

Institution: University of Glasgow (UofG)		
Unit of Assessment: UoA 6 (Agriculture, Veterinary & Food Sciences)		
Title of case study: Driving change and investment in international policy on rabies post-exposure prophylaxis		
Period when the underpinning research was undertaken: 2011–2018		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
1) Prof. Katie Hampson	1) Professor; Reader; Wellcome Research Fellow	1) 2020-present; 2015–2020; 2008–2015
2) Prof. Sarah Cleaveland	2) Professor	2) 2008–present
Period when the claimed impact occurred: 2017–2020		
Is this case study continued from a case study submitted in 2014? No		
<p>1. Summary of the impact</p> <p>Rabies post-exposure prophylaxis (PEP) is a vital tool for reducing rabies deaths worldwide but access to this life-saving treatment is restricted by a lack of consensus, and thus investment, in appropriate treatment regimens. UofG research has provided epidemiological and cost-effectiveness modelling that underpins changes to World Health Organization (WHO) policy on rabies PEP regimens. The WHO's streamlined policy, together with UofG models of the impact of investment in PEP, were instrumental in the 2018 decision by Gavi, the Vaccine Alliance, to add the rabies PEP to their 2021–2025 investment strategy, supporting access to rabies PEP across 57 developing countries.</p>		
<p>2. Underpinning research</p> <p>UofG is at the forefront of research to eliminate canine rabies. Its internationally recognised researchers and rabies programme have made landmark contributions to understanding rabies transmission and to the development and implementation of rabies-control measures. In regions where rabies is still common, rabies PEP is given to people bitten by suspect dogs within 24 hrs and is essential for preventing the fatal onset of rabies. Several safe and effective regimens for PEP vaccine delivery are recommended by WHO, involving intramuscular (IM) or intradermal (ID) injection, often with multiple doses, but these regimens are inconsistently implemented and there are no clear recommendations about which to use in specific settings. In 2010, a Glasgow research team (Hampson and Cleaveland) developed a framework for comparing the cost-effectiveness of a range of existing and experimental PEP vaccination regimens in urban and rural settings [3.1]. This study showed that PEP is a highly cost-effective intervention in all cases, but that a universal switch from IM to ID delivery would improve the affordability and accessibility of PEP for bite victims [3.1].</p> <p>To put the ongoing need for investment in rabies control into context, UofG research led by Hampson performed a comprehensive estimation of the global burden of endemic rabies [3.2]. This study revised the global human rabies mortality up to 59,000 per year and highlighted the disease's economic burden, which is mainly due to premature death (55%), followed by direct costs of PEP (20%), and lost income whilst seeking PEP (15.5%). In 2017, the WHO commissioned Hampson, in recognition of her earlier study [3.1], to lead a quantitative assessment of the benefits and costs of PEP, pre-exposure prophylaxis (PrEP), and rabies immunoglobulin (RIG) regimens (the 'vaccine model') [3.3]. Using the model defined in [3.1] as a basis, this study modelled a range of IM and ID regimens and concluded that a one-week, two-site ID injection was most cost-effective, using between 25–85% fewer vaccine vials than IM injection owing to the smaller vaccine dose needed [3.3]. PrEP was considered unlikely to be an efficient use of resources. The study was reviewed by the WHO IVIR-AC (its immunization and vaccines related implementation research advisory committee), which evaluates evidence for policy recommendations — the first time rabies PEP had undergone this process.</p> <p>In parallel work, Hampson and Dr Caroline Trotter (University of Cambridge) led the first study to consider the impact of a major investment in rabies PEP by 'Gavi, the Vaccine Alliance' (Gavi)— a public-private global health partnership that aims to increase access to vaccines in developing countries. To support the modelling, the WHO formed the WHO Modelling Consortium, consisting of 47 members and 30 academic and government institutions in 18 countries, led by</p>		

