INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

June 2022

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MONKEYPOX 101

HEALTH POLICY AGENCY
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
2022

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newsletter

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INA-RESPOND Newsletter

TRIPOD, PROACTIVE, & ORCHID Study Updates

By: Eka Windari R., I Wayan Adi Pranata, Lois E. Bang, Melinda Setiyaningrum, Nur Latifa Hanum, Retna Mustika Indah, Riza Danu Dewantara

INA102

We submitted 2 papers from the TRIPOD study: #1 "The Characteristics of Drug Sensitive and Drug Resistant Tuberculosis Cases in Indonesia" to the American Journal of Tropical Medicine and Hygiene on 22nd February 2022; and #2 "Performance of Xpert TB/RIF and Sputum Microscopy Compared to Sputum Culture for Diagnosis of Tuberculosis in Seven Indonesian Hospitals" to the Frontiers in Medicine - Infectious Diseases - Surveillance, Prevention, and Treatment on 31 March 2022. We just received comments from 1 reviewer for paper #2. We are preparing the response for paper #1 reviewer for a re-submision.

The subculture process of isolates sent to Bandung BBLK is still ongoing. From 301 baseline samples, 258 were sub-cultured and the mTB DNA was extracted. Eleven of them did not grow and the remaining 32 samples are in process.

RePORT Network's call for abstracts to be presented in the upcoming Annual RePORT International meeting in Cape Town, South Africa on 7-8 September 2022 is for Young Investigators. Candidates may send abstracts for their work on Tuberculosis or a concept plan to use INA RESPOND data to INA-RESPOND Secretariat. The abstract should be sent to the secretariat no further than 21 June 2022. RePORT network will be providing airfare, hotel expenses, as well as an invitation to participate in a poster discussion at the meeting. Young investigators are defined as one of the following:

- faculty members who are no more than five years out from completion of all training; current clinical fellows,
- doctoral students or post-docs; or current medical students or residents.
- completed their last degree by 2014 or after (not more than 8 years of completion).
- The abstracts should be of high scientific quality and should describe work related to the TRIPOD Protocol i.e., any ongoing projects that leverage, or plan to leverage, the established RePORT platform.

INA104

By 31 May 2022, from 4,336 subjects that had been enrolled, 45% of subjects are still ongoing in the study, and 55% of subjects have ended their study. The 3 sites that have end-of-study subjects with more than 75% are Site 610 – RSU Kab Tangerang (80%), Site 530 – Cipto Mangunkusumo Hospital (79%), and Site 570 – Soetomo Hospital (77%).

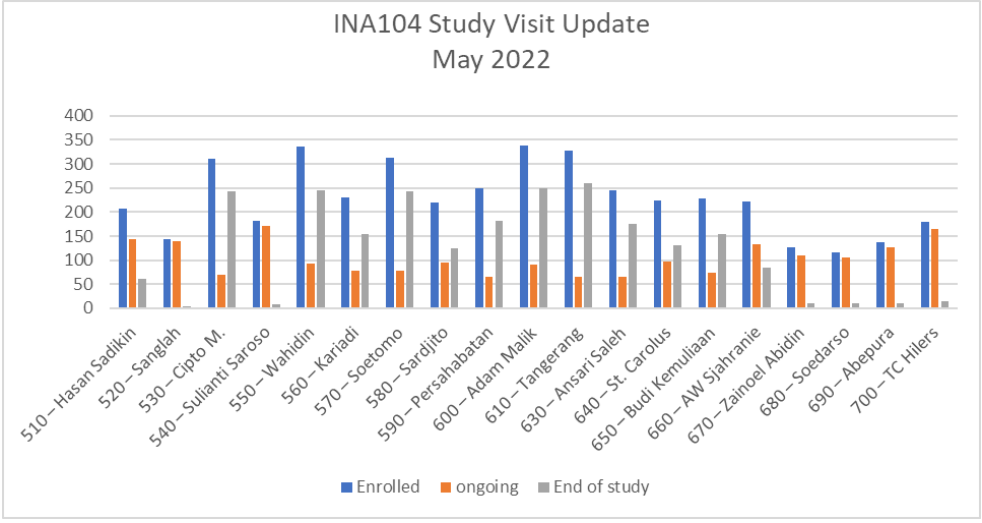

Figure 1. Site's study progress

For the end-of-study subjects, 80% subject had already completed the study until follow-up month 36, 10 % died, 7% are lost to follow-up, and the rest is due to withdrawn consent, moving away to a city without a PROACTIVE Site, HIV negative test, and being suspended (imprisoned).

For the monitoring activity, the study monitor planned to conduct the 3rd monitoring visit to site 520 (Sanglah Hospital) and the 4th monitoring visit to site 690 (Abepura Hospital) in Jun 2022.

Table 1. Subjects' end of study reasons

No	Site	*End of Study Duration/ Complete*	Withdrew Consent	Participants with HIV negative	Moved	Death	Investigator Discretion	Lost to Follow Up	Other	Total
1.	510 – RSUP Dr. Hasan Sadikin	55	1	0	2	4	0	0	0	62
2.	520 - RSUP Sanglah	1	0	0	0	3	0	0	0	4
3.	530 – RSUPN Dr. Cipto Mangunkusumo	221	0	0	0	17	0	6	0	244
4.	540 – RSPI Dr. Sulianti Saroso	0	0	0	2	6	0	0	0	8
5.	550 – RSUP Dr. Wahidin Sudirohusodo	176	0	0	5	24	0	41	0	246
6.	560 – RSUP Dr. Kariadi	129	1	3	0	15	0	7	0	155
7.	570 – RSUD Dr. Soetomo	195	13	0	4	21	0	10	0	243
8.	580 – RSUP Dr. Sardjito	98	1	0	4	4	0	18	0	125
9.	590 – RSUP Persahabatan	132	0	1	0	37	0	11	0	181
10.	600 – RSUP Dr. H. Adam Malik	192	3	0	2	21	0	31	0	249
11.	610 – RSU Kabupaten Tangerang	214	7	0	3	19	0	16	2	261
12.	630 – RSUD Dr. M. Ansari Saleh	160	1	0	1	7	0	6	0	175
13.	640 – RS St. Carolus	127	0	0	0	1	0	2	0	130
14.	650 – RSU Budi Kemuliaan Batam	126	3	0	5	8	0	12	0	154
15.	660 – RSU A. Wahab Sjahranie	73	0	0	2	5	0	5	0	85
16.	670 – RSUD Zainoel Abidin	0	0	0	0	11	0	0	0	11
17.	680 – RSUD Soedarso	0	0	0	0	10	0	0	0	10
18.	690 – RSUD Abepura	0	2	1	1	7	0	0	0	11
19.	700 – RSUD TC Hillers	0	1	0	0	14	0	0	0	15
Total		1899	33	5	31	234	0	165	2	2369

INA107

Based on uploaded CRFs as of 13 June 2022, a total of 184 participants were enrolled in the ORCHID-COVID-19 study, with 115 from site 610 (RSU Kabupaten Tangerang, Tangerang) and 69 from site 521 (RS Universitas Udayana, Denpasar). This study had 173 (94%) participants who completed the visits, with 5 (3%) participants who died during the study. In terms of deaths, 2 participants from site 610 died because of COVID-19 and heart failure, while 3 participants from site 521 died from pulmonary embolism; non-ST-segment Elevation Myocardial Infarction; and non-hemorrhagic stroke & thromboembolism. On the other hand, 6 (3%) participants decided to discontinue his/

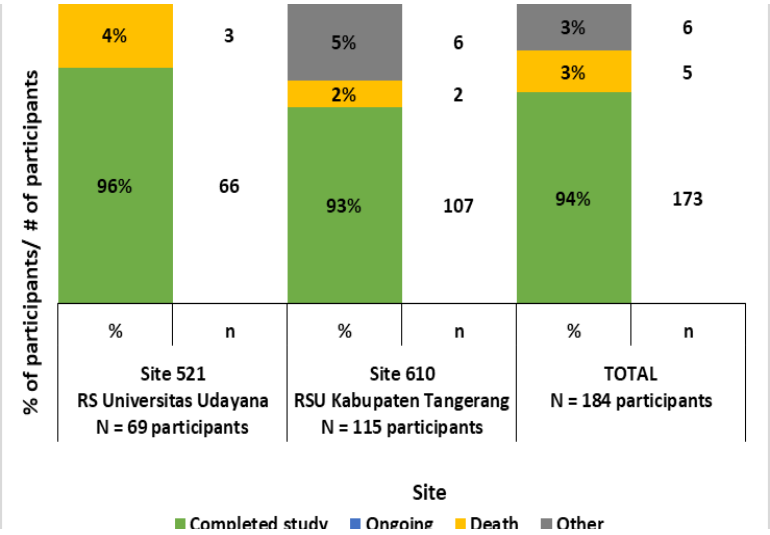

Figure 1. Participant status per site based on uploaded CRF as of 13 June 2022

her participation to the study (categorized as other) (figure 1).

As of 13 June 2022, a total of 153 (83%) participants were COVID-19 positive while 31 (17%) participants were COVID-19 negative. In site 610, the number of participants with positive COVID-19 was 105 (91%) and 10 (9%) participants were negative COVID-19. On the other hand, in site 521, there were 48 (70%) participants with positive COVID-19 and 21 (30%) participants were negative COVID-19 (figure 2).

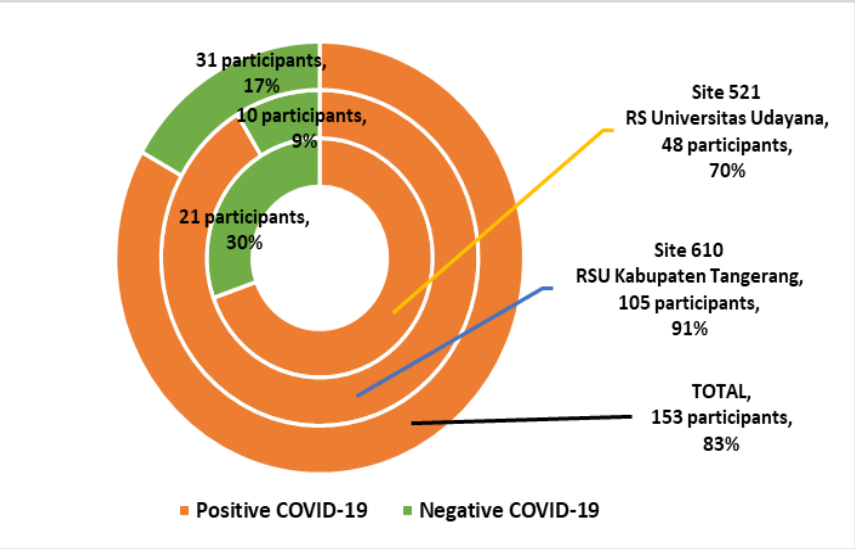

Figure 2. COVID-19 identification at enrolment based on uploaded CRF per 13 June 2022

In site 521, SARS-CoV-2 was identified in 47 (69%) participants based on the pathogen identification data. SARS-CoV-2 and Dengue (confirmed by PCR SARS-CoV-2 and RDT Dengue IgM) co-infections were identified in 1 (1%) participant. Among negative COVID-19 participants, dengue (confirmed by RDT Dengue NS-1) was also identified in 3 (5%) participants. Meanwhile, based on the data from site 610, SARS-CoV-2 was identified in 103 (90%) participants. SARS-CoV-2 and dengue (confirmed by PCR SARS-CoV-2, RDT Dengue NS-1, and RDT Dengue IgM IgG) co-infection were identified in 2 (2%) participants. Among negative COVID-19 participants, influenza (confirmed by PCR) was identified in 2 (2%) participants. Dengue (confirmed by RDT Dengue NS-1 and RDT Dengue IgM IgG) was also identified in 1 (1%) participant. Overall, the pathogens among 25 (14%) COVID-19 negative participants (18 participants from Site 521 and 7 participants from site 610) were still unidentifiable (figure 3).

