Rabies vaccination strategies in the Netherlands in 2018: a cost evaluation

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Background: The risk of contracting rabies is low for travellers. However, the number of Dutch travellers potentially exposed abroad following an animal-associated injury and needing post-exposure prophylaxis (PEP) has increased, resulting in increased costs. Aim: Here, we evaluated the costs and the cost-effectiveness of different pre- and post-exposure interventions in the Netherlands, taking into account the 2018 World Health Organization (WHO) recommendations for the prevention of rabies. Methods: A decision tree-based economic model was constructed. We calculated and compared the cost of different WHO pre-exposure prophylaxis (PrEP) recommendations, intramuscular vs intradermal vaccination and PEP subsequent to increased vaccination coverage in risk groups. We estimated cost-effectiveness, expressed as incremental costs per rabies immunoglobulin (RIG) administration averted, using a societal perspective. Statistical uncertainty regarding number of travellers and vaccination coverage was assessed. Results: Total costs at the national level were highest using previous WHO recommendations from 2012, estimated at EUR 15.4 million annually. Intradermal vaccinations in combination with the current recommendations led to the lowest costs, estimated at EUR 10.3 million. Higher vaccination uptake resulted in higher overall costs. The incremental costs per RIG administration averted varied from EUR 21,300-46,800. Conclusions: The change in rabies PrEP and PEP recommendations in 2018 reduced total costs. Strategies with increased pre-travel vaccination uptake led to fewer RIG administrations and fewer vaccinations after exposure but also to higher total costs. Although larger scale intradermal administration of rabies vaccine can reduce total costs of PrEP and can positively influence vaccination uptake, it remains a costly intervention.

Introduction

Rabies is a preventable infectious zoonotic disease that is responsible for annually roughly 59,000 deaths worldwide [1]. The majority of human rabies cases result from dog bites and following the onset of clinical symptoms, the disease is almost always fatal [2]. While rabies control heavily depends on prevention of rabies in dogs, vaccination of humans is an effective preventive intervention, either before or after exposure to the rabies virus [3,4]. Rabies vaccines are highly effective, safe and well tolerated [5]. For most travellers, the risk of contracting rabies is very low [6,7]. If organised access to medical care is available while travelling, including access to immediate care and rabies immunoglobulin (RIG), travellers may choose not to have pre-exposure vaccination (pr-exposure prophylaxis (PrEP)) [3]. Pre-travel immunisation is expensive and often not covered by health insurance.

An increasing number of Dutch travellers are potentially exposed to rabies virus abroad after an animal-associated incident (AAI) and consult a doctor for post-exposure prophylaxis (PEP) either abroad or after returning home. The National Institute for Public Health and the Environment (RIVM) receives on a daily basis requests for consultations by municipal health services, general practitioners, hospital specialists and medical repatriation organisations about potential rabies exposure accidents among Dutch travellers abroad or after returning home. The number of consultations increased from 184 in 2008 to 350 in 2014 and 450 in 2018 [8]. Consequently, the overall costs for seeking and receiving medical treatment after an AAI has increased.

According to the World Health Organization (WHO) classification, an AAI with potential exposure to rabies virus is defined as a category II or category III injury. A category II injury consists of nibbling of uncovered skin, minor scratches or abrasions without bleeding, while a category III consists of transdermal bites or
scratches, contamination of mucous membrane or broken skin with saliva from animal licks. Depending on the category of exposure, PEP consists of extensive wound washing, administration of a series of rabies vaccines (RV) and RIG [2]. The RV administration varies in time-schedule (Essen vs Zagreb regimen) and injection technique (intradermal (ID) vs intramuscular (IM)). In this study, we considered the IM RV administration of 1 mL vaccine according to the Essen regimen, as the gold standard because that is the recommended regimen in the Netherlands. In the Netherlands, two vaccines are available: Rabipur produced by Glaxo Smith Kline (Marburg, Germany) and Rabies Mérieux produced by Sanofi Pasteur (Lyon, France). In case of a PrEP-naïve individual, not previously immunised but otherwise healthy, both exposure categories need the administration of RV. In case of a category III exposure, RIG is needed in addition. In case PrEP was previously given, only a short series of RV needs to be administered (Table 1). RIG is an expensive and globally scarce product that ideally should be used for those most at risk, which is the local population in endemic countries. Furthermore, an AAI needs a careful and often time-consuming assessment. These assessments frequently take place in stressful circumstances, as PEP needs to be started as soon as possible, preferably within 24 h after the AAI [9].

