# 2025 Vaccinology PBL

The purpose of the vaccinology Problem Based Learning (PBL) exercise is to expose students to real-world vaccinology applications of high contemporary importance particularly for Low- and Middle-Income Countries (LMICs). This year, we are covering two challenge areas – malaria and mpox – in part based on requests from students but also in part because both are of such extremely high current priority that it was hard to ignore either of them. While focussing on vaccines, the PBL gives an opportunity to draw off much other knowledge learned on the IHTM course and deploy it in a problem-solving, interdisciplinary, and impact focussed fashion.

Each of you will be part of a sub-group who will write and present on one of these challenge areas but join all discussions about both. As in previous years, several 'ask the expert' masterclasses – with questions set by you – will provide you with access to hands-on local expert knowledge to ground your advice in real-world reality. This year we will have a strong Africa expert focus. Names and dates will be shared with you in early January.

You will work with colleagues from the National Institute of Public Health, Burundi, who are working on implementation strategies for tackling malaria and mpox, in a two-way partnership, sharing knowledge and experience. Later in the year, we plan an online workshop with CERCLE, the Coalition for Equitable ResearCh in Low-resource sEttings, at which you may be asked to present your findings.

We thank Professors Joseph Nyandwi, General Director of the National Institute of Public Health, Burundi, Andy Pollard, Adrian Hill, and Kevin Marsh of Oxford for their kind support and encouragement. We thank AFOx for generously awarding Roger Ciza an AfOx Catalyst Grant to work with Andrew Farlow to support this activity and to catalyse future collaborations with colleagues in Burundi.

This year's Vaccinology PBL is being organised by Andrew Farlow, NDM, University of Oxford, and Roger Ciza, recent graduate of the University of Oxford IHTM course, an MD, and now researcher and lecturer at the National Institute of Public Health, Burundi.

# Malaria

## Background

Between 2001 and 2015, a substantial expansion of malaria interventions contributed to a 30% reduction of the global incidence of malaria and a 47% decline in malaria mortality rates. About 4.3 million deaths were averted, and the UN Millennium Development Goal (MDG) 6 target – to "have halted by 2015 and begun to reverse the incidence of malaria and other major diseases" – was achieved. Since 2015, progress has slowed, stalled or even reversed in many moderate- and high-transmission countries. In 2024 there were over 240 million malaria cases worldwide and about 627,000 deaths. About 95% were in sub-Saharan Africa, where children younger than five years old made up about 80% of all cases and accounted for about 750 deaths on average every day. Other countries and regions have struggled to maintain progress too. Brazil, after 2017, experienced a reversal in its declining trend. Conflict-stricken regions in the Democratic Republic of the Congo and South Sudan and much of Afghanistan currently experience extremely high malaria prevalence.

The WHO's 'Global Technology Strategy for Malaria' nevertheless envisages by 2030 at least 90% reduction in case incidence and mortality rates from malaria compared to 2015, and elimination in 35 countries. Much hope is pinned on two recently approved malaria vaccines – the first ever for any human parasitic disease – RTS,S/AS01 (GSK and PATH) in 2022 and R21/Matrix-M (University of Oxford and the Serum Institute of India, SII, using Novavax's Matrix-M adjuvant technology) in 2023, to be used in under-five children in moderate to high malaria transmission regions.

## PBL group task

The malaria PBL sub-group is tasked with preparing a report/presentation on:

i) How these new malaria vaccines should be deployed as part of a package of interventions to achieve maximal impact.
ii) Proposed data management frameworks and tools to support countries in achieving this.
iii) Possible future malaria vaccines, especially to support malaria elimination and eradication, and how policy makers and funders should respond now.

The following observations might help to guide your thinking.

# 1) Shaping malaria vaccine deployment strategies

With massive malaria vaccine rollout on the way, it is vital to understand how to achieve efficient deployment. You first need to critically evaluate evidence on the properties and potential roles of these new vaccines, such as: immune response; efficacy; waning/durability of immune response; stability; number of doses needed including the role of booster doses; impact of changing natural immunity; safety profile (adverse events, side effects); and practicability of these vaccines as interventions based on trial data, pilot study evidence (of the phased introduction of RTS,S/AS01 through routine childhood immunization programs in Malawi, Ghana, and Kenya), and early implementation lessons in a range of counties such as Cameroon, Burkina Faso, Ethiopia, and Nigeria.