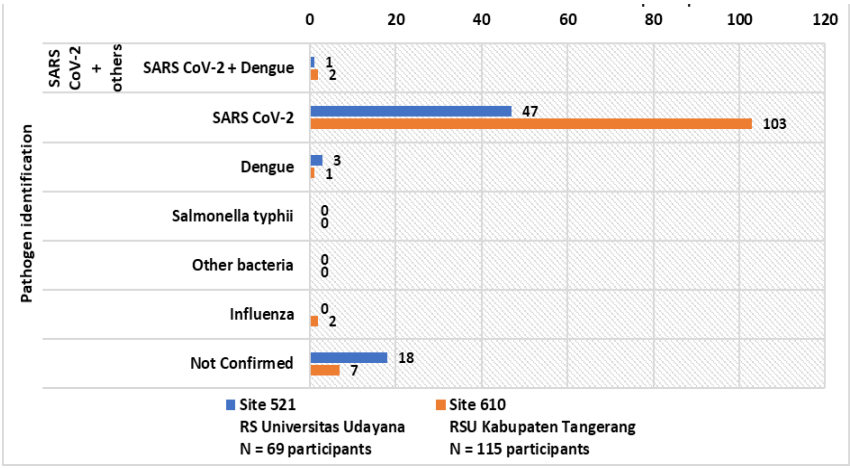

Figure 3. Pathogen identification based on uploaded CRF per 10 May 2022

The annual report for notifying study progress was submitted to local IRB RSU Kabupaten Tangerang on 13 May 2022, and the approval for the continual ethical clearance was given on 20 May 2022. The submission of the annual report for the central IRB (NIHRD/ BKPK) was sent on May 20, 2022. The central IRB will be directed to a new EC/IRB (Poltekkes Jkt II) since central IRB can no longer process any new/ amendment of the protocol. Preparation for the protocol submission is in progress. Meanwhile, preparation for transitioning from protocol Annex 1. ORCHID -COVID-19 to protocol ORCHID General is ongoing.

Several calls with NIAID are held to discuss manuscripts based on the ORCHID-COVID-19 study results. The analysis of data from the FluPRO questionnaire is of particular interest. The FluPRO preliminary analysis was presented and discussed with John Powers. Inputs will be factored into the analysis.

INA-RESPOND Newsletter

MONKEYPOX 101

By: Yan Mardian

First described in 1958, the human monkeypox virus (hMPXV) is a neglected zoonotic pathogen closely associated with the smallpox virus. Medical and public health officials are concerned—and puzzled—by the increasing number of confirmed monkeypox cases in countries outside central and western Africa, where the virus is endemic. Monkeypox is endemic in 10 countries in West and Central Africa, with dozens of cases this year in Cameroon, Nigeria, and the Central African Republic (CAR). The Democratic Republic of the Congo (DRC) has by far the highest burden, with 1284 cases in 2022 alone. Those numbers are almost certainly underestimates. In the DRC, infections most often happen in remote rural areas; in the CAR, armed conflict in several regions has limited surveillance.

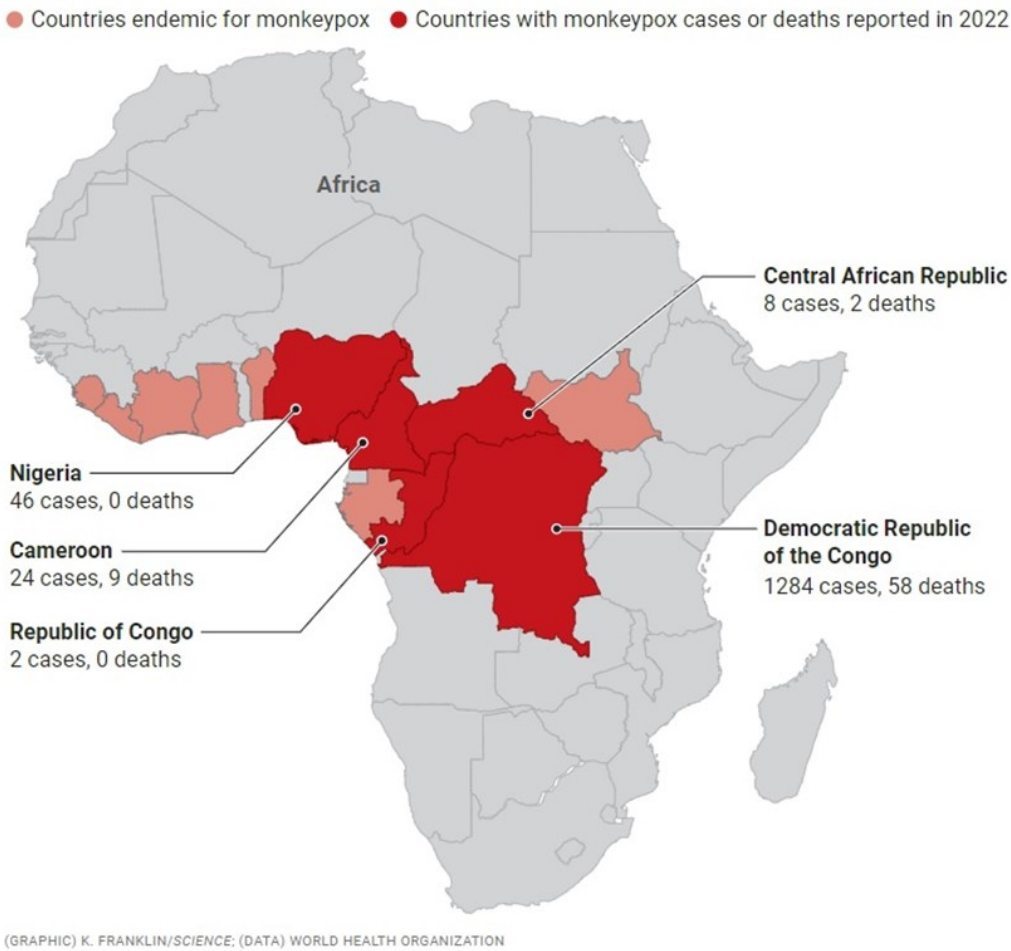

Figure 1. Endemic country for monkeypox. The virus infects squirrel, rat, and shrew species in at least 10 countries in West and Central Africa and occasionally jumps into the human population. So far this year, five countries have reported human cases

As monkeypox stokes here-we-go again fears in a pandemic-weary world, some researchers in Africa are having their own sense of déjà vu. Another neglected tropical disease of the poor gets attention only after it starts to infect people in wealthy countries. On 7 May 2022, the UKHSA (United Kingdom Health Security Agency) confirmed the first case of the human Monkeypox virus (hMPXV) in a case travelling back from Nigeria. The patient had developed rashes few days before travelling to UK but presented to the hospital on the day of his arrival in UK. A reverse transcriptase polymerase chain reaction (RT-PCR) on a vesicular swab was per-

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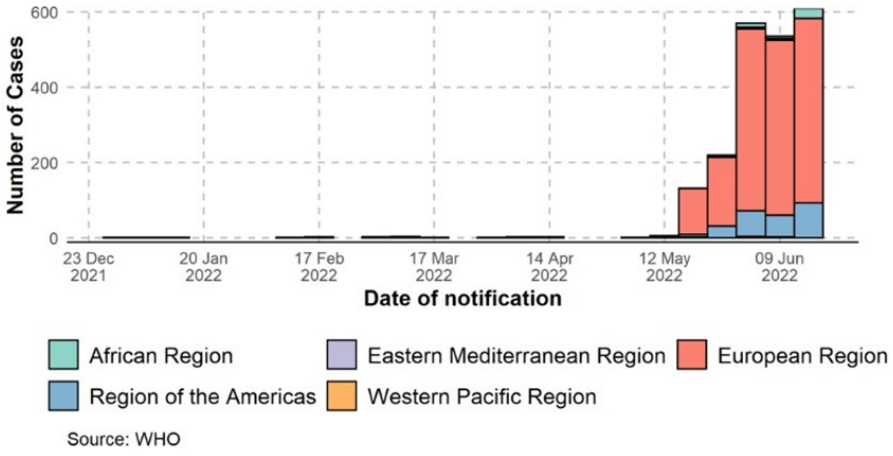


Figure 2. Confirmed cases of monkeypox by WHO region from January 2022 to 15 June 2022. Data as of 15 June 2022 17:00 CEST

formed and hMPXV infection was confirmed. Now, the fire is spreading. Since 1 January 2022, cases of monkeypox have been reported to WHO from 42 Member States across five WHO regions (the Regions of the Americas, Africa, Europe, Eastern Mediterranean, and Western Pacific).

In the past 5 years, scientists have confirmed only 8 cases where travelers carried monkeypox to countries outside Africa, including 2 cases last year in the US. Each was linked to a person who had recently spent time in Nigeria, a country that experienced a resurgence in monkeypox starting in 2017. In those cases, the human-to-human spread was limited; 2 family members became infected in one instance, according to the World Health Organization (WHO). One health care worker who had contact with contaminated bedsheets was infected in another case, report experts in an article published in the CDC's Emerging Infectious Diseases. As of 15 June, a total of 2103 laboratory confirmed cases and one probable case, including one death, have been reported to WHO. The outbreak of monkeypox continues to primarily affect men who have sex with men who have reported recent sex with new or multiple partners. And unlike the previous cases discovered outside Africa, the current outbreaks have occurred in people with no travel history, suggesting that human-to-human transmission is driving the spread. Despite the increase in cases and human-to-human transmission, the risk to the general public remains low, according to a briefing by the WHO.

