# RABIES AND EMERGING INFECTIONS: A ONE HEALTH REVIEW OF THE OLDEST ZOONOSIS IN AN AGE OF NEW SPILLOVERS

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**Abstract**

On 6 July 1885, Louis Pasteur administered the first rabies vaccine to a bitten child, a moment now commemorated annually as World Zoonoses Day. Almost a century and a half later, rabies endures as the most lethal zoonosis known to medicine, claiming an estimated fifty-nine thousand human lives every year despite being entirely vaccine-preventable. This review uses rabies as a lens through which to examine the broader landscape of emerging and re-emerging infections that arise at the animal–human–environment interface. We trace the biology of the rabies virus and its relatives within the genus Lyssavirus, the mechanisms by which the virus invades the nervous system, and the clinical and laboratory features that define the disease. We then summarise the global and Indian burden, the modern pillars of prevention—wound care, post-exposure prophylaxis, mass dog vaccination, the emerging use of oral vaccines and integrated surveillance—and the World Health Organization's "Zero by 30" goal that India has adopted through its National Action Plan for Dog Mediated Rabies Elimination. Turning outward, we ask why the majority of newly emerging human pathogens originate in animals, and we consider the ecological and socio-economic drivers of spillover through detailed examples including highly pathogenic avian influenza H5N1, Nipah virus, SARS-CoV-2 and mpox. Throughout, we argue that the One Health framework is the connective tissue linking the elimination of an ancient disease to preparedness for novel outbreaks, and that veterinarians, positioned at this interface, are indispensable to both endeavours.

**Keywords:** Rabies; lyssavirus; zoonoses; emerging infectious diseases; One Health; Zero by 30; spillover; post-exposure prophylaxis; veterinary public health

## Introduction

Few calendar dates capture the entanglement of animal and human health as neatly as the sixth of July. On that day in 1885, Louis Pasteur and his collaborators inoculated nine-year-old Joseph Meister, who had been savaged by a rabid dog, with a graded series of attenuated rabies preparations derived from dried rabbit spinal cord. The boy lived, and with his survival the modern era of vaccination against zoonotic disease was born. That single act is the reason 6 July is now observed across the world as World Zoonoses Day, an annual prompt to remember that diseases moving between animals and people are neither exotic nor new (Warrell and Warrell, 2004). Zoonoses are infections transmitted naturally between vertebrate animals and humans, and they are caused by the full spectrum of pathogens—viruses, bacteria, parasites, fungi and prions. They are anything but a fringe concern. A foundational analysis of human pathogens found that roughly sixty per cent of the species known to infect people are shared with animals, and the proportion rises further when attention is restricted to pathogens that have emerged recently, the majority of which can be traced to wildlife reservoirs (Taylor et al., 2001; Jones et al., 2008). In other words, the question is not whether the next significant human infection will come from an animal, but which animal, where and when.

Rabies occupies one extreme of this spectrum as the oldest, most thoroughly studied and most uniformly fatal of zoonoses, while a recurring procession of "new" threats—severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), highly pathogenic avian influenza, Nipah virus and mpox among them—occupies the other. Yet treating these as separate problems misses the point. Both ancient and novel zoonoses originate at the

same animal–human–environment interface; both are shaped by how societies rear animals, use land and move goods and people; and both are most effectively confronted through coordinated action spanning the veterinary, medical and environmental sectors. This review therefore uses rabies as a familiar anchor and works outward, examining first the biology, epidemiology and control of rabies in detail, then the wider phenomenon of disease emergence, and finally the One Health philosophy that unites the two. The argument throughout is simple: the very tools and partnerships capable of ending the world's oldest zoonosis are also our best defence against its newest.

**The rabies virus and its relatives**

Rabies is caused by neurotropic viruses of the genus *Lyssavirus* within the family *Rhabdoviridae*, order *Mononegavirales*. The prototype species, rabies virus (RABV), is responsible for the overwhelming majority of human and animal cases worldwide. The virion is enveloped and distinctively bullet-shaped, measuring roughly 180 nanometres in length and 75 nanometres in diameter, and it carries a single-stranded, negative-sense RNA genome about twelve kilobases long. The genome is economical and highly conserved, encoding five structural proteins in the fixed order 3′–N–P–M–G–L–5′: the nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G) and the large RNA-dependent RNA polymerase (L) (Tordo et al., 1986; Fooks et al., 2014).

