Comparison of PEP vaccination regimens including the proposed 4-site ID regimen reduced to a schedule with 3 clinic visits

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Our study provides a framework for evaluating the cost-effectiveness of different regimens and the expected vial use of those regimens in different throughput clinics from the perspective of health providers and bite victims in order to inform policy decisions. Assuming the 4-site regimen can be effectively delivered from 3 rather than 4 clinic visits (i.e. d0: 4 x 0.1mL injections or a single 0.5mL vial divided between 4 sites, d7: 2 x 0.1mL injections, d28: 1 x 0.1mL injection) as proposed in ref. 36 means that the 4-site regimen would use less vaccine and become more cost-effective.

We therefore calculated the cost-effectiveness per rabies death averted for the 3-visit 4-site regimen using the parameter values and methods described in the main text (i.e. based on the costs described in Table 2, and the probability of 0.19 that rabies-exposed bite victims develop rabies in the absence of PEP as per ref 19). Here we compare the cost-effectiveness of the proposed 3-visit 4-site regimen with other regimens in Figure 1, but note that absolute cost-effectiveness varies with locale-specific costs. A more intuitive comparison for health practitioners is vial use (thus relative costs to health care providers). Vial use for the 3-visit schedule of the 4-site ID regimen is compared to other PEP vaccination regimens in Figure 2 and a comparison of the different regimens in terms of their cost to patients is also presented in Table 1.

These analyses imply that evaluation of the 4-site ID regimen using a 3-visit schedule is warranted by WHO, as this could be highly cost-effective for health practitioners and would reduce both indirect (travel and accommodation) and direct (PEP) costs for bite victims. In particular, curtailing the schedule to just 3 visits means that fewer vials would be opened and discarded in lower throughput clinics resulting in greater savings.

As per WHO requirements, clinical data from the administration of the 3-visit schedule for the 4-site regimen would need to be evaluated by WHO in order to include this regimen in their recommendations for its future use. These analyses suggest that clinical trials for this should be a research priority for effective translation to policy.

Table 1. Costs of different PEP vaccination regimens from the perspective of the bite-victim (with vaccination provided free-of-charge, or according to different pricing strategies). The most affordable regimens are highlighted for each strategy. We assume that for each clinic visit patients pay a consultation fee (equivalent to the price of overhead for a clinic visit) and the costs of materials for injections (Table 2, main text).

Regimen	Travel costs only (USD$):		$2.5 per injection:		$3 per injection:		$15 full course:		$10 for 1st and 2nd visits:	
	Near[1]	Far[2]	Near[1]	Far[2]	Near[1]	Far[2]	Near[1]	Far[2]	Near[1]	Far[2]
Updated TRC ID	11.6	56	34.4	78.8	38.4	82.8	29.4**	73.8**	34.4	78.8
4-site ID	11.6	56	34.4	78.8	38.4	82.8	29.4**	73.8**	34.4	78.8
3 visit, 4-site ID	8.7	42	28.4	61.7	31.9	65.2	25.9**	59.2**	30.9	64.2
1-week ID	8.7	42	41.4	74.7	47.4	80.7	26.4**	59.7**	31.4**	64.7**
Essen 4-dose*	11.6	56	54*	98.4*	54*	98.4*	54*	98.4*	54*	98.4*
Zagreb*	8.7	42	50.6*	83.9*	50.6*	83.9*	50.6*	83.9*	50.6*	83.9*

*For all IM regimens, we assume patients pay $10/vial when vaccination is not provided free of charge (Table 2, main text).

[1]High indirect costs are assumed to be $14/visit (worst case scenario in Table 2, main text), which corresponds to patients from rural areas, that have to travel long-distances to a hospital and may need to stay overnight whilst seeking PEP.

[2]Low indirect costs are assumed to be $2.9/visit (best case scenario in Table 2, main text), corresponding to patients from urban areas that only need to travel relatively short distances to obtain PEP.

** When using 0.5mL vials charging $15 for a full course does not recuperate costs for any ID regimen and charging $10 for each of the first two clinic visits does not recuperate costs for the 1-week ID regimen (see figure 3, main text).

