1 and NR2 act as regulatory sequences. Currently classified utilizing genomic surveillance (www.nextstrain.org), MPXV is known by clade I (Congo Basin) or clade II (West Africa) nomenclature [9,10]. When clades were classified, disruptions to ORFs were noted that may explain differences in virulence [11,12].

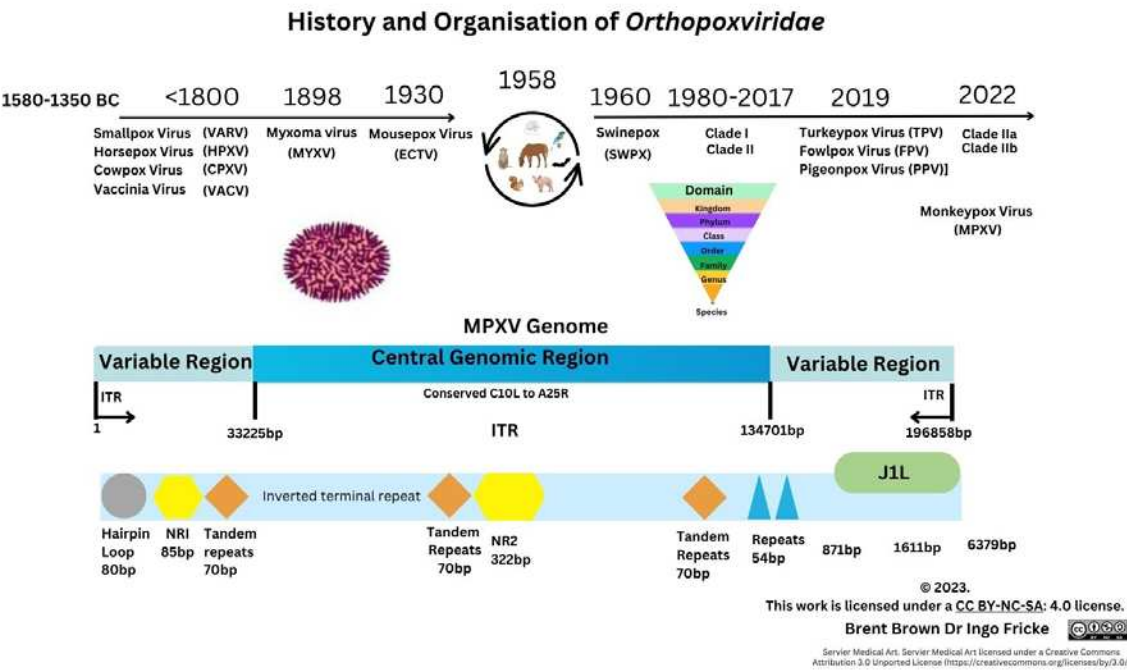


Figure 1. Monkeypox Virus Genome.

Monkeypox virus infects a host through intradermal, oropharynx, and nasopharyngeal routes. Infection accompanied by rashes and lesions that resemble those of MPXV can be like lesions of other viral or bacterial infections. For example, exanthem skin rashes or lesions are associated with epithelial and mucosal cell membrane disruption during infection with *Echovirus*, *Coxsackievirus*, *Cytomegalovirus* (CMV) or *Neisseria meningitidis* (meningococcal disease) [13–16]. In addition, chickenpox lesions caused by *Human herpesvirus 3* (HHV3/VZV) have similarity to those caused by MPOX disease. Viral gene DNA transcription into messenger RNA (mRNA) occurs with translation into protein intracellularly following.

In brief, *Poxviridae* use permeation, adsorption, membrane fusion, and lysis, being four key stages to propagate while interacting with cellular proteins [13]. Globally, MPOX disease has occurred in more than 110 previously non-endemic countries reaching more than 87,543 laboratory confirmed cases worldwide as of 24th May 2023. It is possible that increased usage of diagnostic testing during the COVID-19 pandemic thereby allows greater scientific analysis into MPOX cellular disease mechanisms [18]. Different generations born after 1980, or potentially earlier could have variations in immune responses against OPXV that include MPXV infections [19]. Historical studies estimating mutations in dsDNA OPXVs, like VARV now extinct, indicate that prior to eradication OPXVs may have evolved or mutated at between 1×10^{-5} to 1×10^{-6} substitutions/site/year [20,21]. The current review focuses on existing contributory MPXV proteins and will attempt to clarify immunological responses since the VARV pandemic more than 43 years ago.

Historical and Epidemiology Overview of Monkeypox Virus

Initially, MPXV was isolated in the laboratory from lesions found on imported primates in Copenhagen in 1958, but also subsequently in monkeys and squirrels (1985), together with dormice (*Graphiurus*), rodents (*Cricetomys*), and prairie dogs (2003). These are known to be the primary MPXV hosts [22–25].

Other OPXVs exist in different animal species, for example isolation of *Eptesipoxvirus* occurred (2017) in a microbat (*Eptesicus fuscus*), while some are known to infect cattle (*Capripoxviruses*) that cause lumpy skin disease (LSD) [26–28]. On 25th May 2022, WHO issued a public health statement due to increases of MPXV cases detected. The risk of transmission in vulnerable populations also includes both elderly and children. The information available suggests that children in the endemic area are affected and vulnerable populations in non-endemic could be affected [29]. There is some data on whether MPXV infection affects pregnancy and gestation [30]. From early 2022, the median age of MPXV cases is 34 (range 29–41). Like other OPXVs, MPXV may affect pregnant women more severely than healthy non-pregnant females [31]. Some reports suggest a link between congenital infection and fetal death from virus propagation [31].

Since 2017, surveillance confirmed the existence of subclade IIb B.1. Moreover, subclade IIb A.2 is considered to possess 42 nucleotide mutations, including those of apolipoprotein B mRNA editing enzyme deaminases (APOBEC3) that play a role in outbreaks seen in 2022 [5,10,32,33]. All systems put in place to monitor SARS-CoV-2 can therefore be useful in the context of MPXV surveillance and other pathogens from the OPXV family given the severity of both. At the time of the WHO announcement, it was noted that SARS-CoV-2 prevalence was transitioning between BA.2/4/5 strains at that time. Details on MPXV co-infection remains limited even now [34].

Clades of MPXV can vary by infection fatality rate (IFR), as indicated by clade I (Congo Basin and Nigeria) at up to 10.0%, with the latter clade IIa (West Africa clade) and more recent clade IIb suggested to have an IFR of 1.0%–3.7% [35]. Transmission rates are indicated by R_0 and a recent study by Du et al. indicated that MPXV R_0 is around 1.39 (95% CI: 1.37, 1.42) [36]. R_0 remains a parameter used to define transmissibility in human populations [37,38]. In comparison, 2009 Influenza (H1N1) and 2020 SARS-CoV-2, R_0 was quantified at 1.7 and 2.4 respectively, with other OPXVs (Measles) at 12–18 [39–41]. Between 1980–2000, MPXV remained detected in mostly African countries with cases reported in the Democratic Republic of Congo (DRC), Gabon, Ivory Coast, and the Central African Republic until 2003 in United States of America (USA) [17]. It is notable that research during the DRC outbreak quantified incidence risk between outbreaks of 1981–1986 and 2005–2007. During the 1980s this is suggested at 0.72/10,000 individuals, with latter outbreaks at 14.42/10,000 individuals respectively [42]. Prior articles indicate occurrence in individuals between age 21–40 that may be indicative of lack of immunity to OPXVs like VARV, unknown to date [22]. Between 2009–2014 (n=645) it was confirmed that 80% of prior OPXV outbreaks occurred in children under 15, but analysis indicated either 93% or 98% met the criteria for MPXV infection; however low specificity to the available serological analysis of between 9%–26% respectively was indicated then [6]. Serological diagnostic testing is validated prior to use as a diagnostic for specificity of reagents (e.g., monoclonal antibodies) and was indicated as problematic with OPXVs before and after 2000 due to antibody cross-reactivity with other OPXVs [43–46]. However more recently 119 antigen, DNA and antibody tests are now available subject to specificity and licensing approval (see Supplementary Data S1).