The current WHO recommendations on PEP treatment were presented in 2018 and differed from the previous recommendations mainly on two points: Firstly, the number of needed vaccination doses was lowered by one dose for both PrEP and PEP. Secondly, the dose of RIG was based on the anatomical localisation of the affected area instead of the body weight of the individual [10]. Maximum infiltration of RIG into and around the wound is effective but the benefit from additional infiltration is limited [2,11,12]. The amount of administered RIG is therefore in almost all cases based on the size of the wound. Only the maximum dose of RIG is still assessed by body weight. Since the introduction of the current recommendations, the amount of RIG is estimated to be on average 40% of the quantity that was previously required based on body weight [9,10]. Hence, the 2018 WHO rabies recommendations are expected to have a positive effect on the costs of rabies prevention for the individual traveller and at national level. A schematic overview of the main differences between the 2018 guidelines and those in place before 2018 is given in Table 2.

In the WHO recommendations, rabies vaccinations can be administered either IM or ID. One ID dose is 0.1 mL of vaccine, leading to an immune response comparable with IM administration but at a considerably lower dose, thus saving vaccine and costs [9,13]. A disadvantage is that vaccination staff must be well trained to guarantee full ID instillation of the vaccine and to avoid accidental subcutaneous injection. In the Netherlands, ID administration is used off-label and only practiced for PrEP in a few vaccination centres; a two-site ID vaccination is given twice. Therefore, in this study, ID administration of the vaccine is only considered for PrEP rather than as outlined in the former or current recommendations.

The current WHO recommendations for rabies PrEP and PEP, as implemented in the Netherlands, are expected to have a positive effect on the costs of rabies prevention for the individual traveller and at national level. The ID vaccination can also contribute to cost reduction. In the Netherlands, several studies have focused on clinical outcomes or on the effect of risk behaviour of Dutch travellers on the number of AAI [14,15]. However, to our knowledge, an economic study investigating the possible cost reduction of different rabies prevention approaches is lacking. This study aims to assess the costs and the cost-effectiveness of different preventive interventions for rabies, by systematically comparing different strategies: (i) cost-effectiveness reached with the implementation of the 2018 WHO recommendations, compared with the recommendations before 2018, (ii) costs of ID vs IM vaccination and (iii) cost-effectiveness of an increase in PrEP in Dutch travellers in order to avoid extensive PEP regimens.

**Methods**

We investigated costs of several policy measures for rabies in the Netherlands using a decision tree-based economic model programmed in MS Excel 2010. With this model, costs of different prevention strategies, including their effect on subsequent post-exposure treatment can be calculated and compared per risk group (see chapter Assessment of risk groups), both at

| Category of exposure | PrEP | PEP |
|----------------------|------|-----|
| Category I (intact skin) | None | None |
| Category II (minor scratches or abrasions without bleeding) | Yes, 2 × RV (day 0, 3) | No, 4 × RV (day 0, 3, 7, 14–28) |
| Category III (broken skin; contamination of mucous membrane with saliva) | Yes, 2 × RV (day 0, 3) | No, 4 × RV (day 0, 3, 7, 14–28) + RIG (day 0) |

PEP: post-exposure prophylaxis; PrEP: pre-exposure prophylaxis; RIG: rabies immunoglobulin; RV: rabies vaccination.

Source: [9,10].

**Table 1**

Post-exposure prophylaxis scheme for rabies, the Netherlands, 2018
national level and per person vaccinated before travelling. Two time points were included in the model: before travelling at the travel clinic when a risk assessment is made, and after an AAI when PEP is considered.

Firstly, we assessed the economic impact of the 2018 PrEP recommendations vs former recommendations, both with IM administration of the vaccine. Secondly, we compared ID vs IM administration of PrEP (two-dose administrations). Thirdly, we analysed the effects of a 1.5-fold increase in the uptake of PrEP in risk groups, using IM administration (two applications). We assumed that the increased vaccination uptake would happen because of revised recommendations and only within the traveller population who obtained a medical consultation at Municipal Health Services (MHS), general practitioners (GPs) or another travel clinic before their journey. No additional campaigns to increase the number of travellers requesting a medical consultation before their journey were assumed, hence no additional campaign costs for the MHS and GPs were included.

