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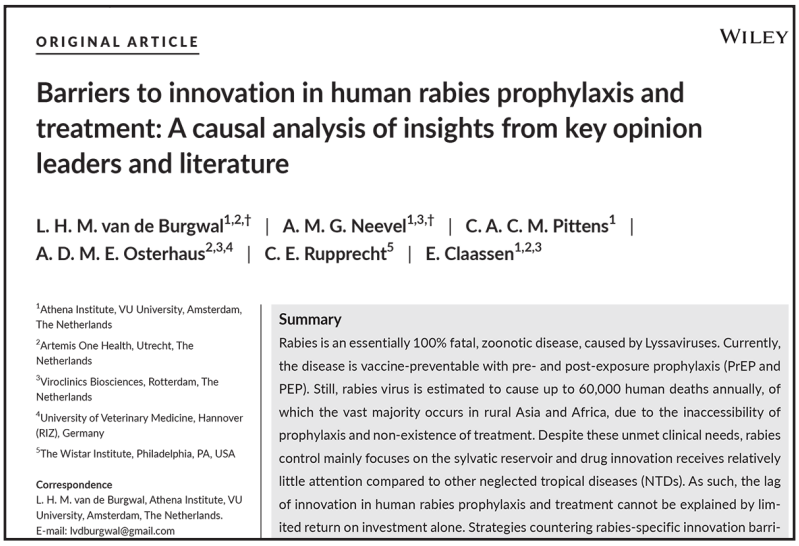
Rabies Experts Highlight Barriers to Innovation in Rabies Education and Treatment



ORIGINAL ARTICLE

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Barriers to innovation in human rabies prophylaxis and treatment: A causal analysis of insights from key opinion leaders and literature

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Summary

Rabies is an essentially 100% fatal, zoonotic disease, caused by Lyssaviruses. Currently, the disease is vaccine-preventable with pre- and post-exposure prophylaxis (PrEP and PEP). Still, rabies virus is estimated to cause up to 60,000 human deaths annually, of which the vast majority occurs in rural Asia and Africa, due to the inaccessibility of prophylaxis and non-existence of treatment. Despite these unmet clinical needs, rabies control mainly focuses on the sylvatic reservoir and drug innovation receives relatively little attention compared to other neglected tropical diseases (NTDs). As such, the lag of innovation in human rabies prophylaxis and treatment cannot be explained by limited return on investment alone. Strategies countering rabies-specific innovation barri-

Broader awareness, increased vigilance, and innovative thinking are more important than ever to address the unmet clinical and societal needs associated with rabies treatment.

Rabies Continues to Pose a Threat to Humans Around the Globe

"Rabies is not rare. Known human cases of rabies are rare in developed countries due to the application of innovation. But, we cannot rest on our laurels." *Charles E. Rupprecht, VMD, MS, PhD, The Wistar Institute, Philadelphia, PA*

Rabies disease in humans is now rare in many areas of the world, including the Americas, Europe, Australia, and parts of Asia and Africa, due to innovation in rabies science and clinical practice.[1,2] Still, rabies deaths in humans do occur, and 95% happen in poorer areas of the world, especially Asia and Africa.[1,3] These deaths highlight the need for greater efforts to combat rabies globally. Additionally, the global persistence of rabies serves as a reminder that healthcare systems should not overlook this pathogen, since rabies is endemic in the natural environment on all continents except Antarctica,[3] and animal exposures may never be completely eliminated since numerous reservoirs exist in wildlife. Therefore, human disease may always remain a threat.

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Since rabies is not a notifiable disease in much of the world, the accuracy of data for the number of infected animals and epidemiology of exposure incidents among humans cannot be validated.[3,4] Some authorities believe that the incidence of rabies infections and deaths in humans may be underestimated by 100-fold.[1] Uncertainty is compounded by the effects of global travel and ecotourism, which may transport people from areas of low rabies incidence to areas of high incidence, with increased potential for exposures through domestic or wild animals.

