



UK Health
Security
Agency

Monkeypox Incident

UKHSA

The challenge of seroepidemiology
Research priorities and laboratory investigations

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Monkeypox Diagnostics

- Frontline Diagnostic MPX testing service provided by UKHSA Rare and Imported Pathogens Laboratory (RIPL)
- Provided input into “interim WHO laboratory testing guidance”.
- Provided protocols and advice to laboratories in UK and worldwide
- Commenced Sequencing pipeline in place ([genomes on virological.org/GenBank](https://virological.org/GenBank)).
- Examining commercial kit offerings;
 - Potential to place the MonkeyPox assay onto the Roche Cobas 6800/8800 systems using the Utility Channel, allows for combined extraction and detection.
 - In-use assay to be modified and transferred in-house (Orthopox & MPX), reagents ordered.
 - Roche’s version using TIB Mbiol: Orthopox established for other Roche systems. MPX in development
 - Working with Thermofisher to evaluate their MPX assay for open platform use

Meeting the diagnostics needs of the response

Lead: Richard Vipond

- Frontline Diagnostic MPX testing service provided by RIPL (CDC MPX-specific assay Li et al 2010)
- Current demand within diagnostic capacity but working to scale up of PCR testing activity
- The limiting factor in UK is need to process and inactivate primary swab sample at CL3/BSL-3
 - Evaluating sample lysis buffer for swab tubes – inactivation at point of collection so no CL3/BSL-3 and facilitates transport
 - Facilitates roll-out of testing without need/overloading CL3 facilities – reduces TAT and increases capacity
 - Can still sequence samples but virus isolation no longer possible
- Evaluating commercial PCR offerings for open and closed platforms for scale up
- Better to use “pre-mix” reagents if we need to run at scale though limited performance data compared to current assay
- Ideally would have assays on high throughput systems compatible with lysis swabs – assays being migrated
- Assessing X-ray irradiation of cultured isolates for control material
- Provision of PCR protocols, extracted control materials and deposition of sequenced isolates into BEI, EVA Global, NCPV under way

Overview of research needs and priorities

Surveillance	Seroepidemiology	How much undiagnosed disease is there? What is the level of asymptomatic infection? How many cases could have been missed due to a presumption of a different cause, e.g. syphilis, herpes?
	Wastewater	Wastewater surveillance
Transmission dynamics	Contact tracing	What proportion of cases are infected in UK? What is the infectious period? What is the incubation period?
	Risk to contacts	Risk of transmission to different groups on the population and contact categories. Risk of transmission in flights What is the serial interval?
		Is there pre-symptomatic or prodromal transmission? How much transmission is asymptomatic / presymptomatic / symptomatic? Viral presence in semen
		What information can we gain about intrinsic transmissibility of West African clade monkeypox?
	Mode of transmission	What are the likely modes of transmission, including is there evidence of airborne transmission? Fomites. Role of large droplets / aerosols/steam rooms Decontamination & mitigations – what is effective and needed in different settings
Biological characterisation and virology	Whole genome sequencing +/- phenotypic Virology	Is there any evidence that this is a new clade or that there has been any biologically significant change compared to previously described West African monkeypox? Can phylogeny provide any information on transmission? In host variation
		Viral dynamics
Clinical characterisation	Case data and ISARIC CCP	What are the symptoms and should the case definition be refined? Does the current syndrome differ from the classical description of WA monkeypox? Is more severe disease experienced by any population subgroup? What are the risks in pregnancy?
Vaccine response and immunology		What is the duration of the serological response to Imvanex after 1 or 2 doses What are the immune responses & vaccination immune response? What are the immunological correlates of protection including cell mediated immunity after vaccination, protection from smallpox vaccine
Therapeutics	Being commissioned	Does early treatment reduce the risk of transmission? Impact on disease progression Does tecovirimat help with reducing isolation period?
Diagnostics & Evaluation		Best site to test, which site goes positive first What would enable home / POC sampling and testing including self-testing? Development of serology test Evaluation of swabs with inactivating buffer to enable community testing
Evaluation of other interventions		What is the effectiveness of contact tracing and activation? How do interventions act synergistically to reduce onward transmission?
Behavioural & other social sciences and equalities considerations		<ul style="list-style-type: none"> - How are the public and affected groups perceiving the risk from Monkeypox? - What is the public understanding of the disease and what actions they need to take? - What proportion of symptomatic cases seek care? - Vaccine acceptability and intended / actual uptake. - What are current levels of adherence to self-isolation?