Each protein has a defined role. The nucleoprotein tightly encases the genomic RNA to form a helical ribonucleoprotein core, shielding it from host nucleases and serving as the template for transcription and replication; the phosphoprotein and the polymerase associate with this core to drive RNA synthesis. The matrix protein bridges the ribonucleoprotein and the envelope, condensing the complex and orchestrating budding of new particles. The glycoprotein, arranged as trimeric spikes that stud the viral surface, is the only protein exposed on the exterior of the virion and is consequently the workhorse of pathogenesis: it recognises host-cell receptors, mediates pH-dependent membrane fusion after endocytosis, and is the principal target of neutralising antibodies and the key antigen in every licensed rabies vaccine (Fooks et al., 2014). Because the glycoprotein governs both virulence and immunity, a single amino-acid change at position 333 can dramatically attenuate the virus—a property exploited in the design of modern oral vaccines discussed later.

RABV is only one member of a larger and still-expanding genus. Early molecular work distinguished several genotypes including Lagos bat virus, Mokola virus, Duvenhage virus, the European bat lyssaviruses and Australian bat lyssavirus, and the genus now comprises well over a dozen recognised species (Table 1) grouped into phylogenetically and immunologically distinct phylogroups (Bourhy et al., 1993). This diversity has practical consequences. Standard rabies vaccines and immunoglobulins protect well against phylogroup I lyssaviruses, which include classical RABV and most bat-associated viruses encountered by people, but offer little or no cross-protection against the more divergent phylogroup II and III viruses. Bats are the ancestral and most prolific reservoirs of lyssaviruses, and the periodic detection of novel bat lyssaviruses underscores that rabies is not a static, single-virus problem but a dynamic family of related pathogens with an enduring capacity to surprise.

**Table 1.** *Representative lyssavirus species, principal reservoirs and vaccine considerations.*

| Lyssavirus (representative) | Principal reservoir | Phylogroup | Standard vaccine protection |
|---|---|---|---|
| Rabies virus (RABV) | Carnivores (esp. dogs); bats in the Americas | I | Effective |
| European bat lyssaviruses 1 & 2 | Insectivorous bats (Europe) | I | Effective |
| Australian bat lyssavirus | Fruit and insectivorous bats | I | Effective |
| Duvenhage virus | Insectivorous bats (Africa) | I | Effective |
| Lagos bat virus | Fruit bats (Africa) | II | Little / none |
| Mokola virus | Uncertain (shrews, cats) | II | Little / none |

**Rabies in animals: reservoirs, transmission cycles and clinical disease**

Because rabies is, at its root, a disease of animals that occasionally spills into people, no account aimed at a veterinary readership is complete without attention to the animal side of the cycle. All warm-blooded mammals are susceptible to infection, but only a limited set of species act as efficient maintenance reservoirs in which the virus is perpetuated. Two broad epidemiological cycles are recognised. The urban or canine cycle, in which the domestic dog is both reservoir and principal vector, dominates the global burden and is overwhelmingly responsible for human deaths in Africa and Asia, including India. The sylvatic

or wildlife cycle is maintained by various wild carnivores depending on geography—red foxes and raccoon dogs in Europe, raccoons, skunks and foxes in North America, jackals and mongooses in parts of Asia and Africa—while insectivorous and haematophagous bats sustain independent lyssavirus cycles, most notably the vampire-bat-transmitted rabies of Latin America (Fooks et al., 2014; Banyard et al., 2013).

The distinction matters for control. Where a single reservoir such as the dog drives transmission, mass vaccination of that reservoir can interrupt the cycle decisively; where multiple wildlife reservoirs are involved, elimination is far more complex and may require species-specific strategies such as oral baiting. Livestock and humans are generally dead-end or spillover hosts: they can be infected and die but rarely transmit the virus onward. This does not make livestock rabies trivial, however. Cattle, buffalo, sheep, goats, horses and pigs are frequently bitten by rabid dogs or wildlife, and bovine rabies in particular inflicts real economic loss on smallholder and pastoralist households for whom a single animal represents substantial wealth.

The clinical course in animals mirrors that in humans, passing through a short prodromal stage of altered behaviour into either a furious or a paralytic phase. In dogs, the furious form brings restlessness, unprovoked aggression, a tendency to bite at objects and other animals, altered vocalisation, excessive salivation from pharyngeal paralysis and, ultimately, convulsions and death; the paralytic or "dumb" form, by contrast, is dominated by progressive paralysis, a dropped jaw and drooling, and may be mistaken for choking or a foreign body, dangerously tempting an owner or veterinarian to perform an oral examination bare-handed. In cattle, rabies often presents with persistent bellowing, straining, hypersalivation, knuckling and ascending paralysis, a picture that can be confused with other neurological or metabolic conditions and that places attending stock-keepers and veterinarians at occupational risk during examination or drenching. For the veterinary professional, three practical imperatives follow: maintain a high index of suspicion for rabies in any mammal with unexplained acute neurological signs, handle suspect cases with rigorous personal protection, and ensure prompt reporting and laboratory submission, because an accurate animal diagnosis directly governs the prophylaxis of every exposed person and animal.