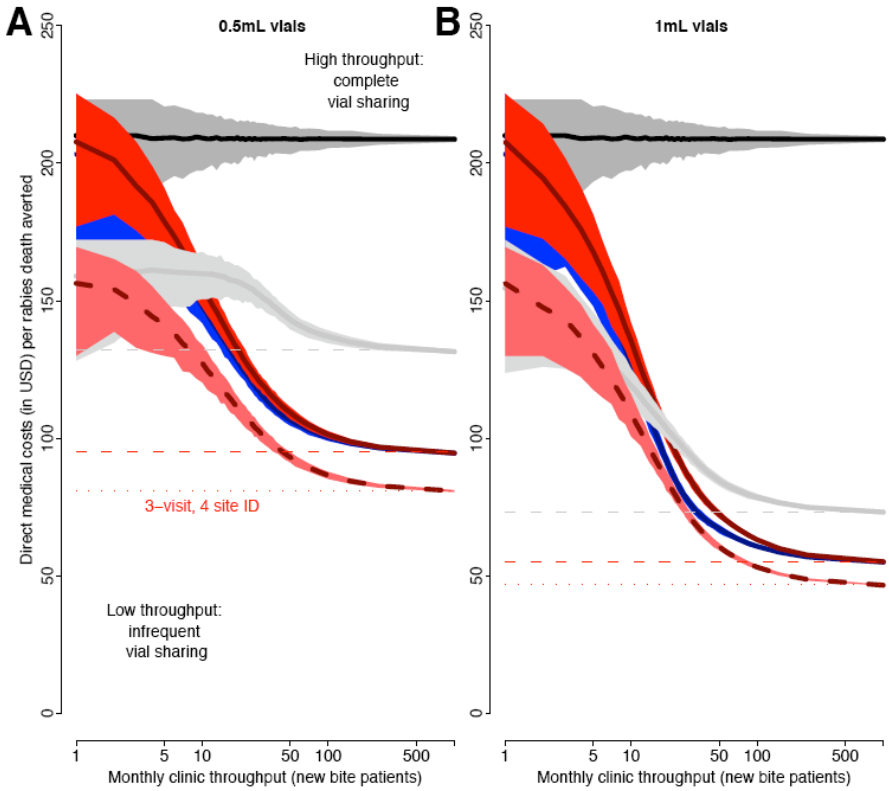

Figure 1. Cost of vaccination per rabies death averted for different PEP regimens according to clinic throughput, illustrating the cost-effectiveness of the proposed 3-visit 4-site ID regimen. Costs for IM administered vaccinations (the Zagreb regimen and the Essen 4-dose regimen are equivalent and shown in black) and ID administered vaccinations (the updated TRC regimen in blue, the 4-visit 4-site in red and 3-visit 4-site in light red shading with the dashed line, and the 1-week in grey) per rabies death averted is plotted against clinic throughput (new animal bite patients presenting for PEP each month). Shading represents 99% confidence intervals resulting from variation in patient arrival dates and the effects on vial sharing. Dashed and dotted lines highlight optimal vaccine use in high throughput clinics. Panel A is based on 0.5 mL vials and panel B on 1 mL vials. Here, we assume that vaccine is perfectly delivered without any wastage (5 complete 0.1 mL injections from a 0.5 mL vial, and 10 complete 0.1 mL injections from a 1 mL vial). Minor reductions in efficiency occur assuming some wastage (notably that a single vial is used on d0 for the 4-site ID schedules) and these are illustrated in Figure 2 showing vial use under this assumption.

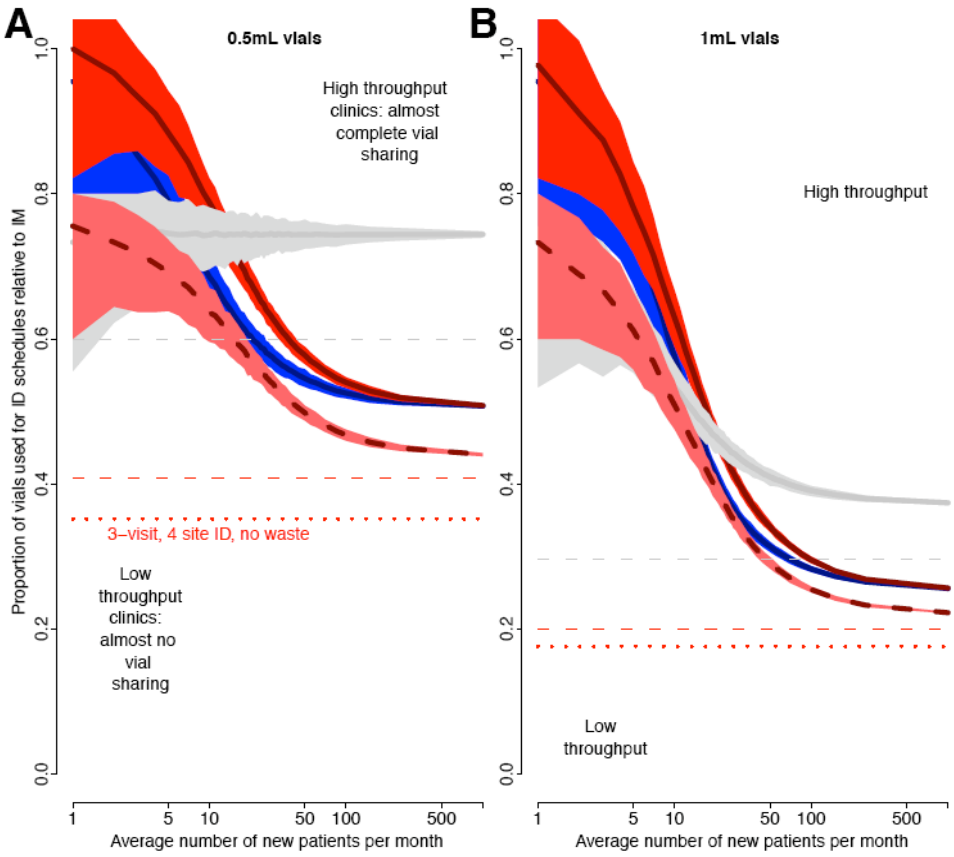

Figure 2: Vial use for ID versus IM (4-dose Essen or Zagreb) administration of PEP according to different patient throughputs and assuming imperfect use (4 x 0.1mL injections from a 0.5mL vial, and 8 x 0.1mL injections from a 1mL vial). Vials use for ID administered PEP (updated TRC ID regimen in blue, 4-visit 4-site ID in red with a solid line and 3-visit 4-site ID in light red with a dashed line, 1-week ID in grey) is plotted as a proportion of vial use under IM regimens against average monthly incidence of newly exposed bite victims. Shading represents 99% confidence intervals resulting from variation in patient arrival dates and the effects on vial sharing. Dashed and dotted lines highlight optimal vaccine use in high throughput clinics assuming no waste. Panel A is based on 0.5mL vials and panel B on 1mL vials. Here, we assume that 4 injections of 0.1mL are obtained from each 0.5mL vial and 8 injections of 0.1mL are obtained from 1mL vials. Note the x-axis is plotted on a log scale.