PEP with vaccinations is indicated for category II exposures, according to WHO recommendations (Table 1). PEP is indicated with vaccine and, for those without PrEP, with administration of RIG for category III exposures (Table 1). We estimated cost differences between the former and current vaccination policies following recommendations of WHO including differences in the amount of RIG. In addition, we calculated cost implications when implementing ID administration of rabies vaccine using the current vaccination policy with two doses as comparator strategy. We present costs of PrEP for several risk groups of travellers (see chapter Assessment of risk groups), both at national level and per vaccinated person. The benefit of higher pre-travel vaccination coverage among risk groups is the reduced use of RIG and a less extensive vaccination scheme after possible exposure. We calculated the incremental costs per (extra) vaccinated person and incremental costs per RIG application averted as an indication of the cost-effectiveness of the prevention strategy. A time horizon of 1 year was considered. The economic model was employed from a societal perspective, including healthcare costs, costs of lost holidays and an impact on evacuation and repatriation of those travellers possibly exposed, costs that would have to be covered by the patients themselves, their travel insurance and/or their health insurance.

### Assessment of risk groups

In 2017, a case–control study was conducted among Dutch travellers to rabies-endemic countries in which the various determinants of possible exposure to rabies virus were investigated [14]. The following risk groups were identified that would be eligible for more intensive rabies prevention: (i) men, (ii) travellers younger than 35 years and (iii) travellers to south-eastern and western Asia as these groups had a higher risk of a rabies-associated incident during travel. In addition, we added (iv) travellers to South America to this list as in South America little or no RIG is available for travellers in case of AAI so that repatriation or evacuation of unvaccinated patients with a category III wound is required [16].

### Pre-travel consultations

In the Netherlands, the decision whether rabies vaccinations are indicated before and/or after an AAI and the actual administration of the vaccinations are provided by MHS, GP services, some hospital’s outpatient clinics and some commercial vaccination centres. The decision-making is based on travel destinations, travel duration, accommodations and activities during travel and on personal conditions including vaccination history. For our model, we used data from travellers consulting the MHS Hart voor Brabant and MHS Amsterdam between 1 July 2016 and 1 July 2017 (for details see Supplement).

### Travellers needing post-exposure prophylaxis

The estimated annual number of people who presented to a healthcare provider because of an AAI while travelling is provided in Table 3. The number of RIG administrations that were actually indicated, and provided once returned to the Netherlands, was based on the registration of RIG therapies by the RIVM in 2017. For the number of administered RIG abroad while travelling, figures from Eurocross Assistance (ECA) were used (see Supplement). We extrapolated the mean number of RIG administrations abroad (n = 64) in the ECA database between 2016 and 2018 to all travellers needing RIG abroad, taking into account the market share of ECA (30%, total n = 213). For incidents where RIG was not indicated, registration data from all Dutch MHS were used. ECA also provided the number of incidents requiring only two vaccinations abroad (for travellers with PrEP). This figure was also extrapolated to the Netherlands. To prevent double counting, travellers from the ECA registry needing PEP who started their

| Rabies vaccination | Current recommendations | Former recommendations |
|--------------------|-------------------------|-------------------------|
| PrEP               | 2 doses                 | 3 doses                 |
| PEP (not previously immunised) | 4 doses | 5 doses |
| PEP (previously immunised people) | 2 doses | 2 doses |
| RIG                | 2–10 mL with a maximum based on body weight | 20/40 IU/kg |

IU: international units; PEP: post-exposure prophylaxis; PrEP: pre-exposure prophylaxis; RIG: rabies immunoglobulin.
The annual number of people possibly exposed to rabies virus, the Netherlands, 2016–2018 (n = 1,400)

| Type of PEP | n  | PreP | Percentages |
|------------|----|------|-------------|
| Category III injury needing RIG and full series of vaccinations | 413 | No | 29.5% |
| Category III injury, no RIG indication, full series of vaccinations | 540 | No | 38.6% |
| Category III injury needing two vaccinations | 285 | Yes | 20.3% |
| Category II injury needing full series of vaccinations | 125 | No | 8.9% |
| Category II injury needing two vaccinations | 37 | Yes | 2.7% |
| Total | 1,400 | NA | 100% |

NA: not applicable; PEP: post-exposure prophylaxis; PrEP: pre-exposure prophylaxis; RIG: rabies immunoglobulin.

17 days after start of PEP vaccination series RIG is not indicated anymore and according to Dutch guidelines, RIG is not indicated for injuries inflicted by monkeys.

regimen abroad with a full series of four vaccinations but further completed their vaccinations at MHS in the Netherlands were not taken into account.

