Infectious disease

Burden of human rabies disease: its potential prevention by means of Rabipur® vaccine

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Summary

Rabies is a zoonotic viral disease transmitted mainly by bites of infected animals, especially dogs, which are responsible for 99% of human cases. Despite being preventable, it remains a neglected disease in low-income countries, with approximately 60,000 deaths per year, mostly concentrated in Africa and Asia. The real worldwide burden of rabies is probably underestimated, as death-reporting systems are inadequate and active surveillance is limited.
Rabies prevention implies two main, non-exclusive strategies: (i) dog vaccination, in order to interrupt virus transmission to humans, and (ii) human vaccination i.e. pre-exposure prophylaxis (PrEP) and Post-Esposure Prophylaxis (PEP) through the use of purified cell-culture and embryonated egg-based vaccines (CCEEVs).
Rabipur® is one of the available anti-rabies vaccines and is indicated for active immunization in individuals of all ages. Its efficacy and safety have been amply demonstrated.
In rabies-free countries, PrEP is indicated for individuals who face occupational and/or travel-related exposure to the rabies virus in specific settings or over an extended period.
Wider use of human rabies vaccination for PrEP and PEP in conjunction with programs to eradicate rabies from animal populations is the challenging goal in order to reduce the burden of disease and achieve zero rabies.

Introduction

Rabies is a zoonotic viral disease of mammals that is transmitted from animals to humans by exposure to saliva or other sources of infectious virus. Exceptional cases of direct human-to-human transmission and indirect transmission via infected transplants have also been reported [1-3].
After a bite by an affected animal, the virus present in the saliva reaches the peripheral nerves and then the brain. Once the rabies virus infects spinal cord neurons, dissemination proceeds quickly throughout the central nervous system by means of fast axonal transport along neuroanatomical pathways. Many neuronal cell types throughout the central nervous system are infected, whereas infection of non-neuronal cells, including astrocytes, occurs much less commonly [4, 5]. Brain infection results in behavioural changes, probably due to the infection of neurons in limbic areas. Subsequently, the rabies virus spreads away from the central nervous system (centrifugal spread) along neuronal pathways, particularly involving the parasympathetic nervous system, to many organs, including the heart, gastrointestinal tract, adrenal medulla, skin and saliva glands.
While all mammalian species are believed to be susceptible, rabies is mainly detected in dogs, wolves, foxes, coyotes and jackals, raccoons, mongooses, skunks and bats [6]. Dogs are responsible for 99% of human cases [7].
Clinically, rabies is characterized by fitful consciousness, hyperactivity, hallucinations and hydrophobia (furious rabies), or paralysis and coma (paralytic rabies), progressing rapidly and inevitably towards death [8].
Rabies is considered to be a neglected disease, as global and national stakeholders and decision-makers lack awareness of its importance and have not prioritized it. Indeed, global funding agencies do not generally provide funding for rabies elimination efforts; this means that rabies remains under-resourced, especially in the areas most affected by the disease. As a result, the burden rabies persists.
Here, we present a narrative overview on rabies disease, focusing on its clinical, epidemiological burden and the opportunity for prevention by means of Rabipur® vaccine.

Characteristics of rabies virus and clinical symptoms of the disease

The rabies virus is a member of the genus *Lyssavirus*, which belongs to the family of *Rhabdoviridae*; these consist of genetically related enveloped viruses with a single non-segmented negative-stranded RNA [9, 10].
The virus contains multiple copies of five structural proteins: virion transcriptase L, glyocoprotein G, nucleoprotein N, phosphoprotein P, and matrix protein M. The G and M proteins are responsible for blocking apoptosis after infection by virulent street of viruses, which is a protective mechanism for the host. The G protein is a major determinant of viral neurotropism. Mutations in the

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G protein reduce or eliminate neuroinvasiveness without impairing the ability of the virus to multiply in cell culture [11-13]. The G protein of the rabies virus is the main antigen responsible for inducing the production of virus-neutralizing antibodies and for conferring immunity against lethal infection by the rabies virus. Located on the surface of the virion, this glycoprotein plays an important role in the host's immune response and facilitates interaction of the virion with host cell receptors.

The incubation period of rabies is reported to range from weeks to years, but mostly lasts 1-2 months on average; indeed, in the majority of cases, incubation takes between 20 and 60 days [14, 15]. Moreover, it has been observed that the incubation period is shorter if the bite occurs in the head rather than in an extremity.

The clinical stages of rabies can be summarized as; incubation, prodrome, acute neurological signs, coma, and death. Once the infection manifests itself clinically, death almost always occurs within 7-10 days. Weakness in the bitten extremities may be evident on primary presentation; subsequently, the disease may progress to either the furious or paralytic form [16-18]. The features of furious rabies are fluctuating consciousness, hydrophobia or aerophobia, inspiratory spasms, and signs of autonomic dysfunction. These may not appear simultaneously, and disappear during coma. Comatose patients with furious rabies may develop flaccid limb weakness, which has frequently been misinterpreted as paralytic rabies. Conversely, ascending weakness of lower motor neurons with only motor disturbance is the initial manifestation of paralytic rabies [17], in which consciousness is preserved until the preterminal phase.

Atypical signs and symptoms of rabies associated with infection by either bat or dog rabies virus variants have been increasingly recognized [15-19]. Transverse myelitis presenting as neuromyelitis optica, and tetanus-like symptoms with locked jaw have been reported [20-22].

Epidemiological burden

The real worldwide burden of rabies is probably underestimated, as death-reporting systems are inadequate and active surveillance is limited [23-25]. Moreover, the widespread unavailability of laboratory diagnosis gives rise to false results, incorrect assessments of rabies epidemiology and, consequently, difficulties in rabies control [26]. Indeed, owing to socio-cultural norms also, laboratory testing of human brain samples is not practical in low- and middle-income countries; hence, the majority of cases of rabies in humans are identified exclusively on the basis of symptoms.

The under-reporting of rabies is complicated by the pathophysiology of the disease itself. Indeed, most individuals with rabies do not present in hospital for diagnosis, since they know that the disease is terminal as soon as the symptoms arise. Moreover, in regions where other diseases with neurological symptoms are common, rabies may be misdiagnosed as these other diseases.

Other methods, such as a probabilistic decision-tree approach, are used in order to calculate the likelihood of a person contracting clinical rabies after being bitten by a dog suspected of having the virus [26]; on the basis of this technique, Knobel et al. argued that canine rabies was responsible for about 55,000 deaths per year across Africa and Asia [23]. However, more data have become available, and the dynamics of the disease has shifted, with a rise in occurrence in some regions and the appearance of rabies in those previously free from the disease [27].

As mentioned above, rabies is an ancient disease with about 60,000 human deaths per year, mostly in Asia and Africa. Most deaths occur in children (approximately 40%), who are more susceptible because of their curious/adventurous nature and their shorter stature, making them more likely to sustain a wound in a higher-risk anatomical location, such as the head [27].

In resource-limited and resource-poor countries, endemic dog rabies, which is sustained by dog-to-dog transmission of the rabies virus, results in an ongoing risk of transmission to humans due to dog bites. Furthermore, rabies in wildlife is still a problem in North America and Europe [27].