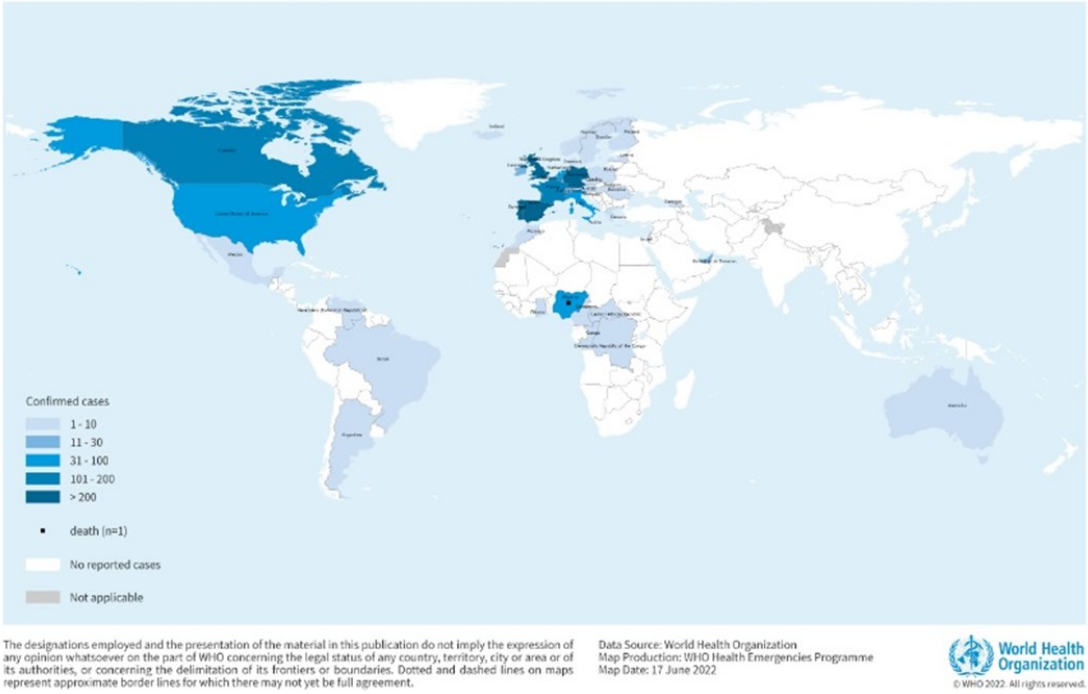


Figure 3. Geographic distribution of cases of monkeypox reported to WHO, between 1 January and 15 June 2022, (n=2103).

1. Virology of MPX

Human monkeypox virus (hMPXV) is a ds DNA virus (~197 kb) of the Orthopoxvirus genus of the Poxviridae family. The subset includes Smallpox (variola), Vaccinia, and Cowpox viruses. hMPXV is a 200 to 250 nm large, brick shaped, enveloped, cytoplasmic virus that binds to glycosaminoglycans to enter the host cells. As an enveloped virus, it has been postulated to alternatively employ the classical apoptotic mimicry mechanism for entry in the host cells.

The virus got its name after it was first isolated in 1958 from smallpox-like vesiculopustular lesions amongst the captive imported monkeys (Java macaques) at the State Serum Institute in Copenhagen, Denmark. The monkeys were reported to suffer from a spontaneous outbreak of fever and rash. Over the next few years, similar outbreaks were reported in monkeys elsewhere. In 1966, the virus was identified as the causative agent behind a widespread outbreak at a zoo in Rotterdam. The virus was believed to have first affected the South American giant anteaters before spreading to various species of apes and monkeys. However, it has only been isolated from a wild monkey—in Africa—once. It appears to be more common in squirrel, rat, and shrew species, occasionally spilling over into the human population, where it spreads mainly through close contact, but not through breathing. Isolating infected people typically helps outbreaks end quickly.

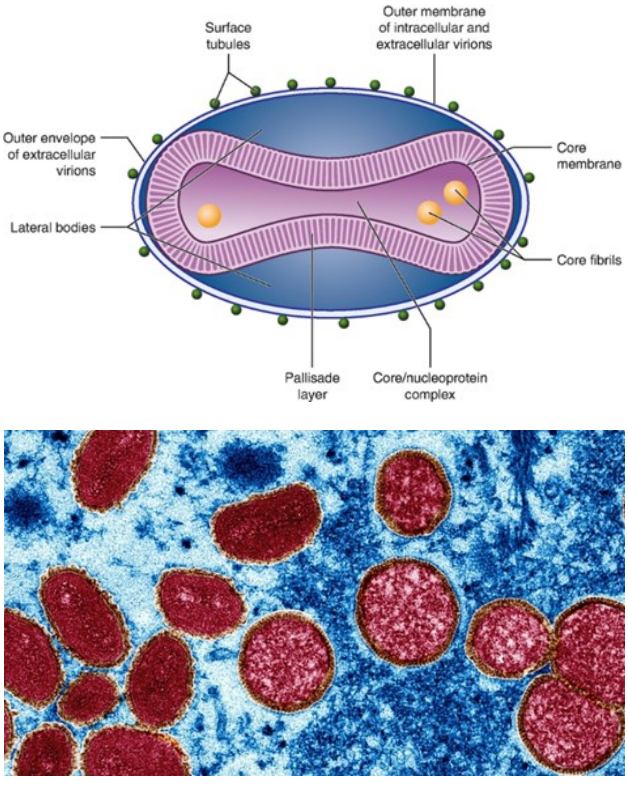


Figure 4. Schematic (left) and electron microscope image (right) depict monkeypox virus particles. On the left are mature, oval-shaped virus particles; on the right are crescent and spherical immature viruses

Human disease was first identified in 1970 in a 9-month-old boy in the Democratic Republic of the Congo and since then most cases have been reported across Central and West Africa. The hMPXV has two described strains – the Central African/Congo Basin (CB) and West African (WA) strains. Historically, the CB clade appears to be more virulent, with a case fatality ratio (CFR) ranging from 1% to 10%, whilst the WA clade is associated with an overall lower mortality rate of < 3%. Recent data for the latter report a CFR of 1.4%. It is important to note that mortality in different settings may differ substantially. Genomic comparative studies have revealed a 0.55-0.56% nucleotide difference between the two strains, with the CB strain possessing 173 functional unique genes compared to 171 of the WA strain. Amongst the virulence genes, 53 out of 56 were found in both strains and showcased 61 conservative, 93 non-conservative, and 121 silent amino acid changes.

The differences in virulence between the two strains has been postulated to stem from the differences in the gene orthologs BR-203 (virulence protein), BR-209 (IL-1β binding protein), and COP-C3L (inhibitor of complement enzymes). Other candidate gene orthologs include the WA strain, specific COP-A49R (unknown function), and COP-A52R (Bifunctional Toll-IL-1-receptor protein). In terms of CB strain specific orthologs, candidate include BR-19 and BR-20 (unknown function). Another crucial gene responsible for difference in virulence in strains is the D14R gene coded inhibitor of complement-binding protein (MOPICE), an important anti-inflammatory factor which is absent from the hMPXV WA strain. However, these genes are not the only factors responsible for virulence, with many more candidates yet to be identified.

Recently, four genomes of the hMPXV isolated during the 2022 outbreak (Germany, USA, Portugal, and Bel-

gium) were published online by various groups of researchers. The 2022 outbreak sequences are a part of a distinct cluster from 2022 within the West African clade. Limited sampling and sequencing of MPXV over the years makes it difficult to generate a hypothesis on the source of introduction for this outbreak. Analysis of the genomes preliminarily hint at very strong bias in mutations of bases Guanine (G) to Adenine (A) and Cytosine (C) to Thymine (T). The enzyme APOBEC3 (Apolipoprotein B Editing Complex), a cytidine deaminase, has been postulated to be responsible for these mutations. A genomic comparison from viral isolates from 2015 to 2022 showed a 30-T base long sequence in the middle of the viral genome, the role of which is yet to be determined.

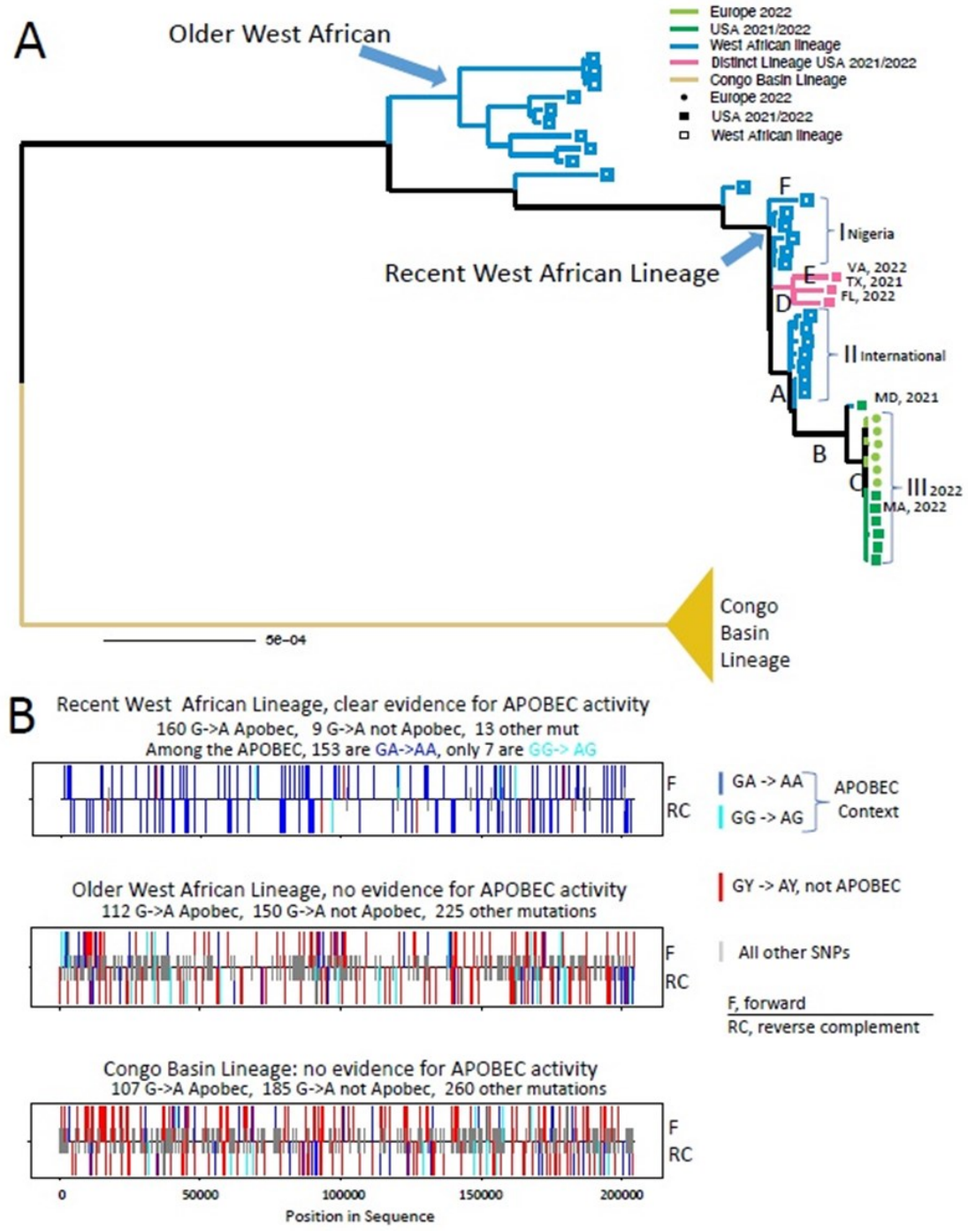


Figure 5. Analysis of APOBEC3 motif mutations in the West African MPXV lineage.