Success with malaria vaccines will depend on how well they are integrated with, and work alongside, existing malaria control strategies. They are not standalone silver-bullet solutions. Real-world vaccine efficacy is a function of the transmission dynamics of malaria, shaped by the complex lifecycles and behaviours of mosquitoes, genetic diversity, environmental factors, and other non-vaccine control strategies.

You will need to factor in the following:

- For maximum efficacy, doses of the current vaccines need to be administered before peak transmission season and align with seasonal malaria chemoprophylaxis (SMC). Given resource constraints, you need to identify which children to target according to age and whether living in areas of low, moderate, or high malaria transmission.
- The routine immunisation schedule for these vaccines consists of three doses and a fourth dose to mitigate waning of vaccine-induced immunity, and a fifth dose one year later in areas where there is substantial remaining risk for malaria in children.
- Nevertheless, to increase uptake of the required number of doses and reduce disruption and costs to health systems, it is better if the malaria vaccination schedule aligns as closely as possible with the current EPI schedule for children aged from 5 months.
- You might explore strategies to combine, according to transmission setting, vaccines with mass drug administration program (MDA), targeted drug administration (TDA), reactive case detection and treatment (RACDT), alongside insecticide-treated bed nets, indoor residual spraying, and antimalarial drugs.
- Given that asymptomatic individuals – who have developed partial immunity from repeated infections and show no or limited symptoms – act as a ‘silent’ reservoir of malaria parasites and source for malaria transmission, you might further explore the role of widespread diagnostic testing and treatment strategies.

- These vaccines modulate the pathway to acquiring natural immunity, such that severe malaria may shift to older ages, the so-called 'rebound malaria'. You will need to factor this in too.
- Even when enough vaccine doses reach high-risk countries, children most at risk of malaria-related adverse health outcomes might not get them. After all, countries where malaria vaccines will be rolled out are home to the largest share of children that EPIs fail to protect. These children often live in the poorest, hardest-to reach settings where non-vaccine malaria interventions also have more limited reach.
- Given the high number of doses needed for vaccine efficacy, you will need to factor in the attitudes and perceptions of caregivers. Studies in Uganda, Ghana, Nigeria, and elsewhere, have highlighted significant disparities in awareness and acceptability of malaria vaccines. Early studies indicate that even in countries and regions with great focus on the roll-out of the RTS,S/AS01 vaccine, uptake falls off as required doses rise. In one study in western Kenya, of children targeted, only about 60% got as far as a third dose and less than a third got as far as a fourth dose (there is no evidence so far on a fifth dose). This reduces vaccine efficacy and undermines messaging about the benefits of the vaccines. Ways to improve uptake and reduce rates of dropout might include aligning the fourth dose with other second-year-of-life vaccines or health interventions (as Ghana has done since 2023), and careful messaging that educates on the limitations in efficacy, because not all children will be protected from malaria even after receiving four doses of the vaccine.
- It is currently estimated that 40–60 million malaria vaccine doses will be needed to meet demand by 2026, rising to 80–100 million doses annually by 2030. Given growing birth cohorts in sub-Saharan Africa and potential use also in pre-elimination and elimination settings, these quantities may yet be an underestimate. A major challenge with RTS,S/AS01 is that the quantity of available doses will not be sufficient to meet demand. Indeed, only 18 million doses have been allocated to 12 African countries between 2023 and 2025. Most malaria vaccine supply will need to come from the R21/Matrix-M vaccine. You should explore frameworks for improving supply response and allocation of vaccines.
- The cost per malaria vaccine dose (estimated at US$2–$4 for R21/Matrix-M and just over $10 for RTS,S/AS01) is only part of the costs. Non-vaccine delivery costs are a significant burden that may overwhelm many endemic countries' health systems. Your financial strategy and malaria roll-out strategy will need to work together to make overall costs stainable.
- You will need to factor in that even when supply is available, fragmented transportation/storage/cold chains, and limited power supply infrastructure may make it hard to guarantee the availability of quality-assured products (not just vaccines) at all points of delivery, especially in remote areas. These infrastructure requirements will need to be incorporated.