Seroepidemiology studies

Lead: John Saunders

- Understanding the potential burden of disease and undiagnosed infection and the behavioural and clinical factors associated with infection is essential for control
- Primary aim is to estimate the prevalence of MPX infection among MSM attending sexual health services
- Secondary aims are to:
 - 1. Estimate the prevalence of MPX infection among other populations
 - 2. Explore the clinical, socio-demographic and behavioural risk factors associated with MPX infection
- Methods: testing for the presence of antibodies to Orthopox species (sera) and monkeypox viral DNA (swabs) on residual samples collected from people aged 16 years and older attending sexual health clinics in the period prior to recognition of the MPX outbreak.
- Various sources of stored samples and proactive recruitment being considered

Monkeypox serology

Lead: Richard Vipond

- UKHSA currently tech-transferring CDC Pox IgG assay
 - Pan-pox IgG assay
 - Coating of plates with whole MVA/Vaccinia virus – cross-reactive antibodies between MPX and MVA/Vaccinia
 - CDC also providing some controls/material. Collaboration with NIBSC for further controls
 - In house preparation of Research reagents for assay (e.g., MVA)
 - Collaboration on IgM assay and strain-specific protein microarray
- No commercial assay, but working with manufacturers to see if commercial kits also available in future (pan-pox)
- Development for:
 - use in clinical cases (in RIPL), MPX PCR negatives with MPX like rash/sores
 - Clinical description of those with confirmed MPX infection/vaccinees
 - Seroepidemiology studies

Detection of monkeypox virus within healthcare and non-healthcare settings

Provision of Rapid Response

Conducting extensive environmental sampling around hospitalised patients to investigate:

- the presence of monkeypox virus on environmental surfaces
- the presence of monkeypox virus in the air and the potential for transmission during different activities (e.g. doffing of PPE; changing of bed sheets)*

Environmental samples analysed via PCR and culture-based virus isolation

Provision of Evidence and Data to Support to Policy and Guidance Teams

IPC and Decontamination sub-cell of the IMT

- Rapid Review: Monkeypox virus – stability, persistence and review
- specialist expertise on decontamination and waste management

Research/Knowledge Gaps – emerging pathogens

Infected individuals contaminate their immediate environment.

- How to effectively decontaminate the domestic/community setting? Incorporation of scientific evidence into existing UK recovery handbook for biological incidents
- What is the risk of fomite transmission? How does surface type (e.g. porous; non-porous) and/or interaction influence transfer efficiency?

Additional slides

- Some more details on capabilities and research needs

Monkeypox – UKHSA animal Models (MIG & BIG)

- Non-Human Primate (NHP) – Very good models for clinical and pathological assessment and preclinical trials
 - Used different infection routes, including aerosol
 - Limited transmission studies
 - Model working at Porton Down, with immunology, virology and pathology tools in place
- Mouse models
 - Many inbred/outbred resistant to infection
 - Some strains good for lethality studies (mostly IFN deficient)
 - Clinical signs and pathology different to human disease
- Other species
 - Prairie dogs and squirrels (not easy to work with)
 - Hamsters quite resistant
 - Infant rabbits have some potential

UKHSA Non-human primate Monkeypox studies

- Lethal infection model for evaluation of smallpox countermeasures
- Challenge strain Central African clade: Monkeypox virus, strain Zaire 79
- *Cynomolgus* macaques of Mauritian origin

Studies:

- Natural history, aerosol (10^5 PFU) and IV (10^7 PFU)
- Assessment of stock viruses
- Vaccine evaluation (aerosol challenge) – ACAM2000 (live vaccinia) and IMVAMUNE® (attenuated vaccinia, i.e. MVA-BN).
- Therapeutic evaluation (IV challenge) – various monoclonals, most recent study employing tecovirimat (TPOXX®) as a positive control.