**Pathogenesis and clinical disease in humans**

The natural history of rabies is a slow journey along the nervous system that ends, almost without exception, in death once it is complete. Infection is usually established when virus-laden saliva is introduced through the bite or deep scratch of an infected animal. After inoculation the virus may persist near the wound for a variable period, sometimes replicating quietly in muscle, before it binds receptors at neuromuscular junctions and enters peripheral nerves. It then travels centripetally toward the central nervous system by hijacking the retrograde axonal transport machinery, a comparatively unhurried mode of spread that explains the disease's characteristically long and variable incubation period (Hemachudha et al., 2013).

That incubation interval, typically one to three months but occasionally much shorter or, rarely, longer than a year, is the single most important window in the entire disease, because it is during this nerve-bound, pre-symptomatic phase that post-exposure prophylaxis can still intercept the virus. Bites to the face, neck and hands tend to produce shorter incubation periods because of richer innervation and proximity to the brain. Once the virus reaches the central nervous system it replicates explosively and then spreads centrifugally back outward along nerves to the salivary glands, skin, cornea and other tissues—dissemination to the salivary glands being precisely what renders the host infectious and perpetuates the transmission cycle (Warrell and Warrell, 2004).

Clinically, human rabies declares itself after a non-specific prodrome of fever, malaise and, classically, tingling or pain at the healing bite site. It then diverges into two recognised forms. The furious or encephalitic form, seen in most patients, is dominated by hyperexcitability, fluctuating consciousness, autonomic instability and the pathognomonic hydrophobia and aerophobia—violent pharyngeal spasms triggered by attempts to drink or by a draught of air. The paralytic or "dumb" form, less common and more easily misdiagnosed, produces ascending flaccid paralysis reminiscent of Guillain–Barré syndrome and a more protracted course. Both forms progress relentlessly to coma and death, usually within days of symptom onset. Despite occasional and heavily publicised reports of survival following aggressive intensive care, there remains no reliable cure once clinical rabies is established, and the case-fatality rate

approaches one hundred per cent (Hemachudha et al., 2013). The histological hallmark, the eosinophilic cytoplasmic inclusion known as the Negri body, reflects accumulations of viral ribonucleoprotein within infected neurons.

**Laboratory diagnosis**

Because the clinical picture can be ambiguous, particularly in paralytic disease, laboratory confirmation is essential for case verification, for guiding the prophylaxis of contacts, and for the surveillance on which any elimination programme depends. Diagnosis is far more straightforward after death than during life. The long-standing gold standard for post-mortem confirmation in both humans and animals is the direct fluorescent antibody (DFA) test performed on fresh brain tissue, ideally sampled from the brain stem and cerebellum, in which fluorescently labelled anti-nucleoprotein conjugates reveal viral antigen with high sensitivity and specificity (Mani and Madhusudana, 2013).

Several complementary techniques have broadened the diagnostic repertoire. The direct rapid immunohistochemistry test (dRIT) achieves accuracy comparable to the DFA test using light microscopy and biotinylated antibodies, making it well suited to field and resource-limited laboratories. Reverse-transcription polymerase chain reaction (RT-PCR) and real-time RT-PCR assays detect viral RNA with very high sensitivity, perform well even on decomposed specimens that defeat antigen-based tests, and permit molecular characterisation that can distinguish field from vaccine strains and trace the geographic origin of an isolate. The pan-lyssavirus LN34 real-time RT-PCR assay, validated across many laboratories and diverse lyssaviruses, exemplifies the move toward robust, standardised molecular diagnostics (Gigante et al., 2018). The older Seller's staining method for visualising Negri bodies, while quick, is insufficiently sensitive and is no longer recommended for primary diagnosis.

Antemortem diagnosis in living patients is considerably more challenging because the virus is sequestered in nervous tissue and shed only intermittently. A combination of specimens—saliva for RT-PCR, skin biopsy from the nape of the neck for antigen and RNA detection, and cerebrospinal fluid or serum for antibodies in unvaccinated patients—improves sensitivity, but a single negative result never excludes the disease, and repeat sampling is often necessary (Mani and Madhusudana, 2013). Strengthening this diagnostic capacity, especially in endemic rural districts, is a recurring priority of national control programmes, since deaths that are never confirmed are deaths that never enter the statistics that drive policy and funding.