- Most malaria deaths worldwide are caused by delays in diagnosis and lack of access to timely appropriate treatment, especially amongst lower socioeconomic groups. Half the world's population cannot get access to health services without incurring financial hardship, which is made worse by substandard quality of services. Less than half of the population at risk of malaria uses an insecticide treated net (ITN). Many with fever do not seek care, and in many places less than half who seek care are tested for parasites anyway. Current vaccines are no panacea for fixing these issues and must not take resources away from health system strengthening.
- On top of the growing threat of resistance to antimalarial drugs and insecticides, the emergence of new vectors and the changing biological behaviour of vectors to avoid exposure to pesticides, means that we need to factor in longer-term risks of resistance to malaria vaccines. The two new vaccines, and most malaria vaccines in development, are based on a single parasite genotype. It is currently unclear if highly resistant genotypes will eventually strongly reduce vaccine effectiveness. Alongside vaccine deployment, this requires an added layer of data monitoring of genotype frequency, conditions for the spread of resistance genotypes, and impact on vaccine effectiveness. Strategies will be needed to limit evolution of resistance to current vaccines and to develop and implement vaccines that are more evolution-proof including combining vaccines that target different life-stages to reduce the spread of resistant genotypes or modifying vaccination programs to use different vaccines in different groups to create a heterogeneity of selection.

# 2) Creating a data system to support locally-tailored strategies and country-driven planning

Per capita population-at-risk funding for malaria has declined, making it even more critical to optimize the use of the limited available resources. This means moving away from a one-size-fits-all set of interventions to be deployed equally everywhere. Each population-at-risk will need a different optimised combination of, timing of, and intervals between, interventions, and methods for monitoring effectiveness of such interventions. But this involves potentially complex targeting and stratification of vaccines and other interventions across heterogeneous population profiles living in resource-limited settings.

The current 'vaccine allocation prioritization index' used by the WHO for determining GAVI eligibility/needs for RTS,S/AS01 malaria vaccines relies on underlying data (on disease burden/transmission, risk of child death) that is between 5 and 10 years old, is not real-time, does not capture trend, and excludes data on important aspects such as resistance to insecticides, drugs, and vaccines. This composite index needs to be

revisited and updated, or replaced with something more local, before it is used in an even bigger priority allocation of more effective malaria vaccines like R21/Matrix-M.

Your second task, working with colleagues on the front-line of scaling up malaria vaccine deployment, is to describe an effective, affordable, locally led and governed information management system for subnational data collection that will support local data-driven stratification and targeting of interventions including vaccines and enable better use of available local resources.

You will need to consider (by asking those with local knowledge and already working on such systems) what types of data this system might realistically contain – which will vary by country according to local malaria situation and resources available. Possible data you might explore include: admissions for malaria to hospitals and health centres and deaths from malaria confirmed by a parasitological test; malaria burden; transmission intensity; entomological, demographic, epidemiological, health system and other factors; data on the efficacy of malaria interventions (including molecular, clinical, and epidemiological evidence of the impact of resistance); climate data from meteorological and satellite sources; population-level information on the coverage of interventions and treatment-seeking behaviour; and operational programmatic data (financial, human resources, logistics and supply chain).

As well as supplying local project management needs, this will feed into evidence-based national malaria strategic plans owned and led by countries to direct resources to the most affected populations and to assess the impact of interventions and better guide future national strategic planning and delivery. You might like to explore new digital, AI, and GIS tools. This is challenging where health systems are weak, suggesting again a major focus on health system strengthening.

Current systems, even for the limited data collected, have been typically set up as tools to satisfy the needs of external donors and funders, and not for local control. If we are to shift from top-down command and control to sustainable local data systems, with countries truly in charge and based on meaningful participation of local communities, how might this look? (be radically honest in your observations).

