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 barriers are important for the acceleration of innovation in human rabies prophylaxis and treatment. Barriers throughout society, science, business development and market domains were identified through literature review and 23 semi-structured interviews with key opinion leaders worldwide. A subsequent root cause analysis revealed causal relations between innovation barriers and a limited set of root causes. Finally, prioritization by experts indicated their relative importance. Root causes, which are fundamental to barriers, were aggregated into four types: market and commercial, stakeholder collaboration, public health and awareness, and disease trajectory. These were found in all domains of the innovation process and thus are relevant for all stakeholders. This study identifies barriers that were not previously described in this specific context, for example the competition for funding between medical and veterinary approaches. The results stress the existence of barriers beyond the limited return on investment and thereby explain why innovation in human rabies medication is lagging behind NTDs with a lower burden of disease. A re-orientation on the full spectrum of barriers that hinder innovation in rabies prophylaxis and treatment is necessary to meet unmet societal and medical needs.

KEYWORDS
barriers, preventive medicine, public health, rabies, root cause analysis, treatment of diseases

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1 | INTRODUCTION

With a life expectancy of approximately 7 days after onset of symptoms, rabies is one of the deadliest infectious diseases (Schnell, Mcgettigan, Wirblich, & Papaneri, 2010). Annually, 26,400–61,000 people reportedly die from rabies (World Health Organization, 2013). The disease disproportionately affects people living in rural areas of endemic countries (Knobel et al., 2005). Children under 15 years of age are at highest risk of being exposed to rabid animals, which leads to a disease burden of 3.7 million disability-adjusted life years (DALYs) (Hampson et al., 2008, 2015).

Rabies does not only affect humans, but other mammals are affected as well. The most prominent groups of reservoir animals are dogs, bats and foxes, but many other animal species have shown to be host to rabies virus (World Health Organization, 2013). The eradication of rabies warrants a One Health approach in which human and veterinary disciplines collaborate to eradicate diseases, as has been instituted before with smallpox by human medicine and rinderpest by veterinary medicine. Importantly, these successes show how diseases can be controlled in resource-poor settings and how they rely on social as well as technical innovation (Mariner et al., 2012). Veterinary approaches for rabies control include mass vaccination, spaying or neutering and culling of (stray) dogs and vaccination of wildlife via oral baits (World Health Organization, 2013). Effects of environmental changes on rabies are still poorly understood (Kim et al., 2014) although climate change is likely to impact the geographical distribution of animal hosts (Rebelo, Tarroso, & Jones, 2010). Consequently, as long as genuine rabies control is lacking in resource-poor settings and rabies cannot be controlled in all host animals, human rabies prophylaxis and treatment is highly needed to decrease the number of human rabies cases.

Currently, the vast majority of rabies deaths are preventable with pre- or post-exposure prophylaxis (PrEP or PEP). Preventive human rabies vaccination has proven to be safe and effective, and is administered to more than 15 million people annually (World Health Organization, 2010). Together with rabies immunoglobulins administered as part of PEP, rabies vaccines prevent in excess of an estimated 327,000 human deaths per year (Knobel et al., 2005). However, these biologicals are expensive, have limited scalability and their administration requires several visits to healthcare providers (World Health Organization, 2013). These characteristics limit their societal impact, especially in developing countries where repetitive access to health care is extremely challenging (Levine, 2011). Social innovations could improve access to these tools by improving local healthcare settings. Simultaneously, technological innovations could improve prophylactic measures in such a way that they address current unmet needs in terms of affordability, scalability and treatment regimens and thereby complement existing veterinary approaches. The need for such technological innovation extends to developed countries, as there are no anti-viral drugs or documented therapies available to treat the invariably fatal disease, once clinical symptoms are manifest.