Lymphadenopathy reactions occur when the lymphatic system, tissues and cells react as with other viral lesions that occur during chickenpox (VZV) infection [6]. More recent surveillance of serology in animals is feasible and has occurred during a 2017 cowpox virus (CPXV) outbreak. For example, in four alpaca herds, seroprevalence was established (range 16.2%–81.6%) alongside monitoring of OPXV (CPXV) spread between rodents and the vole (*Microtus arvalis*) between 2007 and 2017 [47,48]). In December 2019, as the COVID-19 pandemic was recognized by the WHO, investigations examined real-time quantitative polymerase chain reaction (qPCR) cycle thresholds (CT=range 22.6–38.1). This identified in a case study that 88.1% (n=42) of MPXV infected individual sample types obtained from residential surfaces were positive for MPXV DNA. The likelihood of finding DNA was greater on surfaces such as bed linen and tablet screens [49]. Moreover, in 2021, confirmation occurred (CT range 16.1–35.7) that MPXV was isolated from porous surfaces with

viability of up to 15 days (about 2 weeks) [50]. Indeed, analysis confirmed that the amount of infectious MPXV viral load necessary to instigate MPOX disease remains unknown from these investigations [51–53].

Pathogenesis

Clinical manifestations and Diagnosis

Monkeypox (MPOX) disease displays with fever, headache, and myalgia with/or without swelling that may occur within lymph nodes (LNs) indicative of an immune response occurring in germinal centers (GCs). Lymphadenopathy can be accompanied by exhaustion, chills, back pain, sore throat, and malaise [54]. Appearance of lesions together with rashes and/or pustules disturbs skin epithelial cell layers [55,56]. These occur as macular, papular, vesicular or pustular and may also start in the mouth [57]. Initially, a rash begins as macules, progressing to papules, vesicles and pustules before scab appearance after 7–14 days [28,29]. The eschar falls off with epithelial cells and surrounding tissue healing over 2–4 weeks later and renewing. An individual is no longer considered infectious from this time onward [56]. During 2022, it was noted that lesions in certain areas were less or more common [58]. Such clinical signs and symptoms could be mistaken for other viral diseases (e.g., *Varicella zoster*–HHV3), but also bacterial infections like *Treponema pallidum* (syphilis) or lesser virulent poxviruses causing skin lesions like *Molluscum contagiosum* [55].

Diagnostics began testing for MPXV with real-time PCR (polymerase chain reaction) for generic OPXV genes or others (see Supplementary Data S1–5). Assays also utilised include enzyme-linked immunosorbent assay (ELISA), western blot, or tissue protein immunohistochemistry. More recently, clustered regularly interspaced short palindromic repeats (CRISPR), and other biosensors (e.g., CRISPR/Cas12b) are in development that could potentially be suitable for viral detection. These could be more cost effective than traditional diagnostics and potentially more accurate than lateral flow device (LFD) testing [59–63].

During acute infection, real-time PCR is the preferred test as per current WHO guidelines [17]. For example, usage in a variety of cohort studies (n=3) quantified cellular viral load in distinct location of anatomical lesions during MPOX disease. This was noted by sample type as follows: saliva (92.3%), oropharyngeal swabs (86.2%), plasma (51.7%), stool (46.1%), urine (9.5%), and semen (5.7%). Viral particles from MPXV DNA were found in non-lesion sites present (up to 67 days), but also in oropharyngeal swabs, with DNA detectable up to 19 days [64]. Although MPXV diagnostic tests yield satisfactory sensitivity and specificity confirming positive OPXV infections, serology tests in the past could detect other OPXV epitope similarities through cross-reactive antibodies. Recent PCR DNA tests detect specific MPXV genes according to WHO guidelines that include *B6R*, *B7R*, *E9L*, *C3L*, *RPO18*, and *F3L* [65–71]. Currently there are 3 types of MPXV diagnostic test available that include DNA (87), antigen (18), and antibody (14) diagnostics totaling at least 119 to our knowledge (see Supplementary Data S1).

3.2. Cellular Monkeypox and Orthopoxvirus Historical Evolution on Viral Entry

Unlike other viruses, MPXV does not have a unique receptor for cell entry. Many genes encoding proteins and receptors are described and contribute to MPXV virion particle fusion alongside intracellular formation of virion particles. Synthesis of intracellular mature virions (IMV) and enveloped extracellular virions (EEV) occurs. Specific host proteins are affected by MPXV utilising host-synthesized proteins and affecting immune system responses. For example, cytokines (interleukins, IL-1), but also type I/II interferons (IFN) are known to be affected by OPXVs due to protein homology and comparative knowledge of IFN signaling [72–74]. The role of type III IFN in OPXVs remains unclear and are therapeutic targets under investigation in other inflammatory pathologies. [75,76].

Poxvirus cellular protein entry occurs via the phospholipid plasma membrane (PM) and endocytoses dependent on low intracellular pH conditions utilising more than eleven conserved fusion proteins to form an entry fusion complex (EFC) [77–79]. Replication in Guarnieri bodies in

proximity of cell organelles occurs between the Golgi apparatus and endoplasmic reticulum (ER) [80]. Subsequently, MPXV synthesis of other viral proteins described are encoded by early (E), or late gene products (L), that transcribe viral DNA producing RNA translated to produce proteins making the IMV/EEV particle utilising host cell proteins that lyse with variable thickness poxvirus cell membrane layers [80]. Monkeypox virion particle entry requires extra-cellular expressed protein receptors and the intra-cellular proteins as below. Virion particle formation to a stable IMV/EEV requires actin tails synthesised within host cells [81]. It is believed that MPXV and VARV are slightly comparable with estimates of 96.3% genetic homology [82,83].

Historically, VARV and MPXV gene proteins are denoted by restriction endonucleases described by capital letter (HindIII restriction endonuclease fragment), number (position within fragment), but also R/L (denoting direction of transcription). Other reviews dictate that it is unknown how poxvirus gene loss and variation occur [84]. Some reviews refer to COP proteins frequently denoting research on complement inhibition proteins on earlier vaccinia (VACV) strains. Therefore, convention describes researched protein homology in lesser virulent strains of OPXV, initially denoted by VACV, (and COP proteins), but also CPXV (BR derived from CPXV British Green proteins), in which these were first characterised.

History indicates that differences before clade I and clade II MPXV gene transcripts were that these gene transcripts were initially characterised (*A52R*, *A55R*, *B17L*, *C2L* and *E5R*) [85]. Subsequently during the 21st century, research on VACV indicated that another gene transcript, *H3*, is notably homologous between *Chordopoxvirinae* and *Entomopoxvirinae*. Other gene transcripts (*A27*, *A33*, *L1*) had not been confirmed by X-ray crystallography until the 21st century as technological improvements in genome sequencing occurred.

