Institution: University of Glasgow

Unit of Assessment: Unit 6, Agriculture, Veterinary and Food Science

Title of case study: Development of international policy and strategies for prevention, control and elimination of rabies

1. Summary of the impact

Rabies is the most lethal known infectious disease and kills 55,000 people annually worldwide, mainly in Africa and Asia; however, it is almost entirely preventable. Effective vaccines for animals and humans are available, but their use is limited by cost and accessibility. Research undertaken at the University of Glasgow by Professor Sarah Cleaveland and her team has led to the development and adoption of new health and veterinary policies in East Africa, transforming research findings into practical strategies for rabies prevention and control. These strategies reduce the cost of medical treatment (such as post-exposure prophylaxis), increase its effectiveness (by improving compliance) and eliminate the barriers to receiving treatment in some of the world's most disadvantaged communities. Research by the Glasgow team on dog vaccination strategies has also made a major contribution to the recognition by the World Health Organization (WHO) that global canine rabies elimination is feasible, with national and global strategies now focussing on dog vaccination as a cost effective means of reducing human rabies deaths.

2. Underpinning research

Rabies develops in people who are bitten by animals (usually dogs) that are infected with the rabies virus. If left untreated, the disease is fatal in essentially all individuals once symptoms appear. However, preventative vaccination is almost 100% effective, as is 'post-exposure prophylaxis' (PEP) treatment – but this must be administered within 24 hours of exposure to the virus. Despite comparative successes in the control of rabies in Central and South America through mass dog vaccination programmes, the incidence of canine and human rabies in Africa continues to rise, killing around 24,000 people annually (almost half of all cases worldwide). The control and elimination of rabies in Africa and Asia has been hampered by misconceptions about the epidemiology of the disease, the ecology of domestic dogs and the cost of preventing rabies in humans. In particular, policy-makers have often opted for culling 'stray' dogs as the principal strategy for canine rabies control and consider wildlife to be the main source of rabies in Africa.

In on-going research since 2008, a University of Glasgow team, led by Professor Sarah Cleaveland (Professor of Comparative Epidemiology, 2008-present), with Drs. Katie Hampson (Research Fellow, 2009-present), Tiziana Lembo (Postdoctoral Research Associate, 2007-present), Darryn Knobel (Postdoctoral research associate, 2009-2010) has provided key evidence and insight into canine rabies control strategies. These demonstrated that: (i) rabies transmission is not dependent on the density of dogs, therefore the common strategy of indiscriminately culling dogs is likely to be ineffective for rabies control;[1] (ii) contrary to common perceptions among policy-makers in Africa, very few (if any) domestic dogs in Africa are ownerless (or stray) and most are accessible for vaccination;[5] and (iii) mass canine vaccination is feasible and can result in the elimination of rabies in all species, even in wildlife-rich areas of Africa,[3,4] and crucially, is the most cost-effective means to prevent human rabies in rural Africa.[5]

Rabies PEP treatment requires multiple doses, is expensive for developing nations, and places a heavy economic burden on African healthcare systems. In addition, vaccine shortages often occur in Africa. Therefore, PEP is often not available, particularly in rural clinics. This, together with difficulty reaching clinics and poor patient compliance with PEP doses, means that many people die unnecessarily from rabies, particularly those from poor families. In high-throughput clinics, often in urban centres, regimens that use injections into the skin (intradermal delivery) have been recommended as a cost-saving alternative to the conventional injections into the muscle (intramuscular delivery); however, these regimens are rarely used in Africa and have never been evaluated in these settings. In 2010, the research team (Cleaveland and Hampson) simulated different PEP regimens in a range of settings (high-throughput urban clinics and low-throughput rural clinics), identifying the costs to both the health authority (per treatment) and the bite victims, including indirect costs such as travel to clinics. The team found that, irrespective of the type of

clinic, a universal switch from intramuscular to intradermal regimens would reduce the amount of vaccine required (by 20% in low-throughput clinics and by 80% in high-throughput clinics), resulting in significant savings to public health budgets and mitigating the vaccine shortages that occur widely in Africa.[6]

External collaborators: Deborah Briggs (Global Alliance for Rabies Control) (study of PEP cost-effectiveness); Alena Gsell (Swiss Tropical and Public Health Institute, STPHI) (study of ownerless dog populations in Tanzania). The impetus and ideas for the research in the field studies were largely provided by the University of Glasgow team, and the STPHI dog ecology study in Tanzania was embedded within the University of Glasgow field programme.