Costs
Estimated costs were determined for both PrEP and PEP courses, including costs for the vaccine and RIG, administration costs, management costs for handling PEP, costs of lost holidays and costs involved in moving the involved subjects from one facility to another in case the required treatment needed was not available (Table 4). For the administration of RIG some cases needed repatriation to the Netherlands, other cases needed evacuation to another country abroad, for example to a neighbouring country. Hospitalisation costs were not included as an AAI generally does not lead to further treatment and care in a hospital. All costs were indexed to Euros 2017 using Dutch consumer price indexes (www.cbs.nl). Detailed information about costs is provided in the Supplement.

Cost-effectiveness
We calculated the incremental cost-effectiveness ratio (ICER) per (extra) person vaccinated before travelling and the ICER per RIG administration averted as an indication of the cost-effectiveness of the prevention strategy. That means that we divided the difference in total costs by the difference in persons vaccinated before travelling and we divided the difference in total costs by the difference in RIG administrations.

Sensitivity analysis
Statistical uncertainty with respect to the number of travellers to certain regions and to vaccination coverage estimates was considered using the Monte Carlo simulation technique and the add-in software Palisade @Risk 7.5 in which we sampled 10,000 random values from input distributions. All other variables were considered fixed by using average resource utilisation and fixed unit cost prices. Results are presented as means with 95% uncertainty intervals.

Results
Table 5 shows the costs of PrEP and PEP according to the former and current recommendations, and if vaccinations would be administered ID. In all these situations, we considered the current vaccination uptake in combination with the existing number of rabies-associated incidents. The number of visitors to a vaccination centre before travel to a rabies-endemic country was 353,100, of whom 37,300 persons were vaccinated during the visit. Among vaccinated travellers, the number of AAI was 322. Among the 1,078 unvaccinated travellers having an AAI, 665 persons did not receive RIG because of (i) a category II injury, (ii) a category III injury where it was too late for the RIG administration for instance because RIG was not available (RIG has to be given within 7 days after start of PEP vaccination series) or (iii) a category III injury inflicted by monkeys.

Among 953 unvaccinated travellers having an AAI with a category III injury, 413 persons received RIG. Costs were highest following the former recommendations, estimated at EUR 15.4 million annually for the Dutch society (EUR 411 per vaccinated person). Overall costs were lowest when ID vaccinations were administered, estimated at EUR 10.3 million per year (EUR 275 per vaccinated person). Of all persons needing RIG, 9.5% had repatriation costs and 7.4% had evacuation costs.

Results of increasing the vaccination coverage with 150% in the identified risk groups are presented in Table 6 and Table S3 in the Supplement. The largest risk group were people younger than 35 years, followed by people travelling to south-eastern and western Asia. In all risk groups, a higher vaccination uptake led to higher overall costs, despite a decline in management and vaccination costs of possible rabies exposure incidents, and avoided annually between 4 and 60 cases requiring RIG. The costs per averted RIG administration varied from EUR 21,300 to EUR 46,800. The ICER per additional person vaccinated before travelling varied between EUR 98 and EUR 105 per additional vaccinated person. This is also illustrated in Supplementary Figures S1 and S2.

Discussion
This cost evaluation showed that the current WHO rabies PrEP and PEP recommendations, as implemented in 2018 in the Netherlands, were associated with a substantial reduction (16%) in societal costs. An additional cost reduction (33%) could be achieved by offering ID vaccination on a large(r) scale.

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The use of ID administration requires proper planning of the number of travellers who need a rabies vaccination in order to avoid wasting vaccine. Therefore, ID administration would not lead to vaccine savings if there are only a few cases. A hypothetical increased vaccination uptake in the defined risk groups would lead to higher overall costs, despite the smaller number of RIG administrations and a reduced number of vaccinations after an AAI. Even though the costs of RIG administration according to the new recommendations were lower (currently EUR 800 instead of the former EUR 2,000 in the Netherlands), total costs were higher because of higher costs of PrEP when assuming a higher number of travellers vaccinated before travelling. As the incidence of AAI in travellers to endemic countries is low, increasing the vaccination uptake is a costly intervention with an ICER varying from EUR 21,300 to EUR 46,800 per avoided RIG administration. These results are not only relevant for the Netherlands but also for other European countries with a similar healthcare system. The risks of contracting rabies are comparable for travellers from other countries and the costs of preventing rabies will also be similar.