2. Natural History

The incubation period of MPX is usually 6 to 13 days following exposure but can range from 5 to 21 days (10). Although most people recover within weeks, severe complications and sequelae have been reported to be more common among those unvaccinated for smallpox compared with those vaccinated (74% vs 39.5%). It is unclear if there is waning immunity to smallpox vaccination over time; however, studies indicate that smallpox vaccination is approximately 85% effective in preventing MPX. Since prior smallpox vaccination may result in a milder disease course, it is important to ascertain vaccination status in any person exposed to MPX. Evidence of prior vaccination against smallpox can typically be found as a scar on the upper arm. Individuals over 40 to 50 years of age (depending on the country) may have been vaccinated against smallpox prior to cessation of global smallpox vaccination campaigns after the WHO declared eradication of the disease in 1980. Additionally, some laboratory personnel or health workers may have received the vaccine.

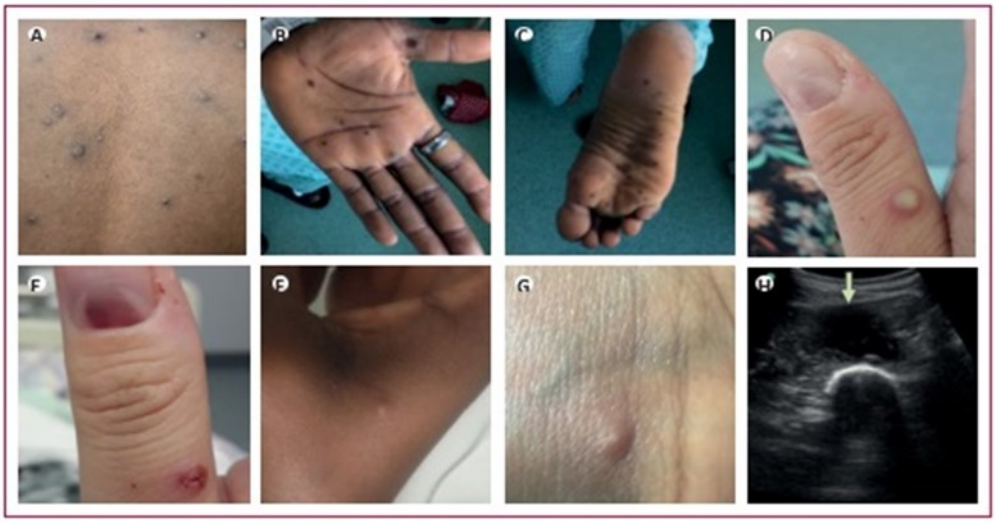
To date, most reported deaths have occurred in young children and immunocompromised individuals, such as those with poorly controlled HIV. A recent study from the Democratic Republic of the Congo reported that in a cohort of 216 patients, there were three deaths in patients < 12 years of age. When compared with survivors, patients with fatal disease had higher MPX viral DNA in blood, maximum skin lesion count, and day of admission AST and ALT values.

3. Signs and Symptoms

MPX can cause a range of clinical signs and symptoms. The initial phase of clinical illness typically lasts 1 to 5 days, during which time patients may experience fever, headache, back pain, muscle aches, lack of energy and lymphadenopathy – which is a distinctive feature of this disease. This is followed by a second phase, which typically occurs 1 to 3 days after fever subsides with the appearance of a rash. The rash presents in sequential stages – macules, papules, vesicles, pustules, umbilication before crusting over and desquamating over a period of 2 to 3 weeks. The lesions range in size from 0.5 to 1 cm in diameter and from a few to several thousand in number. The eruption tends to be centrifugal, starting on the face and extending towards the palms and soles of the hands and feet, and can involve the oral mucous membranes, conjunctiva, cornea and/or genitalia. Observations from current outbreaks in European and North American countries describe lesions starting in the genital area, but more information is needed.

Patients may develop lymphadenopathy – which was described in 98.6% of a cohort of over 200 patients with MPX in the Democratic Republic of the Congo. Oral ulcers are common and may affect a patient's ability to eat and drink leading to dehydration and malnutrition. Inflammation of the pharyngeal, conjunctival and genital mucosae may also occur. A recent large prospective observational study describing the natural history of 216 patients with MPX in the Democratic Republic of the Congo described the most common clinical symptoms to be rash (96.8%), malaise (85.2%) and sore throat (78.2%). The most common findings on physical examination were the classic MPX rash (99.5%); lymphadenopathy (98.6% – the cervical region was most frequently affected [85.6%], followed by the inguinal region [77.3%]); and mouth/throat lesions (28.7%).

Though uncommon, patients with MPX may develop severe and life-threatening complications. For example, the confluence of skin lesions are susceptible to bacterial skin and soft tissue infections such as cellulitis, abscesses, necrotizing soft tissue infections requiring meticulous local wound care; subcutaneous accumulation of fluid in the crusting phase leading to intravascular depletion and shock; and exfoliation resulting in areas of skin that may require surgical debridement and grafting. Other rarer complications include severe pneumonia and respiratory distress, corneal infection which may lead to vision loss, loss of appetite, vomiting and diarrhoea which may lead to severe dehydration, electrolyte abnormalities and shock, cervical lymphadenopathy which may lead to retropharyngeal abscess or respiratory compromise, sepsis, septic shock, and, encephalitis and death. Small studies looking at laboratory abnormalities in patients with MPX indicate that leucocytosis, elevated transaminases, low blood urea nitrogen and hypoalbuminaemia were common features during illness, and that lymphocytosis and thrombocytopenia were seen in more than one-third of patients evaluated.



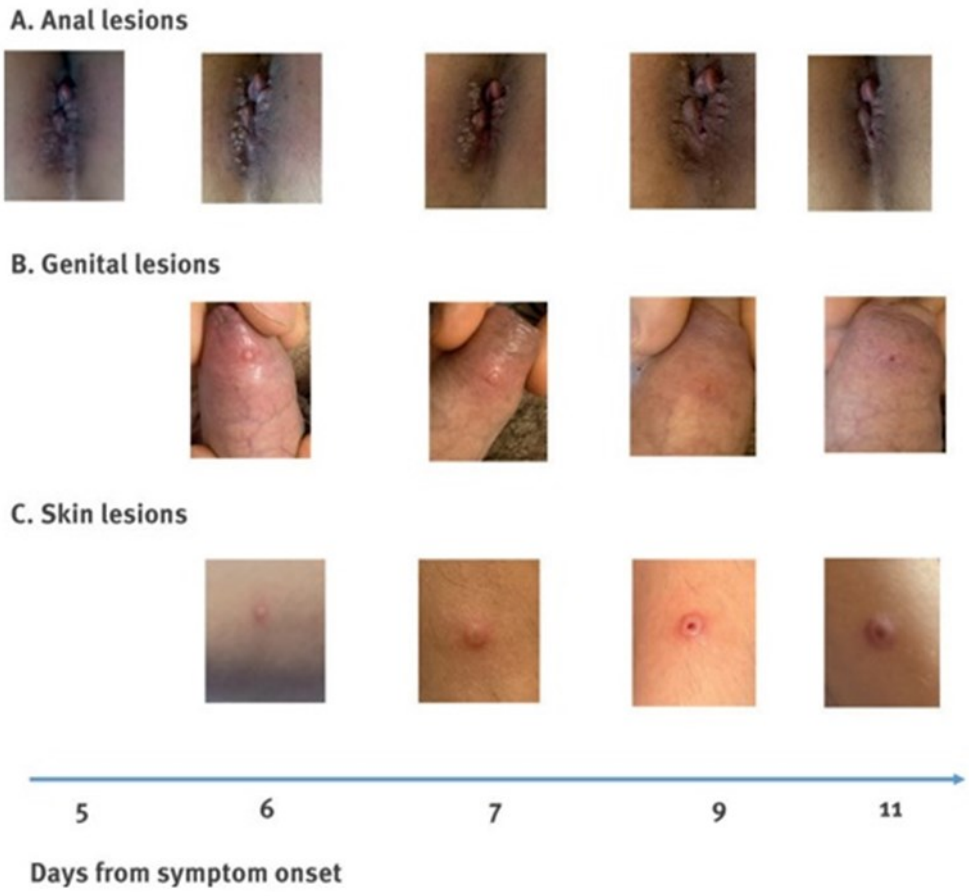


Figure 6. (above) Skin and soft tissue manifestations; and (below) genital manifestation of monkeypox

taminated environments to humans. To date, most information is available from countries in West and Central Africa and less from areas in other WHO regions. MPX virus is transmitted from infected animals to humans via indirect or direct contact. Transmission may occur from bites or scratches, or during activities such as hunting, skinning, trapping, cooking, playing with carcasses, or eating animals, such as non-human primates, terrestrial rodents, antelopes and gazelles, and tree squirrels. The extent of viral circulation in animal populations is not entirely known and further studies are underway.

4. Transmission and viral shedding

Despite decades of circulation in animals with occasional spread to humans, there are limited data available describing transmission and viral shedding of MPX. Available information supports that transmission can occur from animal to human, human to human and from con-

Human-to-human transmission can occur through direct contact with infectious skin or mucocutaneous lesions, this includes face-to-face, skin-to-skin, mouth-to-mouth

or mouth-to-skin contact and respiratory droplets (and possibly short-range aerosols requiring prolonged close contact). The virus then enters the body through broken skin, mucosal surfaces (e.g. oral, pharyngeal, ocular and genital), or via the respiratory tract. The infectious period can vary, but generally patients are considered infectious until skin lesions have crusted, the scabs have fallen off and a fresh layer of skin has formed underneath. Transmission can also occur from the environment to humans from contaminated clothing or linens that have infectious skin particles (also described as fomite transmission). If shaken, these particles can disperse into the air and be inhaled, land on broken skin or mucosal membranes and lead to transmission and infection; one documented health worker infection has been published suggesting MPX virus transmitted through contact with contaminated bedding. Persistence of surrogate pox virus in the environment and on different types of surfaces has been found to last between 1–56 days depending upon the temperature and room humidity; however, there are currently limited data on surface contamination and fomite transmission, aside from contaminated linens. MPX are generally more resistant to environmental conditions and show high stability. No information on the presence of virus in wastewater.

A recent study published in May 2022 from the United Kingdom has reported on the clinical characterization, viral kinetics and polymerase chain reaction (PCR) positivity and response to antivirals in seven patients infected with MPX between 2018 and 2021. All seven patients had MPX viral DNA detected by PCR in skin lesions and in upper respiratory tract samples; six patients had DNA detected in blood; four patients had DNA detected in urine and one person had DNA detected in skin abscesses. Another recent study published in May 2022 on the clinical characterization of 216 patients diagnosed between 2007 and 2011 in the Democratic Republic of the Congo suggested that MPX viral DNA in blood and the upper respiratory tract may be detected prior to onset of rash and that peak viral load may occur very early in the disease course. Data also suggest the MPX scabs contain significant quantities of viral DNA until and including when they fall off and that it is higher than the levels found in the blood and throat. It should be noted that viral infectivity of specimens was not determined. At this time, the significance of these findings in relation to viral transmission and infectious period remains uncertain. More information is needed to better understand other possible modes of transmission and persistence via contact with other bodily fluids (such as breastmilk, semen, vaginal fluid, amniotic fluid or blood) and to better understand transmission by respiratory droplets and aerosols. In the current outbreak countries and amongst the reported MPX cases, transmission appears to be occurring primarily through close physical contact, including sexual contact (oral, vaginal and anal).