Evidence was found during VACV research therefore that *H3* (p35) may not be involved in cell fusion but is involved in OPXV adherence via binding to heparan sulfate and is a plausible immunodominant antigen target [86]. Subsequently, *A46R* and *A52R* proteins were shown to be expressed by the lesser virulent VACV potentially homologous that may antagonize host IL-1 and Toll-like receptors (TLR) responses although not to the extent seen prior [72]. Prior research from *in vitro* studies indicates that *H3/A27* bind to heparan sulphate and *D8* binds to chondroitin/laminin with both *A27/D8* binding to glycosaminoglycans (GAG) [87].

Differences between Smallpox and Monkeypox virus

Shortly around the time of earlier outbreaks of MPXV, reports appeared further clarifying poxvirus inhibitors of complement enzymes (PICES) generic to previous OPXVs, with other proteins indicated key to viral replication, cell structure, transcription and immune responses. These include morphogenesis factors, profilin-like factors, but also DNA ligases and actin tail nucleation proteins.

Based on genomic analysis it was postulated that 5 MPXV genes could affect the immune response that were *D10L*, *D14L*, *B10R*, *B14R*, alongside *B19R* that may explain the differences between virulence of previous MPXV clades [88]. As research evolved it became clearer that three proteins *E3L*, *C3L* and *C10L* were truncated or fragmented in MPXV, present in the virulent VARV, of which one is considered an IFN resistance protein (*E3L*) [85]. The *E3* homologue gene transcript *F3L* of MXPV contains an N-terminal binding domain and a C-terminal dsRNA binding domain that is 88% to 92% similar to VACV. The protein encoded is implicated in affecting pattern recognition receptors (PRRs), retinoic acid-inducible gene I (RIG-I), melanoma-differentiation-associated-protein 5 (MDA5), and oligoadenylate synthetase (OAS). Each is central to sensing both dsRNA and DNA through TLR signaling largely unknown [89,90]. In earlier clades of MPXV therefore it is known that through inhibiting protein kinase R (PKR) and OAS intracellularly that type I/II IFN pathways can be inhibited. Although it is notable that there are four types of OAS enzymes, of which three have typical OAS catalytic activity. The fourth OAS protein (OASL) does not have enzyme catalytic function, but is involved in intracellular signalling that regulates the human anti-viral response.

Gene Transcripts and Proteins during Monkeypox virus Infection

When MPXV fuses with a host PM, a viral particle enters the cytoplasm facilitating cellular replication/synthesis of viral proteins within a host cell by proteins encoded by MPXV genes that may also include *A16L*, *A21L*, *A28L*, *F9L*, *G3L*, *G9R*, *H2R*, *J5L*, and *L5R*. [16,20].

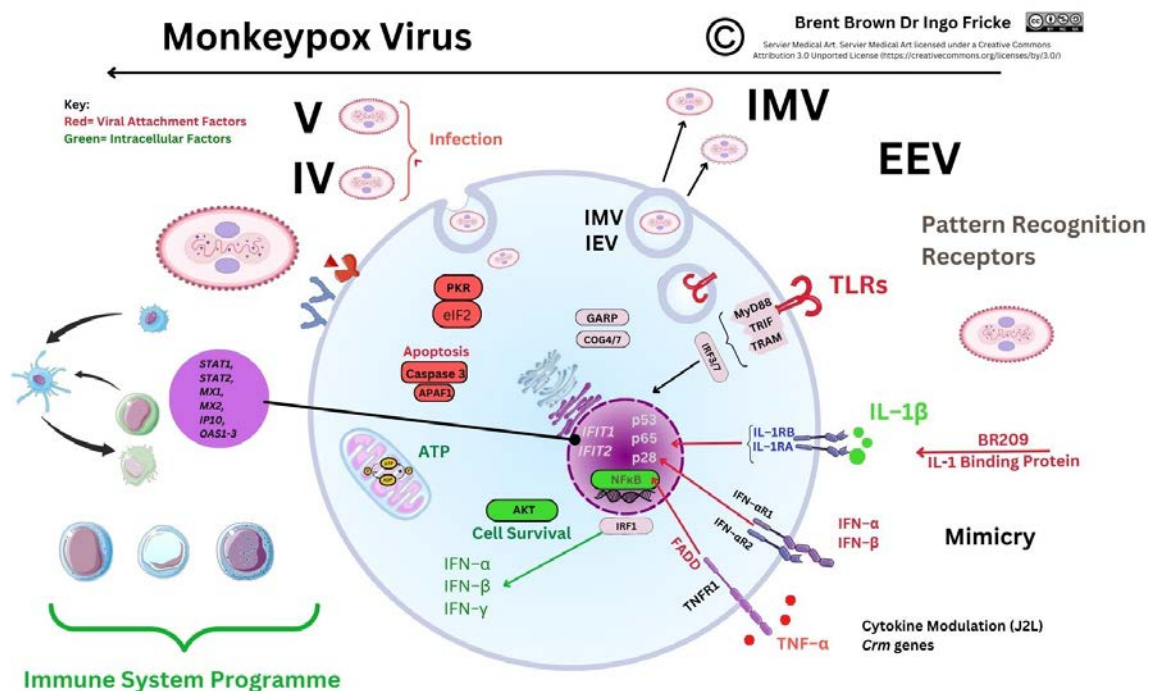
As far as timing and location of OPXV DNA replication occurs, generic DNA synthesis of DNA is detectable within 2 hours of cytoplasmic entry [92]. Differences between MPXV clade I/II occurred with virulence proteins still under validation checks. However, most gene transcripts were initially characterised by OPXV homology with VACV/VARV (*A49R*, *A52R*, *A55R*, *B17L*, *C2L*, *E5R*) [85].

During the 21st century CPXV gene transcripts observed were upregulated during cellular infection (*BR158*, *BR203*, *BR209*). Of these *BR203* protein (221 amino-acids) is considered to effect lymphocyte apoptosis while *BR209* (126–210 amino-acids) is shared between two MPXV clades affecting IL-1 function as an interleukin-1 β (IL-1 β) binding protein. Below is an example of the MPXV genes and proteins outlined herein (see Figure 2 and Supplementary Data S2, S3, S4).

A notable article in 2008 examined MPXV gene transcript expression. This was examined in monocytes with MPXV gene transcripts observed including ribonucleotide reductase (*C10L*) and others [93]. Also described were an array of encoded RNA polymerases (*G6R*, *E7R*, *F4L*) and DNA ligase enzymes (*A50R*) necessary for host cell propagation [93]. Prior reviews suggest that *D14L* is missing in MPXV clade II as well as *B10R* and *B14R* that may affect lymphocyte apoptosis and MPXV virulence [94].

Considerable divergence in OPXV protein naming became more specific with the term monkeypox inhibitor of complement enzyme (MOPICE) being used. While identification of the *D14R* gene transcript encoding missing in MPXV specific proteins is indicative that could previously further inhibit complement pathway C3 and C5 convertases through binding to C3b and C4 complement proteins [88]. These findings were relevant in explaining the change in MPXV complement inhibition and resulting virulence potential change from earlier clades.

Activation by cytoplasmic DNA of the cyclic GMP-AMP synthase (cGAS) and resulting intracellular synthesis of 2',3' cGAMP and stimulator of interferon genes (STING) remains of interest in OPXV research as a regulator of IFN synthesis and gene transcription of other host gene factors (e.g., *IFIT*, *ISG*) including some affecting interferon synthesis.