Despite these unmet medical needs, true innovation in human rabies prevention and treatment has received relatively little attention in past decades. For example, of the 17 World Health Organization (WHO)-defined neglected tropical diseases (NTDs), rabies is among the least studied, despite having a relatively large burden of disease (Bourhy, Dautry-Varsat, Hotez, & Salomon, 2010; Kappagoda & Ioannidis, 2012). What little innovation has occurred in the last 30 years was primarily the result of advances in production methods (Hicks, Fooks, & Johnson, 2012; Wu, Smith, & Rupprecht, 2011).

In addition to NTD-related barriers, the gap in innovation activity compared to other NTDs leads to the assumption that rabies-specific barriers play a role in limiting innovation. For the acceleration of innovation in new human rabies prophylaxis and treatment, it is important to identify and prioritize such barriers. In addition, actions based upon insights in the causal relations among these different barriers may improve progress across the demand-driven value chain. Hence, the objective of this study was to develop a causal tree of barriers in an attempt to define and understand substantive impediments to further innovation in human rabies prophylaxis and treatment.

2 | MATERIALS AND METHODS

2.1 | Innovation framework

For the aim of this study, innovation was defined as “the process of turning an opportunity into new ideas and putting these into widely used practice” (Tidd & Bessant, 2009). When these ideas, in the form of products or services, address unmet needs, societal value is created. The valorization cycle (Figure 1) shows how innovation results
from knowledge exchange between the research, business development, market and society domains (Claassen, 2014). Activities in these domains add societal value to the knowledge before it transfers from one domain to the next (Van Ark & Klasen, 2007). Conceptually, the different steps are taken consecutively; however, iterations are an inherent part of innovation and results of a specific phase may necessitate innovators to go back one or multiple steps before they can continue. Other cases may warrant the skipping of steps or the execution in a different order. The model therefore is not prescriptive for all innovation processes but rather provides a broad conceptual understanding of what steps constitute innovative processes. Furthermore, the model is actor independent which reflects the notion that stakeholders may be active in different phases in the process.

Based upon its definition, innovation starts with unmet needs as opportunities and ends with the feedback of customers and users. The cyclic shape of the model, however, reveals that innovation is a continuous process in which unmet needs are shaped by innovation output. In the context of the current study, despite medical interventions on the market, unmet needs extend to affordability, availability, administration windows and treatment regimens as well as to the lack of effective therapies once clinical symptoms are apparent.

When stakeholders in the valorization cycle who aim to address these unmet needs encounter barriers that hamper their activities, this may hinder progress across the cycle and limit societal impact of innovations.

### 2.2 | Data collection

To identify innovation barriers, key opinion leaders (KOLs), renowned experts in the field of rabies and active in one or more domains of the valorization cycle, were interviewed. The KOL approach was chosen because of the widely dispersed nature of the rabies problem, in terms of geography, affected socio-economic groups and type of medical intervention (PrEP or PEP).

Key opinion leaders on the one hand have direct experience with multiple approaches on different markets and in different contexts and on the other can convey the experiences of a broad network of stakeholders in this field. They can therefore weigh the benefits and drawbacks of innovative approaches, identify barriers and come to an integrated perspective on the important issues at stake. For similar reasons, no patients were approached for this study.

To ensure a comprehensive overview of relevant barriers, KOLs were selected on the basis of the domain of their experience: society, research, industry or market. These included experts working for public health authorities, academic researchers, industrial affiliates and medical doctors, respectively. Selection of KOLs active in research was performed through the network of ASKLEPIOS, a non-commercial consortium that was awarded funding by the European Commission to address the gap in innovation in human rabies treatment, and a web search. All interviewees were asked to suggest further KOLs (“snowballing”), which were also checked for these criteria.

Ultimately, 53 KOLs received an invitation email. The anonymity of the KOLs encouraged participation and enabled them to also discuss more contentious aspects of the problem.

The semi-structured interviews were conducted via phone by two researchers (LvdB and AN) to ensure consistency. Respondents received the interview questions beforehand. A total of 23 semi-structured interviews were conducted with KOLs primarily working in society (5), science (9), business development (6) and market (3) domains (Data S1). The numbers refer to their main area of expertise, as stakeholders can be active in multiple domains. All interviews were recorded and transcribed verbatim.