# 3) The future of malaria vaccines for malaria eradication

Malaria vaccines roughly split into three groups: Pre-erythrocytic vaccines which target the sporozoites and the liver stage; blood-stage vaccines which work at the asexual blood stage; and transmission blocking vaccines (TBV) that target the mosquito midgut protein and the sexual stage antigen of the parasite. The 'Malaria Vaccine Technology Roadmap' set the goal of achieving by 2030 the licensure of

vaccines targeting *Plasmodium falciparum* and *Plasmodium vivax* that: have protective efficacy of at least 75 percent against clinical malaria suitable for administration to appropriate at-risk groups in malaria-endemic areas; and reduce transmission of the parasite and thereby substantially reduce the incidence of human malaria infection and enable elimination in multiple settings.

Your third task therefore is to evaluate emerging technologies and innovations that might enhance future malaria vaccine efficacy and real-world impact, speed development of next-generation vaccines, and make eradicating malaria one day possible.

You might consider exploring the following:

- *Plasmodium falciparum* has a high level of genetic variability, especially in the antigens that could be targeted by vaccines. Such genetic and antigenic diversity, and the parasite's ability to evade immune responses, poses significant challenges to vaccine development.
- Current pre-erythrocytic vaccines provide partial protection. Maintaining high coverage and follow-up booster doses to offset waning immunity can be logistically challenging in low-resource settings. It also raises concerns about the long-term effectiveness of malaria vaccines. Maybe efficacy of such vaccines can be extended with alternative formulations, or by combining them with other interventions.
- RTS,S/AS01 and R21/Matrix-M are pre-erythrocytic vaccines targeting the circumsporozoite protein (CSP) to elicit protective B- and T-cell responses, in an attempt to interrupt infection before the beginning of the blood stage when the fewest parasites are present in the human host. They incompletely prevent human blood-stage infection. While improving malaria morbidity and mortality, a pre-erythrocytic vaccine with 100% efficacy may not be feasible. For malaria elimination, we will need blood-stage vaccines, and transmission-blocking vaccines. The latter would not provide health benefit to an individual but would significantly impact malaria elimination efforts at the community and regional levels.
- Transmission-blocking vaccines could be administered as a standalone product or combined with pre-erythrocytic or erythrocytic vaccines to provide individual and community benefit.
- Though most deaths are caused by *Plasmodium falciparum*, multi-species vaccines might also be needed. For example, zoonotic malaria species *Plasmodium knowlesi*, detected in South-East Asia, creates a wildlife parasite reservoir, not targeted by current human-focused control measures or vaccines, for cross-species transmission to humans. New invading vector species, such as the urban vector *Anopheles stephensi* which has expanded its distribution into the Horn of Africa, may spread and put non-immune populations at risk.

- Powering significant randomised control trials with epidemiological end points is becoming prohibitively expensive. How might trial performance be improved? Consider: i) by identifying the correlates and mechanisms for malaria vaccine performance, especially in endemic regions; ii) use of next-generation sequencing (NGS) in antimalarial (not just vaccine) development, effectiveness evaluation, safety profiling, etc., iii) the role (including in reducing costly and time-delaying preclinical work) of novel bioinformatics/big data/AI tools to leverage parasite and human genomic data to strategically identify candidate vaccine targets that generate precise and accurate immunity (e.g. by identifying genomic regions under positive selection pressure to remain conserved, or identifying essential proteins consistently expressed during distinct life cycle stages that can serve as vaccine targets), and to overcome parasite diversity.
- On route, you might like to evaluate the potential role, and pros and cons, of the mRNA vaccine platform, including the ability to code for multiple antigens to strengthen immune response, but also challenges, such as availability of raw materials, efficiency of delivery, issues with cell targeting, route of administration, vaccine thermostability, side effects, and safety issues.
- In places like India, which is mostly a very low transmission setting and where malaria mortality is low, current malaria vaccines are not ideal. Malaria elimination would be more favoured by vaccines that target both *P. falciparum* and *P. vivax* in all age groups (mortality being highest in the age group >4–5 years) and that prevent transmission.
- You might like to consider hybrid strategies combining malaria vaccines with other novel emerging control measures, such as gene-drive technology to eliminate mosquito populations, use of Wolbachia, monoclonal antibodies, etc.
- What strategies and investments might be needed to achieve the original Malaria Vaccine Technology Roadmap goals in the next ten years?

