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Equitable global allocation of monkeypox vaccines

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A B S T R A C T

With the world grappling with continued spread of monkeypox internationally, vaccines play a crucial role in mitigating the harms from infection and preventing spread. However, countries with the greatest need – particularly historically endemic countries with the highest monkeypox case-fatality rates – are not able to acquire scarce vaccines. This is unjust, and requires rectification through equitable allocation of vaccines globally. We propose applying the Fair Priority Model for such allocation, which emphasizes three key principles: 1) preventing harm; 2) prioritizing the disadvantaged; and 3) treating people with equal moral concern. Post-exposure prophylaxis (PEPV) has the most potential to mitigate harm, and so ensuring countries have sufficient supply for PEPV should be the first priority. And historically endemic countries, which face disadvantages that compound potential harms from monkeypox, should be the first recipients of such vaccines. Once sufficient supply is allocated for countries to apply PEPV, global allocation could move on to pre-exposure prophylaxis (PrEP), again prioritizing historically endemic countries first before distribution to the rest of the global community, based on projected number of cases and vulnerability to harm.

1. Background

As of March 2023, over 86,000 cases of Monkeypox have been confirmed worldwide since the 2022 outbreak [1]. Monkeypox symptoms include fever, muscle aches, headache, fatigue, and painful skin lesions. While symptoms usually resolve in a few weeks, infection can occasionally cause severe illness or even death [2]. Since 2022, 112 people have died from monkeypox, about 15 % in African countries where monkeypox is historically endemic [1]. Youth, pregnancy, and immunocompromise increase the risk of fatal complications, particularly in populations lacking adequate nutrition or good access to healthcare [2–5].

Research indicates that smallpox vaccines can cross-protect against monkeypox [6,7]. Three vaccines have been used or proposed: MVA-BN (referred to as Jynneos, Imvamune, or Imvanex), LC16, and ACAM2000 [8]. MVA-BN uses a virus that is non-replicating and therefore unlikely to cause illness. It is the only monkeypox vaccine suitable for immunocompromised people. MVA-BN is licensed for monkeypox in the US, EU, and Canada, but doses are extremely scarce, in part because its manufacturer had planned to shift to more profitable products before the recent outbreak. As of 17 August 2022, only 1.25 million doses of MVA-BN had been delivered worldwide, 88 % of them to the US [9]. LC16 is a minimally replicating vaccine, deemed sufficiently safe for use in children in Japan but still contraindicated for immunocompromised individuals [8]. Presently, Japan holds the largest LC16 stockpile [10]. By contrast, many countries have stockpiled ACAM2000 to guard against smallpox outbreaks, and the US has authorized Expanded Access to ACAM2000 for use against monkeypox. However, ACAM2000 uses a replicating vaccinia virus that can infect others and cause myocarditis in recipients. Its use is contraindicated in immunocompromised individuals [11].

Because of monkeypox's long incubation period, post-exposure preventive vaccination (PEPV) can prevent infection in those recently exposed to monkeypox. Even when infection does occur, PEPV can lessen the severity and transmissibility of disease. Vaccines can also be offered as pre-exposure prophylaxis (PrEP) to at-risk individuals without recent exposures, but scarcity of vaccines may limit the feasibility and scope of PrEP.

A recurring pattern during global outbreaks is for countries to rapidly obtain vaccines for their own populations, often to the detriment

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of other countries' access. This is sometimes referred to as 'vaccine nationalism'. For example, during the 2009 swine flu outbreak, high-income countries secured most vaccine supply early on [12]. Similarly, during the COVID-19 pandemic, vaccine distribution around the world was highly inequitable [13]. Similar patterns have emerged for monkeypox, as high-income countries have rapidly secured the majority of monkeypox vaccine. Ongoing negotiations over a pandemic treaty may result in better global cooperation concerning vaccine distribution, but such a treaty will not be finalized for some time [14].