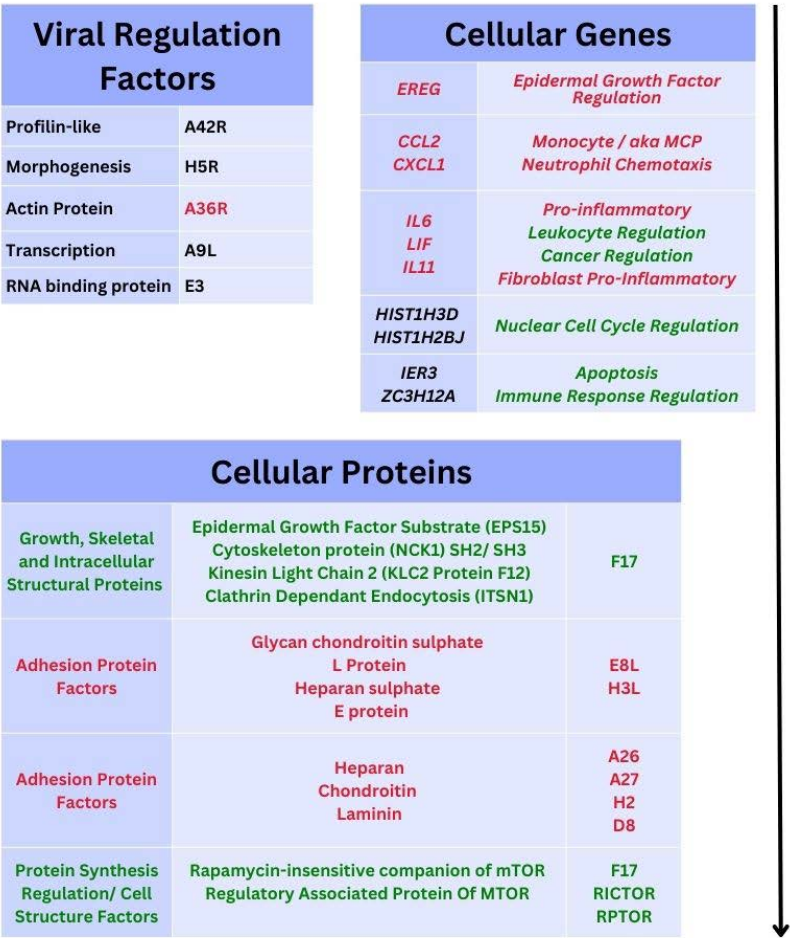


Figure 2. Monkeypox Virus Cell Genes and Proteins.

In 2017, it was confirmed that Golgi—associated retrograde protein complexes (GARP) were the retrograde transporters that the endosomal cellular transport system utilises encoded by four vacuolar protein genes (VPS) (*VPS51–VPS54*) [95]. This was followed up shortly after by the discovery of a 2',3'-cGAMP-specific nuclease, named poxins, in 2018. These were inactivated in VARV and may affect innate immune response signaling [96,97]. Recently, it has been further clarified that after the virion particle enters a host cell, that GARP and eight conserved oligomeric Golgi (COG) proteins may facilitate cell entry, fusion and virion particle formation (COG3/4/7/8) around the endoplasmic reticulum [77,78,95]. Specifically, *VPS52* and *VPS54* knockout MPXV infected cells *in vitro*, incurred significant loss of function in actin tail formation, and as a result these were not required for IMV formation but for maturation towards EEV virion particles [95,98] The same group then further identified this COG complex as being composed of eight heterodimeric proteins of two subtypes (lobe A COG1–COG4 and lobe B COG5–COG8) with COG4/7 considered to be more important for viral fusion and egress [95,98].

3.5. Recent Monkeypox Virus Protein Characterisation and Research

Since October 2022, the first article detailing a specific MPXV protein characterised by crystallography was published to our knowledge. Gene *A42R* (*gp153*), homologous to cellular profilin proteins, was found to be conserved across OPXVs with 98% homology. It has been described that A42R protein may have some affinity to actin whilst simultaneously being a cytotoxic T (Tc) cell epitope, denoted by the cluster of differentiation (CD) molecule, CD8+ [70,71].

Although not involved in MPXV replication, reports in November 2022 documented a novel MPXV protein that may affect intracellular host proteins and be of therapeutic value. Researchers discovered the synthesis of the conserved OPXV enzyme H1 phosphatase during MPXV infection. It is expected to be to dephosphorylate STAT1 and downregulate interferon signaling [99].

While bioinformatics research from earlier MPXV genomic analysis recently implicated, in yet to be peer reviewed reports that ten MPXV genes were upregulated (*IER3*, *IFIT2*, *IL11*, *ZC3H12A*, *EREG*, *NFKBIE*, *IFIT1* and *AREG*) with significance associated to suppression of two anti-viral gene transcripts *IFIT1/2* regulating interferon synthesis [100]. Interestingly it was noted that a chemokine ligand gene transcript (*CXCL1*) was predicted to be significantly activated with *CCL2*, but slightly less so in comparison to CPXV and VACV [101]. Furthermore, the authors predicted upregulation of an early response *IER3* gene transcript [102]; But also, *IL11* upregulation of a potential cytokine protein that could be considered pro-inflammatory in fibroblasts [102–104]. Epiregulin is encoded by the *EREG* gene and is a member of the epidermal growth family (EGF) signaling through EGF receptors present in epithelial cells [105–108]. Furthermore *NFKBIE* noted above follows nuclear transcription of *NF-κB* activation occurring during *myelopoiesis* [109]. Whilst amphiregulin gene transcript (*AREG*) expression is indicative of influence on cell proliferation of keratinocytes and fibroblasts in skin epithelial cell layers [110].

More recently immunoinformatics prediction on potential peptide vaccine candidates to HLA-II DRB*0101 that is highly expressed (99.74%) in global populations is suggestive that a peptide could be designed that would bind to MHC class I/II molecules and stimulate both TLR3 and TLR 4 receptors [111]. These observations indicate HLA alleles may underpin differential immune responses and would be very interesting to see experimental research on.

However other bioinformatics study imply that the top three cellular pathways affected during MPXV infection are cytokines (Tumour necrosis factor (TNF) and IL-17), immune cells (T_H17), and nuclear transcription (NF-κB) pathways [101,112]. These are hypothetical, however given that CXCL1 has a short-half life and as below it is biologically plausible that infection by other factors may upregulate cytoplasmic CXCL1 synthesis leading to neutrophil and monocyte migration during MPXV infection like TNF-α expressed in epithelial cell layers [112].

Orthopoxvirus and Monkeypox Virus 21st Century Immunological Research

Background

Monkeypox virus protein antigens were evidenced around 2001 as replicating in epithelial cells, macrophages (Mφ), dendritic cells (DCs), and fibroblasts utilizing anti-vaccinia polyclonal antibodies and anti-MPXV polyclonal antibodies [113]. Monkeypox virus proteins outlined above are encoded by at least twenty-four gene transcripts that cause cellular changes upregulated 1 day after infection in two other key cell subtypes infected. The immune cell type that matures into Mφ and presents pathogenic antigens, namely monocytes, is better characterised in context of other recent viral infections recently [114]. Orthopoxviruses are known through VACV/MPXV/CPXV research in ability to modulate anti-viral immunity that led to smallpox eradication utilising the first. The role of monocyte markers and Mφs in antigen presentation can be considered further as type I/II IFN remains crucial in viral clearance of infected cells [115–117]. The underlying mechanisms of the success of earlier VARV eradication remain unclear to this day but likely involve a host cell cytotoxic T cell response unknown to date.