# Mpox

## Background

There have been four major mpox outbreaks documented prior to the most recent – in 1970, 1996–1997, 2003, 2018. The current outbreak has been much more extensive. Between January 2022 and August 2024, more than 120 countries recorded mpox cases, with over 100,000 laboratory-confirmed cases and over 220 fatalities. As the outbreak grew, it was declared a public health emergency of international concern (PHEIC) by the WHO on 23 July 2022. Into 2023, the global outbreak subsided and the PHEIC was lifted on 10 May 2023. The emergence in the Democratic Republic of Congo of the new Clade Ib variant of mpox – characterized by enhanced transmissibility particularly through human-to-human contact – and its quick spread to neighbouring African countries and beyond, transformed the virus into a global health threat, and a PHEIC was once again declared on 14 August 2024.

Mpox has been a problem for the 'Global South', particularly Africa, for decades, with little global attention. The re-emergence and expansion of mpox beyond endemic regions in West and Central Africa had been predicted as a possible consequence of a decline in population immunity following smallpox eradication. Smallpox and mpox are genetically similar; immunity to one helps protect against the other, and the smallpox vaccine is about 85% effective against mpox. When smallpox vaccinations stopped after smallpox was eradicated, the world's immunity to mpox declined too. Those who have got mpox in the recent outbreak came from the generations who were not vaccinated against smallpox.

Stopping smallpox vaccinations even though it might protect against mpox had logic at the time. The potential for human-to-human mpox transmission was deemed low. Urbanisation was supposed to reduce exposure to the wild animal reservoir of the mpox virus. The first-generation smallpox vaccines, based on a live virus, came with risks and were not suitable for those with weakened immune systems. However, in the intervening period, the virus has evolved to become more transmissible human-to-human. Big and overcrowded LMIC cities, it turns out, are great for the virus too. Meanwhile, the vaccines have become much safer, and now offer longer protection against mpox.

The poor global response to the mpox outbreak has reminded us, much as COVID-19 did, of the deep faults in the global system to research, develop, manufacture, and distribute vaccines to those who need them most: hoarding by high-income countries of the available mpox vaccines; vaccine nationalism; lack of mpox manufacturing

capacity in LMICs; supply/cold-chain/logistical challenges; and intellectual property (IP) barriers hindering equitable distribution.

The WHO points to global competition for mpox vaccines, with 35 countries vying for access to the 16.4 million currently available doses with very few doses reaching those who most need them, especially in Africa where mpox has been endemic for decades.

# PBL group task

The mpox PBL sub-group is tasked with preparing a report/presentation on:

iv) Appropriate mpox vaccination strategies. Should the focus be global or local, and should or can mpox be targeted for elimination/eradication?

v) Mechanisms for more equitable access to mpox vaccines of those most in need of them, especially in LMICs.

vi) Necessary capacity strengthening needed in LMICs particularly in health research training and health system skills to support the current response and to be more prepared for future outbreaks.

The following observations might help to guide your thinking.

# 1) Strategies for immediate mpox control including vaccination

The following areas might fruitfully be explored:

- Should the global population be mass vaccinated to make sure everyone is protected from mpox and smallpox? Yet, there would not be enough current vaccine to do this, much more vaccine production capacity would be needed, and the costs of mass vaccination would be high. Furthermore, mpox has not spread widely in the general population and it is not clear there would be much population willingness for this approach.
- Or should vaccination be more targeted, as post-exposure prophylaxis or as a pre-exposure measure among high-risk populations, or spatially by high-risk regions? Might ring vaccination (the vaccination of close contacts of confirmed mpox cases) be a more efficient and cost-effective strategy for mpox control and, one day, eradication? But would all groups cooperate? Might the stigma associated with such an approach make it more challenging than a broader vaccination strategy? Could targeting achieve eradication anyway?
- Given the costs and the burden and many competing other needs, how much vaccine protection is needed from pox viruses? Should we tolerate some inevitable ongoing low-level burden or seek to eradicate?
- The two PBL groups might like to compare the challenges of malaria and mpox control and eradication strategies.