Funding: BARDA, NIAID, Bavarian Nordic

In vivo modelling capability

Virology

- Characterised viral stocks (challenge agent)
- Infectious load (swabs, tissues) and neutralisation tests.

Biocontainment

- BSL3 NHP housing for social groups

Aerobiology

- AeroMP-Henderson NHP exposure system
- Head-out plethysmography chamber and exposure mask

Pathology

- Comprehensive, in-house histology and immunohistochemistry techniques
- Substantial pathological experience in the understanding of pathogenesis of monkeypox virus in the NHP animal model, and evaluation of vaccines/therapeutics.
- Immunohistochemical (established) and in-situ hybridisation (current) assays to detect viral antigen and RNA respectively in formalin fixed tissues.
- Quantitative and qualitative pathological assessment and reporting.

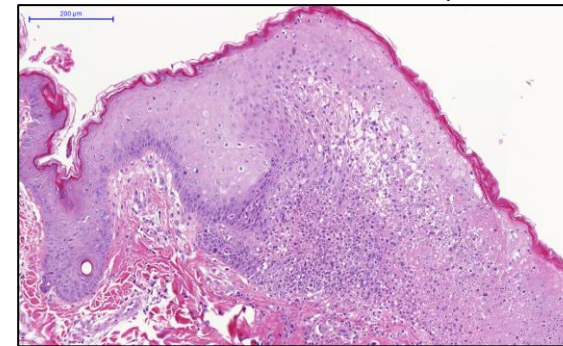


BSL3 NHP
housing

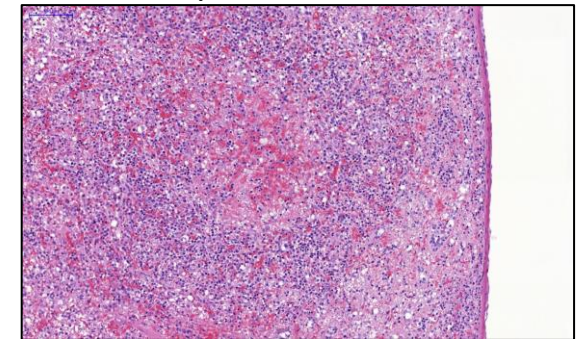


Aerosol infection

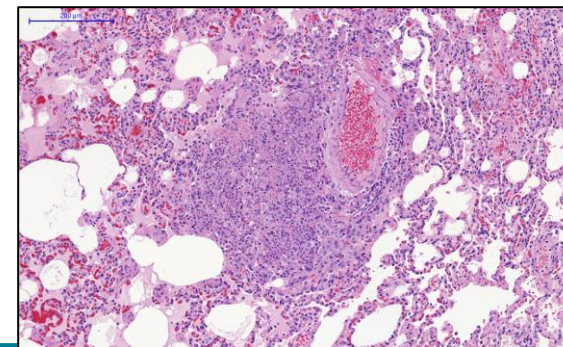
Monkeypox infection (IV) in *Cynomolgus* macaques
(*Macaca fascicularis*)