**Global and Indian epidemiology**

Rabies is present on every inhabited continent and is endemic across much of Africa and Asia. The most widely cited estimate places the global toll at roughly fifty-nine thousand human deaths each year, distributed across more than one hundred and fifty countries, with about ninety-five per cent of fatalities occurring in Africa and Asia (Hampson et al., 2015). Domestic dogs are responsible for up to ninety-nine per cent of human cases, and children under the age of fifteen account for a disproportionate share—close to forty per cent—of deaths, reflecting their height, their tendency to play with animals and their reduced likelihood of reporting minor bites. The burden falls overwhelmingly on poor rural communities with limited access to prompt wound care and biologicals, which is why rabies is classified among the neglected tropical diseases (World Health Organization, 2024).

These global figures are almost certainly underestimates. Rabies surveillance is notoriously weak in the very settings where the disease is most common; deaths frequently occur at home, are attributed to non-specific encephalitis, or are never laboratory-confirmed. The consequence is a vicious circle in which under-reporting masks the true scale of the problem, which in turn weakens the case for the investment that better surveillance would require. Closing this data gap is therefore not a bureaucratic nicety but a precondition for elimination (Hampson et al., 2015).

India carries one of the heaviest rabies burdens of any country, historically estimated at around a third of global deaths. The landmark WHO-supported national multicentric survey conducted in 2003 estimated about twenty thousand five hundred human rabies deaths annually—roughly two per hundred thousand population—and documented that dogs, predominantly strays, were responsible for the great majority of bites, that victims were disproportionately male, rural and unvaccinated, and that many had first resorted to traditional remedies rather than seeking timely medical care (Sudarshan et al., 2007). A more recent community-based survey and modelling study covering 2022–23 reaffirmed the immense scale of exposure, estimating millions of animal bites each year and a substantial, though gradually declining, number

of rabies deaths, while again highlighting persistent under-reporting in routine surveillance (Thangaraj et al., 2025). The combination of a very large free-roaming dog population, high human density and uneven access to prophylaxis makes India simultaneously a major contributor to the global burden and a decisive arena in which the worldwide elimination goal will be won or lost.

To investigate the genetic relationships among Indian rabies virus isolates, a SplitsTree phylogenetic network was constructed using the complete glycoprotein (G) gene sequences of 25 Indian isolates representing domestic animals (dogs and cattle) and wildlife hosts (hyena, mongoose, sambar deer and Himalayan black bear) (Figure 1). The network resolved several well-supported genetic clusters, demonstrating that most Indian rabies virus isolates grouped into closely related lineages irrespective of host species, consistent with frequent interspecies transmission within a shared transmission cycle. Dog-derived isolates were distributed across multiple clusters and frequently grouped with cattle isolates, reinforcing the central role of domestic dogs as the primary reservoir responsible for spillover infections in livestock. In contrast, isolates from wildlife formed distinct or peripheral clusters while remaining genetically connected to the broader canine-associated population, suggesting occasional transmission between domestic and wild carnivores rather than the existence of completely independent wildlife-maintained lineages. Overall, the phylogenetic network highlights the extensive circulation of closely related rabies virus variants across different host species in India and emphasizes the importance of integrated molecular surveillance to understand viral evolution and transmission dynamics.

The network illustrates the genetic relationships among rabies virus isolates obtained from domestic animals (dogs and cattle) and wildlife hosts (hyena, mongoose, sambar deer and Himalayan black bear) from India. Isolates are grouped into genetically related clusters, with branch lengths proportional to genetic distance (scale bar indicates nucleotide substitutions per site). The network demonstrates the close genetic relatedness of canine and livestock isolates, while wildlife-derived isolates occupy distinct but connected positions, reflecting the circulation of rabies virus across multiple host species and the occurrence of interspecies transmission within India.

The economic and social dimensions of this burden are easily overlooked behind the mortality figures. Independent re-evaluation of the rabies burden across Africa and Asia has emphasised that, beyond deaths, the disease imposes enormous costs through the millions of courses of post-exposure prophylaxis administered each year, through livestock losses, and through the psychological trauma inflicted on bite victims and bereaved families (Knobel et al., 2005).