Within limits, countries can permissibly favor procuring vaccines for their own citizens [15]. However, current vaccine access is objectionably disconnected from monkeypox burden. Historically endemic countries have received no vaccines, despite experiencing the highest case-fatality rates, while countries with no deaths have acquired many [16]. And the richest among recently affected countries have received disproportionate access to doses, compared with poorer recently affected countries, like Peru and Brazil, which have the second- and third-highest number of cases and deaths of any country worldwide [1]. The international community can do better.

Recently, Japan committed to providing 25,000 doses of LC16 to Colombia [17], while South Korea announced a donation of 50,000 monkeypox vaccines to the Africa Centers for Disease Control, for further distribution in the region [18]. This raises a fundamental ethical question: Which countries should be prioritized for the vaccines and in what quantities?

To answer this question, we deploy the Fair Priority Model, a framework for the equitable international allocation of vaccines. As we will show, this framework can inform which countries should receive priority in the allocation of scarce vaccines, according to well-established ethical principles of harm prevention, equity and equal moral concern. Initially developed for COVID-19, it provides distinctive guidance for the allocation of monkeypox vaccine among countries [19].

Our focus here is on vaccine allocation for public health rather than research. Obviously, better data would improve the estimates of where doses can prevent the most harm and thereby allow for more equitable allocation of doses among countries. Continuing to improve the evidence base for monkeypox vaccines is thus an ethical imperative. Nevertheless, equitable allocation of vaccines must proceed simultaneously with improvements to the evidence base. The world cannot wait for more robust data before fairly allocating vaccines.

2. Addressing barriers to equitable global allocation of vaccines

Current arrangements highlight three potential barriers to equitable allocation. First, high-income countries have used advance purchase agreements to secure priority access to newly manufactured vaccines, even for lower risk populations. This excludes other countries interested in purchasing vaccines at the market price. Second, countries with stockpiled vaccines have hesitated to share their stockpiles. Third, low-income countries that cannot afford vaccines lack an organized mechanism to access vaccines and largely depend on charity.

Equitable allocation could address these barriers. Instead of allowing advance purchase agreements to reserve all available doses, vaccine manufacturers could set aside a certain portion for global distribution or cap how much any given country can procure. Instead of preserving stockpiles, countries might allocate a portion for the international community, consistent with their commitments to contribute to global response in case of a smallpox outbreak. Finally, countries might establish a global procurement and distribution system similar to PAHO's successful Revolving Fund for Access to Vaccines in the Americas and its distribution of MVA-BN for monkeypox [20,21].

Once some vaccines are available for distribution among countries, the allocating agent must determine what distribution would be equitable.

3. An ethical framework for global allocation of vaccines

The Fair Priority Model guides allocation of monkeypox vaccine using the same ethical principles that it relied on for COVID-19 vaccine allocation: 1) preventing harm; 2) prioritizing the disadvantaged; and 3) treating people with equal moral concern [19].

Harm prevention calls for preventing as much harm as possible per allocated dose. While monkeypox infection is typically self-limiting, vaccination can prevent or alleviate weeks of painful symptoms, which require isolation in order to minimize spread to others and may occasionally lead to hospitalization. Isolation or hospitalization compromise the ability of many people, especially the most economically vulnerable, to maintain their livelihoods, causing additional indirect harms that vaccination can prevent. By reducing transmission, vaccines can also protect non-recipients from harm. Importantly, death is the most serious harm that vaccination prevents. While death from monkeypox infection is rare, it is irreversible and far worse than a few weeks of symptoms. Death deprives someone of a future. The gravity of this harm is increased when people die earlier in life.

Second, equitable vaccine allocation should prioritize populations whose disadvantages make them vulnerable to monkeypox harms. Currently, this may mean preferentially allocating vaccines to countries with high prevalence of conditions, such as untreated immunocompromise, that increase the risk of severe complications. Further preferential allocation may be appropriate as more evidence emerges concerning risk factors that worsen outcomes, such as lack of access to health care, poverty, or malnutrition.

Equal moral concern requires treating people the same when there are no morally relevant differences between them. This does not require identical treatment for everyone. For instance, people who live in a jurisdiction with more virus circulating have a stronger claim to vaccines than others, since their increased risk of infection is a morally relevant difference.