Rabies elimination programs have greatly reduced the mortality associated with rabies disease in countries that have implemented such programs.[3,5] Given that rabies is a 100% vaccine-preventable disease, mass programs to vaccinate canine populations have been a central component of rabies elimination programs.[5] These programs, along with the use of rabies vaccines with human rabies immune globulin (HRIG) for postexposure prophylaxis (PEP) and public awareness campaigns, have reduced the incidence of rabies in dogs by 98% and in humans by more than 95% over the past 3 decades in the Americas.[5] Pre-exposure prophylaxis (PrEP) among people at high risk of infection due to occupational or recreational activities, including travel to areas of high rabies endemicity, is recommended to help reduce the risk of transmission.[1,5] However, as the incidence of canine-transmitted rabies has fallen dramatically, rabies transmission by other mammals, including bats, raccoons, foxes, skunks, and others, has emerged as a public health threat.[5] Therefore, the challenges associated with rabies are still present globally and need to be addressed.

Lack of Awareness of Rabies and the Value of PEP Remain Substantial Barriers to Progress

"The most important barrier to progress against rabies globally continues to be the lack of awareness of rabies as a public health problem." *Charles E. Rupprecht, VMD, MS, PhD, The Wistar Institute, Philadelphia, PA*

Foremost among barriers to clinical progress against rabies is the lack of awareness among stakeholders that rabies is a continuing health problem.[2] This challenge is compounded by the lack of awareness of the need to administer PEP with HRIG and rabies vaccine to prevent the consequences of rabies and also of the need to ensure that patients complete their PEP regimens for optimal prevention.[1,3,4] Several other barriers are known to impede progress in clinical practice, including poor infrastructure and administrative/logistic mechanisms to facilitate initiation and completion of vaccination series, a lack of compliance in administration of vaccines to humans and animals, a lack of consistent availability of vaccines, and inability of governments to provide access against a backdrop of poverty in areas of endemic rabies.[1]

A different approach, exploring barriers to innovation, was undertaken by van de Burgwal and colleagues.[2] These authors recognized that, as in other areas of medicine, technological and societal innovations in rabies prophylaxis need to begin with recognition and prioritization of unmet needs.[2] Their comprehensive review of barriers to innovation in the field of rabies revealed numerous challenges that were categorized into 4 domains: public health and awareness, collaboration of stakeholders, market and commercial issues, and disease trajectory.[2] This analysis led to prioritization of the barriers to societal and clinical progress toward elimination of rabies (Table).[2]

Table. Prioritization of Key Problems Relating to Innovation Barriers in Rabies[2]

Importance[a]	Key problem
1	Lack of awareness of rabies as a health problem
2	Limited (perceived) economic impact of rabies
3	No societal pressure for innovation in human rabies
4	Lack of adoption by governments from endemic countries
5	Limited availability of products
6	Limited research efforts on rabies
7	Lack of operational research
8	Lack of multidisciplinary approaches
9	Lack of healthcare-seeking behavior of PEP
10	Difficult to get clinical evidence for new innovations
10	Limited production capacity
11	(International) coordination problems
12	Lack of translational research and buy-in from industry
13	Lack of direction in research
14	Inherent complexity of rabies research
15	Lack of healthcare-seeking behavior of PrEP
16	Lack of adoption by healthcare professionals
17	High regulation burden for R&D
18	No demand for human rabies control
19	Limited market viability ideas of scientists
20	Limited efficacy of products against some genotypes
21	Limited freedom to operate (due to IP rights)
21	Difficult to combine PrEP and PEP

[a] Some positions are shared by 2 key problems.
IP, intellectual property; R&D, research and development.
Adapted from van de Burgwal LHM, et al. *Zoonoses Public Health.* March 20, 2017. doi:10.1111/zph.12352.