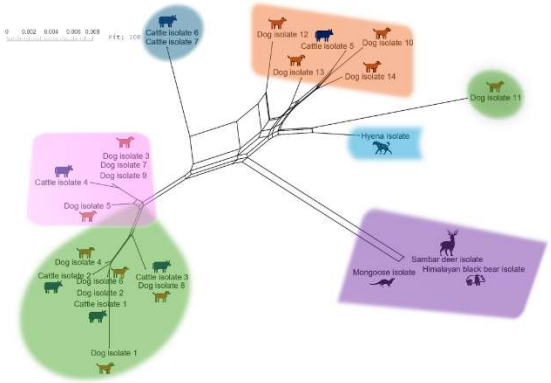


**Figure 1.** SplitsTree phylogenetic network of 25 Indian rabies virus isolates based on complete glycoprotein (G) gene sequences

Because the disease concentrates among the rural poor and among children, and because the costs of prophylaxis can be catastrophic for a low-income household, rabies is as much a problem of equity and poverty as of virology—a point that strengthens, rather than weakens, the moral case for elimination.

## Prevention and control

### *Managing human exposures*

Because rabies is virtually untreatable once symptoms appear yet almost entirely preventable beforehand, everything hinges on correct management of the exposure. The first and most underrated step is immediate, thorough washing of the wound with soap and running water for at least fifteen minutes, supplemented by a virucidal agent such as povidone-iodine; this simple measure alone substantially reduces viral load at the inoculation site. The World Health Organization stratifies exposures into three categories (Table 2) that determine subsequent action: category I, such as touching or feeding animals or licks on intact skin, requires no prophylaxis; category II, comprising minor scratches or nibbling of uncovered skin without bleeding, requires prompt wound care and vaccination; and category III, involving transdermal bites or

scratches, contamination of mucous membranes, or any exposure to a bat, requires wound care, vaccination and the infiltration of rabies immunoglobulin into and around the wound (World Health Organization, 2018).

**Table 2.** *WHO categories of rabies exposure and recommended response.*

| Category | Type of contact | Recommended action |
|---|---|---|
| I | Touching or feeding animals; licks on intact skin | Wash exposed skin; no prophylaxis needed |
| II | Nibbling of uncovered skin; minor scratches or abrasions without bleeding | Wound washing and immediate vaccination |
| III | Transdermal bites/scratches; mucous-membrane contamination; any bat exposure | Wound washing, vaccination and rabies immunoglobulin |

Modern post-exposure prophylaxis (PEP) rests on safe, potent cell-culture and embryonated-egg-based vaccines that have replaced the obsolete and dangerous nerve-tissue (Semple) vaccines of the past. Administered correctly and without delay, PEP is close to one hundred per cent effective. To conserve vaccine and reduce cost, the World Health Organization endorses intradermal regimens, which deliver smaller volumes into the skin and have been shown to be as immunogenic as the traditional intramuscular route—an especially valuable option in supply- and budget-constrained settings such as much of India, where shortened, abbreviated schedules have been evaluated to improve patient compliance (World Health Organization, 2018). For category III exposures, passive immunisation bridges the gap before the vaccine elicits a response: human or equine rabies immunoglobulin has traditionally been used, but supply has always been limited, and the licensing of rabies-specific monoclonal antibodies—including products developed and approved in India—represents a significant advance toward scalable, standardised passive prophylaxis. Pre-exposure prophylaxis, a short vaccine course given in advance, is recommended for people at continual or frequent risk, including veterinarians, laboratory staff, animal handlers and travellers to highly endemic regions.

***Controlling rabies at its animal source***

Treating exposed people one bite at a time can prevent individual deaths but can never eliminate the disease, because it does nothing to interrupt transmission in the animal reservoir. The decisive intervention is mass vaccination of dogs. Both mathematical modelling and decades of field experience indicate that sustaining vaccination coverage of at least seventy per cent of the dog population breaks the chain of transmission and, through herd immunity, protects people far more cost-effectively over time than treating an endless stream of victims (Fooks et al., 2014). In countries with large free-roaming dog populations, mass dog vaccination is most effective when paired with humane dog-population management—in the Indian context, the Animal Birth Control framework of sterilisation and vaccination—and with community education to reduce risky interactions and encourage prompt reporting of bites.

A complementary tool, drawn directly from the history of wildlife rabies control, is oral rabies vaccination (ORV). The distribution of vaccine-laden baits to free-ranging animals achieved one of the great triumphs of veterinary public health: beginning in Switzerland in 1978 and expanding across the continent, ORV campaigns using attenuated and recombinant vaccines eliminated fox-mediated rabies from vast areas of Western and Central Europe, an accomplishment without precedent in the management of disease in a wildlife reservoir (Müller et al., 2015). The same principle is now being adapted to free-roaming dogs that are difficult to catch and inject by hand. Third-generation oral vaccines such as the genetically engineered SPBN GASGAS construct, derived from an attenuated vaccine strain and rendered highly safe by modifications at glycoprotein codon 333, have been endorsed as a tool for dog rabies elimination and are under field evaluation in several countries; their use in tropical settings such as India will, however, demand careful attention to vaccine thermostability and the cold chain (Vos et al., 2025).