Our results are in line with a previous modelling study by Hampson et al. [17]. In that study, WHO recommendations for use of human rabies vaccines were modelled to inform prophylaxis regimens to prevent human rabies. The ID vaccination regimen was recommended as it is less costly and treats more patients when vaccine is in short supply. In a cost evaluation of Le Guerrier et al. it was found that PrEP given routinely to Canadian travellers heading for rabies-endemic regions was far too costly and therefore not indicated [18], in contrast to people living in endemic countries, where routine PrEP vaccination programmes can be an efficient use of resources [19]. The Strategic Advisory Group of Experts on Immunization (SAGE) committee stated that PrEP, as a large scale public health intervention, is not cost-effective and would have acceptable costs only in areas where RIG is rarely administered and the dog bite incidence exceeds 6% [2]. PrEP can play a valuable role in protecting high-risk populations in remote areas, especially where the risk of bat rabies is not easily controlled [9]. Kessels et al. systematically reviewed cost-effectiveness of national programmes implementing PrEP for high-risk populations in remote settings [20].

This study has several strengths and limitations. One of the strong points was the use of model input data from different MPH and a recently conducted
case–control study. The first limitation concerns the period of data collection, during which the old vaccination recommendations still applied. It is plausible that the vaccination uptake will go up as the number of necessary doses and consequently the costs and efforts for the traveller decrease. Secondly, because of data restrictions, the model contained a time horizon of only 1 year while vaccination offers lifelong immunological memory, thereby underestimating the benefits of improved vaccination coverage, which accumulates with every next trip to a rabies-endemic region. At present, decisions to vaccinate before travelling are typically made on the basis of an individual risk–benefit assessment and individual willingness to pay for the vaccine [21]. If future travel is incorporated into the considerations of risk exposure, the decision regarding vaccination might change. Finally, we did not include in our model costs for medical assistance organisations and costs for increasing the vaccination uptake among risk groups such as campaign costs, thereby underestimating total costs.

PrEP is indicated for individuals who face occupational and/or travel-related exposures to rabies virus in specific settings or over an extended period of time [9]. Many travellers are not aware of the health risks during their travel. Lammert et al. evaluated a large cohort of international travellers who obtained a pre-travel health consultation at clinics in the United States that provide health advice for international travellers [22]. They found that a large part (28%) of travellers who sought pre-travel health advice rejected some of the recommended vaccinations. A lack of concern about the associated illnesses was the most frequently mentioned reason to refuse the vaccines. More specifically, Marano et al. assessed rabies risk perception among individuals who travelled to rabies-endemic countries [23]. Within the subsample of travellers at higher risk for rabies, a large part (83%) was aware of the basic characteristics of rabies. However, only 8% reported receiving PrEP vaccination within the past 3 years. On addition, vaccination costs and a short time period until travel proved to be barriers for rabies vaccination [15]. Therefore, additional effective education about rabies risks seems necessary for high-risk groups.

Other preventive measures to be taken in endemic countries such as One Health approaches have proven (cost-)effective in controlling rabies in different areas of the world [24,25]. For example, an economic evaluation performed in rural India indicated that a combination of a dog vaccination campaign, sterilisation of free-roaming dogs and PEP in humans after dog bites is likely to provide the optimal scenario for cost-effective prevention of human rabies [26]. In Chad, besides mass dog vaccination, improved communication between human health and veterinary workers was imperative to prevent human rabies deaths through the appropriate use of PEP [27]. Also in Tanzania, integrated control programmes proved to be cost-effective [28]. In the first place, these measures contribute to protection of the local population and have also positive externalities (are beneficial) for (international) travellers.

There is some evidence that vaccination schemes can be further simplified, as Jonker and Visser found promising results that vaccinating with a single dose was already sufficient to induce an adequate anamnestic antibody response in all subjects, at least for 1 year [29]. However, a single PrEP vaccination is only viable if additional scientific evidence on efficacy of this reduced PrEP scheme becomes available. In Europe, rabies is a very rare infectious disease and it is almost always associated with travel to an endemic country [30]. It remains important to inform the public, especially those travelling to endemic areas, about the risk of contracting rabies and to consider PrEP for those with increased risk. This study revealed that

| Table 5 |
|---|
| Annual costs of rabies PrEP and PEP using different regimens, assuming no change in vaccination uptake, the Netherlands, 2018 |
| | Former recommendations IM | Current recommendations IM | ID |
| National costs for prevention (before travel) in EUR | | | |
| Consultation | 7,050,700 | 6,807,800 | 6,807,800 |
| Vaccination | 5,878,700 | 3,927,200 | 1,353,100 |
| Total (before travel) | 12,929,400 | 10,735,000 | 8,160,900 |
| National costs for prevention after an AAI in EUR | | | |
| Vaccinations and RIG | 1,401,300 | 1,086,400 | 1,086,400 |
| Consultation and coordination | 480,900 | 480,900 | 480,900 |
| Repatriation | 64,800 | 64,800 | 64,800 |
| Evacuation | 56,400 | 56,400 | 56,400 |
| Lost holidays | 423,000 | 423,000 | 423,000 |
| Total (after potential exposure) in EUR | 2,426,400 | 2,111,500 | 2,111,500 |
| Grand total (national costs) in EUR | 15,355,800 | 12,846,500 | 10,272,400 |
| Costs in EUR per person vaccinated before travel | 411 | 336 | 275 |