Subsequently, a literature search was conducted. Within the PubMed database, a search syntax combining “rabies” with synonyms...
of the words “barrier” and “medication” (Data S2) led to the retrieval of 110 academic papers discussing such barriers (Figure 2). To ensure topicality and current relevance, only papers published between January 2009 and March 2015 were included. A total of 70 papers mentioned barriers to innovation in human rabies prevention and treatment (Data S3). The parts of the papers discussing innovation barriers were highlighted for later analysis.

Next, a focus group discussion was organized to initiate a root cause analysis (RCA). A total of 14 participants of the ASKLEPIOS consortium participated in the focus group discussion during the 3rd International One Health Congress on March 17th 2015 in Amsterdam. The principal investigators and members of the advisory board were selected for participation to ensure extensive expertise covering public health, veterinary health and virology backgrounds (Data S1). After presenting and discussing all innovation barriers, participants were divided into four groups, with each group analysing the barriers in one domain (Figure 1) to establish a sequence of events between innovation barriers. This enabled the identification of key problems, causal factors and root causes, or the most basic causes that are still relevant and specific for the key problem in question. Participants could also add missing causal factors or root causes and were encouraged to discuss the results. The participants next switched groups and discussed the RCA of another domain.

Lastly, to increase practical relevance of the findings, a bigger and more international group of KOLs was approached for quantitative prioritization of the innovation barriers. The key problems were used to develop an online questionnaire, as these would be the most visible. The respondents were asked to prioritize the key problems, based on their own experience as well as on the hampering effect on innovation. The relative importance of the latter could be indicated by the distribution of 100 points (more points being more hampering) over the five barriers that hamper innovation the most. In a comments box, KOLs were able to leave any additional barriers.

The questionnaire was pilot-tested and distributed through the web survey programme SurveyMonkey®. The questionnaire was distributed among 172 KOLs selected through a web search and KOLs were encouraged to send the questionnaire to colleague rabies experts. During the participant selection, a special focus was on KOLs with rabies-related experience in endemic settings and developing countries. The definition of KOL was adapted for the anonymous questionnaire, and responses of all respondents having at least 5 years work experience in the field of rabies or holding at least a MSc degree were included. A reminder was sent after 7 and 11 days to increase the response rate.

### 2.3 Data analysis

The interviews and subsequently relevant literature text were analysed according to the grounded theory approach (Corbin & Strauss, 1990). Open coding led to the initial conceptualization of the interview data into distinct concepts, which were established independently by two researchers (LvdB and AN). Where the two researchers differed on concepts attributed to the data, a dialogue was started to exchange ideas and interpretations in order to ensure reflexivity. Subsequently and iteratively, axial coding led to the aggregation of these concepts in categories and subcategories. The resulting innovation barriers, defined as factors hampering activities in the innovation process, were formulated as abstract constructs. Next, during selective coding, the contexts and circumstances under which these barriers occurred led to the assignment of innovation barriers to one or multiple domains and phases of the innovation cycle (Figure 1; Gioia, Corley, & Hamilton, 2013). Theory building occurred during the integration of the categories and subcategories in abstract constructs after which the theory was grounded by re-evaluating whether these categories and constructs fit the original data. Iteratively, abstract constructs, categories and subcategories were reformulated to ground the theory in the data. After this initial analysis of interview data, the literature data were analysed. During this process, the same two researchers used open, axial and selective coding which enabled consistency with the coding processes of the interviews. Again, abstract constructs were formulated, checked against the initial data and integrated into the resulting innovation barriers (Gioia et al., 2013).

After the focus group discussion where the RCA was initiated, the two primary researchers (LvdB and AN) conducted a subsequent iterative RCA where all relations between innovation barriers were grounded in the data from the qualitative interviews and the literature and drafted an integrated RCA. The integrated RCA was then sent to all participants of the focus group discussion, who were enabled to provide comments on the internal logic of the RCA. The adaptations were again grounded in the data and adapted accordingly in a third evaluation round until consensus among experts was reached.