Underpinning all of these interventions is surveillance. Without reliable, timely information on where bites and cases are occurring in both animals and people, programmes cannot target resources, measure progress or demonstrate freedom from disease. Integrated Bite Case Management (IBCM), an intersectoral approach in which animal-health and human-health workers jointly investigate bites to determine the rabies status of the biting animal, is promoted as a cost-effective way to sharpen surveillance, rationalise the use of expensive biologicals and link the veterinary and medical sectors in practice.

***The economic case and the evolution of rabies vaccines***

A persistent obstacle to dog vaccination is the perception that it is expensive, yet the economics point firmly the other way over any reasonable time horizon. Modelling and field studies of integrated dog–human rabies control have shown that, although mass dog vaccination carries upfront costs, it becomes cost-effective and ultimately cost-saving compared with relying indefinitely on human post-exposure prophylaxis, because it reduces the very exposures that generate demand for costly biologicals (Zinsstag et al., 2009). Framing dog vaccination as an investment that pays dividends in averted human treatment and averted deaths is central to sustaining the political will that elimination requires.

The vaccines themselves embody more than a century of progress since Pasteur. The hazardous nerve-tissue vaccines of the twentieth century, prone to severe neurological adverse events, have been almost entirely replaced by safe and potent cell-culture and embryonated-egg-based vaccines for human use, and by highly effective inactivated vaccines for parenteral use in animals. A further generation of recombinant and genetically engineered constructs underlies the oral vaccines now deployed in wildlife and under evaluation in dogs. Research continues into thermostable formulations that would relax the cold-chain demands so limiting in tropical field conditions, and into next-generation platforms; the broad goal across all of this work is the same—cheaper, safer, more heat-stable and more easily delivered immunisation for both the animal reservoir and the exposed human (World Health Organization, 2018; Vos et al., 2025).

**Toward elimination: Zero by 30 and India's NAPRE**

The recognition that rabies is both preventable and, in principle, eliminable has crystallised into a global goal. Under the banner "Zero by 30", the World Health Organization, the World Organisation for Animal Health, the Food and Agriculture Organization and the Global Alliance for Rabies Control—collaborating as United Against Rabies—have set the target of ending human deaths from dog-mediated rabies by the year 2030 (Abela-Ridder et al., 2016). The strategy is explicitly phased, moving from start-up through scale-up to a final mop-up period, and it rests on three interlocking objectives: making people safe through accessible PEP, eliminating the disease at source through dog vaccination, and ensuring that programmes are driven by sound data and multisectoral collaboration. Rabies has also been incorporated into the World Health Organization's 2021–2030 road map for neglected tropical diseases, and the inclusion of human rabies vaccines within the investment strategy of Gavi, the Vaccine Alliance, has improved the prospects for affordable access in low-income countries.

India has translated this global ambition into national policy. The National Action Plan for Dog Mediated Rabies Elimination (NAPRE), developed under the National Centre for Disease Control and launched jointly by the health and animal-husbandry ministries, sets out a route to a rabies-free India by 2030 built explicitly on the One Health approach (National Centre for Disease Control, 2021). Its human-health components include strengthening the availability of PEP, training health workers, improving surveillance of bites and clinical rabies, and public communication; its veterinary components encompass estimating and managing the dog population, mass dog vaccination, and mapping of high-risk areas. The declaration of rabies as a notifiable disease and the creation of a national One Health coordination network are intended to bind these elements together. Formidable challenges remain—among them the scale of the free-roaming dog population, gaps in surveillance and laboratory capacity, uneven implementation across states, and the perennial difficulty of sustaining political attention and funding for a disease of the poor—but the strategic architecture for elimination is now in place, and the experience India accumulates will be instructive for every other high-burden country.

**The science of spillover and the drivers of emergence**

Stepping back from rabies reveals a broader and more unsettling pattern. "Emerging" infectious diseases are those that are newly recognised, newly evolved, or expanding into new hosts, geographies or vectors, while "re-emerging" diseases are familiar infections resurging after a period of decline. What unites the great majority of them is an animal origin combined with human activities that intensify contact between people and animals (Figure 2). The drivers are by now well characterised: deforestation and the conversion of wild habitat for agriculture; the encroachment of expanding cities and settlements on forest edges; the intensification and crowding of livestock and poultry production, which creates ideal conditions for pathogens to amplify and mutate; live-animal markets and the legal and illegal wildlife trade, which assemble

unnatural mixtures of species at high density; the unprecedented speed and volume of global travel and commerce; and, increasingly, a changing climate (Jones et al., 2008).