According to the latest epidemiological reports, rabies remains a cause for alarm, mainly in Asia, Africa, the Middle East, Latin America and the Caribbean [28-31]. Furthermore, towards the end of the last century, rabies re-emerged in China, and it spread in historically free islands such as Flores and Bali (Indonesia) [31, 32].

Notably, rabies transmission is linked to the socio-economic status of a country, with a high prevalence of the disease being detected in poor areas [26, 33, 34]. Indeed, it has been documented that the incidence and transmission of rabies are negatively correlated with economic development [33-35]. In El Salvador, for example, the country's economic and social crisis has hindered rabies control programs. Furthermore, the capacity for vaccine manufacture and procurement influences the status of rabies in a country [33-35]. Another relevant issue is the high cost of post-exposure rabies programs in developing countries, which is not sustainable by most residents.

Canine and wildlife-mediated rabies burden

A possible strategy for controlling rabies disease is to vaccinate dogs. The cost of vaccinating dogs, which can limit human exposure and curb the spread of the disease, is negligible [36, 37]. However, the lack of funding hinders this action in the developing countries. In the countries where the dog's vaccination is widely implemented good results have been achieved. For example, the United States is one country that has maintained a significant investment in dog vaccination, with the cost being estimated as $0.11/person/year [3, 38].

However, the recent pandemic affected the implementation of mass vaccinations for dogs (interruptions to mass dog vaccination campaigns and disruptions in vaccine supply). Consequently, after the COVID-19 emergency, a sudden spike in rabies cases and dog-bite-induced deaths in India and many other countries were registered.

Fig. 1. Occurrence of canine rabies [40].

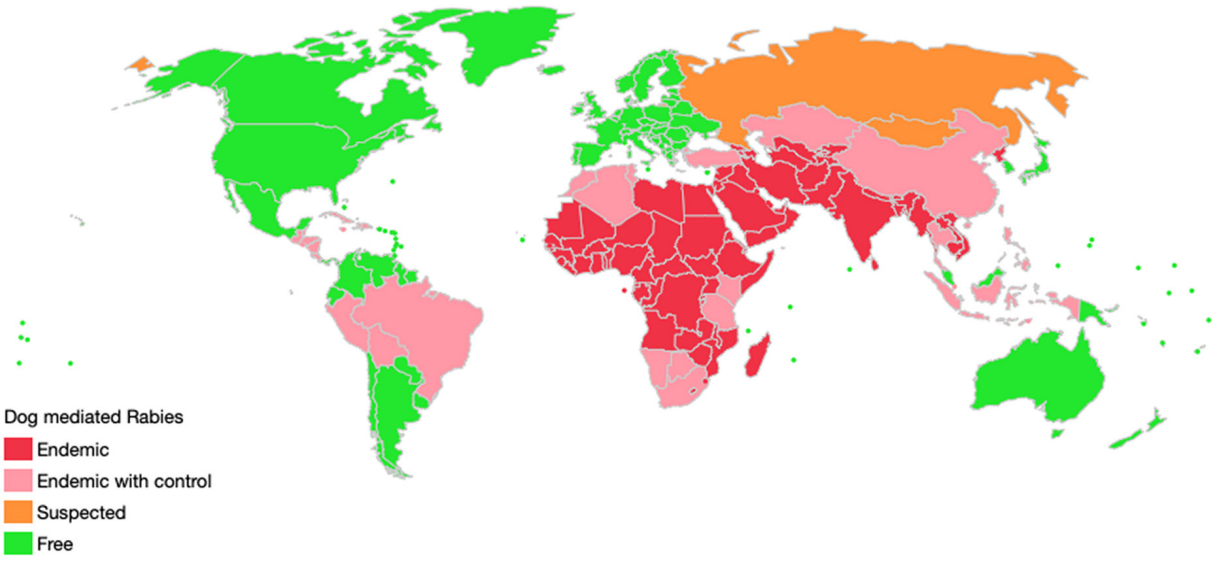
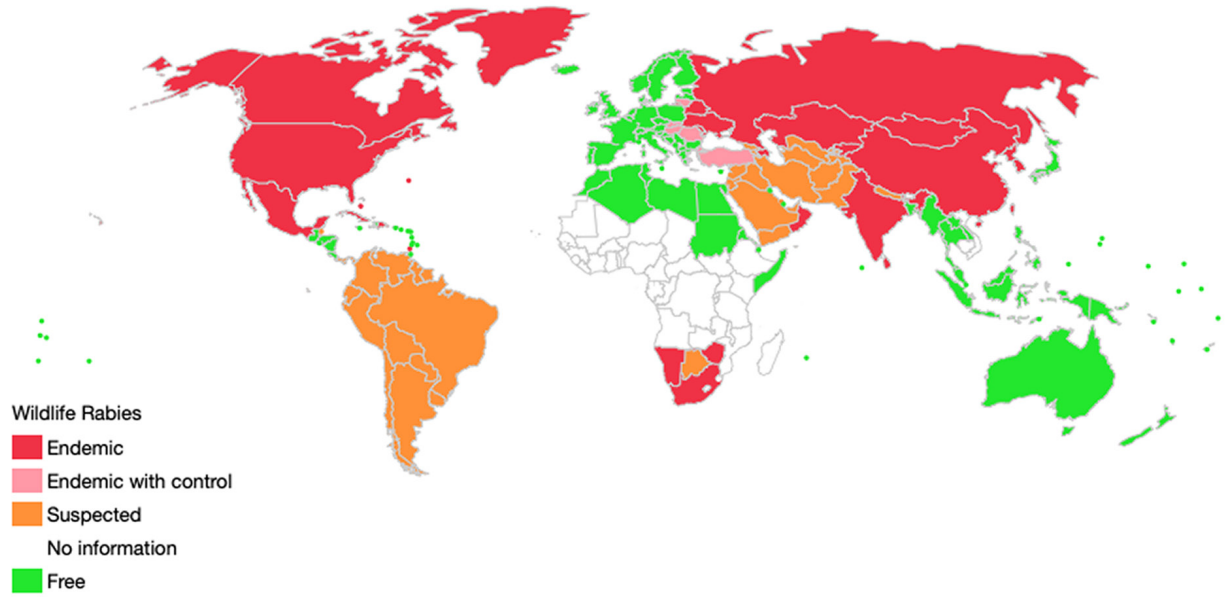


Fig. 2. Occurrence of wildlife-mediated rabies [40].



Monitoring canine rabies and wildlife is critical for the control and elimination of disease [39].

Figure 1 shows the occurrence of canine rabies [40]. Dog-mediated rabies has been eliminated from Western Europe, Canada, the United States, Japan and some Latin American countries. Australia and many Pacific Island nations have always been free from dog-mediated rabies. Nevertheless, these countries may still report imported cases and incur costs for maintaining disease freedom or the surveillance of endemic transmission in wildlife. In South America, efforts to eliminate canine rabies have been enormously successful.