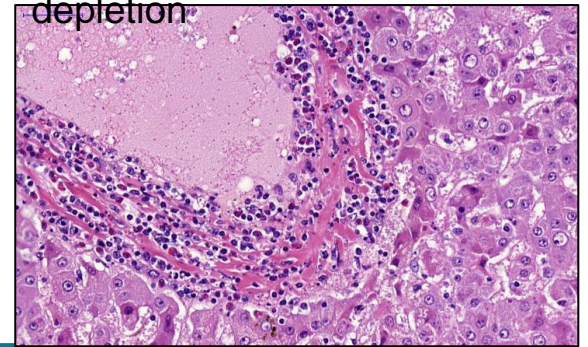
Skin – early lesion



Spleen – severe lymphoid
depletion



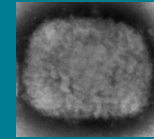
Lung – focal necrotising
pneumonia



Liver – arteritis

Research: MPXV inactivation with X-rays

UKHSA Virology & Pathogenesis Group



- Supports genome recovery & nucleic acid detection
 - Avoids protein denaturation (*c.f. heating, cross-linking of surface proteins*)
 - Chemical-free & environmentally responsible, (*avoids use of radioactive gamma source, (inc. security and decommissioning costs)*)
- **Rapid provision of non-infections samples to partners (*c.f. SARS-CoV-2*)**
- **Validation of non-infectious small volumes of irradiated MPXV - underway**
 - **Distribution through WHO-CC (Special Pathogens), NCPV & EVAg**

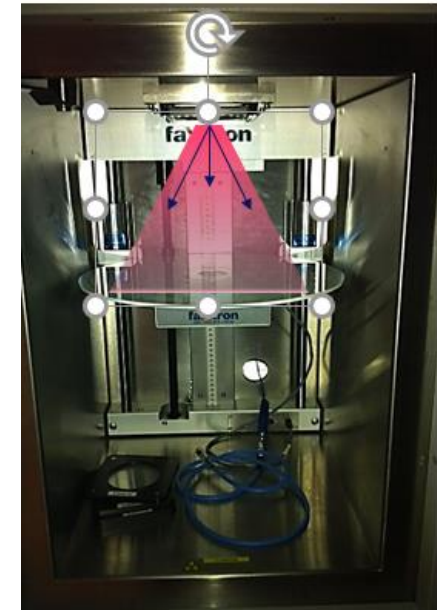
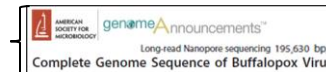


FUNDING GAP: Up-scaling for large volumes of MPXV^(inc. Pathogen X) & structural characterisation

Other MPXV activity enabled and provided by V&P group

Isolation & banking^(Priority UK cases), Distribution^(National / International inc. 2018 stocks), RIPL support^(diagnostics), Production & distribution of DNA stds, Sci. advice, Genomic sequencing methods re-BPXV research

Sequencing of new isolates re-low Ct levels in clinical samples



Some of the research gaps in more detail

1. Protection for groups contraindicated for the old live vaccine (Eczema, Pregnant, Immunocompromised) with *Imvamune* vaccine (especially young children) and have the licenced drugs available to treat those with disease.

Questions: Do two doses of ***Imvamune* protect children** with Eczema?

Can we test this using a **neutralisation assay**?

Can we develop **T-cell assays** to test this as well?

What is the **duration of the *Imvamune* response**?

2. **Transmission of Mpx to/from pets and spill over to wildlife species**, has MPX found a wildlife **reservoir** outside Africa?

The HAIRS group has produced a good RA document about animal/human transmission, but there are many facts missing

3. Infected individuals contaminate their immediate environment.

- How to **effectively decontaminate** the domestic/community setting? Incorporation of scientific evidence into existing UK recovery handbook for biological incidents
- What is the risk of **fomite transmission**? How does **surface type** (e.g. porous; non-porous) and/or **interaction** influence transfer efficiency?

4. Up-scaling for **large volumes of MPXV** (inc. Pathogen X) & structural **characterisation of pathogen**;

- (i) Funding for a **dedicated pathogen irradiation** staff base, CL3 lab inc. roller bottle culture, and preparative ultra-centrifuges; with additional funds for structural / validation studies (e.g. colleagues at Diamond). This would facilitate response activities.
- (ii) **Rapid diagnostics** V&P would do (i) standard PCR and (ii) rapid LAMP type approaches.
- (iii) Why do the **West African and CB-MPXVs** have different pathogenicities?