The climate dimension deserves particular emphasis because it reframes emergence as a problem of the near future as well as the present. Modelling of the global mammalian virome under projected climate and land-use change predicts that as species shift their ranges toward cooler refuges they will meet in novel combinations, especially in the biodiverse and densely populated highlands of Asia and Africa, generating thousands of first-time encounters between previously isolated mammals and an estimated multitude of new opportunities for viruses to jump hosts by 2070—a process the authors argue may already be under way in today's warmer world (Carlson et al., 2022). Rabies, an old disease maintained largely in domestic dogs, is comparatively insulated from these forces, but it shares with every emerging zoonosis the same fundamental interface and the same dependence on cross-sectoral vigilance. Understanding that interface through concrete examples is the surest way to see why.

It is worth dwelling on why spillover is, in fact, a rare and contingent event rather than a constant one, because those understanding shapes prevention. A widely adopted framework conceives of animal-to-human transmission as a hierarchical series of barriers that a pathogen must overcome in sequence: it must be present and prevalent in a reservoir host, be released into the environment, survive long enough outside the host, reach a human in a sufficient dose and by an appropriate route, and finally overcome the within-human barriers to establishing infection (Plowright et al., 2017). Each barrier offers an opportunity for intervention, and crucially, the pathways for superficially different diseases—rabies, Ebola, Nipah—share the same upstream architecture of reservoir distribution, pathogen prevalence and human–animal contact. This means that measures reducing contact at the ecological source can lower spillover risk across many pathogens at once.

Environmental drivers (deforestation, land-use change, urbanization and climate change) together with anthropogenic factors (intensive livestock production, wildlife trade, global travel and increasing human population density) increase human–animal interactions, facilitating pathogen transmission from wildlife reservoir hosts to humans. Successful spillover occurs through a series of sequential barriers, including pathogen maintenance in the reservoir, environmental shedding, survival outside the host, human exposure, establishment of infection and subsequent human-to-human transmission. Climate change further amplifies spillover risk by altering species distributions and creating novel host interactions, while tropical regions experiencing rapid ecological change represent major hotspots for emerging infectious diseases. Understanding these interconnected ecological and anthropogenic drivers provides the basis for implementing One Health strategies aimed at preventing the emergence and re-emergence of zoonotic diseases, including rabies, Ebola, Nipah and SARS/COVID-19.

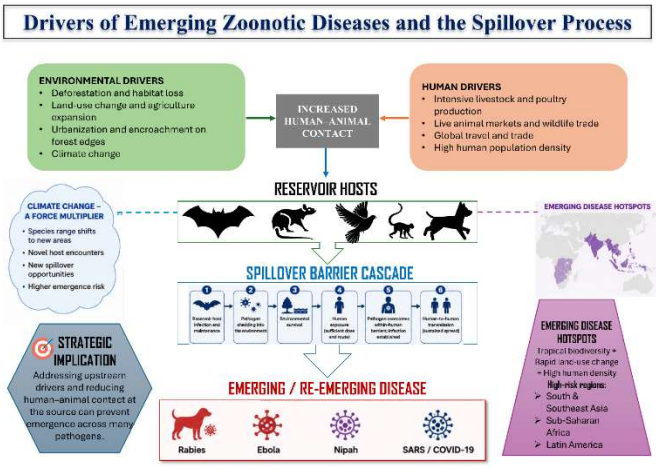


**Figure 2.** Conceptual framework illustrating the drivers of zoonotic disease emergence and the spillover process

Geographic and ecological analyses reinforce where attention should fall. Mapping of emerging zoonotic events and their correlates has identified hotspots concentrated in tropical regions rich in wildlife diversity and undergoing rapid land-use change (Figure 2), frequently overlapping with dense and growing human populations (Allen et al., 2017). These same analyses make the case for a shift in strategy: rather than waiting to detect and respond to outbreaks once they reach humans, the more cost-effective long-term approach is to predict and prevent emergence by targeting its upstream drivers, an argument advanced forcefully in the wake of repeated pandemic threats (Morse et al., 2012). South and Southeast Asia, where this review's readership is concentrated, sit squarely within these high-risk zones, which lends the abstract science of spillover an immediate regional urgency.