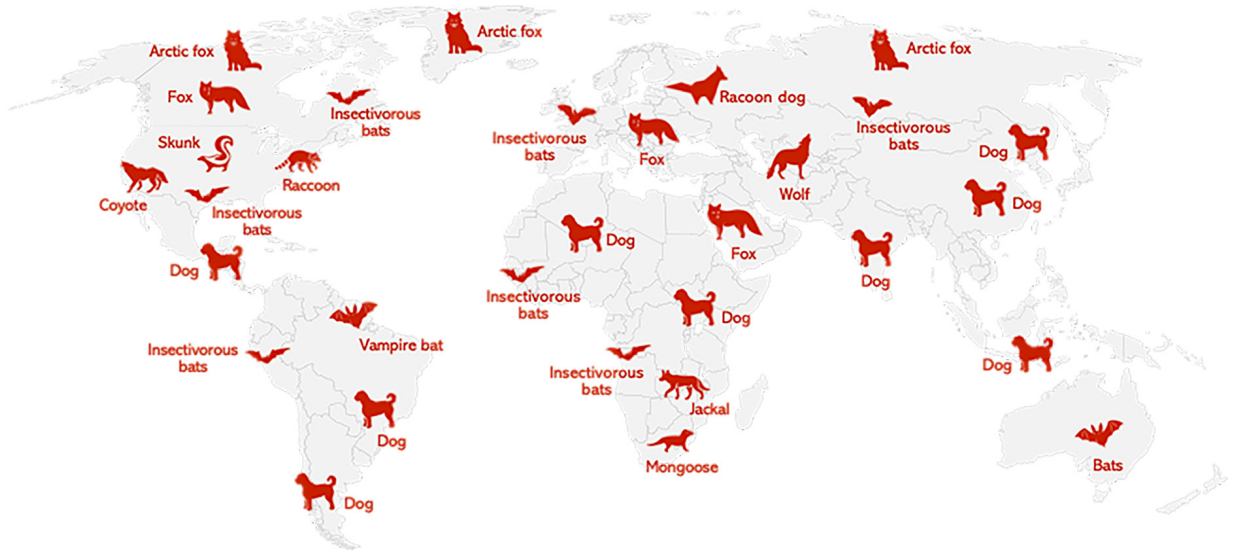
Figure 2 shows the occurrence wildlife-mediated rabies [40]. Other animals, such as bat species, are also reservoirs for the rabies virus. As can be seen, rabies virus vectors and reservoir species are widespread.

It is well recognized that carnivora (carnivores) and chiroptera (bats) are the canonical mammalian orders responsible for the maintenance and onward transmission of rabies Lyssavirus. However, the role of most species within these orders is not yet completely known and is continually changing as a result of contemporary host shifting (Fig. 3) [41, 42].

Human rabies burden

Figure 4 reports the worldwide prevalence of rabies (human cases per 100,000 pop.). The data refer to 2010 and the 2019-2021 period [43].

Fig. 3. Global distribution of mammalian rabies reservoirs and vectors [41, 42].



Although the number of rabies cases has decreased significantly, the prevalence of the disease is still high in many countries. In Asia, the continent with highest number of cases, 35,172 human deaths per year are estimated to occur. The cost of Post-Exposure Prophylaxis (PEP) is highest in Asia, with estimates up to US$ 1.5 billion per year. India accounts for 59.9% of rabies deaths in Asia and 35% of deaths globally. In Central Asia and the Middle East, the numbers of human deaths are estimated to be 1,875 and 229 per year, respectively [44]; however, limited information is available on the burden of disease in these areas.

Recently, the age-standardized incidence was evaluated by a Chinese research group [45]; the global incidence was seen to have decreased from 24,745 cases in 1990 to 14,076 cases in 2019. Moreover, the estimated number of rabies cases in 2030 will be close to 5,810. Nevertheless, achieving zero rabies remains a challenging goal [46].

A total of 21,476 human deaths due to dog-mediated rabies [47] are estimated to occur each year in Africa. It is estimated that Africa spends the least on PEP and consequently has the highest human mortality. Improving access to PEP and reducing the prevalence of dog-mediated rabies could save a significant number of lives. In Latin America and the Caribbean, a concerted effort by the Pan American Health Organization and sustained control in the region has led to a significant decrease in cases of human and dog rabies. Today, bat-mediated rabies accounts for the majority of human cases in the Americas [48].

According to the latest available ECDC report (2022), no human lyssavirus infections were reported in Europe in 2020 and 2021. By contrast, human lyssavirus infections were reported in 2019 and 2018 [49]. However, travel-associated human rabies cases have sometimes occurred in Europe, as reported in recent years. Specifically, in 2018-2019, cases were reported in countries of the European Union, including four travel-related cases and one EU-acquired non-rabies lyssavirus infection caused by European bat lyssavirus 1. In particular, the cases occurred in travelers returning from Morocco (N = 2), Tanzania (N = 1) and India (N = 1). In 2019, France reported an EU-acquired infection due to European bat lyssavirus 1 (EBLV-1) [49]. Finally, one travel-related case was reported in the United Kingdom in 2018.

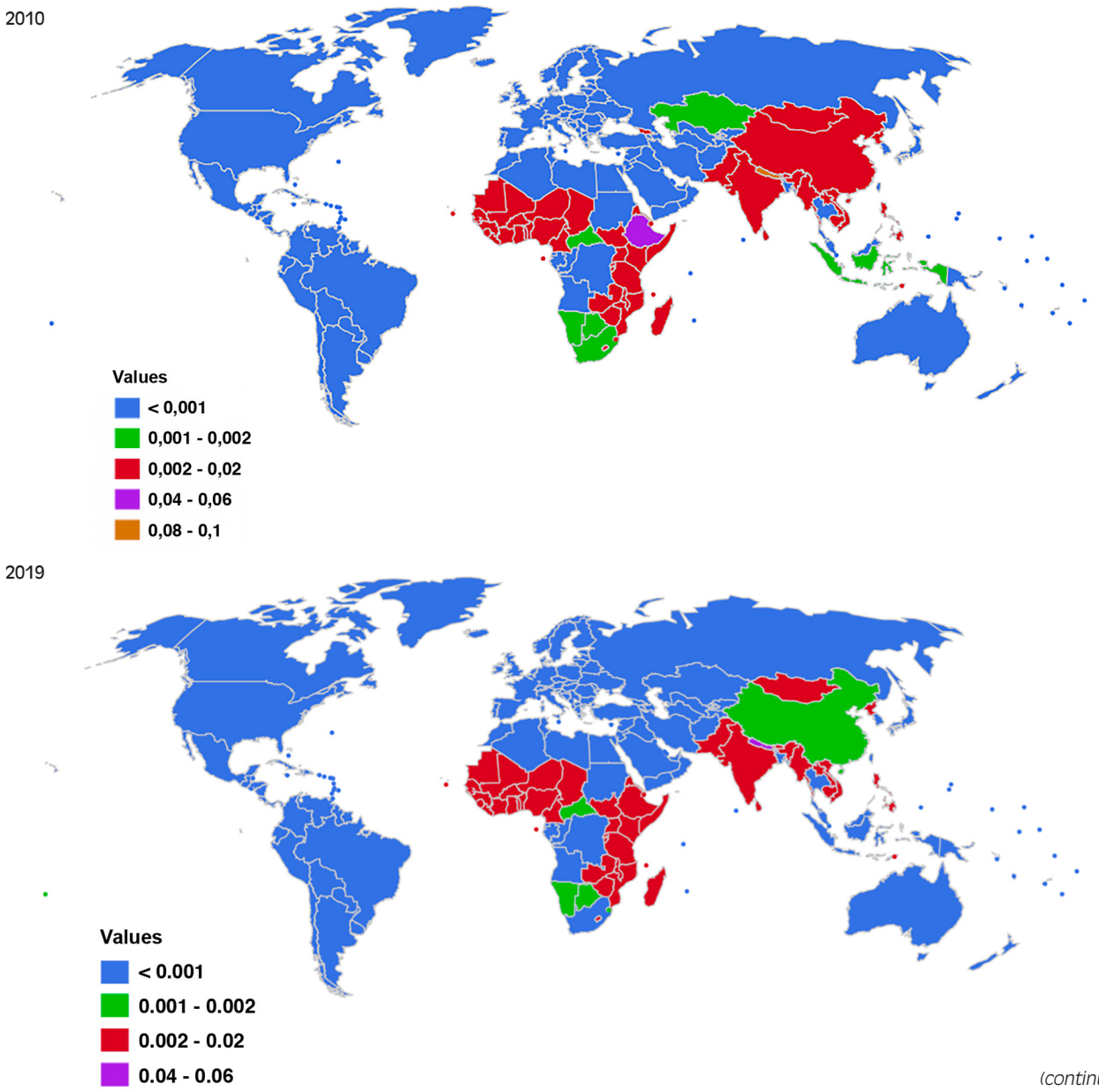
Preventive opportunity in Europe: focus on Rabipur® vaccine