It is therefore necessary to consider the role of TLRs in MPXV which are both intracellular/extracellular transmembrane proteins. There are ten known TLR types in humans, but specifically five may be more relevant to immune cell recognition of OPXV infection, like TLR2/3/4/5/7/10, acting as cell membrane and vesicular sensors during viral and/or bacterial infections [118–121]. Below is an example of TLR perspective in OPXVs (see Figure 3).



Therefore, as OPXVs express IL-18 binding protein homologues, this represents a potential route of OPXV immune response modulation affecting delayed type II IFN- γ release. In addition, all OPXVs contain serpin genes with serpin 2 (*B13R*) in earlier MPXV clades [127,128]. There are 180 serine proteases regulated by 37 serine protease inhibitors (SERPINS) in humans that regulate

haemostasis, inflammation, tissue remodeling, or angiogenesis. Furthermore, other roles for TNF modulation by homologous virus encoded receptors (TNFSFR1B/p75; TNFR2) is plausible as cytokine release modulators (Crm) are known in OPXVs [128,129].

Immunological Response during OPXV Infection

Immunological responses to OPXVs occur across natural environments in hosts but MPXV specifically, which are dependent on at least four key factors that include B cells, T cells alongside APCs (monocytes, Mφs, DCs) and natural killer (NK) cells. In recent serological studies investigating residual VARV immune responses 23 years after eradication. It was observed (n=204) that residual immune cell memory to VACV remained during the 2003 MPXV United State of America (USA) outbreak in 2003. This was measured by B cell antibodies present in a total of 68.5% of those receiving one dose and 79.5% of those receiving two doses age over age 35 [130]. Estimates of smallpox immunity longevity are largely unknown [131,132].

Shortly after Hammarlund et al. during 2008 examined MHC expression during MPXV infection to show that, in comparison to VACV, MHC expression was comparatively not affected by either synthesis or maturation indicative of a role of T cell receptor signalling and that antigenic peptide fragments were presented. [133]. During *in vivo* research (2013) reports indicated increases of total NK cells during MPXV infection in combination with a significant reduction in the overall percentage of a specific NK cell phenotype (CD56^{dim}CD57⁺) [134]. Below is shown overall immune responses (See Figure 4).

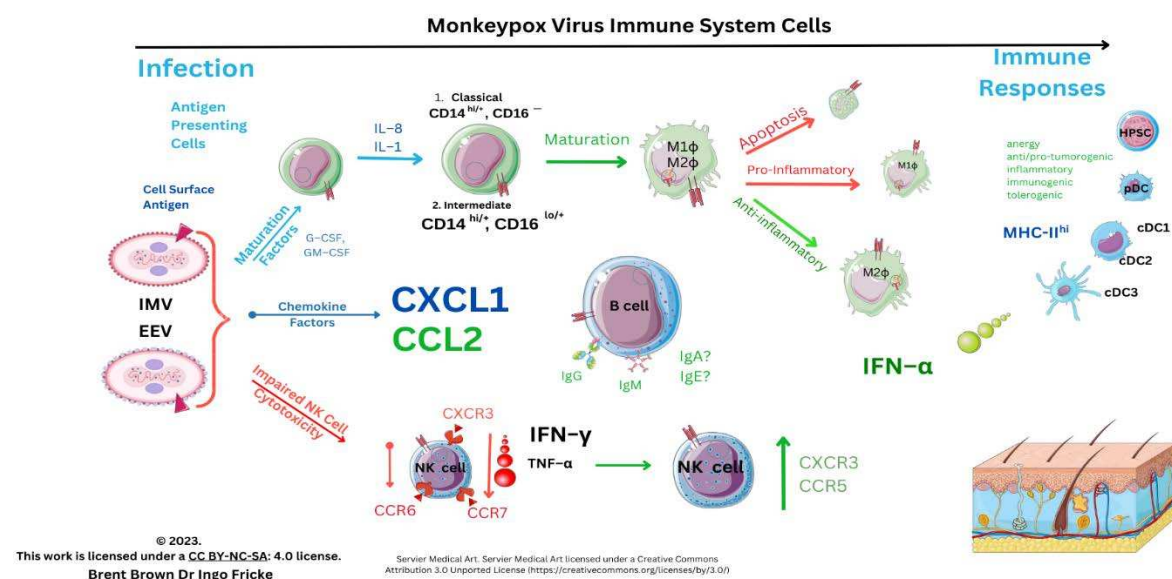


Figure 4. Immune Responses to Monkeypox virus.

In a recent MPXV analysis in 2022 (n=17) it was confirmed that up to 3 days after MPXV infection there is a temporal reduction of CD4⁺ T cells with an increase in CD8⁺ T cells representing helper T_H and cytotoxic T_C cells, respectively. Within the adaptive T cell compartment, naïve T (T_N cells (CD45RA⁺CD27⁺)) increase alongside increases in effector T memory cells. (T_{EM} / CD45RA⁺CD27⁻). During MPOX disease, T cells observed had concurrent increases in CD38 receptors within both T cell (CD4 / CD8) compartments normalising at around three weeks [135]. Summary reports were indicative of a OPXV T_H1 cell specific profile but notably there was no difference in immune cells between either HIV or non-HIV affected individuals, the significance of which remains unknown. Notably, these authors indicated that between 2–4 days after infection, key chemokine changes in NK cells occurred that were CXCR3, CCR7, and CCR6 which were temporarily reduced. Furthermore between days 5–8 NK cell frequencies were expanded significantly before reducing [134,136]. In contrast, NK cell chemokines expressed were upregulated including CXCR3 and CCR5 at days 7–8. The role of NK cells during MPXV infection is unknown currently. Recent transcriptome NK cell

transfection research indicated gene transcript upregulation of *granzyme B/K* alongside both *TNF- α* and *TRAIL* genes in comparable other DNA viruses and could be indicative of release from other cytotoxic T cells or $\gamma\delta$ T cells [137–139]. Other authors concur that CD160 in the context of viral infection affecting NK cells could be a worthy target of investigation [138–140].

Immunological Responses to Monkeypox Virus and Orthopoxviruses

It is notable that the longevity of protection provided by initial vaccinia vaccines was unknown with CD nomenclature not designated until the 1980s. In 2005 during *in vivo* research, investigators examined antibody responses and T cell responses utilising VACV to find that that memory B cells expressing CD20 were essential to OPXV B cell plasmablast generation, but also that the T cell response could be abrogated with host survival [114,141]. Therefore, it is notable, at least with SARS-CoV-2 infection, where there was appearance of MHC downregulation on certain immune cell subtypes, that this may not be the case with MPXV. Interestingly, here it was seen that infected CD14⁺ monocytes could still produce type II IFN (IFN- γ) and TNF- α but indeed be non-responsive to host and VACV infected cells with NK cell phenotypes clarified (CD56⁺, CD16⁺, CD16-CD56⁻, CD16⁺ CD56⁺) [136].