Hampson and Trotter. Hampson and Trotter developed a multidisciplinary modelling framework (the 'impact model') [3.4] to integrate epidemiological and economic burden data generated by the consortium to predict the impact of investment into PEP treatment across 67 Gavi-eligible countries and to model different outcome scenarios [3.4]. These scenarios included the scaling up of mass dog vaccinations and limiting wasteful PEP use by undertaking integrated bite case management—an approach to assessing the rabies status of the biting dog. Of vital importance to the impact model were UoG field studies that assessed how access to PEP can be improved [3.5, 3.6]. One study addressed uncertainty about treatment-seeking behaviour in Tanzania and provided empirical estimates of the risk of death following a rabid dog bite in the absence of PEP or following late or incomplete PEP [3.5]. This vital work provided the first demonstration that even in a very resource-poor country, ID vaccination can be easily adopted by health workers. A second study performed in Madagascar revealed the health improvements that are possible when PEP is provided for free: 84% of rabies-exposed people sought PEP (90% of whom completed), while also reducing vaccine use by 50% through use of an ID regimen [3.6].

The impact model showed that an investment to fund rabies PEP would prevent ~489,000 deaths of the 1 million forecasted to occur across 67 developing countries between 2021–2035, and that the number of vials needed globally (73 million) would remain the same if the ID regimen is used [3.4]. The study thus supports a case for increased investment in PEP by the global community and provides a tool to address specific scenarios needed by stakeholders.

3. References to the research

1. **Hampson K, Cleaveland S**, Briggs D. (2011) Evaluation of cost-effective strategies for rabies post-exposure vaccination in low-income countries. *PLoS Negl Trop Dis*. 5(3):e982 (doi: [10.1371/journal.pntd.0000982](https://doi.org/10.1371/journal.pntd.0000982))
2. **Hampson, K.** et al. (2015) Estimating the global burden of endemic canine rabies. *PLoS Neglected Tropical Diseases*, 9(4), e0003709. (doi:[10.1371/journal.pntd.0003709](https://doi.org/10.1371/journal.pntd.0003709)).
3. **Hampson K**, Abela-Ridder B, Bharti O, Knopf L, Léchenne M, Mindekem R, Tarantola A, Zinsstag J, Trotter C. (2018) Modelling to inform prophylaxis regimens to prevent human rabies. *Vaccine*. 7. pii: S0264-410X(18)31519-6. doi:[10.1016/j.vaccine.2018.11.010](https://doi.org/10.1016/j.vaccine.2018.11.010).
4. **Hampson, K.**, Trotter, C. Ventura, F., Steenson, R., Mancy, R. and WHO Rabies Modelling Consortium (2018) The potential impact of improved provision of rabies post-exposure prophylaxis in Gavi-eligible countries: a modelling study. *Lancet Infectious Diseases*, 19(1): 102–111 (doi: [10.1016/S1473-3099\(18\)30512-7](https://doi.org/10.1016/S1473-3099(18)30512-7))
5. Changalucha J, Steenson R, Grieve E, **Cleaveland S**, Lembo T, Lushasi K, Mchau G, Mtema Z, Sambo M, Nanai A, Govella NJ, Dilip A, Sikana L, Ventura F, **Hampson K**. (2018) The need to improve access to rabies post-exposure vaccines: Lessons from Tanzania. *Vaccine*. 8. pii: S0264-410X(18)31243-X. doi: [10.1016/j.vaccine.2018.08.086](https://doi.org/10.1016/j.vaccine.2018.08.086)
6. Rajeev M, Edosoa G, Hanitriaina C, Andriamandimby SF, Guis H, Ramiandrasoa R, Ratovoson R, Randrianasolo L, Andriamananjara M, Heraud JM, Baril L, Metcalf CJE, **Hampson K**. (2018) Healthcare utilization, provisioning of post-exposure prophylaxis, and estimation of human rabies burden in Madagascar. *Vaccine*. S0264-410X(18)31520–2. (doi: [10.1016/j.vaccine.2018.11.011](https://doi.org/10.1016/j.vaccine.2018.11.011))