5. Differential diagnosis.

The rash which develops in MPX may resemble other infectious diseases or other conditions, including varicella zoster virus (VZV, chickenpox), herpes simplex virus (HSV), primary or secondary syphilis, disseminated gonococcal infection (DGI), foot and mouth disease, chancroid, lymphogranuloma venereum (LGV), granuloma inguinale, molluscum contagiosum, measles, scabies, rickettsia pox, chikungunya, zika virus, dengue fever, vasculitis and other bacterial skin and soft tissue infections. Often, the rash caused by VZV can be confused with MPX but can be distinguished as the rash in varicella generally progresses quicker, is more centrally located than the centrifugal distribution of MPX, is in multiple stages of development (rather than the same stage as seen in MPX) and patients usually do not have lesions on their palms and soles. Additionally, patients with VZV typically do not have lymphadenopathy, which is a hallmark of MPX.

Despite the clinical differences between these two diseases, a study from the Democratic Republic of the Congo reported co-infection with MPX/VZV with an incidence of 10–13%. Patients with co-infection reported fatigue, chills, headache and myalgias. These individuals were less likely to report signs/symptoms of oral sores, axillary lymphadenopathy, cough or sore throat. Patients with co-infection had a higher lesion burden than seen with VZV alone but a lower rash burden than seen with MPX alone raising the suggestion that co-infection with these two viruses could modulate severity of the overall infection – an area for further investigation.

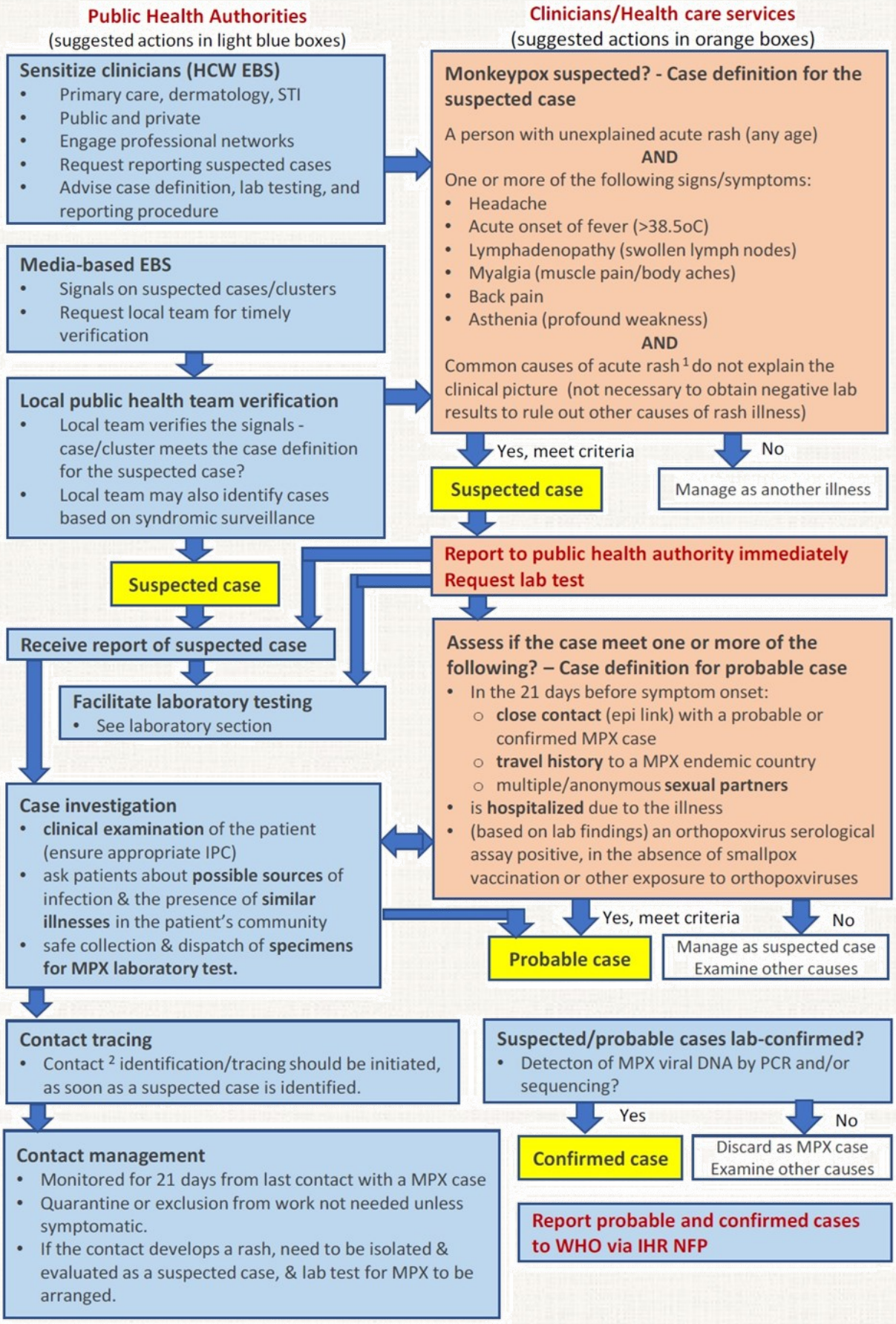


Figure 7. MPX surveillance, investigation and contract tracing

6. Diagnostic Test

The recommended specimen type for laboratory confirmation of monkeypox is skin lesion material, including swabs of lesion surface and/or exudate, roofs from more than one lesion, or lesion crusts. Swab the lesion vigorously, to ensure adequate viral DNA is collected. Both dry swabs and swabs placed in viral transport media (VTM) can be used. Two lesions of the same type should be collected in one single tube, preferably from different locations on the body and which differ in appearance.

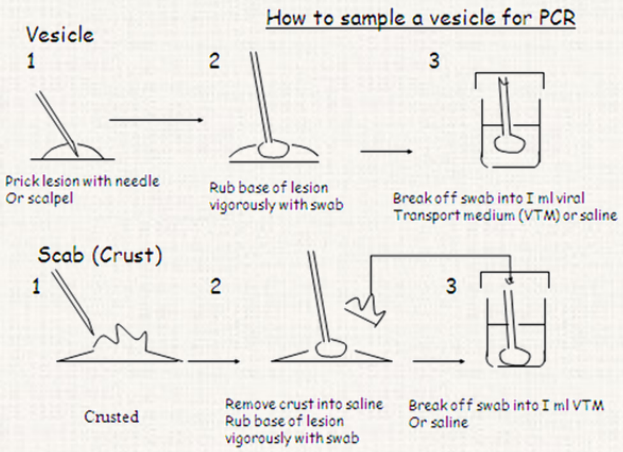


Figure 8. Guidance of specimen collection from lesion.

Testing for the presence of MPXV should be performed in appropriately equipped laboratories by staff trained in the relevant technical and safety procedures. Confirmation of MPXV infection is based on nucleic acid amplification testing (NAAT), using real-time or conventional polymerase chain reaction (PCR), for detection of unique sequences of viral DNA. PCR can be used alone, or in combination with sequencing. Several groups have developed validated PCR protocols for the detection of OPXV and more specifically MPXV, some of which include distinction of Congo Basin and West African clades. Some protocols involve two steps, in which the first PCR reaction detects OPXV, but does not identify which species. This can then be followed by a second step, which can be PCR-based or utilize sequencing, to specifically detect MPXV. Before an assay is utilized to test human clinical specimens within a laboratory, it should be validated and/or verified within the laboratory by appropriately trained staff.

7. Treatment and vaccines

Many people infected with monkeypox virus have a mild, self-limiting disease course in the absence of specific therapy. However, the prognosis for monkeypox de-

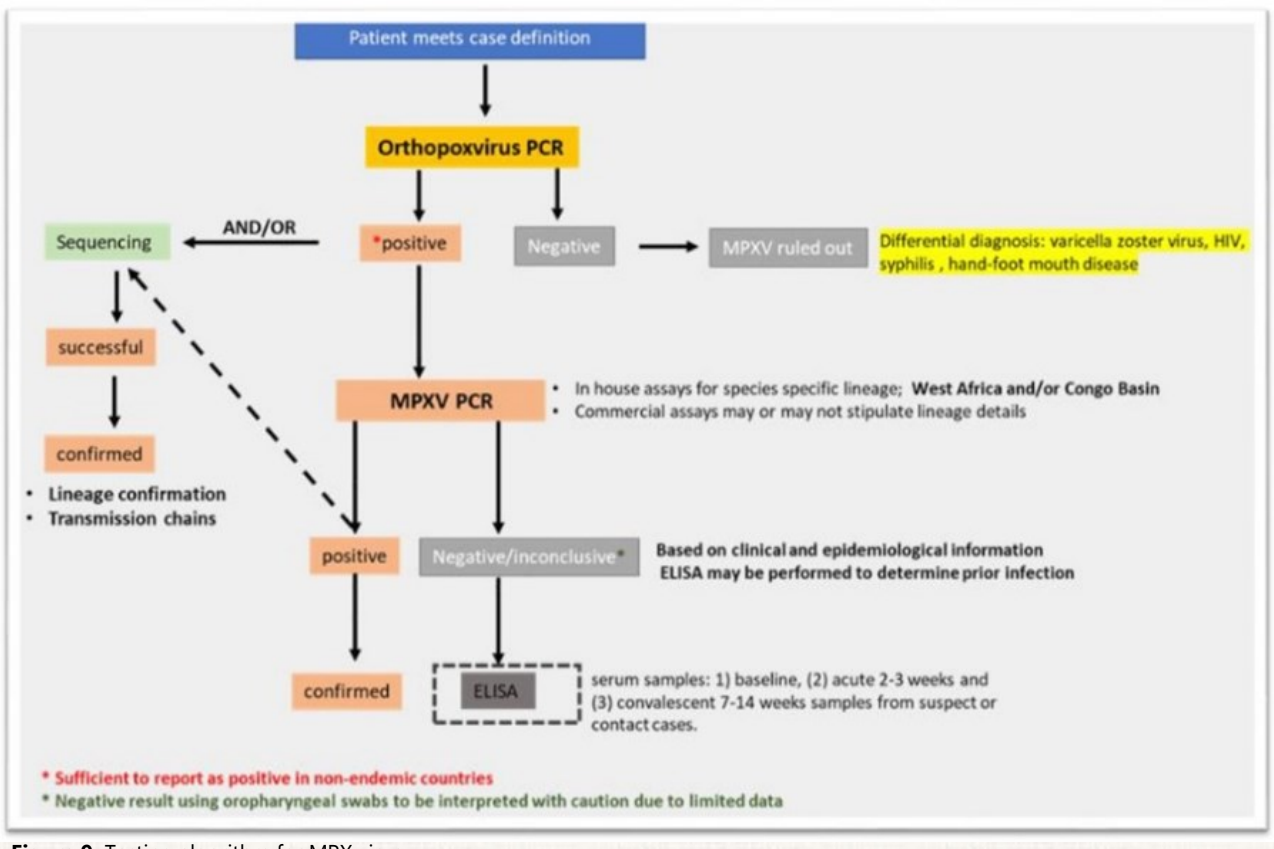


Figure 9. Testing algorithm for MPX virus.