Lastly, questionnaire results were imported to Microsoft Excel for further analysis. Compliance with inclusion criteria was checked using the demographic information. Comments boxes were compared with the earlier identified barriers and checked for new barriers. Final ranking of barriers was based on the total points allocated to the key problem.
3 | RESULTS

3.1 | Root cause analysis

Axial coding of the text from interview transcripts and literature resulted in 209 and 106 innovation barriers, respectively. Selective coding led to the integration of these barriers into 136 abstract constructs. Grounding of the resulting theory after the focus group discussions resulted in a final total of 119 barriers (Data S4). The results of the root cause analysis are visualized in a causal tree (Figures 3–7). From the RCA, 43 unique root causes were identified which were categorized into four main types (see Table 1). The figures provide a structural overview of how a multitude of key problems is caused by a relatively limited set of root causes. Some root causes come back in more than one domain and hamper innovation across different domains of the innovation process.

A total of 23 key problems were identified, of which five occurred within the society domain (see Figure 3). These barriers

![FIGURE 3](https://wileyonlinelibrary.com) Causal tree on society domain. From left to right: per phase of the society domain the innovation barriers (key problems, causal factors and root causes), each having its own unique number. Colours refer to the domain from which the root causes originate: society (pink), business development (blue) and market (grey). Type: public health and awareness (H), disease trajectory (D), collaboration of stakeholders (S) and market and commercial (M). Dx, Diagnosis. [Colour figure can be viewed at wileyonlinelibrary.com]

**TABLE 1** Four types of root causes

| Short | Full name | Description | No |
|-------|-----------|-------------|----|
| H     | Public health and awareness | (Non-medical) prevention methods, influencing the adoption of medical products, and care for patients | 15 |
| S     | Collaboration of stakeholders | Integration of activities of different stakeholders | 8 |
| M     | Market and commercial | Adoption of and return on investments for innovations | 10 |
| D     | Disease trajectory | Diagnosis, pathogenesis, prophylaxis and treatment of rabies encephalitis | 10 |

*a Name as indicated in Figures 3–7.

*b Number of root causes of this type.
referred to a lack of perceived unmet need (lack of awareness of rabies as a health problem and limited (perceived) economic impact of rabies) and a lack of demand articulation (no societal pressure or lobbying, no demand for human rabies control and international coordination problems). The causal analysis revealed nine root causes that play a role in these key problems, of which one from the disease trajectory type, two of the public health and awareness type, three of the market and commercial type and three of the collaboration between stakeholders type. Furthermore, two innovation barriers with their origin in another domain led to these key problems.

Within the science domain, seven key problems were found (see Figure 4). These problems related to barriers within the idea phase (lack of operational research, lack of multidisciplinary approaches and lack of research efforts in general), to barriers within the research phase (inherent difficulties with rabies research and a lack of direction in research) and to barriers within the realization phase (limited market viability of ideas from scientists and limited Freedom to Operate). The causal analysis identified 11 root causes for these key problems, of which two were from the disease trajectory type, two of the public health and awareness type, two of the market and commercial type and four of the stakeholder collaboration type. Furthermore, two innovation barriers resulting from another domain led to key problems in this domain.

The business development domain encountered four key problems (see Figure 5). The problem with the most causal factors and root causes was the lack of translational research and buy-in from industry, due to the limited (perceived) return on investment for rabies