- The mpox outbreak underscores the importance of a One Health approach, which emphasizes the interconnectedness of human, animal, and environmental health. Since mpox can be transmitted through wildlife, particularly rodents and non-human primates, One Health tools are essential for early detection, prevention, and control of the virus. What does this mean in practice in LMICs and how might such tools be integrated with a suitably adapted vaccine approach? How is the necessary collaboration between public health, veterinary, and environmental agencies achieved to monitor zoonotic reservoirs, manage human-animal interactions, and mitigate the risk of future outbreaks?
- In healthcare settings, infection control measures are critical because of the high risk of mpox transmissions. High-income country advice is that patients should be placed in single-patient rooms with closed doors, their movement limited, and PPE should be properly disposed of after use to prevent contamination. The WHO talks of the need for scaled up (devolved) testing, financial support for those isolating at home, case management with therapeutics such as tecovirimat, and the production of rapid guidance, including clinical guidelines, in the face of ongoing clinical and epidemiological uncertainties. What are the practical realities in LMICs and how might they respond to some of this advice? What international financial support should be given?
- Surveillance has intensified across affected countries, and the WHO and Africa CDC are supporting the implementation of real-time reporting systems and community-based surveillance programs, including in high-risk areas such as Internally Displaced People's (IDP) camps. Who should pay for this?
- Note that there is a strong association between severe mpox and HIV, suggesting further targeting considerations.
- Risk communication and community engagement (RCCE) efforts are also needed.

## 2) Strategies to improve global distribution of and access to mpox vaccines

The global distribution of the mpox vaccine has faced many challenges, especially in ensuring equitable distribution and access for vulnerable populations.
The following areas might be fruitfully explored:

- The manufacturing capacity for vaccines is concentrated in a few countries – in the United States, Japan, and Europe – making LMICs reliant on these regions for mpox vaccine supply. To remove such dependency, there is great need to expand local domestic production of vaccines. And this needs to go beyond fill and finish. Although, vaccine production facilities have been set up by foreign pharmaceutical companies across Africa, these still produce less than 1% of all vaccines used in Africa.

- Even when vaccines are available, their distribution is often inequitable. Could the limited current supply of mpox vaccines be better used by, for example, setting up country prioritization mechanisms (defining which countries get first and how big a share each gets) based on ethical principles that challenge the current disconnect between disease burden and vaccine access? How would these mechanisms work in practice or are they "pie in the sky"? For example, should countries with elevated risk profiles and limited resources and therefore worse outcomes, be given higher priority? Nigeria, Ghana, and Cameroon have fewer than 1% of total worldwide mpox cases but have recorded 15% of global mpox fatalities since 2022. Should these countries not get more doses than nations with much fewer cases and more resources to tackle those cases? What criteria might be developed to support prioritisation based on projected cases, case severity, potential risk factors, and local resources?
- What lessons of COVAX (COVID-19 Vaccines Global Access) might be applied to mpox and could such a mechanism be adapted to include mpox vaccines? COVAX was designed to be an end-to-end coordination mechanism encompassing research and development and manufacturing, policy guidance, vaccine portfolio development, regulatory systems, supply allocation and country readiness assessments, transport logistics, vaccine storage and administration, and the monitoring of country coverage and absorption rates. Which bits of COVAX worked well and which did not?
- Expanding the manufacturing capacity in LMICs could involve transferring technology to these regions, fostering partnerships between pharmaceutical companies and local producers, engaging the public, business, academic, and civil society sectors.
- Yet, what is the role of pharmaceutical monopolies and unwillingness to relinquish Intellectual Property (IP) and technology rights in limiting production? Sometimes vaccine-related patents have much more lucrative global vaccine markets.
- Vaccine R&D and manufacturing need qualified personnel, which needs training, and specialized infrastructure.
- How much investment do local governments and international stakeholders need to make in manufacturing capacity and delivery mechanisms in LMICs (including stable electricity supply and adequate cold chains)?
- It might be worth exploring the nuance of the three current vaccines recommended by the WHO to offer protection against mpox. All are based on live vaccinia virus. All need to be stored and distributed through a cold chain operating at temperatures well below 0°C. All are in limited supply for different reasons. 'Fourth generation' vaccines are under development.
- The ACAM2000® 'second-generation' vaccine is recommended by the US CDC but there are concerns over adverse effects, especially among the

immunocompromised, but there is a total of about 100 million doses currently available.

