

- 10 Commons RJ, Simpson JA, Thriemer K, et al. Risk of *Plasmodium vivax* parasitaemia after *Plasmodium falciparum* infection: a systematic review and meta-analysis. *Lancet Infect Dis* 2019; **19**: 91–101.
- 11 Recht J, Siqueira AM, Monteiro WM, Herrera SM, Herrera S, Lacerda MVG. Malaria in Brazil, Colombia, Peru and Venezuela: current challenges in malaria control and elimination. *Malar J* 2017; **16**: 273.
- 12 Thriemer K, Bobogare A, Ley B, et al. Quantifying primaquine effectiveness and improving adherence: a round table discussion of the APMEN Vivax Working Group. *Malar J* 2018; **17**: 241.
- 13 Brito MA, Peixoto HM, Almeida AC, et al. Validation of the rapid test Carestart(tm) G6PD among malaria vivax-infected subjects in the Brazilian Amazon. *Rev Soc Bras Med Trop* 2016; **49**: 446–55.
- 14 Llanos-Cuentas A, Lacerda MV, Rueangweerayut R, et al. Tafenoquine plus chloroquine for the treatment and relapse prevention of *Plasmodium vivax* malaria (DETECTIVE): a multicentre, double-blind, randomised, phase 2b dose-selection study. *Lancet* 2014; **383**: 1049–58.



## Improving the provision of rabies post-exposure prophylaxis

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In 2015, WHO and its partners set the ambitious objective<sup>1</sup> to reach zero human deaths from dog-mediated rabies by 2030, after the concept of effective One Health interventions.<sup>2</sup> Mass dog vaccination is expected to be an important part of any successful strategy.<sup>3,4</sup> In *The Lancet Infectious Diseases*, the WHO Rabies Modelling Consortium<sup>5</sup> reminds us that effective and timely post-exposure prophylaxis, administered to humans bitten by rabid dogs to prevent the fatal onset of rabies, is another essential tool for success.<sup>5</sup> Through the analysis of a wide range of data collected in multiple countries and the use of multilayer mathematical models, the authors show that increased investment in post-exposure prophylaxis by Gavi, the Vaccine Alliance, would be extremely cost-effective and could substantially reduce disease burden. The study is particularly timely because Gavi is currently reconsidering rabies vaccine investment.

Preparation of such assessment required the Consortium<sup>5</sup> to overcome several major challenges. First, any assessment of post-exposure prophylaxis needs to account for a very diverse set of factors.<sup>6</sup> For example, it must be based on a good understanding of dog populations, how they are structured, how they interact with humans, how they can be affected by the spread of rabies, and how that spread might be mitigated by dog vaccination.<sup>7</sup> Furthermore, the likelihood that a bitten person will seek, obtain access to, and complete post-exposure prophylaxis treatment depends on cultural, economic, geographical, and logistical factors (eg, awareness in the population, accessibility to post-exposure prophylaxis centres, direct and indirect costs, effective stockpiling, and delivery of vaccines). Several of these factors have historically been poorly characterised and might exhibit strong spatial heterogeneities. A major strength of the analysis<sup>5</sup> is that it benefited from tremendous efforts by Gavi to reduce some of these knowledge gaps by supporting rabies field

studies. Consequently, the diversity of data the authors used to build their assessment is quite impressive, both in terms of data type and geographical coverage. A second achievement of the paper is that the authors developed a multidisciplinary modelling framework in which these data could be integrated in a coherent way, making it possible to generate rabies incidence dynamics in dogs and the associated human exposures under various epidemiological scenarios, while also capturing economic, behavioural, and logistical aspects.<sup>5</sup>

The new data and modelling framework therefore constitute an important improvement to past studies; future iterations of the work are likely to lead to additional refinements. Of course, still too many countries have little or no data available, and more field studies targeting these places are needed. Some aspects of the assessment could also be improved further. For example, in some circumstances, free provision alone might be insufficient to increase health-care seeking and accessibility. Indeed, the lack of infrastructure might make it impossible for exposed populations (especially those living in rural remote areas) to travel to clinics and access post-exposure prophylaxis,<sup>8</sup> even if vaccines are freely available. To this regard, further investments are needed to improve the accessibility to post-exposure prophylaxis via point-of-care and decentralised integrated dog bite management centres (IDBCs).<sup>9</sup> The geographical distribution of these IDBCs is a crucial issue in many developing countries and will require important efforts from national authorities.<sup>8</sup> The education of populations to increase awareness and perception of the risks related to dog bite exposure and rabies is another complex issue that is starting to be addressed by stakeholders but should be promoted further.<sup>10</sup>

Hopefully, Gavi and other national and international stakeholders and donors will keep on supporting field studies so that all these aspects can be better

characterised and accounted for in future assessments of rabies control strategies.