As previously described, rabies is an infection that can be transmitted when a person is bitten, scratched or even just licked by an infected animal, especially if the skin is not intact. Contact with animal traps that have been licked or bitten by infected animals can also cause infections in humans.

Rabies prevention implies two main, non-exclusive strategies: (i) dog vaccination, in order to interrupt virus transmission to humans, and (ii) human vaccination *i.e.* Pre-Exposure Prophylaxis (PrEP) and Post-Exposure Prophylaxis (PEP) through the use of purified cell-culture and embryonated egg-based vaccines (CCEEVs) [46].

The initial rabies vaccine was created by Louis Pasteur in 1885, who used the dried spinal cord of infected rabbits. Subsequently, rabies vaccine production was directed towards sources of virus propagation in materials free from neural tissue. Cell-culture-based and embryonated egg-based vaccines were therefore developed. In embryonated egg-based rabies vaccines, the complete embryo is used for virus propagation. By contrast, cell-culture-based vaccines contain the rabies virus that has been propagated in cell substrates (*e.g.*, primary hamster kidney cells, human diploid

Fig. 4. The worldwide prevalence of rabies (human cases per 100,000 pop.) in 2010, 2019, 2020 and 2021 (available data on August 2024) [43].



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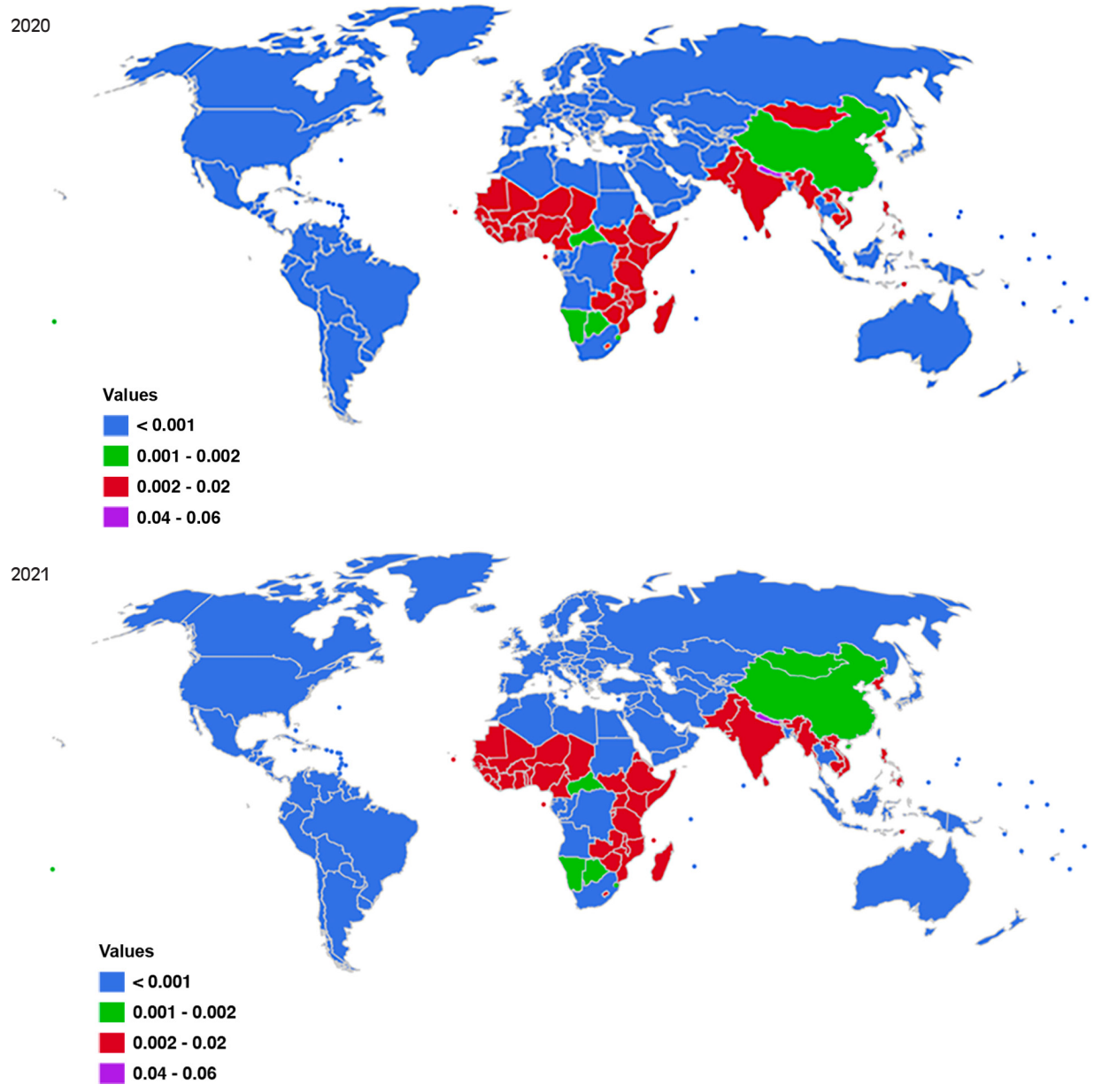
cells, chick embryo cells or Vero cells) [3]. Since 1984, the World Health Organization (WHO) has strongly recommended modern, concentrated, purified CCEEVs [3]. All CCEEVs are able to promptly induce a high level of virus-neutralizing antibody response to the G protein of the rabies virus. The WHO-specified minimum serum antibody concentration of 0.5 International Unit (IU)/mL is widely used as a measure of adequate seroconversion after vaccination. In most individuals, irrespective of age or nutritional status, this level is reached by day 7 to 14 [3].

