

Models to support policy to improve rabies prevention and guide elimination

Thumbi Mwangi - clinical assistant professor at the Paul G Allen School for Global Animal Health - Washington State University, and a Wellcome trust fellow in public health and tropical medicine based at the Kenya Medical Research Institute.

Katie Hampson - Wellcome trust senior research fellow based at the University of Glasgow in the UK. She started working on rabies during her PhD at Princeton University.

Rabies epitomizes all the challenges of zoonotic diseases. Although the virus circulates primarily in domestic dogs, rabies causes the most concern when it spreads from animals to people, typically via a rabid dog bite. Rabies has the highest case fatality rate of any known infectious disease and causes a horrifyingly painful death, leaving families, communities and healthcare workers traumatized. Fortunately there are extremely effective vaccines that, if administered promptly after an exposure, will prevent the fatal onset of rabies. Yet despite these lifesaving vaccines, human deaths inevitably occur, because the human vaccines are very expensive, not widely available and because not all bite victims know that they need to seek care. As long as rabies continues to circulate in domestic dog populations there is an ongoing risk of human deaths. That is what motivates the need for mass dog vaccination programs which can interrupt transmission in the reservoir and eliminate the disease at its source.

International organizations recently declared their joint commitment to eliminate human deaths from dog-mediated rabies by the year 2030 (1). Their approach is underpinned by intersectoral collaboration, focusing on improving access to post-exposure vaccines, scaling up mass dog vaccination to levels sufficient to break transmission, and engaging all stakeholders, from local communities to politicians and national governments, who, by working together can rid the world of this preventable disease. As part of the 'Zero by thirty' campaign, international organizations have taken major steps to catalyse progress.

Intradermal PEP regimen

In 2016 the WHO convened a Strategic Advisory Group of Experts (SAGE) working group to review the latest evidence on human rabies prevention. One challenge is that the course of post-exposure prophylaxis (PEP) to prevent rabies after an exposure is complicated. Furthermore, bite victims are often delayed in starting their PEP course because they need to raise funds to pay for the vaccines, or they need to find a health facility with the vaccines in stock. Even the costs for travel and accommodation to complete the course can be

substantial, given that PEP is usually only available in major urban centres.

Various PEP regimens are recommended, some administered via the intramuscular (IM) route and some via the intradermal (ID) route. Each require different volumes of vaccines administered on different days and typically take around one month to complete, however the new abridged ID regimen is completed in one week. The clinical evidence suggests that all these regimens are extremely effective in preventing rabies (5). Experience from East Africa, and other parts of the world, indicates that delays in bite patients receiving vaccine are the main cause of PEP failures, whereby human deaths occur despite a patient receiving some sort of post-exposure vaccination. A priority is therefore to make sure that these vaccines are available immediately to rabies-exposed patients. This is where the benefits of ID vaccination become clear: in the event of an outbreak where limited vaccine is available, the same stockpile can treat over five times more patients using the new abridged ID regimen compared to IM regimens that are currently used (3).

ID regimens for rabies post-exposure vaccination have been recognized as safe and effective for over two decades (4), but have not been widely adopted. This is perhaps because of the complexity of different regimens or because ID vaccination may appear trickier than IM administration. However, TB vaccination via the ID route has been routine for decades and health workers typically say that administration is very straightforward. Another issue is the practicality of sharing vaccine vials for ID use. Unused vaccine must be discarded at the end of each day because once a vial has been opened there is a risk of contamination. Discarding expensive yet lifesaving vaccine likely feels perverse for a health worker, in contrast to IM regimens where the whole vaccine vial is used and vaccine is never discarded. However, health workers often need to refer emergency patients elsewhere because of vaccine stock outs, which are predicted to occur much less frequently under ID vaccination, even with the discarding of partially used vials.

On the basis of the SAGE recommendations, the

WHO updated its position on rabies vaccines (5), and now recommends universal use of ID vaccination, highlighting the new abridged ID regimen as the simplest and least expensive option for patients and governments alike. Gavi, the Vaccine Alliance, recently shortlisted rabies as being among the diseases under consideration for its 2020-2035 vaccine investment strategy, with their final decision due towards the end of this year. As part of the WHO rabies modelling consortium we examined what a Gavi investment could mean for rabies, both in terms of improving access to post-exposure vaccines and in the context of scaled up dog vaccinations (6).

Cost-effectiveness of PEP regimens and dog vaccinations

Building on previous modelling work (2), we compared different PEP regimens to understand their relative costs and benefits, including the use of the new abridged ID regimen (3). We then examined what the impact of improved access to PEP would mean under a range of different scenarios. Our modelling work shows that a universal switch to the new abridged ID regimen would cost less than is currently spent on PEP over the Gavi 2020-2035 time period, whilst treating many more people - over 15 million more bite victims (6). We assumed that Gavi support would enable bite victims to receive PEP free at the point-of-care and that this reduces delays that bite victims often face in trying to raise money to pay for PEP. As a result we estimate almost 500,000 additional human rabies deaths could be averted, compared to the current situation. In most Gavi-eligible countries, bite victims currently pay the full cost of PEP. Without a major player like Gavi facilitating a switch to more efficient vaccination regimens, bite victims are likely to bear the brunt of this market failure – which results in preventable deaths.

In most rabies-endemic countries resources are primarily focused on preventing rabies through post-exposure vaccination of those bitten by rabid dogs. While post-exposure vaccination is critical to preventing human rabies deaths, it does not interrupt transmission in the reservoir host population, so costs continue to rise and as some people do not receive vaccination some still die of rabies. Where investments have been made in dog vaccination, human deaths have declined accordingly - yet investment and collaboration across sectors to tackle rabies at its source remains a major challenge.

We therefore considered in our model the situation whereby mass dog vaccination effort is scaled up as part of the ‘Zero by thirty’ global strategy. Under this scenario, a Gavi investment is still highly cost-

effective, and the global target of zero dog-mediated human rabies deaths can be achieved. One potential concern for Gavi, and for countries tackling rabies in general, is how to prevent the escalation of costs for provision of PEP even when the incidence of rabies declines. This is because with greater awareness of the need to seek care in the event of a dog bite, and of the need to provide PEP, precautionary use of PEP rises. However, we modelled a scenario with the use of integrated bite case management (IBCM) to address this concern (7, 8). We found that IBCM dramatically increases the cost-effectiveness of PEP, whilst also acting as a sensitive tool to improve detection of rabies (9), which is critical as elimination is approached.

Like many zoonoses, rabies has until very recently been very much a neglected disease, with thousands of deaths occurring every year in low- and middle-income countries. But recent in-country prioritization exercises have highlighted that rabies is a priority for countries like Kenya. By modelling the different tools that can be applied to help us to reach the 2030 target, we hope to support governments and international agencies and demonstrate how, through collective action, human deaths from dog-mediated rabies can be eliminated. What this shows us for now is that we need to use both human and animal vaccines more effectively to deliver on this possibility.

Thumbi Mwangi - clinical assistant professor at the Paul G Allen School for Global Animal Health - Washington State University, and a Wellcome trust fellow in public health and tropical medicine based at the Kenya Medical Research Institute. His research focuses on linkages between human and animal health, and leads the implementation research for rabies elimination in Kenya. thumbi.mwangi@wsu.edu

Katie Hampson - Wellcome trust senior research fellow based at the University of Glasgow in the UK. She started working on rabies during her PhD at Princeton University. Her work involves a combination of fieldwork, analysis and modelling, and her current fellowship focuses on the elimination of dog-mediated rabies. katiehampson@gmail.com

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