3. References to the research

1. Hampson K., Dushoff J., Cleaveland S., *et al*. (2009) Transmission Dynamics and Prospects for the Elimination of Canine Rabies. *PLoS Biol* 7: e1000053. doi:10.1371/journal.pbio.1000053.
2. Hampson, K., Cleaveland, S., and Briggs, D. (2011) Evaluation of cost-effective strategies for rabies post-exposure vaccination in low-income countries. *PLoS Negl Trop Dis*. 5: e982. doi:10.1371/journal.pntd.0000982
3. Lembo T. *et al*. (2010) The feasibility of eliminating canine rabies in Africa: dispelling doubts with data. *PLoS Negl Trop Dis*. 4: e626. doi:10.1371/journal.pntd.0000626
4. Beyer, HL. *et al*. (2012) The implications of metapopulation dynamics on the design of vaccination campaigns. *Vaccine*, 30:1014-1022. doi: 10.1016/j.vaccine.2011.12.052
5. Fitzpatrick M.C., Hampson K., Cleaveland, S. *et al*. (2013) Cost–effectiveness of canine vaccination to prevent human rabies in rural Tanzania. Ann Intern Med. (*In press Nov 2013,* PDF available on request)
6. Gsell A.S, Knobel D.L., Cleaveland S. *et al*. (2012) Domestic dog demographic structure and dynamics relevant to rabies control planning in urban areas in Africa: the case of Iringa, Tanzania. *BMC Vet Res.* 8: 236. doi:10.1186/1746-6148-8-236

Grant funding

i. Canine Rabies Elimination Demonstration Project, Bill and Melinda Gates Foundation (2008-2012) $ 9,996,674, awarded to Dr François Meslin, World Health Organization ($68,312 awarded to Sarah Cleaveland as technical adviser). (Peer reviewed)

ii. Development and implementation of an effective surveillance system for rabies in southern Tanzania using innovative technologies. UBS Optimus Foundation (2008-2011), £487,500 awarded to Katie Hampson and Sarah Cleaveland as co-PIs. (Peer reviewed)

4. Details of the impact

The work of Professor Sarah Cleaveland and the University of Glasgow rabies group has had a strong impact in several African countries and at a global level. Their research has led directly to major changes in policy, influencing decisions made by government health and veterinary authorities in Tanzania and Kenya. In Tanzania, this work led to the development and adoption of new standard operating procedures for measures that both control rabies in animal populations and prevent rabies from developing in humans. In Kenya, the team is currently developing a national rabies control and prevention plan for the Kenyan government. At the global level, the team's efforts have led to the drafting of a resolution on the global elimination of canine-mediated human rabies to be taken forward at the WHO World Health Assembly in May 2014, which is the vehicle for controlling the budget and policy decisions of the WHO.

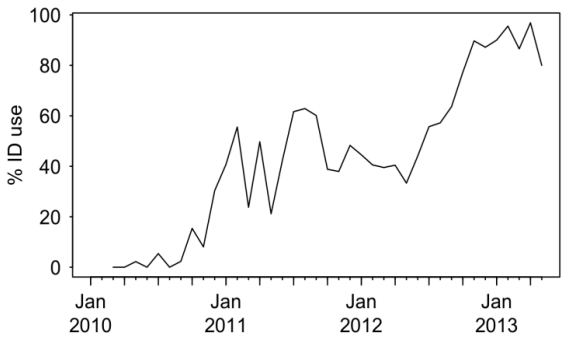
In 2009, Cleaveland helped to develop a cost effective package for sustainable canine rabies control at a WHO/Bill & Melinda Gates Foundation Consultation.[a] The consultation recommended financial mechanisms by which canine rabies control can be sustained through cost savings in PEP, essentially adopting a 'one health' approach, where solutions to rabies control are addressed as a joint concern of both veterinary and medical authorities. Cleaveland's work was debated at the WHO level, demonstrating both the significant health problem posed by rabies and the potential for global uptake of the work of University of Glasgow research, which could lead to effective eradication of the disease.