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- 1 WHO. Global framework for the elimination of dog-mediated human rabies. [http://www.who.int/rabies/control/Poster\\_Global\\_framework\\_for\\_the\\_elimination\\_of\\_dog-mediated\\_human\\_rabies.pdf](http://www.who.int/rabies/control/Poster_Global_framework_for_the_elimination_of_dog-mediated_human_rabies.pdf) (accessed Oct 26, 2018).

- 2 Cleaveland S, Sharp J, Abela-Ridder B, et al. One Health contributions towards more effective and equitable approaches to health in low- and middle-income countries. *Philos Trans R Soc Lond B Biol Sci* 2017; **372**: 20160168.
- 3 Abela-Ridder B, Knopf L, Martin S, Taylor L, Torres G, De Balogh K. 2016: the beginning of the end of rabies? *Lancet Glob Health* 2016; **4**: e780–81.
- 4 Zinsstag J, Lechenne M, Laager M, et al. Vaccination of dogs in an African city interrupts rabies transmission and reduces human exposure. *Sci Transl Med* 2017; **9**: eaaf6984.
- 5 WHO Rabies Modelling Consortium. The potential impact of provision of rabies postexposure prophylaxis in Gavi-eligible countries: a modelling study. *Lancet Infect Dis* 2018; published online Nov 21. [http://dx.doi.org/10.1016/S1473-3099\(18\)30512-7](http://dx.doi.org/10.1016/S1473-3099(18)30512-7).
- 6 Hampson K, Cleaveland S, Briggs D. Evaluation of cost-effective strategies for rabies post-exposure vaccination in low-income countries. *PLoS Negl Trop Dis* 2011; **5**: e982.
- 7 Lembo T, Hampson K, Kaare MT, et al. The feasibility of canine rabies elimination in Africa: dispelling doubts with data. *PLoS Negl Trop Dis* 2010; **4**: e626.
- 8 Tarantola A, Bianchi S, Cappelle J, et al. Rabies postexposure prophylaxis non-completion after dog bites: estimating the unseen to meet the needs of the underserved. *Am J Epidemiol* 2018; **187**: 306–15.
- 9 Amparo ACB, Jayme SI, Roces MCR, et al. The evaluation of animal bite treatment centers in the Philippines from a patient perspective. *PLoS One* 2018; **13**: e0200873.
- 10 Hasanov E, Zeynalova S, Geleishvili M, et al. Assessing the impact of public education on a preventable zoonotic disease: rabies. *Epidemiol Infect* 2018; **146**: 227–35.

## Knowledge advances and gaps on the demand side of vaccination



Vaccination is one of the most successful and cost-effective interventions for preventing and controlling infectious diseases. In addition to providing direct protection for vaccinated individuals, vaccination also induces indirect protection for the community by slowing transmission of diseases.<sup>1</sup> This effect, in turn, reduces the risk of infection among susceptible individuals and helps to prevent disease outbreaks. However, the success of vaccines depends on high levels of vaccination uptake. Supply-side factors, such as inadequate access to vaccines, remain important contributors to suboptimal vaccination uptake.<sup>2</sup> But, ensuring that individuals decide to take-up available vaccines is an additional challenge. Several studies have shown that increased numbers of individuals globally are questioning vaccines, seeking alternative vaccination schedules, and deciding to delay or refuse vaccination.<sup>3</sup>

Encouragingly, there is growing international focus on the demand side of vaccination. Various international working groups have been established in this regard—one on vaccine hesitancy within WHO,<sup>4</sup> one on vaccine

confidence within the US National Vaccines Advisory Committee,<sup>5</sup> and one on vaccine demand under the leadership of UNICEF.<sup>6</sup> The 2017 Assessment Report of the Global Vaccine Action Plan also recommended that all countries develop strategies to increase acceptance and demand for vaccination.<sup>2</sup> Furthermore, academic publications examining the scope and drivers of vaccine demand have increased substantially over the past decade,<sup>3</sup> together with the number of systematic reviews synthesising this evidence (appendix).

As an emerging focus and field of research, it is timely to reflect on the knowledge advances that have been made and the current gaps requiring attention going forward. A first major development has been the depolarisation of individuals as either anti-vaccines or pro-vaccines. Research in this area has shed light on the porous continuum of vaccine attitudes and behaviours, thus challenging previous perspectives of a simple dichotomy between vaccine acceptance and rejection. Various terms have been developed to capture this spectrum: hesitancy, confidence, trust, acceptance, demand, and uptake. However, there is

See Online for appendix