Rabipur® is an inactivated, purified chick embryo cell culture rabies vaccine for human use. One dose contains ≥ 2.5 IU of rabies antigens in 1.0 mL dose of lyophilised inactivated rabies virus of the Flury low egg passage (LEP) strain, polygeline, salts and sucrose as excipients, and trace amounts of amphotericin B, chlortetracycline, neomycin, human serum albumin and chicken proteins (*e.g.,* ovalbumin) [50].

The vaccine was first approved in Germany in 1984, and subsequently in the UK in 2016. At the time of development of the vaccine, a six-dose Essen regimen of PEP was officially recommended by the WHO. Consequently, Rabipur® was initially assessed in clinical trials involving six 1.0 mL intramuscular (IM) doses for PEP, and was licensed as such. According to WHO guidelines, the PEP six-dose Essen regimen produced an adequate antibody response [3]. Subsequently, the shorter Zagreb regimen used an abbreviated schedule of two doses on Day 0 and one dose on Days 7 and 21 (2-1-1).

Fig. 4 (*follows*). The worldwide prevalence of rabies (human cases per 100,000 pop.) in 2010, 2019, 2020 and 2021 (available data on August 2024) [43].



Rabipur® is indicated for active immunization PrEP and PEP against rabies in individuals of all ages, according to official recommendations [50]. The recommended dose for both primary immunisation and boosters is 1.0 mL.

To date, Rabipur® has been authorized in 15 European Economic Area (EEA) countries and in 8 non-EEA countries: UK, Switzerland, Australia, Canada, Japan, New Zealand, Singapore and the USA.

Pre-exposure prophylaxis of Rabipur® vaccine

Primary immunization involves three doses administered according to the conventional day 0, day 7, day 21 (28) or the rapid regimen (days 0, 3, 7), available in Europe, in unvaccinated individuals (Tab. I). The rapid regimen should only be considered for adults aged 18-65 years who are not able to complete the conventional PrEP regimen within 21 or 28 days before protection is required (Tab. I). Alternatively, in immunocompetent individuals, the one-week regimen with 2 doses can be used: at time 0 and after 7 days. This new product information is available from October 2023 [50] (Tab. I). Evidence for a shortened PrEP regimen is consistent with the latest recommendations from the WHO, the US Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) [51] and several European national rabies guidelines.

The conventional 3-dose regimen should be implemented in immunocompromised individuals. The rapid regimen and the one-week schedule with 2 doses on days 0 and

Tab. I. Primary immunization schedules in individuals never previously vaccinated [50].

	Conventional schedule	Accelerated schedule	One-week regimen
1 dose	Day 0	Day 0	Day 0
2 dose	Day 7	Day 3	Day 7
3 dose	Day 21 (28)	Day 7	

7 may be administered, if accompanied by serological testing at 2-4 weeks after the first rabies vaccine administration, to assess whether an additional vaccine administration is needed. Consultation with an infectious disease specialist or an immunologist is advised.
Booster doses are generally recommended every 2-5 years. The timing of booster administration after vaccination with the rapid regimen has not yet been established. In accordance with official recommendations, serological testing for the presence of antibody titers ≥0.5 IU/mL should be conducted to assess the need for booster doses. Rabipur® may be used as a booster vaccine in subjects previously immunized with any rabies vaccine derived from human diploid cells [50].
The vaccine may be used for pre-exposure prophylaxis during pregnancy and in breastfeeding women if it is considered that the potential benefit outweighs any possible risk to the fetus and the infant [50].

Post-exposure prophylaxis of Rabipur® vaccine

Regarding PEP, this should begin as soon as possible after exposure.
Table II summarizes recommendations for PEP by type of exposure.
In-post-exposure prophylaxis of previously unvaccinated individuals, the vaccine should be administered according to Table III [50].
In previously vaccinated individuals, post-exposure prophylaxis consists of two doses administered on days 0 and 3. Rabies immunoglobulin is not indicated in such cases.
In immunocompromised individuals with category II and III exposures (Tab. II), 5 doses should be given in combination with comprehensive wound management and local infiltration of rabies immunoglobulin.
In view of the almost invariably fatal outcome of rabies, there is no contraindication to post-exposure prophylaxis in pregnancy and in breastfeeding women.

Immunogenicity of Rabipur® vaccine

The immunogenicity of Rabipur® has been assessed in more than 50 clinical trials since 1983, in both PEP and PrEP regimens, using both IM and Intradermal (ID) administration. The trial populations have consisted of adults and children aged ≥12 months [3]. A concise overview of the main studies is provided below.
A double-blind comparative clinical trial carried out by Vodopija I. et al. [52] evaluated the immunogenicity of three tissue culture rabies vaccines by using a commercial human diploid cell vaccine (HDCV) lot as the comparator. Two different vaccination regimens, a pre-exposure schedule, and an abbreviated 2-1-1 post-exposure schedule (two doses of the vaccine applied bilaterally on day 0, with subsequent single doses given on days 7 and 21) were tested. In both regimens, purified chick embryo cell vaccine and purified Vero rabies vaccine induced an antibody response equivalent to that of HDCV. The 2-1-1 regimen rapidly induced a high antibody titre response, peaking on day 14.
Subsequently, a study by Nicholson KG et al. [53] investigated the response and persistence over two years of antibody titres elicited by a purified chick embryo cell culture rabies vaccine and a human diploid cell strain rabies vaccine. An antibody response was detected in all subjects on day 14, the highest titres being found after two intramuscular 1.0 mL doses administered on days 0, 7 and 21. In total, 177 volunteers were enrolled. By comparison, a schedule of immunization on days 0, 28 and 56 induced the highest titres 21 days after the final injection; on both schedules, antibody titres persisted equally over two years. Neutralizing antibody titres were lower after ID vaccination with 0.1 mL than with 1.0 mL IM on days 0, 7 and 21; when given on days 0, 28 and 56, however, the responses were comparable.
Analogously, a study that evaluated the antibody response and duration and the anamnestic response to boosters over a 2-year period found that vaccination with Rabipur® via an IM or ID regimen resulted in an adequate immune response by day 28, which was sustained on day 365 [54]. This clinical trial [54] assessed the immunogenic effects of a purified chick embryo cell (PCEC) rabies vaccine administered ID or IM. Four arms were involved: *i.e.* ID PrEP, IM PrEP, ID Booster, and IM Booster vaccination. In total, 130 adult volunteers participated in the clinical trial. Subjects undergoing IM administration received the vaccine according to the ACIP recommendations: PrEP, three 1 mL (2.5 I.U.) rabies vaccine doses (days 0, 7, and 21) or a routine booster of one 1 mL dose. The ID groups followed the same schedule, but the volume of the doses administered was different [volume of 0.1 mL (0.25 I.U.)]. The researchers found a similar rate of increase in rabies virus neutralizing antibody titres 14-21days after vaccination in both the ID and IM groups. The GMTs values elicited by ID vaccination were slightly lower than those elicited by IM vaccination, in both naïve and booster groups, and these differences were statistically significant. Fourteen days after completing vaccination, all individuals developed neutralizing antibody titres above the minimum arbitrary. Antibodies remained above the set threshold until the end of the trial, 160 days after the completion of vaccination.
Jaijaroensup W et al. [55] investigated the immunogenicity of rabies post-exposure booster injections in subjects

Tab. II. Recommendations for Post-Exposure Prophylaxis (PEP) [50].

