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Good news for travellers, but what do rabies vaccines say about Global Health?

Over the last 150 years vaccination regimens for rabies have evolved dramatically. Starting from Pasteur's experimental vaccination of Joseph Meister in 1885,¹ nerve tissue vaccines that were lifesaving during their time have since been replaced by safer, more efficacious cell culture vaccines and increasingly simplified schedules of post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP). The Lancet has championed these advances, culminating in WHO's 2018 position statement recommending 1-week abridged intradermal PEP and 2-dose PrEP.² In the latest advance, published in *Lancet Infectious Diseases*, Overduin and colleagues show that PrEP can be reduced to a single shot.³

Rabies vaccines do not fit the standard vaccination paradigm and their complexity requires explanation. These vaccines administered promptly after exposure (i.e. PEP) prevent the fatal onset of rabies which would otherwise occur in around 1 in 5 rabid dog bite-victims.⁴ For severe exposures involving multiple and deep bites to the most risky sites such as the head and neck, rabies immunoglobulins are also indicated as part of PEP. Immunoglobulins provide passive protection at the wound site, giving more time for active immunity to kick in. Alternatively, PrEP primes the immune system so that in the event of exposure, only a shortened 1-day PEP regimen is required, without the need for immunoglobulins. For these reasons rabies PrEP is often stipulated for travellers, typically from wealthy rabies-free countries, when visiting low-income rabies-endemic countries. Overduin & colleagues' rigorous randomised controlled trial demonstrates that the anamnestic antibody response to a single intramuscular vaccination is non-inferior to currently recommended two-visit regimens,³ making PrEP a more appealing travel vaccine.

PrEP access for all – not just travellers from the Global North – is a strong ethical position⁵ and this research makes widespread PrEP a more tangible idea. However, it also begs for introspection from the global health community. PrEP is not routine in the Global North because rabies has long been eliminated from domestic dog populations. In low- and middle-income countries (LMICs) dog rabies still circulates endemically, but PrEP is not offered and immunoglobulins are often unavailable. More people in LMICs die of dog-mediated rabies *every day*, than have died of dog-mediated rabies in the Global North *this century*. Despite science that has improved PrEP and PEP, rabies deaths have been reducing at a glacial pace. How can we do better?

COVID-19 starkly brought home truths of vaccine inequity. The term 'vaccine apartheid' was coined as the Global North hoarded vaccines at the expense of the Global South. Rabies today reflects a century-long vaccine apartheid. Each of the many thousands of deaths that occur annually is a health system failure – where rabid bite victims have not accessed post-exposure vaccines i.e. universal health coverage is lacking. These vaccines are expensive, because as an emergency medicine the scale of production is smaller than for routine childhood vaccines. In many LMICs a vicious cycle exists. Patients struggle to pay out-of-pocket for these vaccines, so health facilities prefer to stock cheaper, more reliably purchased commodities and supply deteriorates. This dire situation has driven effort to improve PEP access, resilience to stockouts,

and indeed market forces, through dose-sparing regimens.⁶ Gavi, the Vaccine Alliance's proposed commitment to rabies post-exposure vaccines from 2021 was a welcome and long-advocated opportunity to redress this inequity. Reassuringly, Gavi recently announced intentions to un-pause investment in human rabies vaccines halted by the pandemic.⁷ While Gavi support should save hundreds of thousands of lives,⁸ human vaccines will not directly affect the number of people exposed nor the trauma of rabies-exposure. With dog rabies circulating unabated, PEP will remain an emergency medicine, even with PrEP.

A further learning from COVID-19 is the importance of One Health. Emerging diseases with pandemic potential are invariably zoonoses. Rabies is a slow-burn pandemic, spread by colonial empires, trade and migrations over centuries.⁹ Dog vaccines are the quintessential One Health intervention used to eliminate dog-mediated rabies from the Global North. Moreover, dog vaccines are an unambiguous (global) public good.¹⁰ Their benefits should be extended to the Global South.

Every few years, a tragic rabies death will make headline news in the Global North, following a traveller's return from a rabies-endemic country. Hopefully, the latest research will translate rapidly into improved PrEP practices to lessen the risk of these occasional individual tragedies. Can Gavi now catalyse global health leadership and action to prevent these tragedies that occur every few minutes in the Global South? The latest PrEP can protect an army of dog vaccinators working towards One Health; all of our vaccines - animal and human - need effective deployment so that no one has to face this abhorrent disease.

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