Up to 2007 other studies (n=76) examined the overall OPXV response to indicate that anti-OPXV IgM and IgG antibodies produced by B cells were key to immunological responses with IgM only associated with MPXV or rather OPXV infection [142]. As above, LN swelling can occur after infection indicative of germinal centre (GC) leukocyte production, however the exact mechanisms remain unclear. It was indicated with another OPXV (VARV) that upregulation occurs of gene transcripts *PKR*, *STAT1*, *STAT2*, *MX1*, *MX2*, *IP10*, *OAS1*, *OAS2* and *OAS3* as well as both type I IFN and type II IFN gene transcripts [11]. It is notable that, during MPOX disease, *in vivo* research showed immune cells secrete or express IL-1RA, IL-2, IL-6, IL-8, IFN- γ , CCL2, CCL5, G-CSF, GM-CSF with sCD40 upregulated, of which two (G-CSF and GM-CSF) are known M ϕ differentiation factors [143]. Moreover, recent *in vitro* cell culture, it was seen that there was statistically significant expression of other gene transcripts encoding chemokines, cytokines and growth factors that also include *CXCL1*, *IL11*, *CSF2* but also *PTX3* [144]. *CXCL1* protein was confirmed *in vitro* to be upregulated in CPXV and MPXV monocytes in other studies alongside IL-1 and IL-8, which would therefore make it possible that these are classical or intermediate monocytes [145].

There have been suggestions that MPXV clades selectively down-regulate host cellular responses through reports comparing West African and Congo Basin clades (I/II). So far, it is indicated that MPXV reduces fibroblast growth factor (FGF) signaling, B cell receptor (BCR), growth hormones and the apoptotic signal Fas (CD95) pathway with defective phosphorylation of both c-met and c-kit transcription factors with caspase 3 [114,146–148]. Recently of relevance it has been acknowledged in transcriptome reports that the protein signaling pathways now emerging include G protein coupled receptors (GPCRs), heat shock proteins (HSP60/70), histamine, plasmin alongside multiple histone markers [149]. Therefore, further clarifying some of the unknown into how atypical monkeypox vesicular rashes may occur. As we discussed in our last article chemokine receptors and ligands can be considered directional system markers that influence cytotoxic cell immune responses, some of which are considered therapeutics targets [114,150].

In 2013, it was seen that there was potentially a cross OPXV CD8 T_c specific epitope in one of two peptides from E9L (aa 562–570), with a possible third CD8 T_c epitope (107–115 amino-acids) that could be an immunodominant T cell epitope [136,151]. In December 2022, it was further clarified that there were potentially a further 318 CD4⁺ and 659 CD8⁺ T cell epitopes specific to OXPVs [152]. In mid-2022, in a yet to be peer reviewed report, further reports started to clarify that 124 amino-acids within the MPXV A35R protein generates a comparable frequency of B Cell (CD19⁺) IgG from plasmablasts. Researchers compared MPXV infection to VACV immunized individuals to conclude that A35R/H3L could be a potential additional serological B cell marker [153].

Background to Vaccinia and Orthopoxvirus Role in Cellular Research

As VARV was eradicated, adapting usage of modified vaccinia as a vector occurred, and cellular mechanisms underlying this immunogenicity is required. Originally, during VARV outbreaks, VACV was utilised in immunisation until the late 1970s during which ongoing research showed that serial passage of a vaccinia strain (denoted by a strain from Ankara), attenuates VARV infection. This attenuation could have potential beyond that originally envisaged. Subsequent research and the discovery of dendritic cells (DCs) by Steinman and Cohn in 1973 at the Rockefeller University was a key milestone. Shortly after, Kohler and Milstein discovered how to produce specific monoclonal antibodies [154]. Dendritic cells were further characterised recently using single cell RNA sequencing [147]. Furthermore, DCs are unique in being able to express elevated levels of type I IFN early in infection, but also elevated levels of MHC class II molecules. These affect both innate and adaptive immune system compartments in viral pathologies and cancer [114,155–158]. Approximately 50 years after the original discovery, the complexities of DCs are still being discovered. It is known that DC maturation and cellular differentiation may have potential anti-tumorigenic effects and anti-viral tolerance but also stimulatory effects. It is commonly believed that the original T_H cell response is required to be immunologically beneficial, but that this can be affected by two other APCs (monocytes and Mφs).

In 2011, the role of vaccinia virus, denoted as modified vaccinia Ankara (MVA), was researched utilising CPXV *in vitro* to explore the differential response amongst leukocytes [159]. Uniquely, MVA has a modulatory effect on DC maturation that may direct other APCs to induce a T_H and T_C response [160]. It was shown that DCs express a chemokine, CCR7, expressed by most immune cell phenotypes; but in addition, CXCL10, TNF- α , IL-6 and importantly IL-12 were found that are representative chemokines and cytokines that can influence immune cell maturation and proliferation, whilst being expressed during VACV cellular infection [158,159,161].

Therefore, the usage of CPXV in research which shares much homology with other OPXVs has further clarified non-productive infection of DC cell phenotypes. Notably, DCs can be broadly classified into plasmacytoid (pDC), myeloid derived (mDC), and into three further sub-types, cDC1, cDC2, but also cDC3 that remain crucial [114,162]. Dendritic cells can develop into immunogenic or inflammatory monocytic cells. The tolerogenic profile can be anergic, as well as pro-tumorigenic or anti-tumorigenic in characteristic recognizing pathogenic antigens and/or tumor associated antigens (TAAs).

Unique properties of OPXVs indicate that DCs have been shown to be permissively infected by certain types within this family of viruses, where myeloid and monocyte-derived (mDCs) show vacuolar formation with loss of characteristic dendrites and syncytial cell formation. On the other hand, mDCs excessively vacuolate while immature pDCs show less vacuolation and syncytial cell formation. Cowpox virus infection was shown to differentially inhibit DCs during maturation with suppression of TLR stimulated cytokine responses from early CPXV viral proteins. Alternatively in 2018, a cowpox protein (CPXV012) inhibited proteins linked to the ER lumen which are associated with transporting antigen presentation proteins (TAP). It is known that DCs can present antigens either dependent or independent of TAP, that is localised within the ER lumen. Therefore, resultant effects on $\beta 2$ microglobulin, and MHC class I modulation could interfere with consequent viral peptide presentation by immune cells [163,164].

More recently in 2020, Pereira et al. used mass cytometry to investigate expression of seventeen cell surface receptors in leukocytes after *ex vivo* infection of human whole-blood samples with MVA to show downregulation for most of the characteristic cell surface markers in specific leukocytes [165]. This MVA infection resulted in significant downregulation of CCR5 in CD4⁺ T cells, CD8⁺ T cells, B cells, and three different DC populations but upregulation of MHC Class II (HLA-DR) expression on DCs [165]. Furthermore, Pereira et al. indicated that MVA-infected APCs can directly transfer endogenous viral proteins into the MHC-II pathway to efficiently activate CD4⁺ T cells. To this end, through *in vivo* research and chemical inhibitors, it was elucidated that subcellular pathways including proteasomes and autophagy processes have a further role in endogenous MHC class II peptide presentation. Surprisingly, involvement of both transporter associated with antigen

presentation (TAP), and lysosomal associated membrane protein 2 (LAMP-2) did not occur [166]. Therefore, MHC class I/II antigen presentation during intracellular OPXV infection is crucial to understanding how permissive infection affects cellular apoptosis.