Exposure category	Type of exposure to a rabid animal or suspected domestic or wild exposure [a] or exposure to an animal that cannot be analyzed	Recommended prophylaxis
I	The animal was touched or fed. Licking of intact skin. Contact with secretions or excretions of a rabid animal or human on intact skin.	None, if a reliable history can be gathered.
II	Light bite on unprotected skin. Superficial scratches or abrasions without bleeding.	Administer the vaccine immediately [b]. Discontinue treatment if the animal remains healthy for an observation period of 10 days [c] or if the animal tests negative for rabies on appropriate diagnostic techniques performed in a reliable laboratory.
III	Single or multiple transdermal bites [d] or scratches, licking of damaged skin. Contamination of mucous membranes with saliva (e.g. licks). Exposure to bats [e].	Administer rabies vaccine immediately and rabies immunoglobulin preferably as soon as possible after starting PEP. Rabies immunoglobulin can be injected up to 7 days after administration of the first dose of the vaccine. Discontinue treatment if the animal remains healthy for a 10-day observation period or if the animal tests negative for rabies on appropriate diagnostic techniques performed in a reliable laboratory.

[a] Exposure to rodents, rabbits or hares does not routinely require post-exposure prophylaxis.
[b] If an apparently healthy dog or cat from or one from a low-risk area is placed under observation, postponement of the start of treatment may be justified.
[c] The observation period refers only to dogs and cats. Except for animal species that are threatened or in danger of extinction, other domestic or wild animals suspected of rabies must be euthanized humanely and their tissues examined for rabies antigen by means of appropriate laboratory techniques.
[d] Bites, especially on the head, neck, face, hands and genitals, are considered category III exposures, owing to the abundant innervation of these areas.
[e] Post-exposure prophylaxis should be considered in the case of contact between a human and a bat, unless the exposed person can exclude a bite or scratch, or on exposure of a mucosa.

Tab. III. Post-exposure immunisation regimens for previously unvaccinated individuals [50].

	Essen regimen (5 doses)	Zagreb regimen (4 doses)	Reduced Essen regimen (4 doses)[2]
1st dose	Day 0	Day 0, 2 doses[1]	Day 0
2nd dose	Day 3		Day 3
3rd dose	Day 7	Day 7	Day 7
4th dose	Day 14	Day 21	Day 14
5th dose	Day 28		

[1] One injection in each of the two deltoids or thigh sites.
[2] This shortened Essen regimen may be used as an alternative for healthy, immunocompetent individuals provided they receive wound care plus rabies immunoglobulin in category III (Tab. II) as well as in category II (Tab. II) exposures and a WHO-prequalified rabies vaccine.

who had previously received pre-exposure vaccination. Specifically, 138 veterinary students underwent intradermal or intramuscular pre-exposure vaccination. They then received booster injections one year later [55]. One year later, individuals who had undergone intradermal rabies pre-exposure vaccination with 0.1 mL on days 0, 7, and 28 had a lower post-exposure booster antibody response than those who had received the pre-exposure series intramuscularly. A significant number of the former showed an unsatisfactory early anamnestic response. Residual neutralizing antibodies, 1 year after the preexposure vaccination, were also significantly higher in the intramuscular than in the 0.1 mL dose intradermal group. However, all study subjects had antibody titers above the minimum recommended level of 0.5 IU/mL by day 14. The authors concluded that not all subjects who had undergone intradermal pre-exposure vaccination were fully protected during the first 5 days after exposure. Thus, in the case of severe rabies exposure, rabies immunoglobulin injected into bite wounds and followed by a complete post-exposure vaccine series might be indicated.

Starting from the rationale that conventional rabies PrEP and Japanese encephalitis (JE) primary series vaccination regimens each require up to 4 weeks for completion and sometimes may not be feasible in individuals who need these immunizations on short notice, another study [56] investigated an accelerated regimen. Specifically, a Phase 3b study, randomized, controlled, observer-blind study evaluated the immunogenicity of the concomitant administration of a purified chick embryo cell culture rabies vaccine and an inactivated, adsorbed Japanese encephalitis vaccine according to an accelerated (1 week) regimen in comparison with the conventional regimens (4 weeks). A total of 661 healthy adults (18 to ≤65 years) were randomized to the accelerated or conventional vaccine regimens: Rabies + JE-Conventional; Rabies + JE-Accelerated; Rabies-Conventional; JE-Conventional.

Independently of the rabies vaccination regimen, ≥97% of subjects reached an adequate levels of rabies virus-neutralizing antibody concentrations (≥0.5 IU/mL) up to day 57, with percentages of subjects with concentrations ≥ 0.5 IU/mL on day 366 ranging between 68% in the Rabies + JE-Accelerated group and 80% in the Rabies-Conventional group. The Rabies + JE-Accelerated group displayed high JE neutralizing antibody titers at all-time points. These findings provided evidence that the accelerated PrEP rabies and JE vaccination regimens constitute a valid alternative in the short-term to recommended conventional regimens. The concomitant administration of these two vaccines does not compromise immune responses to any of the vaccine antigens, particularly when short-term protection is required.

"Boostability" after single-visit PrEP with rabies vaccine was demonstrated in a randomised controlled non-inferiority clinical trial [57]. Specifically, single-visit IM PrEP induced an anamnestic antibody response that was non-inferior to that of the two-visit IM schedule; single-visit ID PrEP, however, did not. The fold increases in antibody titers elicited by the single-visit IM and the single-visit ID schedule, respectively, were 2.32 (95% CI: 1.43-3.77) and 1.11 (95% CI: 0.66-1.87) times as high as that elicited by the standard schedule.