A fourth ethical principle, reciprocity, can sometimes be relevant to allocating scarce resources fairly. Reciprocity prioritizes those who have worked to mitigate the problem at hand—currently, monkeypox outbreaks. However, there are no reasonable metrics for contribution at the international level. Moreover, rewarding contribution would tend to favor high-income countries that are better placed to develop vaccines, in part due to advantages resulting from historical inequities. Further prioritization of these countries is unlikely to advance the goals of harm prevention or prioritizing the disadvantaged. As a result, the Fair Priority Model does not consider Reciprocity.

While these principles are the same as with COVID-19 vaccine allocation (and global vaccine allocation more generally), their deployment here must be informed by the relevant features of the current monkeypox outbreak. In what follows, we suggest an allocative approach that is quite different from what was warranted for COVID-19. This is to be expected, due to the substantial differences in which populations are most vulnerable to harm and infection for the two pathogens, as well as the nature of vaccination. For example, while post-exposure prophylaxis through vaccination was not viable in the case of COVID-19, this approach has been recommended in the context of monkeypox [8].

4. Two allocation phases: PEPV vs PrEP

Given the effectiveness of PEPV against monkeypox, there are strong reasons to prioritize PEPV in global allocation. By targeting individuals whose recent exposure increases their risk of infection, PEPV is likely to reduce deaths, symptoms, and transmission more than pre-exposure prophylaxis (PrEP), which targets people at comparatively lower risk of infection. The initial phase of global allocation should supply sufficient doses for PEPV based on a country's currently documented case numbers and projected case growth. Once global vaccine supply exceeds what is needed for PEPV, either because of reductions in spread or increased vaccine production, a second phase of allocation for PrEP

should begin, targeting groups at high risk of infection or who are more vulnerable to harm if infected. This approach is in some ways analogous to the strategy of prioritizing post-exposure prophylaxis over pre-exposure prophylaxis for rabies vaccines when there is a critical shortage [22].

Allocating PEPV based on confirmed cases will deprioritize countries with little capacity for or interest in surveillance. Although PEPV-based allocation will incentivize surveillance, lower-income countries may need support from higher-income countries in building surveillance capacities to support vaccine distribution [23]. Prioritizing the disadvantaged may also suggest upward adjustment of case estimates for countries with poor surveillance capacity.

Countries with no monkeypox cases would receive no doses during this initial PEPV phase. Vaccine would do far less good in these countries than in countries experiencing cases of monkeypox. Countries excluded from the PEPV allocation might still be eligible for doses in the PrEP phase.

International allocation cannot dictate how any given country will actually use its allocated doses. For instance, some countries may opt for PrEP instead of PEPV because they are unable to rapidly reach infected individuals and their contacts. However, prioritizing for PEPV still helps realize harm reduction, because it sends more doses to regions with high current and expected case numbers.

5. Prioritizing high-risk, underserved countries

Within each allocation phase, countries should be prioritized based on the ethical principles. This prioritization could specify the order in which countries receive required doses or how large a share countries receive from a given tranche. Under either method, historically endemic countries should receive the highest priority for monkeypox vaccines. After that, priority should be determined using countries' projected cases and severity of outcomes (Table 1 and Fig. 1).

Historically endemic countries have for decades been burdened with the only significant harms from monkeypox, yet there has been little international attention to this burden up to this point [24]. Since 2022, Nigeria, Ghana, and Cameroon have recorded about 15 % of the world's monkeypox deaths, despite experiencing less than 1 % of the world's cases [1]. While some other historically endemic countries have reported no cases or deaths since 2022, this probably reflects their relatively low surveillance and diagnostic capacities rather than reality [3]. Moreover, a disproportionate number of those who have died in historically endemic countries are children, who have not yet had a chance at a full life [25]. This makes the harm of their death even more morally serious than it would be in the case of adults. By contrast, for example, the UK and France, each with many more cases than historically endemic countries, have reported no deaths.

Table 1
Priority Tiers for Allocating Monkeypox Vaccines.