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**FIGURE 4** Causal tree on science domain. From left to right: per phase of the science domain the innovation barriers (key problems, causal factors and root causes), each having its own unique number. Colours refer to the domain from which the root causes originate: society (pink), science (purple) and business development (blue). Type: public health and awareness (H), disease trajectory (D), collaboration of stakeholders (S) and market and commercial (M). IP, Intellectual Property; FTO, the ability to conduct research activities without the risk of infringing IP rights of others. [Colour figure can be viewed at wileyonlinelibrary.com]
**FIGURE 5** Causal tree on business development domain. From left to right: per phase of the business development domain the innovation barriers (key problems, causal factors and root causes), each having its own unique number. Colours refer to the domain from which the root causes originate: society (pink), science (purple), business development (blue) and market (grey). Type: public health and awareness (H), disease trajectory (D) and market and commercial (M). ROI, Return on Investment; RCT, Randomized Controlled Trial; Dx, Diagnosis; RA, Regulatory Authority; R&D, Research and Development. [Colour figure can be viewed at wileyonlinelibrary.com]
medications, among others. Further key problems in the evaluation phase related to the difficulties that industry partners encountered with obtaining clinical evidence for new innovations and the regulatory burden for research and development. Finally, in the upscaling phase, a key problem related to the limited production capacity of biologicals was found. The key problems in this domain were the result of 11 domain-specific root causes, of which two disease trajectory related, five public health and awareness related and four market and commercial related. Furthermore, 10 innovation barriers originating from another domain, including root causes from the stakeholder collaboration type, contributed to the occurrence of these key problems.

Finally, within the market domain, seven key problems were identified (see Figure 6 and Figure 7). Two of these problems were encountered in the market introduction phase, namely a limited availability of products and the difficulty to combine PrEP and PEP, which were found to hinder the efficient completion and re-vaccination of individuals and thus the societal impact of vaccines. In the context of innovation, this means that any novel medical intervention that is to be used as add-on to existing interventions will face these difficulties. The remaining five problems all related to the reception of new innovations in the market. Next to products not being efficacious against all genotypes, a general lack of adoption was found by governments of endemic governments, by healthcare professionals and by patients. This is reflected in, among others, a lack of healthcare-seeking behaviour and compliance for PrEP and PEP, but caused by several underlying problems (Figure 7); 12 domain-specific root causes were identified to contribute to causing these key problems of which five of the disease trajectory type, five of the public health and awareness type, one of the market and commercial type and one of the stakeholder collaboration type. Furthermore, 11 innovation barriers that originated in other domains played a role in causing key problems in the market domain.

3.2 | Prioritization

A total of 75 respondents involved in human rabies filled out the survey (completion rate 100%). Analysis of the comments revealed no
FIGURE 7  Causal tree on market domain (2). From left to right: for the customer feedback phase the innovation barriers (key problems, causal factors and root causes), each having its own unique number. Colours refer to the domain from which the root causes originate: society (pink), business development (blue) and market (grey). Type: public health and awareness (H) and disease trajectory (D). Dx, Diagnosis; Ig, Immunoglobulin. [Colour figure can be viewed at wileyonlinelibrary.com]
new barriers. According to respondents, the most hampering barriers occur in the societal domain: lack of awareness of rabies as a health problem; limited (perceived) economic impact of rabies and; no societal pressure/lobbying for innovation in human rabies (Table 2). The order of barriers that are experienced by respondents differs from the order of barriers that respondents think hamper innovation the most.

| Importance | Key problem* | Domain | Experience |
|------------|--------------|--------|------------|
| 1          | Lack of awareness of rabies as a health problem | So     | 1          |
| 2          | Limited (perceived) economic impact of rabies | So     | 2          |
| 3          | No societal pressure for innovation in human rabies | So     | 7          |
| 4          | Lack of adoption by governments from endemic countries | M      | 5          |
| 5          | Limited availability of products | M      | 5          |
| 6          | Limited research efforts on rabies | Sc     | 4          |
| 7          | Lack of operational research | Sc     | 9          |
| 8          | Lack of multidisciplinary approaches | Sc     | 3          |
| 9          | Lack of healthcare-seeking behaviour of PEP | M      | 6          |
| 10         | Difficult to get clinical evidence for new innovations | BD     | 11         |
| 11         | Limited production capacity | BD     | 13         |
| 12         | (International) coordination problems | So     | 8          |
| 13         | Lack of translational research and buy-in from industry | BD     | 16         |
| 14         | Lack of direction in research | Sc     | 10         |
| 15         | Inherent complexity of rabies research | Sc     | 15         |
| 16         | Lack of healthcare-seeking behaviour of PrEP | M      | 14         |
| 17         | Lack of adoption by health care professionals | M     | 11         |
| 18         | High regulation burden for R&D | BD     | 18         |
| 19         | No demand for human rabies control | So     | 16         |
| 20         | Limited market viability ideas of scientists | Sc     | 12         |
| 21         | Limited efficacy of products against some genotypes | M     | 20         |
| 22         | Limited freedom to operate (due to IP rights) | Sc     | 19         |
| 23         | Difficult to combine PrEP and PEP | M     | 17         |

*Full name can be found in Figures 3–7.