Tanzania: Human post-exposure prophylaxis and dog vaccination

Between 2008 and 2012, Cleaveland led the 'Canine Rabies Elimination Demonstration Project', funded by the WHO/Bill & Melinda Gates Foundation in Tanzania. At the outset of the project period in 2008, Cleaveland and the Glasgow team (Hampson and Lembo) worked with the senior health and veterinary authorities in Tanzania to develop new national Standard Operating Procedures for both human intradermal PEP and mass canine vaccination, advising on planning, implementation logistics and vaccine options. These were adopted by the Tanzanian authorities in 2009, representing a significant achievement in African public health policy.[b,c]

In 2009 (Nov-Dec), Cleaveland, Hampson and Dr Tiziana Lembo worked with Tanzanian veterinary officials and collaborators from the WHO and United States Centre for Disease Control (CDC) Rabies Team to deliver primary training on the new PEP standard operating procedures to 30 clinicians in Tanzania and on the delivery of mass dog vaccination schemes to 35 district veterinary officers. These training sessions were complemented by the training of 22 lab technicians in rabies surveillance techniques (as part of a separately funded programme of implementing effective rabies surveillance in Tanzania; UBS Optimus Foundation, 2008-2011). The aim was for each of these trained professionals to train others and for the nation to build specialist capacity in the veterinary, medical and surveillance aspects of rabies control.

The project also included research by both Cleaveland and Hampson (University of Glasgow) on new strategies for human PEP regimens. Working in a project area covering the South-East of Tanzania, the team promoted the use of human PEP vaccination by the intradermal route through training workshops with medical officers from the Ministry of Health, conducted in collaboration with the WHO. This was based on research showing it to be a simpler, cost-effective replacement for intramuscular vaccination, due to the lower volume dose required. As a result, since early 2010, the use of intradermal PEP in the project region has increased from 0% to >80% of PEP vaccinations given (see Figure).[d] Issues of PEP regimen compliance to prevent treatment failure have also been improved through a mobile phone text-based reminder service initiated by Hampson in the project area.[d]



Kenya: Informing a national rabies policy

During 2012, Cleaveland was working with the CDC base in Nairobi, which catalysed the establishment of the Zoonotic Disease Unit (ZDU) within the Government of Kenya. Through this collaboration, Cleaveland's expertise in rabies was sought during a large rabies outbreak in the city of Kisumu in western Kenya, and Cleaveland provided operational advice to the veterinary field teams, and organised supplies of vaccine. As a result of this, a plan to develop a national rabies control strategy was initiated by the ZDU, and Cleaveland invited to develop the outline and framework, which was presented to the Kenyan Veterinary Association in April 2013.[e] The strategy document, which encompasses human PEP, dog vaccination and rabies surveillance in a step-wise approach, is being finalised within the Government of Kenya, and has thus been the subject of national policy discussion.

Rabies Blueprint

The 'Rabies Blueprint' is a web-based resource (caninerabiesblueprint.org), launched in June 2010, providing a step-by-step guide for health authorities in rabies-endemic areas. It was conceived and steered by Lembo and the Glasgow team in collaboration with the Partners for Rabies Prevention, an independent group of rabies experts from international agencies. The Rabies Blueprint combines all of the relevant existing rabies control guidelines, addressing the responsibilities of each stakeholder, legislative frameworks, costs and implementation strategies. Within the first year the site had 46,000 visitors (over 2,000 per month) from 157 countries, 1,719 cities and five continents.[f] The Blueprint has been used in many regions with a high incidence of

rabies, such as Africa (Uganda and Benin) and Asia (Afghanistan and Indonesia). For example, the Asia co-ordinator of the NGO 'Global Alliance for Rabies Control' uses the Rabies Blueprint for planning their programmes and operational activities in the Philippines and Indonesia, describing it as a '*valuable tool for training and implementation of dog rabies control programs*' and has cited its use in the WHO strategic framework for rabies elimination in South East Asia (2012).[g,h]

