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Reply to ‘Alternative abridged preventive regimens against rabies for children in high endemic countries’

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In our paper we conclude that “PrEP is very costly and should only be considered when exposure incidence is extremely high.” Our conclusion was on the basis of a case study in Chad and a simulation study. For the Chad study, we used the schedules currently recommended in this country. Implementing PrEP in this case was tremendously costly relative to other interventions to prevent rabies deaths. Affordability of routine PrEP in addition to feasibility is an important consideration for rabies-endemic countries that face other health challenges. In our simulation, we take a broader look at the conditions that might support routine PrEP. Here we model the relative cost of PrEP vs PEP per course; this approach is therefore agnostic to the precise schedule used and spans all the regimens highlighted in the corresponding letter, including RIG as part of PEP in vaccine-naive patients and dose-sparing ID regimens for both PrEP and PEP (e.g. the 2-visit PrEP and 1-visit PEP booster). Nonetheless, we find that in most cases, where RIG is not used, it is highly unlikely routine PrEP would be cost-effective in comparison to PEP only. This is not to say that PrEP is not effective, rather that the number of children who would receive routine PrEP is enormous relative to those bitten and in need of PEP.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Caroline Trotter reports consulting payments from GSK in 2018 and an honorarium from Sanofi-Pasteur in 2015 on unrelated topics. Jakob Zinsstag, Rolande Mindekem and Monique Léchenne were funded by a grant from the 2015 Gavi Learning Agenda.

Cost-effectiveness of PrEP improves as bite incidence increases, supporting our conclusion that PrEP could be considered when exposure incidence is extremely high. The letter suggests that we run our model in Cambodia. Indeed, this example is to our knowledge the highest reported incidence of dog bites (not all of which will be from rabid animals of course) in the published literature [1]. The study authors propose that “adapted control policies for prevention education, canine population control and [canine] vaccination are urgently needed” rather than routine PrEP for children [1]. A recent analysis from the Philippines confirmed that bite incidence would have to be much higher than any published estimate (and moreover, that a very high proportion - 30–40%- of bites would need to be from rabid animals) for a universal PrEP + PEP program to be cost-effective [2]. We are confident that our conclusions are broadly valid, but recognise that models informed by local epidemiology could help in assessing the relative effectiveness and cost-effectiveness of routine PrEP compared to other interventions, particularly when exposure is high and those at risk cannot access timely PEP, e.g. remote Amazonian communities subject to vampire bat rabies outbreaks [3].

Pragmatic PrEP and PEP regimens requiring fewer clinic visits (ideally single dose) have valuable potential for human rabies prevention. But, randomized controlled trials (RCTs) to inform their adoption raise ethical difficulties given that rabies is 100% lethal and validated, highly effective interventions (PEP) exist. In the absence of RCTs, evidence of survival in PEP non-completers can inform on the efficacy of reduced dose regimens, for example, through the accumulation of well-documented case histories within a standardized database [4]. A consequential consideration is whether PrEP programmes might compromise PEP availability. A PrEP programme in the Philippines ended after four years because increased rabies exposures led to a vaccine shortage; priority was therefore given to the immunization of people involved in canine vaccination campaigns [3]. In many Low- and Middle-Income Countries PEP shortages remain chronic with deaths occurring as a direct result [5]. We emphasize that adequate PEP access at national and regional levels be prioritized over routine PrEP. Debate on PrEP and PEP regimens should be tempered as mass dog vaccinations are scaled up, together with education and awareness campaigns as we strive for the ‘Zero by 30’ goal. Elimination of dog-mediated rabies equitably alleviates risk irrespective of healthcare access, unlike PrEP and PEP, which until Universal Health Care is achieved, inevitably leave the most marginalized behind.

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