Grants

1. Hampson, Wellcome Trust Fellowship Awards (various), GBP3.47 million, 2007–2022
2. Hampson & Trotter, World Health Organization, GBP64,354 (to UofG), 2016

4. Details of the impact

Canine rabies is an infectious viral disease that is universally fatal following the onset of clinical symptoms. Rabies transmitted from domestic dogs is responsible for over 99% of human deaths from the disease. Annually, it causes ~59,000 human deaths worldwide, 3.7 million disability-adjusted life years (DALYs) and costs the global economy USD8.6 billion. Effective and timely rabies PEP is a vitally important tool for reducing rabies deaths while canine rabies remains endemic. But in Africa, it is often unavailable in the communities that need it most, while in Asia it is resourced at great cost and used wastefully to treat all dog bites.

UofG modelling research has delivered vital data for international policy and investment strategies. This work provided a crucial framework that supported new global policy on rabies

PEP by the WHO. This policy, together with the models that predict the impacts of PEP investment, provided the basis for a decision by Gavi (<http://www.gavi.org/>) to add rabies PEP to their global vaccine investment strategy. Gavi brings together key global stakeholders, including WHO, the World Bank, UNICEF, governments of donor and developing countries, the vaccine industry in developed and developing countries, research agencies and philanthropic organizations, such as the Bill & Melinda Gates Foundation, which are each represented on Gavi's executive board.

Engagement with Gavi

In 2013, Gavi considered investing in rabies PEP as part of their 2015–2021 vaccine investment strategy (VIS). In an expert consultation, to which UofG's Prof. Hampson contributed, Gavi considered a range of factors but decided in November not to support rabies PEP. In their decision, they cited key knowledge gaps that limited the feasibility of vaccine implementation, including a lack of consensus on PEP treatment regimens (10 different regimens were recommended and in use at the time), uncertainty about PEP demand and treatment-seeking behaviour, and the cost-effectiveness of different investment scenarios [A]. Gavi instead elected to fund a USD2 million 'learning agenda', awarded to WHO, to address these gaps for their next investment decision in December 2018.

Revision of WHO policy on rabies vaccines

A crucial step towards Gavi investing in rabies vaccination was for WHO to develop an updated consensus position statement on rabies PEP to address discrepancies between its earlier recommendations (2010) and how PEP was being used in endemic regions, and to consider evidence for newly proposed regimens that could be evaluated. To facilitate this work, in 2016 the WHO established a Strategic Advisory Group of Experts (SAGE) working group on rabies vaccines whose role was to develop practical and feasible recommendations to prevent human rabies. Concurrently, WHO used Gavi learning agenda funding to commission Hampson and Trotter to undertake two key modelling studies—the vaccine model [3.3] and the impact model [3.5]. In April 2017, WHO convened a meeting of the WHO Modelling Consortium to develop a consensus on the modelling approach and, through SAGE, to commission a portfolio of research from across the consortium, to address Gavi's learning agenda and to feed data to the modelling studies led by Hampson and Trotter.

From June 2017, Hampson and Trotter discussed the findings of the vaccine model study with SAGE during several meetings, with SAGE endorsing a final, clear position on shorter and less costly PEP regimens in October 2017 [B]. The WHO published their position paper in April 2018 [C], ahead of Gavi's investment shortlisting in June 2018 [C]. The WHO 2018 position paper draws on evidence about the magnitude of the global rabies burden established by Hampson et al. in 2015 (global burden study) [3.2] and the pivotal findings from the Gavi-funded/WHO-commissioned PEP modelling work [3.3], stating: "*ID administration of rabies vaccines provides a cost-saving and dose-sparing alternative to IM vaccination. ID PEP regimens use at least 25% less vaccine vials than IM PEP regimens. As numbers of patients seen in clinics increase, ID regimens become increasingly cost-effective, using up to 85% less vaccine vials*" [C]. A summary document published by the chair of SAGE explicitly sets out the updates to WHO's position on vaccine regimens, stating that, "*WHO now also recommends newer, shorter vaccine regimens that reduce costs, quantity of vaccine, and number of clinic visits...*" citing the UofG research [3.1, 3.3, 3.4] throughout as background to changes [B].