**TABLE 2** Prioritization of innovation barriers. Some positions are shared by two key problems. The positions that differed ≥5 between importance and experience are highlighted in italic.

**TABLE 3** Relative attention to neglected tropical diseases. Comparison of the burden of disease in 1000s of disability-adjusted life years (DALYs) and the attention given to the disease in trials per 1000s of DALY

| DALYs | Order in terms of innovation effort | Number of trials | Sample size | Trials/DALYs | Sample size/DALYs |
|-------|-----------------------------------|-----------------|-------------|--------------|------------------|
| 1     | 12                               | 5,777           | 73          | 9,996        | 0.013            |
| 2     | 5                                | 3,796           | 160         | 46,887       | 0.042            |
| 3     | 9                                | 2,329           | 54          | 10,420       | 0.023            |
| 4     | 3                                | 2,090           | 184         | 23,039       | 0.088            |
| 5     | 8                                | 1,780           | 45          | 6,756        | 0.025            |
| 6     | 4                                | 1,702           | 142         | 35,026       | 0.083            |
| 7     | 13                               | 1,525           | 10          | 2,840        | 0.007            |
| 8     | 7                                | 667             | 22          | 1,772        | 0.033            |
| 9     | 10                               | 666             | 15          | 1,064        | 0.023            |
| 10    | 11                               | 665             | 14          | 1,306        | 0.021            |
| 11    | 12                               | 616             | 24          | 2,374        | 0.039            |
| 12    | 2                                | 484             | 62          | 25,182       | 0.128            |
| 13    | 1                                | 198             | 120         | 14,772       | 0.606            |

*Based on Kappagoda and Ioannidis (2012).*
4 | DISCUSSION

Despite the existence of pressing societal and medical unmet needs in terms of affordability, accessibility and the development of therapeutics (Ertl, 2009; Levine, 2011), little successful innovation has been realized in human rabies treatment (Bourhy et al., 2010) since the development of the first rabies vaccine during the 19th century. Rabies suffers from a lack of attention which is disproportionate to its position in the top five of NTDs (Kappagoda & Ioannidis, 2012). This is not unique for rabies however, as there seems to be no relation between the actual impact of NTDs and the innovation efforts for specific NTDs (Table 3). The prioritized key problems presented in this study indicate that in the case of rabies, a lack of attention is primarily due to a lack of awareness, economic impact and societal pressure (Table 2). These factors are less relevant for diseases with a chronic nature, such as leprosy, onchocerciasis and leishmaniasis, which indicates an invariable discrepancy.

The limited efforts can be attributed to both industry and public–private partnerships that aim to accelerate drug development for several other diseases, but not rabies. Neither philanthropic programmes of industry nor initiatives such as the Bill & Melinda Gates foundation, the Foundation for Innovative New Diagnostics (FIND) and the Drugs for Neglected Diseases initiative (DNDi) have rabies on their agenda. Surprisingly, interviews nor scientific literature mention the lack of funding for distribution and usage of the products as a barrier, suggesting that organizations like the Global Alliance for Vaccination and Immunization (GAVI) are purely seen as solutions to the problem. This way, the existence of challenges they experience, such as the risk of displacing funds to the black market, is voided (GAVI, 2013).