pends on multiple factors, such as previous vaccination status, initial health status, concurrent illnesses, and comorbidities among others. Currently there is no treatment approved specifically for monkeypox virus infections. However, antivirals developed for use in patients with smallpox may prove beneficial against monkeypox. The following medical countermeasures are currently available from the Strategic National Stockpile (SNS) as options for the treatment of monkeypox:

- Tecovirimat (also known as TPOXX, ST-246)

  TPOXX is an antiviral medication that is approved by the United States Food and Drug Administration (FDA) for the treatment of smallpox in adults and children. Data are not available on the effectiveness of tecovirimat in treating monkeypox infections in people, but studies using a variety of animal species have shown that tecovirimat is effective in treating disease caused by orthopoxviruses. Clinical trials in people showed the drug was safe and had only minor side effects. US-CDC holds an expanded access protocol (sometimes called "compassionate use") that allows for the use of stockpiled tecovirimat to treat monkeypox during an outbreak. Tecovirimat is available as a pill or an injection. For children who weigh less than 28.6 pounds, the capsule can be opened, and medicine mixed with semi-solid food.

- Vaccinia Immune Globulin Intravenous (VIGIV)

  VIGIV is licensed by FDA for the treatment of complications due to vaccinia vaccination including eczema vaccinatum, progressive vaccinia, severe generalized vaccinia, vaccinia infections in individuals who have skin conditions, and aberrant infections induced by vaccinia virus (except in cases of isolated keratitis). CDC holds an expanded access protocol that allows the use of VIGIV for the treatment of orthopoxviruses (including monkeypox) in an outbreak. Data are not available on the effectiveness of VIG in treatment of monkeypox virus infection. Use of VIG has no proven benefit in the treatment of monkeypox and it is unknown whether a person with severe monkeypox infection will benefit from treatment with VIG. However, healthcare providers may consider its use in severe cases. VIG can be considered for prophylactic use in an exposed person with severe immunodeficiency in T-cell function for which smallpox vaccination following exposure to monkeypox virus is contraindicated.

- Cidofovir (also known as Vistide)

  Cidofovir is an antiviral medication that is approved by the FDA for the treatment of cytomegalovirus (CMV) retinitis in patients with Acquired Immunodeficiency Syndrome (AIDS). Data is not available on the effectiveness of Cidofovir in treating human cases of monkeypox. However, it has shown to be effective against orthopoxviruses in in vitro and animal studies. CDC holds an expanded access protocol that allows for the use of stockpiled Cidofovir for the treatment of orthopoxviruses (including monkeypox) in an outbreak. It is unknown whether or not a person with severe monkeypox infection will benefit from treatment with Cidofovir, although its use may be considered in such instances. Brincidofovir may have an improved safety profile over Cidofovir. Serious renal toxicity or other adverse events have not been observed during treatment of cytomegalovirus infections with Brincidofovir as compared to treatment using Cidofovir.

- Brincidofovir (also known as CMX001 or Tembexa)

  Brincidofovir is an antiviral medication that was approved by the FDA on June 4, 2021 for the treatment of human smallpox disease in adult and pediatric patients, including neonates. Data is not available on the effectiveness of Brincidofovir in treating cases of monkeypox in people. However, it has shown to be effective against orthopoxviruses in in vitro and animal studies. CDC is currently developing an EA-IND to help facilitate use of Brincidofovir as a treatment for monkeypox. However, Brincidofovir is not currently available from the SNS.

Various smallpox vaccines, containing vaccinia virus, provide cross-protection against other orthopoxviruses (OPXV), including monkeypox, therefore national health authorities should conduct a risk assessment and consider whether arranging immunization for health care workers, including laboratory personnel, and other staff that are at risk of exposure to individuals or specimens with MPXV is required. Vaccination against smallpox was

Table 1. Summary of Regulatory Licencing Antivirals for Monkeypox

	Tecovirimat	Brincidofovir	Cidofovir
Treatment dose, route, duration (adults) *(65,66,71,73,76)*	**Dose** Oral 600mg PO every 12 hours Intravenous* 3 kg to < 35 kg: 6 mg/kg every 12 hours 35 kg to < 120 kg: 200 mg every 12 hours > 120 kg: 300 mg every 12 hours *Must be administered over 6 hours **Duration** 14 days	**Dose** Oral < 10 kg: 6 mg/kg 10–48 kg: 4 mg/kg > 48 kg: 200 mg (20 mL) **Duration** Once weekly for 2 doses, on days 1 and 8	**Dose** Intravenous 5 mg/kg IV once weekly Must be given with oral probenecid: 2 grams 3 hours prior to each dose and 1 gram at 2 and 8 hours after completion of the infusion Must be given with at least 1 L of 0.9% normal saline over a 1–2 hour period before each infusion **Duration** Once weekly × 2 weeks, then once every other week (based on treatment for CMV retinitis)
Treatment dose, route, duration (paediatrics) *(65,66,71,73,76)*	**Dose** Oral 13–25 kg: 200 mg every 12 hours 25–40 kg: 400 mg every 12 hours > 40 kg: 600 mg every 12 hours Intravenous* 3–35 kg: 6 mg/kg every 12 hours 35–120 kg: 200 mg every 12 hours > 120 kg: 300 mg every 12 hours *Must be given over 6 hours **Duration** 14 days	**Dose** Oral < 10 kg: 6 mg/kg 10–48 kg: 4 mg/kg > 48 kg: 200 mg (20 mL) **Duration** Once weekly for 2 doses, on days 1 and 8	**Dose** Intravenous 5 mg/kg IV once weekly Must be given with oral probenecid: 2 grams 3 hours prior to each dose and 1 gram at 2 and 8 hours after completion of the infusion Must be given with at least 1 L of 0.9% normal saline over a 1–2 hour period prior to each infusion. **Duration** Once weekly × 2 weeks, then once every other week (based on treatment for CMV retinitis)
Dosage forms and strength	**Capsules:** 200 mg orange and black *(65)* **Intravenous:** IV injection single-dose 200 mg/20mL *(71)*	**Tablets:** 100 mg, blue, oval shaped *(73)* **Suspension:** lemon-lime flavoured suspension containing 10 mg/mL *(73)*	**Intravenous:** supplied as single-use vials 75 mg/mL for intravenous infusion *(76)*
Use in pregnancy	No data from the use in pregnant women *(65,66)*	Not recommended Administration to small animals resulted in embryotoxicity, decreased embryo-fetal survival, and/or structural malformations. It is recommended to use an alternative therapy if feasible *(73)*	Pregnancy class C No adequate well controlled studies in pregnant women *(76)*

Use in breastfeeding	Unknown whether medicine or metabolites are excreted in human milk *(65,66,70)*	In studies with lactating rates, brincidofovir was detected in milk but not plasma of nursing pups *(73)*	Unknown *(76)*
PEP dose, route, duration (adult)	No data	No data	No data
Mechanism of action	Inhibits activity of the orthopoxvirus VP37 protein and inhibits viral envelope formation *(65,69,70,72)*	Inhibits polymerase mediated synthesis of DNA *(73)*	Inhibits DNA polymerase *(79,80)*
Licensed for smallpox	European Medicines Agency (2022)*(65)* US Food and Drug Administration (2021)*(66)* Health Canada (2021)*(67)*	US FDA (2021) *(73)* EMA (2016)	US CDC (EA-IND)
Licensed for monkeypox	European Medicines Agency (2022) *(65,70)* US CDC (EA-IND protocol)	US CDC (EA-IND protocol)	US CDC (EA-IND)

demonstrated through several observational studies to be about 85% effective in preventing monkeypox. Thus, prior smallpox vaccination may result in milder illness. Evidence of prior vaccination against smallpox can usually be found as a scar on the upper arm. Because the smallpox vaccine provides cross-protection from other OPXV, experts have suggested that the upward trend in monkeypox cases is due in part to the decline in smallpox vaccinations in the post eradication era.

A non-replicating vaccine consisting of the modified vaccinia Ankara strain known as MVA-BN was approved for prevention of smallpox (which was declared eradicated in 1980) in 2013. In 2019 it was also approved for the prevention of monkeypox by two stringent regulatory authorities. This vaccine can also be considered for prevention of monkeypox in the occupational setting. Some countries have maintained strategic supplies of older smallpox vaccines from the Smallpox Eradication Programme (SEP) which concluded in 1980. These first-generation vaccines held in national reserves are not recommended for monkeypox at this time, as they do not meet current safety and manufacturing standards. Many years of research have led to development of new and safer (second- and third-generation) vaccines for smallpox, some of which may be useful for monkeypox and one of which (MVA-BN) has been approved for prevention of monkeypox. The supply of newer vaccines is limited and access strategies are under discussion (see table 2, page 18.)

Based on currently assessed risks and benefits and regardless of vaccine supply, mass vaccination is not required nor recommended for monkeypox at this time. Human-to-human spread of monkeypox can be controlled by public health measures including early case-finding, diagnosis and care, isolation and contact-tracing. All decisions around immunization with smallpox or monkeypox vaccines should be by shared clinical decision-making, based on a joint assessment of risks and benefits, between a health care provider and prospective vaccinee, on a case-by-case basis. Post-exposure prophylaxis (PEP): for contacts of cases, PEP is recommended with an appropriate second- or third-generation vaccine, ideally within four days of first exposure (and up to 14 days in the absence of symptoms), to prevent onset of disease. Pre-exposure prophylaxis (PrEP) is recommended for health workers at high risk of exposure, laboratory personnel working with orthopoxviruses, clinical laboratory personnel performing diagnostic testing for monkeypox, and outbreak response team members as may be designated by national public health authorities.

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Table 2. Smallpox and monkeypox vaccine options.