ID: intradermal administration; IM: intramuscular administration; PEP: post-exposure prophylaxis; PrEP: pre-exposure prophylaxis; RIG: rabies immunoglobulin.
The table presents averages with 95% UI. Note that in Table 4 total costs per vaccinated persons are presented, whereas in Table 5 the incremental costs per additional vaccinated person are presented, and they are therefore not comparable. For full details see Supplementary Table S3.

## Table 6
Costs, RIG administrations and ICER as a result of a 1.5-fold increased rabies vaccination uptake for diverse risk groups, the Netherlands, 2018

| Risk group | Travellers <35 years | Travellers to south-eastern and western Asia | Men | Travellers to South America | Travellers having at least one risk factor | Travellers having all risk factors together |
|------------|---------------------|------------------------------------------|-----|-----------------------------|------------------------------------------|------------------------------------------|
| Additional vaccinated persons | 11,970 | 9,800 | 8,570 | 1,800 | 17,290 | 3,410 |
| 95% UI | 2,850–22,100 | 1,880–18,530 | 1,280–16,540 | −3,280–6,730b | 51,60–31,160 | −1,750–8,810b |
| Avoided number of RIG administrations | 45 | 41 | 29 | 4 | 60 | 16 |
| Additional costs | 1,206,000 | 966,400 | 867,100 | 188,900 | 1,755,100 | 333,100 |
| 95% UI | 226,000–2,413,900 | 421,000–2,290,000 | 77,400–1,819,800 | −391,900–765,300b | 482,700–3,341,000 | −260,600–941,800b |
| ICER: Incremental costs per additional vaccinated person | 101 | 99 | 101 | 105 | 102 | 98 |
| 95% UI | 82–116 | 71–116 | 0.75–118.0 | 71–151 | 88–116 | 26–181 |
| ICER: Incremental costs per avoided RIG administration | 26,970 | 23,760 | 30,370 | 46,750 | 29,220 | 21,320 |
| 95% UI | 9,530–52,460 | 5,790–49,510 | 5,323–64,110 | −129,950–229,830 | 14,250–53,000 | −24,010–70,190b |

ICER: incremental cost-effectiveness ratio; RIG: rabies immunoglobulin; UI: uncertainty interval.

This group consist of men younger than 35 years travelling to south-eastern and western Asia.

b Owing to low numbers in this specific risk group, the UI are not interpretable.

The table presents averages with 95% UI. Note that in Table 4 total costs per vaccinated persons are presented, whereas in Table 5 the incremental costs per additional vaccinated person are presented, and they are therefore not comparable. For full details see Supplementary Table S3.

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Conflict of interest

None declared.

Authors’ contributions

Conceptualisation: AWMS, MJJM, EABO. Data curation and validation: AWMS, MJJM, MRH. Modelling: MJJM, EABO. Writing original draft: AWMS. Writing review and editing: MJJM, MRH, SEB, LGV, CMS, WLMR, FSL. Agree with manuscript results and conclusions: all authors.