The 1-year boostability of a three-dose rabies PrEP schedule in individuals undergoing immunosuppressive monotherapy was evaluated in a very recent clinical trial [58]. Individuals on immunosuppressive monotherapy with a conventional immunomodulator or a TNF-alpha inhibitor (TNFi) for a chronic inflammatory disease underwent a three-dose IM PrEP schedule (days 0, 7, 21-28) with 1 mL Rabipur®, followed by a two-dose simulated PEP schedule (days 0, 3) after 12 months. Rabies neutralizing antibodies were assessed at the baseline, on day 21-28 (before the third PrEP dose), day 60, month 12 and month 12 + 7 days. The primary outcome was 1-year boostability, defined as the proportion of patients with a neutralizing antibody titre of ≥0.5 IU/mL at month 12 + 7 days. Secondary outcomes were GMTs and factors associated with the primary endpoint. The 1-year boostability was 90% with a GMT of 6.16 (95% CI: 3.83-9.91). All participants seroconverted at some point in the study. An early response to PrEP (on day 21-28) was significantly associated with 100% boostability (Odds Ratio 51; 95% CI: 5.0-6956, $P < 0.01$). In summary, the vaccination schedule investigated was immunogenic in patients on immunosuppressive monotherapy, with all participants seroconverting at some point in the study, though not all participants were able to mount a quick recall response after boosting (90%).

Good immunogenicity in children and pregnant women has been obtained in several studies [3].

Data from several clinical trials have demonstrated Rabipur® to be immunogenic with an acceptable safety profile in children for both PEP and PrEP. A study in children aged 2-15 years who had single IM doses (1.0 mL) on days 0, 7 and 28 for PrEP showed adequate immune response (≥ 5 IU/mL) by day 14 after vaccination in 100% of children [3, 59]. Similar findings have been observed in children aged 12-18 months receiving IM or ID Rabipur® on days 0, 7 and 28 with concomitant administration of Japanese encephalitis vaccine [3, 60].

A PEP study assessing Rabipur® immunogenicity was carried out in children bitten by either confirmed or suspected rabid animals (mainly dogs, followed by monkeys, cats and mongoose). Two hundred and seventy-one children aged 1-13 years received PEP on Days 0, 3, 7, 14, 30 and 90. The serological response was adequate with a maximum immune response 10–15 days after the last vaccination. The vaccine was well tolerated, and no failures were observed [3, 61].

Another clinical case-study reported on the vaccination with Rabipur® of a newborn baby after her mother developed clinical rabies during pregnancy following a dog bite 3 months prior to giving birth. A healthy baby was delivered, following which the baby received a total of five doses of Rabipur®: 1.0 mL IM at birth and a four-dose series (Days 3, 7, 14 and 30). At the age of 2 years, the child was healthy and developing normally [3, 62].

The administration of Rabipur® in pregnant women for PEP has been documented in a retrospective case series on two pregnant women who had WHO category III exposure to a suspected (Tab. II) rabid animal at gestational week 12. Each of the pregnant women got a total of five doses on days 0, 3, 7, 14 and 28 (Essen regimen) and equine rabies immunoglobulin. Both vaccine and equine rabies immunoglobulin were well tolerated with no reports of systemic or local adverse events. The women had normal deliveries of healthy babies with no evidence of congenital abnormalities [63]. There is a clear consensus that pregnancy is not a contraindication to rabies PEP [3].

Efficacy of Rabipur® vaccine

While immunogenicity of a vaccine is a surrogate parameter of efficacy, vaccine effectiveness can be assessed by investigating survival rate in subjects exposed to confirmed rabies who received the vaccine regimen. Indeed, real survival data are available following administration of Rabipur® to patients who have been exposed to rabies. Giesen A. et al. in their vaccine profile assessment reported that the individuals bitten by proven rabid animals who received Rabipur® survived over the study period (survival rate:100%) [3]. Specifically, a prospective clinical trial assessing the efficacy of a 0.1 mL dose of Rabipur® administered ID was conducted in 113 patients presenting with category III exposure (Tab. II) from laboratory-confirmed rabid animals. Patients were vaccinated and monitored monthly for 1 year post exposure. The vaccine was well tolerated, and no severe adverse events were reported. All patients survived 1 year post exposure, confirming the efficacy of vaccine [64]. This demonstrated efficacy comes from robust data collected from several hundred patients of different ages, including children [3].

There are very rare cases in which clinical rabies has

developed in immunologically healthy people despite apparently correct PEP regimen, including wound treatment and timely administration of RIG and vaccine. A systematic review reported few probable vaccine failure cases in which Rabipur® was administered in one case, Rabipur® and a purified Vero cell rabies vaccine were given in a second case and an unknown vaccine in a third case [3]. More recently, a case of atypical initial clinical rabies symptoms that led to delayed diagnosis was reported. The patient died despite appropriate PEP and administration of Rabipur [3]. Physicians should be advised that immediate and correct PEP management without delay according to official recommendations is essential for patient survival.

Safety of Rabipur® vaccine

Many data have been collected on the safety profile of Rabipur®, including information gathered before vaccine licensing and in the post-authorization period [3, 65].

The main safety results from clinical trials are reported below.

Healthy volunteers from among hospital staff and veterinary students, who were randomly assigned to regimens using purified chick embryo cell PCEC vaccine, alone or together with human rabies immunoglobulin, did not experience severe Adverse Events (AEs), with only mild or moderate injection site pain being reported [66]. Two years later, in 125 patients who had received 3, 5 and 6 doses on days 0, 3, 7, 14, 30 and 90 after exposure to rabid animals, no systemic reactions were registered. Erythema, swelling and pain were among the local reactions reported [67].

Rabipur® administered in a three-dose series and followed by a 2-year booster has proved safe, with tenderness and pain at the injection site (~50%), redness and swelling (~35%), headaches, slight fever and malaise (~20%), joint pain (1.4%) and brief episodes of enlarged nymph nodes (4.3%) being reported [54].

Comparable findings emerged from a study by Briggs DJ et al. [68], in which the safety profile was positively confirmed, the most frequently reported concomitant medical condition being 'allergy' (7.2%).

In 620 healthy volunteers, mild local side-reactions were observed in less than 2% of the vaccinees. No serious general reactions were reported or seen after 2200 injections (except for three cases of urticaria) [69].

A 10-year post-marketing surveillance study was carried out in India; this confirmed the good safety profile of PEP and PrEP with Rabipur®. Specifically, the vaccine was well tolerated in a cohort of 1289 individuals, including children aged ≥1 year. Only 4% of subjects reported AEs, which were mainly mild or moderate. The most frequently reported local adverse reactions were injection-site pain (2.1%) and injection-site induration (1.1%). Mild fever (37.2-37.8°C) occurred in six subjects (0.5%) following the third or fourth vaccination, and lasted 12-24 h [3, 70].

Another relevant post-licensure safety study was conducted in the USA from 1997 to 2005. This showed that, on approximately 1.1 million doses of vaccine, 336 AEs were reported after Rabipur® administration, approximately 30 events per 100,000 doses. Twenty-four (7%) of the AEs were considered serious by the reporters; there were no reports of death. The authors concluded that the evaluation of Vaccine Adverse Event Reporting System reports did not suggest a high frequency or unusual pattern of serious or other medically important AEs, and that most AEs were non-serious and consistent with pre-licensure safety data [65].

Many decades of global use of Rabipur® has confirmed the safety and tolerability profile observed in clinical trials. The overall rate of reports of adverse reactions is approximately 12.3 events per 100,000 doses. The vast majority (nearly 80%) of events reported in Asia, Europe and the USA were non-serious reactions recorded during clinical trials. The most often reported symptoms are: systemic reactions, such as headache, dizziness, influenza-like illness and associated symptoms (*e.g.*, fever, asthenia and myalgia), and local injection-site-related reactions (*e.g.,* redness, swelling and pain) [3, 50].