Vaccine (Manufacturer)	Licensed for smallpox (country, type, date)	Licensed for monkeypox (country, type, date)	Considerations	Presentation	Injection materials
MVA-BN (Bavarian Nordic) 3rd generation	EU: Imvanex has been authorised under exceptional circumstances (2013) Canada: Full MA (2013) USA: Full MA (2019)	USA, full MA (2019) Canada, full MA (2019)	Very limited supply Liquid-frozen formulation, approved for use in the general adult population Two doses four weeks apart	Liquid frozen or lyophilized (freeze-dried) Single dose vials (Multidose vials possible)	Needle and syringe (sub-cutaneous administration)
LC16 (KM Biologics) 3rd generation	Japan - Full MA (1975) USA - EIND (2014)	No	Approved for use in infants and children (all ages) as well as adults (all ages)	Freeze-dried Multidose vials	Bifurcated needle
ACAM2000® (Emergent BioSolutions) 2nd generation	USA - Approved	USA - EIND for PEP	Approved for use in adults aged 18 – 64 years of age. Earlier production by Sanofi Pasteur approved in France.	Freeze-dried Multidose vials	Bifurcated needle
Vaccinia, various strains* **from national production** 1st generation	Various countries Various national production (SEP), held by various countries	No	Regular potency testing recommended	Liquid frozen or lyophilized vials or ampoules	Bifurcated needle

EU: European Union (European Medicines Agency). USA: United States of America (Food and Drug Administration. Canada: Health Canada. MA: market authorization. EIND: Emergency investigational new drug programme of the US Food and Drug Administration. PEP: post-exposure prophylaxis. SEP: Smallpox eradication program. **For example: Wetvax/APSV; Lister/Elstree or Lancy-Vaxina.

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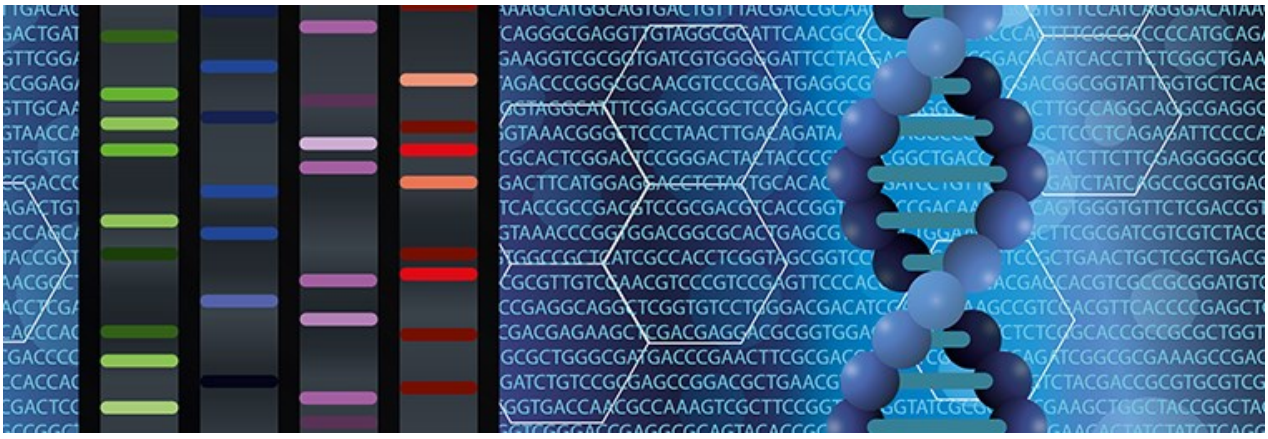
INA-RESPOND Newsletter

SEQUENCING INITIATIVES FROM SMALL TO LARGE SCALE

By: Aaron Neal



The COVID-19 pandemic may finally be nearing its end. Borders are re-opening, postponed trips are happening, mask mandates are expiring, and the fear that gripped the world for the past two years has faded thanks to intense public health efforts and a global vaccine race. As we reflect on ways that the world has changed due to the pandemic, the spillover of terms like 'PCR' and 'sequencing' into the common vocabulary is noticeable. Everyone is familiar with PCR now, and sequencing has grown from a nice-to-have test to an essential technology for the future of public health. While PCR is relatively simple and easy to scale up within existing healthcare systems, routine DNA and RNA sequencing present greater challenges. Let us consider the technology behind sequencing and examples of its implementation at different scales to understand the challenges and opportunities sequencing presents for our future.

"Did you have the Omicron variant?" "I had Delta a few months ago." These are common points of conversation that many of us have heard by now, and we all likely know that a SARS-CoV-2 variant is determined by sequencing. At the smallest scale, such as at the INA-RESPOND Reference Laboratory, a handful of patient samples can be processed and sequenced one at a time on a delicate instrument called a Sanger Sequencer. The 3500 Genetic Analyzer used by INA-RESPOND is a Sanger Sequencer that can identify the precise genetic code of a known target, such as the SARS-CoV-2 S-gene, if the correct DNA primers are used. When compared to reference databases such as GISAID, the strings of A, T, G, and C bases generated by the 3500 Genetic Analyzer can be mapped to known sequences deposited by other scientists to determine viral characteristics, such as variant identity or viral evolution.

Scaling up from Sanger Sequencing, we have "Next-generation sequencing," a buzzword that essentially means high-throughput sequencing with fewer pre-processing steps. Rather than producing a single sequence result of a known target, next-generation sequencing instruments such as the Nanopore MinION used by the INA-RESPOND Reference Lab can generate millions or billions of sequences during an experiment. These sequences can be computationally processed and overlapped using bioinformatics analysis pipelines to produce highly refined sequences of known and unknown targets. Instead of processing one COVID-19 specimen at a time, the MinION can examine 24 or more specimens at once if they are uniquely barcoded and

pooled together. Like the MinION, Illumina sequencing instruments such as the NextSeq 1000 can produce millions of sequences in just a few hours. The scientific community's rapid shift to next-generation sequencing has resulted in hundreds of thousands of sequences and invaluable data on the genomes of humans and pathogens alike.

As more and more countries begin to incorporate sequencing into national surveillance programs and healthcare systems, scaling-up activities from a single lab to an entire country becomes increasingly complex and challenging. The Indonesian Ministry of Health recently formed the Biomedical Genome-based Science Initiative (BGSI) to apply the promises of sequencing to critical research areas in Indonesia, including cancer, aging, and infectious diseases. While the Initiative is well -supported and will develop an initial network of 17 sequencing centers, coordinating such complex experiments and the subsequent data analysis will be difficult. Luckily, existing models of sequencing centers and institutions exist, particularly at the U.S. National Institutes of Health.

Among the 27 Institutes and Centers of the NIH, the National Human Genome Research Institute (NHGRI) is specifically focused on nucleic acid sequencing. NHGRI has been a key player in genomics since its formation in 1989 when it led the U.S. Government's contribution to the Human Genome Project. The technology and experiments pioneered at NHGRI, as well as the ethical guidelines and policies it has developed concerning human genome data, have fundamentally shaped the landscape of modern sequencing. Today, NHGRI balances its priorities of human genome sequencing, bioinformatics tool development, and sequencing technology development with serving as a technical resource for other NIH Institutes and Centers. Rather than developing internal sequencing programs on topics like cancer, heart disease, or infectious diseases, NHGRI works closely with subject matter experts in Institutes like the National Cancer Institute (NCI), the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute of Allergy and Infectious Diseases (NIAID) to pursue collaborative projects within those Institutes. The technical knowledge of NHGRI combines with the research questions of expert investigators to produce strong scientific projects that benefit the entire NIH and international communities.

Sequencing at NIH, though reliant on expertise at NHGRI and research questions from other Institutes and Centers, extends beyond wet-lab experiments and into the world of bioinformatics. Once an experiment is finished and complex sequence data collected, NIH investigators can run analyses on the 105,000+ processor Linux cluster Biowulf maintained by the Center for Information Technology (CIT). The raw computational power provided by Biowulf is combined with cutting-edge genomic analysis tools developed by the National Library of Medicine (NLM) and the National Center for Biotechnology Information (NCBI), the home of PubMed and your favorite analysis tools like BLAST. This final step in the sequencing journey turns millions or billions of indecipherable genetic codes into meaningful genomic data that can be used to control pandemics, understand cancers, pinpoint causes of heart disease, and save lives. And the best part of this system is that most of the resources developed and used by NIH investigators are freely available to the international research community.

As Indonesia and other countries consider high-throughput, national-scale sequencing initiatives, there may be lessons to learn from the assembly line-like model of the NIH, where multiple Institutes and Centers of hundreds of scientists specializing in each step of the sequencing pipeline come together to produce the most robust and valuable data possible.

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INA-RESPOND Newsletter

STEP IT UP FOR YOUR HEALTH! HOW MANY STEPS DO WE NEED EVERY DAY?

By: Edrick Purnomo Putra

Have you ever heard of the renowned recommendation of "10,000 steps daily" to get health benefits? This slogan seems to have been around and firmly stuck in our memory all this time. But do we need to walk 10,000 steps daily? It's time to revisit this popular recommendation and look at the newest evidence regarding this matter.

Before we jump into counting steps, it would be better to look back at where walking plays a part in our daily physical activity. Physical activity is defined as any physical movement involving muscle contraction and energy expenditure. Physical activity is divided into four domains, i.e., domestic, occupational, transportation, and leisure time.1 Doing exercise and sports are included in the leisure time domain.2 By this definition, walking can be a part of any physical activity domain.

Looking at the history, the 10,000 steps/day slogan originated in 1965 by a Japanese company, Yamasa Clock and Instrument Company, when the company was selling the first commercial pedometer named Manpo-Kei, which translates as 10,000-steps meter. The slogan was first used as a marketing campaign to promote interest in fitness after Tokyo Olympic Games in 1964. This slogan was not backed with scientific evidence then, yet it remains famous until now, even used by modern activity trackers.3

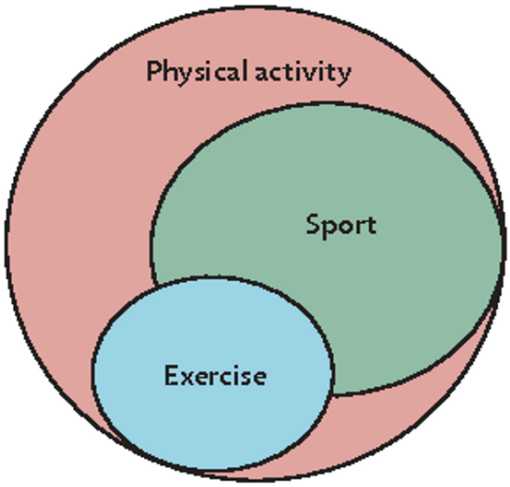

Figure 1. Physical activity classification.[2]

Now, does this marketing campaign live up to its promise? Let's look at the current scientific evidence to find the answer. A prospective cohort study of 18,289 US women with a mean age of 72 years from the Woman's Health Study was done between 2011 and 2015. They agreed to participate by wearing an accelerometer during waking hours for seven days. Among these older women, as little as approximately 4,400 steps per day was significantly related to lower mortality rates than about 2,700 steps per day. Mortality rates significantly decreased with more steps per day and eventually plateaued at approximately 7,500 steps per day. This study also showed that stepping intensity was not clearly related to the mortality rate.3

Another prospective cohort study, part of the Coronary Artery Risk Development in Young Adults (CARDIA) study, was conducted from 2005 to 2006, and the data were analyzed from 2010 to 2021. This study included a total of 2,110 Black and White men and women aged 38 to 50 years old. The participants wore accelerometers for seven consecutive days in waking hours and followed for a mean period of 10.8 years. The result showed that taking approximately 7,000 steps per day or more was associated with a 50 to 70% lower mortality risk while taking more than 10,000 steps per day was not associated with a further reduction in mortality risk.4 A similar study was

published in 2020 with 4,840 US adults aged at least 40 years in the National Health and Nutrition Examination Survey. The result showed that a more significant number of steps was associated with a lower all-cause mortality rate in adults, but the mortality rate reduction leveled off around 12,000 steps per day and above.5 Both these studies showed no association between stepping intensity and mortality.4,5