This study identified 119 distinct innovation barriers, of which a limited set of 43 are root causes. The 43 root causes were categorized in only four main types that have their effect across the valorization cycle; 48 of 119 innovation barriers were identified only through the interviews and focus group discussion with KOLs and were not yet described in literature. This study thereby contributes to the understanding of innovation barriers by providing a comprehensive overview of documented and previously not described barriers in the field of rabies innovation.

The analysis shows that innovation in human rabies prophylaxis and treatment is hampered in all stages of the valorization cycle and barriers hinder activities for all stakeholder groups. A barrier that was prominently mentioned is the limited return on investment which is a direct cause of the neglect by industrial parties (Figure 5: 13b). In past decades, this return of investment has been the focus of studies and strategies to control NTDs, such as the establishment of public–private partnerships to make R&D cost-effective (Frew, Liu, & Singer, 2009). This study substantiates the existence of a limited perceived return on investment (ROI) but the RCA shows how a lack of knowledge on the market can hamper innovation by influencing the perception of the market size (Figure 5: 13b and 13e). Importantly, barriers beyond this limited ROI are also revealed and activities in the market domain, not the business development domain, appear to encounter most barriers (44/119). Moreover, the top three most important key problems are perceived to be in the society domain (Table 2). Although involvement of the private sector is essential to achieve societal impact of innovation (Claassen, 2014; Reperant, Van De Burgwal, Claassen, & Osterhaus, 2014; Taylor, 2013), the current study thus pinpoints numerous innovation barriers and root causes in other domains on which specific actions should be taken to prevent a cascade of events leading to a lack of innovation.

Fifteen of 43 root causes are of the public health and awareness type, which makes it the major root cause for the lack of innovation (Table 1). The effect of this limited public health and awareness extends to most stakeholder groups: researchers, industry, healthcare professionals, patients and public health authorities. Even if a new product would be able to successfully complete the development stage, once it enters the market, its adoption depends greatly on the local healthcare system and the awareness of the general public. One striking example of how the societal impact of human rabies PEP can be hampered in the market domain is the implementation of the intradermal administration route, one of few innovations in recent years, that suffers from confusion caused by an abundance of regimens, thereby leading to its use being restricted by some regulatory authorities due to limited clinical evidence (Warrell et al., 2008; Figure 7: 21a). However, adoption is also hampered from the patients’ side, among others, due to limited awareness and knowledge among risk groups (Figure 7: 22b). In recent years, rabies experts worldwide have launched programmes to increase awareness (such as “World Rabies Day”) but with effective and in some endemic countries free vaccines available, many rabies deaths still seem to result from a lack of healthcare-seeking behaviour (Taylor, 2013). The lack of actions in response to these initiatives and, thus, limited relevance of public health measures, warrants operational research on how to improve these programmes (Figure 7: 22j). The data derived from such research enable the accurate estimation of the potential impact as well as the implementation of human rabies prophylaxis and treatment, which may increase innovation efforts.

The lagging results of international efforts to innovate in the field of human rabies can also be explained from the limited collaboration amongst stakeholders. This study shows that the rabies field is not insensitive to common valorization barriers and that steps between domains are often skipped. Stakeholders from some domains act within their own discourse without being connected to other domains, as was shown before for other fields of public health (Claassen, 2014; Pronker, 2013; Van Den Nieuwboer, Van De Burgwal, & Claassen, 2016). This becomes especially evident from the limited number of innovations that are successfully transferred from the science to the business domain (Figure 4: 10c and 12a). The transfer could be improved if stakeholders would expand their activities to other domains or share their knowledge, thereby gaining understanding on the dynamics of other domains (Figure 4: 10a). Additionally, stakeholders operating within the same domain are facing barriers related to the lack of integration of their activities. In the society domain, the different stakeholders appear to favour either a human or a veterinary approach and to compete, rather than work together towards a common goal of rabies control (Figure 3: 4d and 5b). Today, innovators in the rabies
field are encouraged to apply a One Health approach, thereby considering human, animal and environmental factors. Although environmental factors are often neglected, climate change is important and may affect the population dynamics of various reservoirs, such as in the Arctic with transmission of rabies viruses among different species of foxes or potential impacts among bat populations, for example New World vampire populations (Kim et al., 2014; Lee, Papes, & Van Den Bussche, 2012). Although the wide range of other wildlife hosts makes complete rabies eradication impossible today, animal rabies control programmes have been successful in Europe and showed considerable results in Latin America (Cleaveland, Lankester, Townsend, Lembo, & Hampson, 2014). Rabies thereby serves as precedent for a successful One Health approach, which tackles the problem at the source and reduces costs on the long run (Bogel & Meslin, 1990; Zinsstag et al., 2009). Implementation of animal rabies control programmes is a costly process but shows to be cost-effective within 7–15 years, depending on the size of the dog population (Abbas, Kakkar, & Rogawski, 2014; Bogel & Meslin, 1990; Zinsstag et al., 2009). Besides saving costs, long-term commitment to these programmes would delay human exposure for up to 6 years, thereby drastically lowering the burden of disease (Zinsstag et al., 2009). As these approaches are facing barriers of their own (Cleaveland et al., 2014), improved collaboration between medical and veterinary stakeholders could ensure the most efficient control of rabies disease.