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Possible Paths Ahead

"We will not be able to achieve our global goals if we cannot continue to make major headway against rabies, and to transfer innovative technologies from developed to developing countries." *Charles E. Rupprecht, VMD, MS, PhD, The Wistar Institute, Philadelphia, PA*

The analysis by van de Burgwal and colleagues supports the conclusion that innovation in rabies prevention, diagnosis, and possible treatment has not benefited sufficiently from societal engagement and investment.[2] Little has changed since the development of the first rabies vaccine, which was based on nerve tissue–extracted antigens, and the subsequent shift away from this type of vaccine to cell-culture vaccines.[1,2] In fact, rabies generally receives less attention as an area of investment and innovation than other neglected tropical diseases, despite having a higher burden of disease.[2] Key opinion leaders say the lack of attention and innovation in rabies stems from a lack of disease awareness, a lack of economic impact of rabies because the vast majority of clinical cases occur in areas of Asia and Africa, and the lack of societal pressure for change.[2] Their analyses can help various stakeholders focus on the barriers to innovation that are more relevant and actionable to them.[2]

Possible areas of innovation that may prove valuable in the prevention/management of rabies in the future may include:

- Vaccines that could be administered at reduced doses or on less burdensome vaccination schedules[1]
- Single-dose vaccinations to achieve a protective immunologic response, while improving compliance without the need for multiple, follow-up injections[1]
- Vaccines with enhanced immunogenicity, such as bivalent live vaccines, to improve clinical efficacy[1]
- Plant-based vaccines[1]
- Vaccines containing adjuvants to enhance potency of rabies vaccines[1]
- Oral vaccine administration, especially for mass-vaccination campaigns among canine populations[1]
- Monoclonal antibodies for administration to provide passive immunity[1]
- Monoclonal antibodies for use in direct rapid immunohistochemical diagnostic tests to improve rabies surveillance[1]

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To learn more about barriers to innovation in rabies and perspectives on addressing these barriers, download the van de Burgwal and colleagues publication.

All quotations in this article were provided by Charles E. Rupprecht, VMD, MS, PhD, in a personal interview on April 7, 2017.

IMPORTANT SAFETY INFORMATION

Rabies vaccine and HyperRAB® S/D (rabies immune globulin [human]) should be given to all persons suspected of exposure to rabies with one exception: persons who have been previously immunized with rabies vaccine and have a confirmed adequate rabies antibody titer should receive only vaccine. HyperRAB S/D should be administered as promptly as possible after exposure, but can be administered up to the eighth day after the first dose of vaccine is given.

HyperRAB S/D should be given with caution to patients with a history of prior systemic allergic reactions following the administration of human immunoglobulin preparations.

The attending physician who wishes to administer HyperRAB S/D to persons with isolated immunoglobulin A (IgA) deficiency must weigh the benefits of immunization against the potential risks of hypersensitivity reactions. Such persons have increased potential for developing antibodies to IgA and could have anaphylactic reactions to subsequent administration of blood products that contain IgA.

As with all preparations administered by the intramuscular route, bleeding complications may be encountered in patients with thrombocytopenia or other bleeding disorders.

Soreness at the site of injection and mild temperature elevations may be observed at times. Sensitization to repeated injections has occurred occasionally in immunoglobulin-deficient patients. Angioneurotic edema, skin rash, nephrotic syndrome, and anaphylactic shock have rarely been reported after intramuscular injection so that a causal relationship between immunoglobulin and these reactions is not clear.

Administration of live virus vaccines (e.g., MMR) should be deferred for approximately 3 months after rabies immune globulin (human) administration.

HyperRAB S/D is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent that can cause disease. There is also the possibility that unknown infectious agents may be present in such products.

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REFERENCES

1. Kaur M, Garg R, Singh S, Bhatnagar R. Rabies vaccines: where do we stand, where are we heading? *Expert Rev Vaccines.* 2015;14(3):369-381. **2.** van de Burgwal LHM, Neevel AMG, Pittens CACM, Osterhaus ADME, Rupprecht CE, Claassen E. Barriers to innovation in human rabies prophylaxis and treatment: a causal analysis of insights from key opinion leaders and literature. *Zoonoses Public Health.* March 20, 2017. doi:10.1111/zph.12352. **3.** World Health Organization. What is rabies? http://www.who.int/rabies/about/en/. Accessed April 14, 2017. **4.** Kole AK, Roy R, Kole DC. Human rabies in India: a problem needing more attention. *Bull World Health Organ.* 2014;92(4):230. **5.** World Health Organization. Rabies fact sheet. http://www.who.int/mediacentre/factsheets/fs099/en/. Updated March 2017. Accessed April 13, 2017.

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