- The LC16m8 'third generation' vaccine has limited possibility for scaling up outside Japan, where it is manufactured.
- The Jynneos 'third generation' vaccine, also known as Imvamune or Imvanex, is a non-replicating, Modified Vaccinia Ankara (MVA) vaccine, approved by the U.S. Food and Drugs Agency and European Medicines Agency for the prevention of smallpox and mpox. This vaccine represents a significant advancement in vaccine technology, as it is designed to be safer than earlier generations of smallpox vaccines, particularly for individuals with HIV infection or other immunocompromised conditions. The vaccine is administered in a two-dose regimen, with doses administered four weeks apart, which is essential for the development of a strong and lasting immune response. It can be used post-exposure but needs to be administered within four days to prevent the onset of the disease. If administered 4-14-days post-exposure, it may not entirely prevent mpox but can significantly reduce the severity of symptoms. Despite its effectiveness, production of the Jynneos vaccine by its only manufacturer, Bavarian Nordic, has been limited. The United States holds as precaution about 1.1 million vials of this vaccine on top of most of the 100 million doses of ACAM2000. The European union has similarly been on a buying spree.

## 3) Research, training, and other capacity strengthening to be ready for future mpox outbreaks

Strong public health infrastructure, international collaboration, and boosted research, especially in LMICs, is needed to mitigate the impact of mpox and to prepare for future outbreaks. You might like to explore the following:

- A significant contributor to vaccine access inequality, especially in LMICs, is the underreporting of mpox cases. This is especially so in central and west Africa. Weak health surveillance systems in rural areas prevent the early detection of mpox cases, which leads to the underreporting of cases. As a result, hotspots of mpox are not identified early, and vaccines (and other resources) cannot be allocated to such areas. How might health surveillance systems in these regions be strengthened to support mpox vaccine allocation? Of note, Africa CDC has been taking a leading role in this.
- Consider designing an early warning system for a country incorporating robust data collection and data sharing mechanisms.
- With the ending of smallpox vaccinations, many skills have been lost and not strengthened over the years. Much new medical training is needed to support the rolling out of vaccines; for example, smallpox vaccinations needed skilled technique with a special needle that scrapes the skin. Scientific skills are needed

too, because of the paucity of high-quality scientific data. High-quality specimens need to be collected, stored, and transported correctly.

- The inequitable distribution of research resources needs to be tackled. During the 2022 mpox outbreak, the research focus was on the mpox strain circulating in Europe and the U.S, with much less focus on the strain circulating in Central Africa. Where the impact of mpox has been greatest, there has been a limited number of clinical trials dedicated to evaluating vaccines such as Jynneos and antiviral treatments such as tecovirimat. Diagnostics need to be improved too. This may need large-scale randomized clinical trials to assess efficacy and safety of such interventions.
- The precise global distribution of mpox is uncertain due to case ascertainment bias in some countries (encompassing a lack of diagnostic testing, clinical misclassification, and incomplete surveillance). Although transmission chains have been relatively small in previous outbreaks, a decline in population immunity may lead to more sustained epidemics as the basic reproduction rate rises.
- Uncertainty remains over the exact reservoir and the mechanism of how the virus is maintained in nature. Tools are needed like rapid sequencing of the virus to identify how long it has been circulating in humans or in animal reservoirs. This will need the equitable sharing of sequence data from multiple countries.
- We do not really know what the current reproduction number is, the extent (if any) of an animal reservoir, and what strategies will drive it down.
- Because of the One Health angle, pathogen sharing must involve data on animals too.
- No specific correlate of protection against mpox infection has been identified though some vaccine studies indicate that antibody levels may be a correlate of protection.
- Global health financing and the current global public health institutional structure clearly need to be overhauled to be much more fit for purpose. How might insights from the current mpox outbreak inform this reshaping and future strategies, particularly around strengthened surveillance, diagnostic capabilities, LMIC research capacity, and equitable vaccine production and distribution?