Priority tier	Country characteristic	Ethical justification
Tier 1	Historically endemic countries	Harm prevention: Highest mortality rates, ongoing need, likely Priority for disadvantaged: No access to vaccines at present
Tier 2A	Countries with higher projected case rates and larger vulnerable populations	Harm prevention: Higher projected cases/larger vulnerable populations → more suffering/death vaccines could prevent Priority for disadvantaged: weigh vulnerable populations (e.g., % of population immunocompromised) particularly heavily
Tier 2B	Countries with higher projected case rates but smaller vulnerable populations, OR countries with lower projected case rates but larger vulnerable populations	
Tier 2C	Countries with lower (or no) projected case rates and smaller vulnerable populations	
Excluded	Countries that decline vaccine supply	Harm prevention: allocation would be wasted, no harm would be prevented through allocation

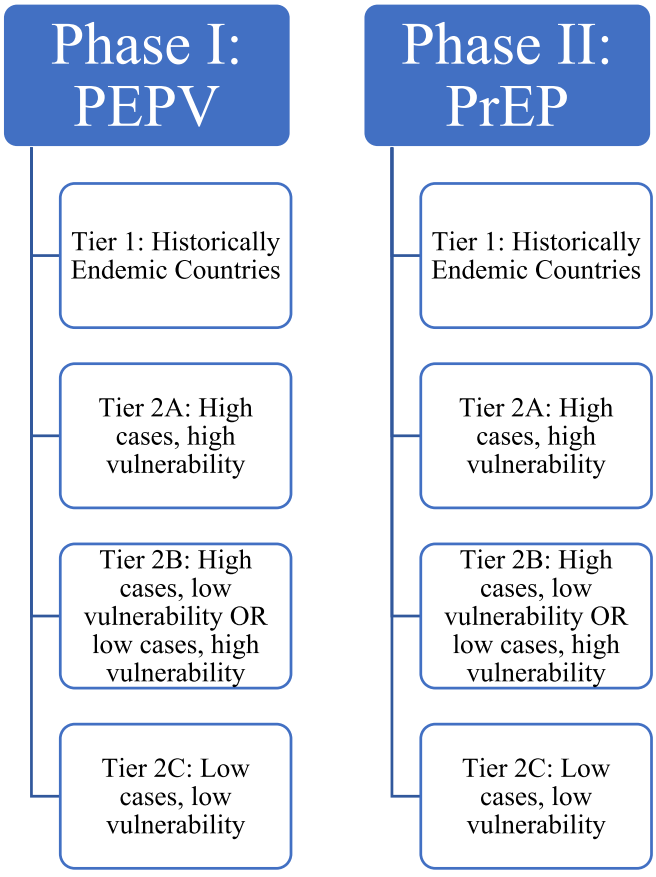

Fig. 1. Allocation Within Phases.

As a result of this asymmetry, vaccination has the potential to save substantially more lives per dose in the historically endemic countries than elsewhere. Harm reduction favors prioritizing these countries. Because their populations face disadvantages, such as high rates of untreated immunocompromise, that heighten their vulnerability to monkeypox, mitigating disadvantage reinforces prioritizing these countries.

Crucially, vaccines should be allocated only where they will be effectively delivered. Some historically endemic countries might need outside assistance with cold-chain infrastructure, diagnostics, and contact tracing, in order better to deliver monkeypox vaccine to their vulnerable populations. Not making this a high priority would be a gross failure to mitigate their disadvantages.

6. The ethical significance of monkeypox becoming endemic in new countries

Should vaccines be distributed to prevent monkeypox from becoming endemic in countries? The experience of first-time monkeypox outbreaks in 2022 made some nations anxious about it becoming endemic, but preventing endemicity is not intrinsically important. Rather, the case for preventing endemicity is that it could prevent future cases and deaths from monkeypox. In the Fair Priority Model, these factors are already given high priority. The importance of preventing endemicity is accounted for by harm-reduction over time.