Ten root causes have their origin in market and commercial aspects and affect innovation for innovation in human rabies medication across the valorization cycle. Such barriers include the complexity of the market structure (Figure 5: 13m), implying that market analysis is essential, and the costs of innovative products (Figure 5: 13n). Root causes of this type also affect other domains such as the society domain, in which the erroneous idea that rabies does not affect livestock hampers the perceived economic impact and thus the perceived need for innovation (Figure 3: 2d). In addition, once this barrier has been overcome and an innovative product has been developed, it encounters a number of barriers in the market domain. One of these barriers for example involves the packaging of multiple doses per vial leading to a wastage of PEP doses (Figure 7: 17f).

Lastly, disease trajectory barriers reflect the lack of fundamental knowledge on viral pathogenesis and immune system responses. This is contrary to the prevailing idea that all is known about rabies (Figure 4: 7c) and this study indicates a clear need for more basic research. Although rabies is an ancient disease, the importance of biomedical innovations for rabies is further increasing. For example, a decline of vultures in some developing countries may result in an increase of carcasses and the number of stray dogs, influencing disease dynamics to an extent that conventional surgical dog sterilization techniques are unable to provide adequate contraceptive compensation for (Maenhoudt, Santos, & Fontbonne, 2014; Markandya et al., 2008). Moreover, the emergence of novel Lyssavirus species that are divergent from phylogroup I and cause rabies-like diseases can limit the relevance of current vaccines (Evans, Horton, Easton, Fooks, & Banyard, 2012). The large number of animal species transmitting rabies makes true global eradication highly unlikely and the market for disease specific medical interventions stable, if not growing.

To improve effectiveness of future activities, stakeholders can use this study as a tool to identify the barriers most relevant to them, based on the specific activities of stakeholders, the specific medical need that they aim to meet, the geographical location of their activities or the social status of their target group. Besides, stakeholders should transcend their activities in a collaborative effort and increase societal pressure, which is less often directly experienced but seriously affects the innovation process (Tables 2 and 3). The causal tree and prioritization study reveal a qualitative and quantitative degree of importance, in the barriers that have to be overcome to accelerate innovation. Root causes are fundamental rather than symptomatic barriers and tackling them thus has the greatest impact (Braun, 2002) although this may also be most difficult to achieve due to their systemic nature. Acknowledging the restricted field of expertise of KOLs involved in the early stages of data collection, the prioritization of key problems included the insights of a more international group of KOL, and no new barriers were added by this group. The prioritization furthermore adds a practical component to the study and highlights which root causes and cascades of barriers are most important to tackle. The current study emphasizes the needs to look at barriers beyond a limited return on investment in the business development domain and to include barriers in the society, science and market domain. A reorientation on fundamental root causes and intermediary causal factors for symptomatic key problems is necessary to address the lack of innovation in current rabies interventions and to be prepared for possible altered dynamics in rabies epidemiology in the future.

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