Since the optimum step count per day is still unclear, a meta-analysis study is needed. A meta-analysis in 2020 included 17 studies, with five reporting all-cause mortality, four reporting cardiovascular risk, and eight reporting dysglycemia outcomes. For every 1,000 daily step count increase from baseline, all-cause mortality risk is reduced by 6-36%, and cardiovascular disease risk is reduced by 5 -21%, yet reports on dysglycemia outcomes were inconsistent. Health benefits are present below 10,000 steps per day. However, the dose-response relationship is unclear, and the minimum threshold is still lacking in data.6

Another meta-analysis in 2021 tried to establish the dose -response relationship, which was missing from the previous meta-analysis. This study included seven prospective cohort studies and suggested certainty for a strong inverse association between daily steps and all-cause mortality risk within counts of 2,700 to 17,000 steps per day. This study showed that even a modest increase in daily steps might be associated with lower mortality risk. However, this study still failed to determine the optimum daily count step for health promotion.7

The latest meta-analysis in 2022 includes 15 prospective cohort studies (seven published and eight unpublished studies) from Asia, Australia, Europe, and North America, with a total of 47,471 adults and 3,013 deaths. This study is the first to provide an evidence -based threshold for the optimum number of steps per day associated with lower all-cause mortality risk. This is also the first study that presented an optimum number of steps varied by age. For adults aged 60 years and older, mortality risk progressively reduced with around 6,000-8,000 steps per day, and among adults younger than 60 years, 8,000-10,000 steps per day progressively reduced mortality risk.8

All studies mentioned above have already proved that health benefits from walking occur at levels less than the famous reference value of 10,000 steps every day. However, most people are still unable to fulfill the optimum number of steps to gain health benefits. A study in the US, named America On the Move, reported that adults took an average of 5,117 steps daily.9 While achieving the needed number of steps per day may seem like a personal matter, physical activity as a way to promote health should concern society and government. A greater approach is needed to create awareness and behavioral changes. An interesting multi-strategy community-based study called "10,000 Steps Ghent" in 2005 implemented a whole community intervention with one year follow up. Local media campaigns, environmental approaches, sale and loan of pedometers, and several local physical activity projects were implemented in the community in the city of Ghent by the Department of Movement and Sport Sciences Ghent University in collaboration with the city and provincial government, insurance company, and local health promotion services. After one year, the number of people reaching the 10,000 steps daily increased by 8%, and average daily step were also

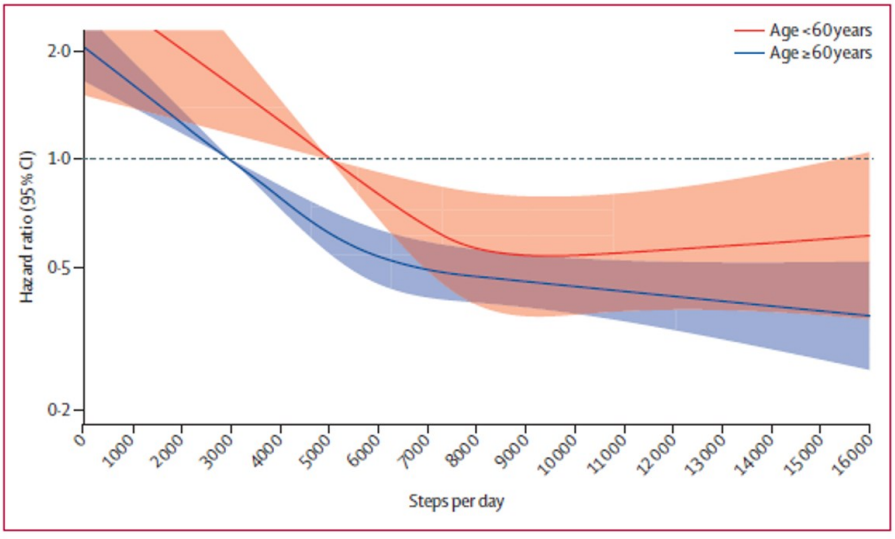

Figure 2. Dose-response association between daily steps and mortality, by age group.[8]

increased compared to a control community from another city.10 This study showed that active community-based intervention with multi-strategy approach succeeded in increasing physical activity level in the community after one year of intervention. Sadly, after one year, the intervention stopped, and a four-year follow-up study was conducted in 2009. The follow-up study concluded that the positive effects were not maintained after four years but a decrease of physical activity from the baseline seen in the comparison community was prevented.11

So, what can we take from these studies? It is evident that increasing our physical activity by increasing daily step count gives us health benefits, but the optimum number of steps needed is less than the popular recommendation of 10,000 steps per day. Yes, a long-term community-based approach will be a great advantage, but we must start from ourselves. For inactive people, you can start by increasing your daily steps; as the studies above said, even a modest increase in your daily steps can reduce mortality risk. And for those who are already active and achieve more than 10,000 steps per day, it doesn't mean you need to be less active. It will help if you always stay active while remembering that more doesn't always equal better. Also, remember that we still need to do exercise. WHO Guidelines 2020 on physical activity recommended that adults do at least 150-300 minutes of moderate intensity, or 75-150 minutes of vigorous intensity of aerobic physical activity per week. Muscle-strengthening exercise at moderate or greater intensity on two or more days per week.12 Attaining the optimal daily step count is essential, but it's not the only thing. Instead of stressing the number, we should focus more on adding movement to our daily life and staying active. Let's be active because every move counts!

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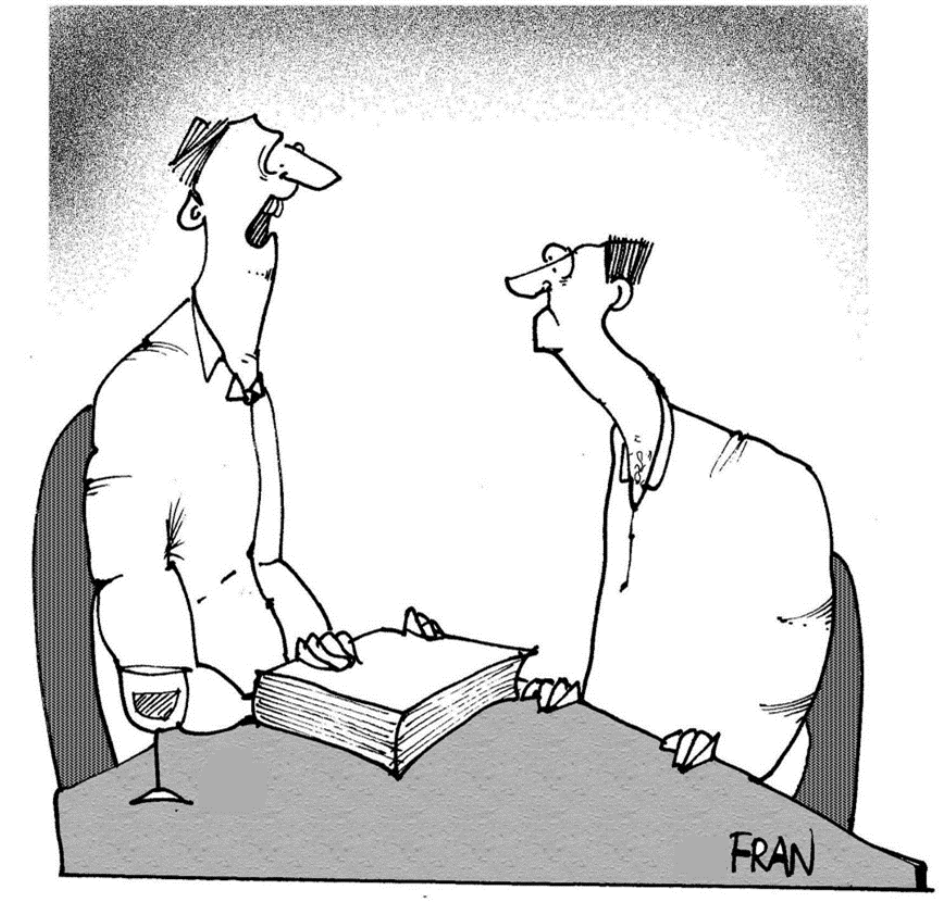
INA-RESPOND Newsletter

PLAGIARISM – HOW BIG IS OUR SIN?

By: Aly Diana

COMIC CORNER



Plagiarism is derived from Latin word "plagiarius" which means "kidnapper," who abducts children; and it entered Oxford English dictionary in 1621. In 1999, the Committee on Publication Ethics (COPE) defined plagiarism as "Plagiarism ranges from the unreferenced use of others' published and unpublished ideas including research grant applications to submission under new authorship of a complex paper, sometimes in a different language. It may occur at any stage of planning, research, writing or publication; it applies to print and electronic versions."

There are several forms of plagiarism, for example: 1) Verbatim plagiarism, when we copy paste from published articles without putting any references; 2) Mosaic plagiarism, when we mix own words in someone else's ideas or in another word copy paste in a patchy way; 3) Paraphrasing, when we rewrite any part/ paragraph from published articles without putting any references – as change a few words does not make it our own; 4) Self plagiarism, when we use a big portion of our published works to create a new publication.

Sorry, I have to copy paste this part – but I will definitely put it in quote and put the references. Promise! FYI, the statements below have not been accepted globally, but it's kind of nice to get a general idea on what is considered major/minor plagiarism.

"Major plagiarism could be defined as:

Any case involving:

- unattributed copying of another person's data / findings, or
- resubmission of an entire publication under another author's name (either in the original language or in translation), or
- verbatim copying of >100 words of original material in the absence of any citation to the source material, or
- unattributed use of original, published academic work, such as the structure, argument or hypothesis/idea of another person or group where this is a major part of the new publication and there is evidence that it was not developed independently.

Minor plagiarism could be defined as:

- verbatim copying of <100 words without indicating that these are a direct quotation from an original work (whether or not the source is cited), unless the text is accepted as widely used or standardized (e.g., the description of a standard technique) from another work (whether or not that work is cited)
- close copying (not quite verbatim, but changed only slightly from the original) of significant sections (e.g., >100 words) from another work (whether or not that work is cited)

Source: Liz Wager, 2011. How should editors response to plagiarism? COPE discussion paper. https://publicationethics.org/files/COPE_plagiarism_disc%20doc_26%20Apr%2011.pdf

Currently, there are many plagiarism detection software available, both paid and free. The main job of the software is to compare our article or our words with other already published research articles or repositories. Usually the software will generate a similarity report showing the proportion of our works that similar with things out there. However, even if we use quote and reference correctly, it will still be reported as similar with the original resources. Therefore, the numerical results generated by plagiarism detection software should be looked more carefully. The overall report is more important than just the number. And yes, getting help from the plagiarism detection software is actually very helpful!

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