There are also evidentiary challenges to making endemicity prevention an independent allocation criterion. Assessing how to prevent

endemicity would depend on modelling more speculative than that needed to prevent cases or deaths. Furthermore, even in countries with many vaccines, it is unclear that preventing endemicity is even possible. Hence, allocation should not aim at preventing endemicity [26].

7. Extending priority to other nations based on projected cases

After prioritizing historically endemic countries, vaccine allocation within a given phase should be based on a combination of vaccines' ability to prevent monkeypox cases and mitigate harm among those infected. Low rates of death mean that countries' risk of harm is better represented by case numbers and the number of people at elevated risk of severe outcomes which includes immunocompromised people, young children, and pregnant people. The share of vulnerable people can differ substantially across countries: in some countries the percentage of all adults who have unsuppressed HIV is over 3 %, while in others it is below 0.1 %; [27] and some have over 40 % of residents under age 15, while others have fewer than 15 % children below that age [28]. Prioritizing the disadvantaged suggests giving extra weight to factors like HIV prevalence or rates of immunocompromised individuals, since these disadvantages exacerbate harm from monkeypox.

8. Conclusion

The consistent pattern of global vaccine inequity has recurred with monkeypox. The Fair Priority Model as outlined above is a means to ensure international distribution of vaccines is informed by robust ethical principles. This is in contrast with the way COVID-19 vaccines were initially allocated via COVAX based on population levels [29]. As we have shown, the Fair Priority Model can provide a detailed framework on the sorts of factors that should affect which countries receive priority in vaccine allocation.

In future, rather than reacting to each successive emergency *ad hoc*, the world would be better served if there were an institution capable of using these principles in future global health crises to allocate scarce medical resources for crisis response before they are distributed to the highest bidders. The current pandemic treaty draft entrusts such a responsibility to the World Health Organization [14]. Should that treaty be enacted, the Fair Priority Model could be deployed in future outbreaks as we suggest above for monkeypox.

Author contributions

All authors contributed equally to the writing of this manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: GP reports grants from Greenwall Foundation and personal fees from the American Society of Clinical Oncology Post and WHO, outside the submitted work. EE reports personal fees from United Health Group, personal fees from BC/BS Dana Point, CA, personal fees from CBI/Informa, personal fees from Rise Health, personal fees from Galien Foundation, personal fees from WellSky, personal fees from Rightway, personal fees from Signature Healthcare Foundation, personal fees from Healthcare Leaders of New York, personal fees from Medimpact, personal fees from Massachusetts Association of Health Plans, personal fees from Princeton University, personal fees from Philadelphia Committee on Foreign Relations, personal fees from Yale University, personal fees from Hartford Medical Society, personal fees from American Association of Health Colleges (AAHC), personal fees from Hawaii Medical Services Association, personal fees from Advocate Aurora Health, travel fees from Macalester College, travel fees from DPharm conference, travel fees from UCSF Department of Urology, Travel fees from Oak CEO Summit, travel fees from Peterson Foundation, grants from Laura and John Arnold Foundation, grants from Humana, grants from Signify Health, grants from Hawaii Medical Services Association, grants from University of Miami, grants from Freeman Foundation, grants from Patient Centered Outcome Research Institute, other from Biden/Harris Transition COVID-19 Committee, other from WHO COVID-19 Ethics & Governance WG, other from HIEx Health Innovation Exchange Partnership, other from World Health Organization, outside the submitted work; and Dr. Emanuel was an unpaid board member at Village MD (end 2021) and since 2022 serves as an External Advisory Board Member of Village MD. He was an unpaid board member at Oncology Analytics (end 2022), an unpaid board of advisors member at Cellares, a member of the unpaid board of advisors for Notable, a member of the unpaid board of advisors for HIEx Health Innovation Exchange partnership sponsored by UN. He is an advisory board member for Peterson Center on Healthcare and an Advisory Board member of JSL Health Fund. He is a venture partner at Oak HC/FT. He is an Advisor to Clarify Health. He was a partner at Embedded Healthcare (ended June 2022) and at COVID-19 Recovery LLC (ended March 2021). All other authors have no declarations.

Data availability

NA

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