References

1. Hampson K, Coudéville L, Lembo T, Sambo M, Kieffer A, Attlan M, et al. Estimating the global burden of endemic canine rabies. PLoS Negl Trop Dis. 2015;9(4):e0003709. https://doi.org/10.1371/journal.pntd.0003709 PMID: 25881058
2. SAGE working group. Background paper: proposed revision of the policy on rabies vaccines and rabies immunoglobulins. Geneva: World Health Organization; 2017. Available from: https://www.who.int/immunization/sage/meetings/2017/october_1_Background_paper_WO_RABIES_final.pdf?ua=1
3. Crowcroft NS, Thampi N. The prevention and management of rabies. BMJ. 2015;350(jan14 26):g7827. https://doi.org/10.1136/bmj.g7827 PMID: 25589091
4. Lankau EW, Cohen NJ, Jentes ES, Adams LE, Bell TR, Blanton JD, et al. Prevention and control of rabies in an age of global travel: a review of travel- and trade-associated rabies events—United States, 1986-2012. Zoonoses Public Health. 2014;61(5):305-16. https://doi.org/10.1111/zph.12071 PMID: 23870674
5. World Health Organization. Rabies vaccines: WHO position paper, April 2018 - Recommendations. Vaccine. 2018;36(37):5500-3. https://doi.org/10.1016/j.vaccine.2018.06.061 PMID: 30107991
6. Steffen R, Behrens RH, Hill DR, Greenaway C, Leder K. Vaccine-preventable travel health risks: what is the evidence--what are the gaps? J Travel Med. 2015;22(1):1-12. https://doi.org/10.1111/jtm.12171 PMID: 25378212
7. Carrara P, Parola P, Brouqui P, Gautret P. Imported human rabies: how do we learn from the past? Clin Infect Dis. 2013;57(5):e2209. https://doi.org/10.1093/cid/cit855
8. Eurocross Assistance. Steeds meer reizigers maken melding van mogelijke besmetting met hondsdoel. (More and more travellers report possible rabies infection). Leiden: Eurocross Assistance; 2018. Dutch. Available from: https://www.eurocross.nl/nieuws/2018/steeds-meer-reizigers-maken-melding-van-mogelijke-besmetting-met-hondsdoel/
9. World Health Organization (WHO). WHO expert consultation on rabies: third report. Geneva: WHO; 2018. Available from: https://apps.who.int/iris/handle/10665/272364
10. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Rabiës richtlijn. [Rabies guideline]. Bilthoven: RIVM. [Accessed: 2 Oct 2019]. Dutch. Available from: https://lci.rivm.nl/richtlijnen/rabies/richtlijn. [Rabies guideline]. Bilthoven: RIVM. [Accessed: 2 Oct 2019]. Dutch. Available from: https://www.who.int/immunization/sage/meetings/2017/october_1_Background_paper_WO_RABIES_final.pdf?ua=1
11. Bharti OK, Madhusudana SN, Gaunta PL, Belludi AY. Local infiltration of rabies immunoglobulins without systemic intramuscular administration: An alternative cost effective
approach for passive immunization against rabies. Hum Vaccin Immunother. 2016;12(3):837-42. https://doi.org/10.1080/21645515.2015.1085142 PMID: 26317441

12. Bhatti OK, Madhusudana SN, Wilde H. Injecting rabies immunoglobulin (RIG) into wounds only: A significant saving of lives and costly RIG. Hum Vaccin Immunother. 2017;13(4):762-5. https://doi.org/10.1080/21645515.2016.1255834 PMID: 28277089

13. Kong LY, Vincellette J, Laplante G, Duchesne JA, Libman M, Barkati S. Intradermal pre-exposure rabies vaccination in a Canadian travel clinic: 6-year retrospective observational study. CMAJ Open. 2016;2(2):E168-75. https://doi.org/10.9778/cmajopen.2016.00098 PMID: 26936332

14. Bantjes S, Haverkate M, Ruis H, van den Hoogen G, Croughs P, Mijtak A, et al. Predictors of possible rabies exposure in travelers: a case-control study. Eur J Public Health. 2018;28(6):942.

15. Wieten RW, Tawil S, van Vugt M, Goorhuis A, Grobusch MP. Risk of rabies exposure among travelers. Neth J Med. 2015;75(3):219-26. PMID: 26067801

16. van Dee L, Dimaandael M, Bantjes S, Haverkate M, van Kessel R. Rabiescasuistiek in de GGD-regio Utrecht. [Rabies in the MHS region Utrecht]. Infectieziekt Bulletin. 2018;29(6). Dutch. Available from: https://magazines.rivm.nl/2018/03/infectieziekt-bulletin/rabies%20casus%20in%20de-ggd-regio-utrecht-o

17. Hampson K, Abela-Ridder B, Bhatti O, Knopf L, Léchenne M, Mindekem R, et al. Modelling to inform prophylaxis regimens to prevent human rabies. Vaccine. 2019;37(Suppl 1):A166-73. https://doi.org/10.1016/j.vaccine.2018.11.071 PMID: 30554795

18. LeGuerrier P, Pilon PA, Deshaies D, Allard R. Pre-exposure prophylaxis for the international traveller: a decision analysis. Vaccine. 1996;14(2):167-76. https://doi.org/10.1016/0264-410X(95)00110-M PMID: 8867415