It was further explored that MVA could produce a reduction in BCL-2 expression as a key regulatory protein inducing cellular apoptosis [167]. Other cellular markers CD80, CD86 and CD83 are known as B and T cell signaling molecules expressed during DC maturation [168–171]. However, smallpox genes, through MVA research, have clarified that early gene expression during DC infection occurs during maturation on either immature or mature mDCs [168,170,172].

In addition, DC maturation is known to occur and produce IFN- α , within 18 hours of infection with apoptosis occurring simultaneously through virus antigen specific MHC class I peptide dependent CD8⁺ Tc responses. [173]. Type I IFNs have been found to be differentially elicited in cDCs, and not pDCs, during MVA infection via transcription factors (IRF3/IRF7) mediated by the IFN receptor (IFNAR1) sensitive to both type I IFNs, IFN- α and IFN- β . This occurs through the cGAS/STING pathway and is dependent on TLR3 and Tank-binding kinase 1 (TBK1). Laboratory studies of MVA in DC infection clarify that endosomal or lysosomal enzymes, like cathepsin B, can attenuate this IFN response through VACV E gene transcripts producing virulence factors affecting IRF3 and *IFNB* [174]. Furthermore, cDC IFN synthesis and secretion could be independent of melanoma differentiation-associated protein (MDA-5), mitochondrial antiviral signaling protein (MAVS), TLR3, or Toll/IL-1R domain-containing adaptor-inducing IFN- β (TRIF) [90,174].

Cell cycle virulence genes like p28 have also been implicated in playing a role in OPXV infection. For example, during ectromelia (ECTV) and CPXV infection of M ϕ [117]. It has been indicated that OPXVs have modulatory functions, and other authors suggest there are unknown ubiquitinating ligands intracellularly that regulate p28 [117,175]. Deficiency of p28 was investigated *in vivo* to show abrogation of OPXV replication in M ϕ cells. Moreover, p28 is active in DCs and NK cells and forms a subunit of the cytokine IL-27 that is produced by DCs. Uniquely, p28 appears to perform a multi-functional role in not only DC/NK cells but is also key in the proteasomal degradation of p53 affecting both tumour cell regulation and bacterial infection [125,175]. The exact nature and effects of pattern recognition receptors (PRRs), damage activated molecular patterns (DAMPs) and how these relate to IFN stimulation and release from multiple immune cell subtypes remains unknown [176,177]. Therefore, both IL-12 and IL-2 represent both cellular inhibitory and maturation cytokines that can be secreted by DCs and regulate both type I and type II IFN secretion as well as maturation of other immune cells.

Background to Therapeutics, Prevention and Therapy

Current data available indicates that smallpox vaccination prior to MPXV infection may have a protective effect against MPXV and prevent symptoms. Younger generations have not received these since 1980 [54,55]. At present, there are three smallpox vaccines utilised, that are ACAM2000® (IMVAMUNE), and Aventis Pasteur smallpox vaccines (APPSV) in the USA [180]. Two of these vaccines are ACAM2000® (IMVAMUNE) is utilised in active immunization against smallpox disease in high-risk populations and comprises of live vaccinia virus utilised during MPXV outbreaks [180]. Additionally, a third vaccine from Bavarian Nordic (MVA-BN) is distributed under two brand names that are modified strains of Vaccinia Ankara-Bavarian Nordic virus (MVA-BN). Currently, these are approved as JYNNEOS™ (MVA-BN strain) in the US; but also, IMVANEX (European Union), and IMVAMUNE in Canada. With the exception of JYNNEOS™ the other vaccines were originally authorized for use against smallpox and are under intensive monitoring by the WHO, Center for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), European Medicines Agency (EMA) and others (see Supplementary Materials) [181,182]. Recent articles that have not yet been peer reviewed, have investigated to indicate that vaccine effectiveness of 1st generation to 3rd generation smallpox vaccines adapted to target MPOX disease appears in the range 58%–89% [183]. Below are some of the historical perspectives (See Figure 5).

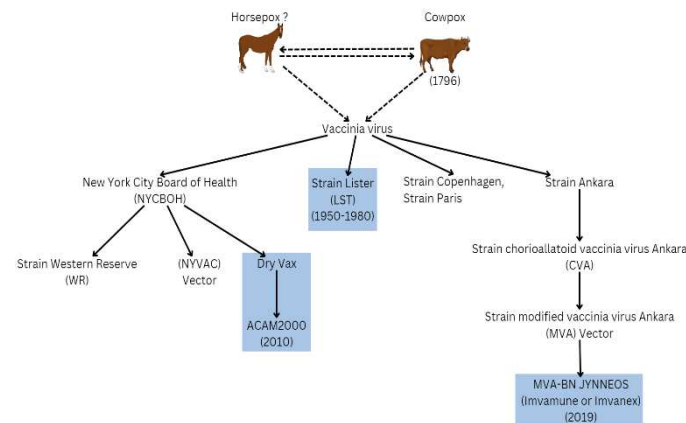


Figure 5. Historical perspectives of *Orthopoxviridae* since 1796.

For specific antiviral therapy in adults and children weighing over 13kg, early indications that an antiviral tecovirimat approved in the European Union (EU) may be beneficial (see Supplementary Materials). Other antivirals of consideration for MPXV infections include intravenous vaccinia immunoglobulins (VIGIV), and brincidofovir [184,185]. These indications potentially could include the treatment of other OPXV infections like VACV, MPXV, and cow poxvirus (CPXV), although this would need to be confirmed. Tecovirimat is considered an OPXV inhibitor with brincidofovir a broader range DNA polymerase inhibitor. Since 2005, tecovirimat was considered a relevant therapeutic to target OPXVs infection, the original name was ST246, that could inhibit extracellular virion production. This occurred from conserved F13L viral host protein and was active against not only VACV, but also MPXV, CXPV, but also ectromelia (mousepox), and camel poxvirus but not the B5R protein in the first two (see Supplementary Materials) [186]. Tecovirimat was initially discovered at the National Institute of Allergy and Infectious Diseases (NIAID), in Bethesda, with other departments under the National Institute of Health (NIH). It was developed by a cooperation between Viropharma with scientists at the United States Army Medical Research Institute of Infectious Diseases (USAMRIID). Since then, it has been manufactured by Siga Technologies, a pharmaceutical company conducting research on bioweapons defense developing the drug under a governmental contract following a U.S. request by tender. Due to its significance for bioterrorism, the FDA granted tecovirimat fast-track status. On July 13, 2018, the FDA announced approval of tecovirimat under the brand name TPOXX® as a prior OPXV anti-viral indicated *in vitro* to have no kidney cytotoxic effects. An EU marketing authorization under exceptional circumstances was granted in January 2022 [187]. Other antiviral drugs considered for the treatment of MPXV infections include brincidofovir (CMX001) developed by Chimerix and marketed under the brand name tembexa. Brincidofovir is an experimental anti-viral agent against several viruses and is a competitive substrate inhibitor of viral dsDNA polymerases [188]. Brincidofovir has been conjugated to a lipid for slower plasma release, that is then cleaved and metabolized to the active ingredient cidofovir diphosphate intracellularly for plasma release to prevent extracellular virion release [185,188]. However, it is also effective against EBOV (see Supplementary Materials) [189–192]. Brincidofovir has been shown to be effective against a variety of viruses including herpes simplex virus 1 (HSV1), adenovirus (AdV), BK polyomavirus, poxviruses, and EBOV [189–192]. No specific recommendations concerning management of HIV patients having a risk of exposure to MPXV have been made at the date of this report, although further information may become available and recently a phase 2/3 clinical trial evaluation (NCT) was completed evaluating MVA-BN (NCT02038881/NCT02977715) [193,194]. As of 21st February, there are currently 20 registered clinical trials listed as awaiting, or in progress (see Supplementary Data S5).