Influencing strategic policy on global health

In September 2012, Cleaveland and Hampson were invited to a WHO Expert Consultation on rabies held in Geneva, Switzerland, bringing together the leading practical evidence for discussion and providing a platform to ratify operational recommendations to be advocated at government level. This Consultation urged the WHO to continue to advocate human rabies prevention through the elimination of rabies in dogs and to promote wider use of the intradermal route for human PEP, which University of Glasgow research has shown to reduce the volume and therefore the cost of the cell-cultured vaccine by up to 80%.[i]

> *'The research conducted by the team has contributed substantially to progress on for example the global burden of rabies and the cost-effectiveness of intradermal rabies post-exposure prophylaxis and rabies surveillance. The published results of that research have contributed to updating relevant recommendations of the WHO Expert Consultation on Rabies.'* – Director, Dept. of Control of Neglected Tropical Diseases, WHO.[j]

Owing to the significant body of work on rabies from Cleaveland, Hampson and Lembo, and the resulting impacts on rabies control in East Africa, Cleaveland has become a prominent expert adviser at the world health level. She is the leading international adviser for rabies on the WHO Neglected Zoonotic Disease working group of the Scientific and Technical Advisory Group for Neglected Tropical Diseases (STAG-NTD); Glasgow research has thus been pivotal in the prioritisation of canine rabies elimination as a top priority of the working group.[j,k]

The report by the STAG-NTD[k] has resulted in global canine rabies elimination being identified as a priority of the WHO and contributed to a WHO resolution on rabies in Africa being officially tabled for discussion at the World Health Assembly in May 2014, thereby stimulating policy discussion at the highest inter-governmental level.

5. Sources to corroborate the impact

a. Human and dog rabies prevention and control. Report of the WHO/Bill & Melinda Gates Foundation Consultation. Annecy, France, 7–9 October 2009 WHO/HTM/NTD//NZD/2010.1
b. Rabies Post-Exposure Prophylaxis Standard Operating Procedures (2009), Ministry of Health and Social Welfare and Ministry of Livestock Development and Fisheries, Tanzania; available on request.
c. Dog Vaccination Campaigns Standard Operating Procedures (2009), Ministry of Livestock Development and Fisheries, Tanzania; available on request.
d. Zacharia Mtema (2013) PhD Thesis, University of Glasgow (Data also presented in: 'Data review report for the WHO-BMGF rabies elimination demonstration project in Tanzania', 2013); available on request.
e. Statement provided on behalf of the Kenyan Ministry of Health and Ministry of Agriculture, Livestock development and Fisheries; available on request.
f. Lembo T, on behalf of the Partners for Rabies Prevention (2012) The Blueprint for Rabies Prevention and Control: A Novel Operational Toolkit for Rabies Elimination. *PLoS Negl Trop Dis* 6(2): e1388. (doi:10.1371/journal.pntd.0001388) (Rabies Blueprint website)
g. Statement provided by Coordinator for Asia, Global Alliance for Rabies Control, Philippines; available on request.
h. Strategic Framework for Elimination of Human Rabies Transmitted by Dogs in the South-East Asia Region, WHO (2012) (Rabies Blueprint cited on p.13).
i. WHO Expert Consultation on Rabies, 2nd report (2013) WHO Technical Report Series No. 982.
j. Statement provided by Director, Department of Control of Neglected Tropical Diseases, WHO, Geneva; available on request.
k. Report of the WHO Strategic and Technical Advisory Group for Neglected Tropical Diseases (2012).