Gavi invest in rabies PEP in their 2021–2025 investment strategy

Drawing on the IVIR-AC validated PEP regimens, the impact modelling study [3.4] was able to offer key insights into the health impact (future deaths averted), costs and value for money of various scenarios of investment in these PEP regimens, both with and without additional rabies control programmes. Hampson & Trotter shared these findings iteratively and responsively with Gavi to address the board's questions [D]. In November 2018, Gavi announced the addition of rabies PEP to their 2021–2025 investment strategy [E]. The Gavi board's documentation cited as strategic rationale for the investment case: 1) the WHO recommendations on the choice of regimen (2-site, 1-week ID regimen); and, 2) the UofG-Cambridge modelling projections, citing

Hampson and Trotter [D, F]. The Head of Policy at Gavi said, “*The estimates that Dr Hampson and Trotter used formed the basis of our projections on future demand for and impact of rabies PEP. This was a critical foundation for determining financial implications for Gavi, the relative cost-effectiveness of rabies PEP and other important criteria to support the Board’s ultimate decision to approve the investment case... The synthesis of research contributed by UofG researchers helped to simplify what had been a complicated investment proposition—contextualising the global burden and identifying a universal and simple strategy*” [D].

Rabies PEP is for the first time one of Gavi’s strategic goals, opening an investment window across the 57 countries eligible to apply for Gavi vaccine support for the next five years, which could prevent an estimated 489,000 deaths from rabies.

Emerging secondary impacts on national vaccination policies

Despite significant disruption to international discourse in 2020 ahead of the Gavi investment window, and in response to the WHO position on rabies PEP, several countries have changed, or are in the process of updating, their rabies PEP policies to bring them into line with WHO recommendations. Currently the Philippines, Nepal and Bhutan have revised guidelines; Bangladesh, Côte d'Ivoire, Madagascar and Cambodia are in the process of revising [G]. In India, Pakistan and Tanzania implementation has been more regional. In India the state of Himachal Pradesh [issued new guidelines](#) in response to the WHO position statement [H]. UofG researchers led by Hampson have also supported a switch to the 1-week ID regimen in the 28 districts of South Eastern Tanzania and in the Mara region in North West Tanzania.

5. Sources to corroborate the impact [PDFs uploaded for all listed items]

- A. Rabies Vaccine Investment Strategy (Background document), Gavi Alliance, November 2013
- B. Overview of the SAGE process: O'Brien et al. (2018). The WHO position on rabies immunization – 2018 updates. *Vaccine*. (doi: [10.1016/j.vaccine.2018.10.014](https://doi.org/10.1016/j.vaccine.2018.10.014)) [*UofG studies cited, refs. 1 (global burden 3.2), 4 (modelling paper 3.3) and 9 (Gavi impact study 3.4)*]
- C. Rabies Vaccines: [WHO position paper](#) – April 2018. *Weekly epidemiological record* No.16, WHO, p. 201–20 [*cites UofG research refs. 2 (global burden 3.2) and 32 (modelling paper 3.3), p. 208*]
- D. Testimony from Head of Policy, Gavi The Vaccine Alliance, Geneva
- E. [Vaccine Investment Strategy](#). Gavi board meeting, 28–29 November 2018 (see Section C(e), p.7—rabies PEP approved) [PDF file]
- F. [06a - Annex C: Rabies Investment Case](#). Gavi Vaccine Investment Strategy Programme and Policy Committee Meeting 18-19 October 2018 [PDF file] [*pp.17–21, 25–26 highlight data from Glasgow-Cambridge modelling study. Hampson and Trotter listed as experts consulted (p.43) and research sources cited (p. 44)*].
- G. Personal communication with Project Manager/Consultant in neglected zoonotic diseases at the World Health Organization (2016–October 2020)
- H. [Guidelines for rabies prophylaxis and intradermal rabies vaccination in Himachal Pradesh 2019](#)