Discussion

The first question in addressing the topic of pathogenic infections like MPOX is whether prior outbreak caused by any pathogen will evolve. Currently, there is low likelihood or risk with

suggestions that the indicative R_0 is 1.39, however both VARV and MPXV remain infectious diseases with the former extinct in nature. Although OPXVs may share some homologous protein structure, the virulence, pathogenicity and transmission seen with VARV before 1980 require analysis. It was seen before and after 2017 that MPXV in endemic countries had increased in localised countries. Transmission requires close contact, and unlike SARS-CoV-2, MPXV infection has demonstrated comparatively less mortality, although some cases present with severe forms of disease (particularly immunocompromised individuals). Contagion, when symptomatic is usually noticeable, and is dependent on social, healthcare and other factors. Therefore, the chances of un-noticed transmission is limited. Given that MPXV has adjusted between climates or is now more visible due to technological advance and geographical surveillance, MPXV appears a potential health threat regardless of low fatality and transmission rates [195]. Risk factors remain unclear. This was emphasized in a routine recent survey in the UK screening blood donations for transfusion ($n=10896$), at a time of high prevalence of circulating MPXV, by PCR to the *TNFR* gene and a non-variola OPXV gene. Whilst this study aimed to establish potential contamination of blood donations, it was therefore confirmed following the MPXV outbreak, the absence in general population of MPXV infection measured by antibodies. Therefore this serves as a useful reminder of surveillance tools, but more importantly the impact viruses may have undetected [114,196]. In addition, the risk of animal pet transmission can be considered since the increase in clade IIb MPXV cases of summer 2022. Recent reports clarify no pet transmission in cats or dogs, ($n=154$) currently, at least in the UK, in households with confirmed MPXV infections [197]. With regards to the contribution of T cells during co-infection with immune-deficiency disorders, this remains unknown, although emerging reports examining whether quantifying high or low T cells below or above 350 cells per mm^3 could represent potential use in clinical settings detail what has been conducted (see Supplementary Materials) [198]. At the time of drafting this report, R_0 describing the transmissibility of the original infectious pathogen has previously been estimated with smallpox in the range 5.5–6.8; however, MPXV R_0 data requires further clarification, and although estimates have been described, transmission rate remains unclear currently. Much research draws similarities between OPXV proteins of VACV, HPXV, CPXV and MPXV due to homology, as we describe above, however both require further clarification within research protocols available. The MPXV infection 2022 outbreak currently has not yet classified MPXV as a sexually transmitted infection (STI) by the WHO [199]. Even though it is logical to consider that underlying immunosuppression may affect the outcome of MPXV disease, this assumption is yet to be determined. Studies conducted in Africa during earlier outbreaks reported cases of co-infection which are variable globally [200–205].

Limitations

Homologous proteins described and current serological assays remain in development largely unknown in 2000 with OPXV prevalent across host animal populations. Data outlined above has been checked on genomic sequencing databases, like UniProt, whilst some undergo validation. Information. Therefore Supplementary Data and Materials clarify this further.

Conclusions

In conclusion, there are currently 88,122 confirmed cases of MPXV globally since 2022 up until 5th July 2023. Even though the MPXV causal agent of MPOX disease could be considered milder than other OPXVs with lower fatality rate, MPOX disease is still a major issue as a public health threat. The surveillance, research and prophylaxis will require further prioritisation. Medical scientists and physicians necessitate further knowledge of the complexities of proteins, immunological mechanisms and pathogenesis. This is pertinent to MPXV infection to expand on our findings, further clarifying missing literature, whilst improving guidance on potential therapeutic targets and individual health outcomes worldwide. With SARS-CoV-2 research extensive, in comparison, OPXVs remain of scientific interest. Surveillance of other existing OPXVs, like CPXV, appears comparatively more diverse in understanding zoonotic transmission across many of the species historically known. With VARV eradicated in nature some years ago, similarly to prior HPXV, further investigations into

OPXVs will require further research. Smallpox experimentation is outside the remit of Biosafety Level 4 (BSL—4) laboratories and is currently banned and subject to WHO guidelines due to the incidence and severity of prior eradicated VARV as the only human virus to have ever been eradicated.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org: **Figure 1:** Monkeypox virus genome; **Figure 2:** Monkeypox Virus Cell Genes and Proteins; **Figure 3:** Toll—like receptor perspectives during OPXV infection; **Figure 4:** Immune Responses to Monkeypox virus; **Figure 5:** Historical perspectives of *Orthopoxviridae* since 1796; **Supplementary Data S1:** Example Serology Assays; **Supplementary Data S2:** Known MPXV / host entry cell protein interactions; **Supplementary Data S3:** Known MPXV / host exit cell protein interactions; **Supplementary Data S4:** Potential MPXV / host immunomodulatory proteins; **Supplementary Data S5:** Clinical trials registered, awaiting, or in progress since 2017. The following supporting information can be downloaded at: Monkeypox virus, complete genome — Nucleotide — NCBI (nih.gov); xref:embl—MT903340 in UniProtKB search (183) | UniProt; GISAID — hMpxV Variants Dashboard; 2022 MPXV Outbreak Global Map | Mpox | Poxvirus | CDC; Multi—country monkeypox outbreak: situation update (who.int); Monkeypox: public health advice for gay, bisexual and other men who have sex with men; What to Do If You Are Sick | Mpox | Poxvirus | CDC | mvanex | European Medicines Agency (europa.eu); JYNNEOS Vaccine | Mpox | Poxvirus | CDC; MVA—BN smallpox vaccine | Bavarian Nordic (bavarian—nordic.com), Nextstrain / monkeypox / hmpxv1; Pox host—virus interactions ~ ViralZone (expasy.org); Mpox (monkeypox) testing: submit sample — GOV.UK (www.gov.uk); BHIVA rapid statement on monkeypox virus; FDA approves the first smallpox treatment (sciencenews.org); A47R — A47R — Monkeypox virus (monkeypox) | UniProtKB | UniProt; FDA approves the first drug with an indication for treatment of smallpox | FDA; dec_154165_en.pdf (europa.eu); Tecovirimat SIGA | European Medicines Agency (europa.eu); Search Orphan Drug Designations and Approvals (fda.gov); Chimerix's Brincidofovir Given To Dallas, Nebraska Ebola Patients (forbes.com); Chimerix Announces Emergency Investigational New Drug Applications for Brincidofovir Authorized by FDA for Patients With Ebola Virus Disease (NASDAQ:CMRX) (archive.org); Chimerix to Conduct Ebola Drug Trial — WSJ; Smallpox (who.int); www.proteinatlas.org

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List of Abbreviations

Protein Kinase R (PKR), Signal Transducer And Activator Of Transcription (STAT1/2), Interferon—induced GTP—binding protein (MX1/MX2), Interferon gamma—induced protein (IP10), OAS (2'—5'—oligoadenylate synthetase 1 OAS1/2/3), Granulocyte Monocyte Colony Stimulating Factor (GM—CSF). Colony Stimulating Factor (CSF) and Pentraxin 3 (PTX3), GMP guanosine

monophosphate (GMP), adenosine monophosphate (AMP). For other protein abbreviations not listed see www.reactome.org.

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