19. Anothaisintawee T, Julienne Genuino A, Thavorncharoensap M, Youngkong S, Rattanavipapong W, Meeyai A, et al. Prophylaxis. Vaccine. 2019;37(Suppl 1):A146-53. https://doi.org/10.1016/j.vaccine.2018.11.071 PMID: 30554795

20. Kessels JA, Recuenco S, Navarro-Vela AM, Deray R, Vigilato LM, et al. On the path to rabies elimination: The need for risk communication. Travel Med. 2019;26(Suppl 1):S3-9. https://doi.org/10.1093/jtm/tty062 PMID: 30476212

21. Barkati S. Intradermal pre-exposure rabies vaccination in a Canadian travel clinic: 6-year retrospective observational study. CMAJ Open. 2016;2(2):E168-75. https://doi.org/10.9778/cmajopen.2016.00098 PMID: 26936332

22. Lammert SM, Rao SR, Jentes ES, Fairley JK, Erskine S, Walker AT, et al. Refusal of recommended travel-related vaccines among U.S. international travellers in Global TravEpiNet. J Travel Med. 2016;24(4):taw075. https://doi.org/10.1093/jtm/taw075 PMID: 27795502

23. Marano C, Moodley M, Melander E, De Moerloose L, Nothdurft HD. Perceptions of rabies risk: a survey of travellers and travel clinics from Canada, Germany, Sweden and the U.K. J Travel Med. 2019;26(Suppl 1):S3-9. https://doi.org/10.1093/jtm/tay062 PMID: 30476212

24. Cleaveland S, Lankester F, Townsend S, Lembo T, Hampson K. Rabies control and elimination: a test case for One Health. Vet Rec. 2014;175(8):188-93. https://doi.org/10.1136/vr.g4996 PMID: 25172649

25. Rysava K, Miranda ME, Zapatos R, Lapiz S, Rances P, Miranda LM, et al. On the path to rabies elimination: The need for risk assessments to improve administration of post-exposure prophylaxis. Vaccine. 2019;37(Suppl 1):A64-72. https://doi.org/10.1016/j.vaccine.2018.11.066 PMID: 30573356

26. Fitzpatrick MC, Shah HA, Pandey A, Bilinski AM, Kakkar M, Clark AD, et al. One Health approach to cost-effective rabies control in India. Proc Natl Acad Sci USA. 2016;113(5):14574-81. https://doi.org/10.1073/pnas.1604975113 PMID: 27996161

27. Lechenne M, Mindekem R, Madjadinan S, Oussiguiéré E, Moto DD, Naissengar K, et al. The importance of a participatory and integrated one health approach for rabies control: the case of N’Djamena, Chad. Trop Med Infect Dis. 2017;2(3):243. https://doi.org/10.3390/tropicalmed2030043 PMID: 30270900

28. Lankester F, Davis A, Kinughi S, Yoder J, Bunga C, Alkara S, et al. An integrated health delivery platform, targeting soil-transmitted helminths (STH) and canine mediated human rabies, results in cost savings and increased breadth of treatment for STH in remote communities in Tanzania. BMC Public Health. 2019;19(1):1398. https://doi.org/10.1186/s12889-019-7737-6 PMID: 31660915

29. Jonker EF, Visser LG. Single visit rabies pre-exposure priming induces a robust anamnestic antibody response after simulated post-exposure vaccination: results of a dose-finding study. J Travel Med. 2017;24(5). https://doi.org/10.1093/jtm/tax033 PMID: 2893127

30. European Centre for Disease Prevention and Control (ECDC). Rabies – Annual epidemiological report for 2018. Stockholm: ECDC; 2019. Available from: https://www.ecdc.europa.eu/en/publications-data/rabies-annual-epidemiological-report-2018

31. Zorginstituut Nederland. Rabies vaccin merieux flacon 2,5IE + solvens 1ml. [Rabies vaccine merieux vial 2.5IE + solvens 1ML]. Diemen: Zorginstituut Nederland; [Accessed: 18 Sep 2019]. Dutch. Available from: https://www.zorginstituutnederland.nl/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg

32. Gemeenschappelijke Gezondheidsdienst (GGD). Reisvacunaties. Tarieven. [MHS tariffs]. [Accessed: 18 Sep 2019]. Dutch. Available from: https://www.ggdreisvacunaties.nl/tarieven

33. Vaccinatiecentrum. Prijzen vaccinaties en medicatie. [Tropical health advice and vaccination. Prices of vaccines and medications]. [Accessed: 18 Sep 2019]. Dutch. Available from: https://vaccinatiecentrum.nl/index.php/vaccinaties-en-medicatie/prijzen

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