Rabipur® is generally well tolerated in children. The studies reported typical adverse reactions as fever, fatigue, and pain and redness at the injection site. No serious adverse reaction related to the vaccine occurred [3].

Rabies as a travel risk

All travellers to rabies affected countries, especially in Asia and Africa, should avoid contact with dogs, cats and other animals whenever possible, and seek advice on the need for rabies vaccination prior to travel.

Any individual who has been bitten, scratched or licked by an animal in a country where rabies is endemic, or has had direct contact with a bat in those countries, should take immediate action by washing the wound or site of exposure abundantly with soap and water, and seek local medical advice without delay, even if they have been previously vaccinated [1].

When administered promptly after exposure, a course of rabies vaccine is extremely effective in preventing the disease. If such exposure occurs abroad, travellers should also consult their doctor or the travel medicine specialist of their Local Health unit on return, in order to complete the course of rabies treatment. If they cannot receive medical advice abroad, travellers should contact their doctor promptly upon return, in order to be assessed [71].

In Europe, most human rabies cases involve travellers bitten by dogs or other animals in rabies-enzootic countries. Therefore, European travellers visiting rabies-enzootic countries should be aware of the risk of being infected with the rabies virus if they come into physical contact with mammals. They should also consider pre-exposure vaccination according to the criteria recommended by the WHO.

In this regard, travel clinics and public health authorities in the EU/EEA should reinforce their prevention

campaigns and advise travellers visiting countries with a moderate or high risk of rabies (i) to be aware of the possibility of acquiring rabies infection through physical contact with mammals, (ii) to undergo PrEP vaccination in accordance with the criteria recommended by the WHO, and (iii) to immediately seek medical attention in the event of being bitten or scratched by mammals [72]. Dedicated communication campaigns should be developed to target different groups of travellers and levels of awareness, and the use of social media to reach these subjects should be explored. In addition, travellers should be reminded to follow veterinary rules and regulations when travelling with pets. Finally, EU/EEA citizens should only acquire pets through authorised channels. Several practical guidelines from different countries are available and are useful tools for healthcare workers [72-77].

Rabies as an occupational risk

Workers in certain occupations may face a higher risk of exposure to rabies. Such individuals include those who work with rabies in laboratory settings, veterinarians, veterinary students, animal handlers, animal control and wildlife officers, those involved in outdoor recreational activities, forestry workers, and wildlife guides in at-risk areas, missionary workers traveling to certain countries, and recipients of transplants, particularly corneas [78, 79]. However, the at-risk population could well be wider, but it is not easy to identify all risk groups in the general population.

Several factors can increase a person's risk of contracting rabies. These include living in an environment where wild animals abound, living in areas with poor sanitation or far from vaccination services, traveling to or living in countries where rabies is more common, and engaging in activities that carry a risk of contact with wild animals, such as camping, hiking or caving [80].

For workers in occupations that are at high risk of rabies infection, PrEP is recommended, followed by a booster dose in the event of exposure [78].

For healthcare workers, routine precautions, including wearing gowns, goggles, masks and gloves, are recommended when providing care for persons suspected of having clinical rabies. In the event of exposure, public health officials should adopt specific criteria to identify high-risk contacts and provide immunization.

Transmission of the virus to healthcare workers caring for a patient infected by rabies has never been documented. However, the admission of a human rabies case to hospital often creates great anxiety among staff, who fear contamination. Theoretically, transmission could occur through direct contact the broken skin or mucosa, saliva, tears, oropharyngeal secretions, cerebrospinal fluid or neural tissue of an infected individual. The care of a rabies patient requires only standard precautions against infection, which consist of the basic preventive measures applied in many other common diseases. These should be sufficient to prevent transmission to staff. Preventing anxiety among healthcare workers should therefore be an achievable goal.

Discussion and Conclusions

Carnivores, especially of the *canidae* family, constitute the principal reservoir of the rabies virus, and are responsible for maintaining the infectious cycle, and hence for the persistence of rabies disease. Canine rabies accounts for 99% of the human death toll, causing more than 60,000 human deaths annually. However, bat species and other wildlife mammals are also a major reservoir of the virus and a threat for human health.

Countries in Asia and Africa carry the heaviest disease burden, and the available data are underestimated due to several reasons: i) inadequate surveillance systems not able to keep track of the number of rabies cases diagnosed and the number of people who have been treated for the disease, ii) PrEP and PEP shortages, and iii) lack of the necessary staff and infrastructure to conduct patient management. In this context, the Global alliance for vaccine immunization (GAVI) recently announced intentions to resume investment in human rabies vaccines, which was halted by the COVID-19 pandemic [81].

The majority of the EU/EEA countries are free from rabies in mammals, as elimination of the disease (no enzootic circulation of the virus and low number of imported cases) had been achieved by 2020. However, the international travels and illegal importation of potentially infected animals, mainly dogs, poses a risk to public health.

The WHO regards rabies as a neglected disease and promotes efforts to establish wider access to appropriate treatment for humans.

The "One Health" approach is the most promising strategy for achieving the global goal of eliminating canine-mediated human rabies by 2030. The 'Zero by 30' framework is a global strategy to effect pragmatic changes in approximately 100 countries over the decade. It advocates a unified surveillance mechanism and a collaborative alliance between human and animal healthcare, thereby enabling better financial and resource management by participating countries [82, 83].

Rabies is entirely preventable. Significantly raising the perception of this disease as a global health challenge demands international attention and active support in order to save lives. There is a need for rabies education and initiatives to raise awareness, including information on wound treatment (first aid) and PEP. Each of the many thousands of deaths that occur annually is a universal health system failure, in that victims of rabid bites have not accessed post-exposure vaccines, *i.e.*, in practice, universal health coverage remains an unavailable model.

Rabipur® is one of the available anti-rabies vaccines,

and is indicated for active immunization in individuals of all ages. Its efficacy and safety have been amply demonstrated.
As regard as PrEP, in clinical trials carried out in unimmunised subjects almost all subjects achieved an adequate immune response 3 to 4 weeks after the end of a primary series of three injections.
About prophylaxis in humans living in rabies-free countries, PrEP is indicated for individuals who face occupational and/or travel-related exposure to the rabies virus in specific settings or over an extended period.
Considering PEP, in clinical trials Rabipur® elicited adequate neutralising antibodies in almost all subjects by day 14 or 30, when administered according to the 5-dose (day 0, 3, 7, 14, 28; 1.0 mL each, intramuscular) Essen regimen or 4-dose (day 0 [2 doses], 7, 21; 1.0 mL each, intramuscular) Zagreb regimen.
The good safety profile of the vaccine observed in clinical trials is confirmed by the post-licensure surveillance.
Wider use of human rabies vaccination for PrEPand PEP in conjunction with programs to eradicate rabies from animal populations would be the right direction in reducing the burden of disease.

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Conflicts of Interest statement

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Author's contribution

All authors equally contributed to this manuscript.

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