**Case studies of emerging zoonoses**

***Highly pathogenic avian influenza (H5N1)***

Few pathogens illustrate the restless adaptability of zoonotic viruses as vividly as highly pathogenic avian influenza (HPAI). The H5N1 subtype, and in particular the clade 2.3.4.4b viruses, has circulated widely in wild aquatic birds and domestic poultry, causing devastating outbreaks and culling, and has repeatedly spilled over into a growing range of mammals. The most striking recent development came in 2024, when H5N1 of this clade was detected in dairy cattle in the United States—a host and a route not previously associated with the virus—with subsequent infection of farm workers exposed to affected animals and their milk (Caserta et al., 2024). The significance lies less in the immediate human toll, which has so far been limited, than in what the event signals: each new mammalian host represents another opportunity for the virus to acquire the mutations that would allow efficient human-to-human transmission. HPAI is therefore monitored intensively as a pathogen of genuine pandemic potential, and its control depends on exactly the kind of integrated animal–human surveillance that One Health prescribes.

***Nipah virus***

Nipah virus (NiV) is a henipavirus of the family *Paramyxoviridae* whose natural reservoir is fruit bats of the genus *Pteropus*. It is a textbook example of a bat-borne emerging infection and one of particular relevance to the Indian subcontinent. India first encountered the virus in outbreaks in Siliguri, West Bengal, in 2001, where nosocomial transmission within a hospital drove a high case-fatality rate (Chadha et al., 2006). Since 2018 the state of Kerala has experienced recurrent outbreaks, the largest of which, in Kozhikode and Malappuram districts, involved direct spillover from bats followed by human-to-human transmission and a case-fatality rate exceeding ninety per cent (Arunkumar et al., 2019). Subsequent outbreaks in Kerala have continued at intervals, typically small in size but consistently lethal, and frequently without an identifiable intermediate host, with spillover attributed to consumption of fruit or sap contaminated by bat secretions. Crucially, there is as yet no licensed vaccine or specific antiviral therapy for Nipah, and management relies on supportive care and rigorous infection control. The virus's high lethality, its capacity for human-to-human spread and the absence of countermeasures explain why it features prominently on the World Health Organization's list of priority pathogens for research and development.

***SARS-CoV-2 and the lesson of COVID-19***

The COVID-19 pandemic was the most consequential zoonotic event in living memory, and the weight of scientific evidence points to a natural origin at the animal–human interface. Detailed epidemiological and genomic analyses place the earliest human cases in and around the Huanan Seafood Wholesale Market in Wuhan, where live mammals susceptible to SARS-CoV-2 were sold, and environmental sampling found viral genetic material concentrated in precisely the section of the market where such animals were traded (Worobey et al., 2022). Genomic studies further suggest that the early epidemic comprised distinct viral lineages consistent with more than one spillover event, and comprehensive reviews of the accumulated evidence conclude that the data point to zoonotic emergence linked to the wildlife trade rather than to laboratory activity (Holmes, 2024). Whatever residual uncertainty remains about the precise sequence of events, the policy lesson is unambiguous: the conditions that brought diverse, stressed wild animals into close, high-density contact with humans created the opportunity for a catastrophic spillover, and reducing such conditions is central to preventing the next one.

***Mpox***

Mpox, caused by an orthopoxvirus historically maintained in African wildlife, demonstrates how a long-neglected zoonosis can abruptly assume global importance. For decades mpox was regarded as a sporadic disease confined largely to forested regions of Central and West Africa, arising from spillover with limited onward spread. That picture changed dramatically in 2022, when a clade of the virus seeded sustained human-to-human transmission across many countries and prompted the World Health Organization to declare a public health emergency of international concern, a step repeated as the situation evolved (Bunge et al., 2022). Waning population immunity to orthopoxviruses following the cessation of routine smallpox vaccination, together with ecological disruption and increased human contact with reservoir species, has been implicated in its resurgence. Mpox underscores that the inventory of emerging threats is not fixed: pathogens can move from obscurity to global emergency within a single transmission season.

***Other zoonoses of regional and global concern***

Beyond these headline examples lies a long tail of zoonoses that variously threaten global health and

weigh heavily on specific regions, and several deserve individual mention because they illuminate recurring themes. The filoviruses Ebola and Marburg, which cause explosive and highly lethal haemorrhagic-fever outbreaks in Africa, are associated with fruit bats as reservoir hosts, with spillover often linked to contact with bats or with infected non-human primates and other wildlife (Leroy et al., 2005); their potential for international spread was made vivid by the West African Ebola epidemic of 2013–16. Hendra virus, the close Australian relative of Nipah, was traced to pteropid fruit bats as its natural reservoir and spills from bats to horses and thence to the people who care for them, a transmission chain that elegantly demonstrates the role of an amplifying domestic intermediate host (Halpin et al., 2000). The Middle East respiratory syndrome coronavirus circulates in dromedary camels and continues to cause sporadic, sometimes severe human infections, underscoring that livestock as well as wildlife can serve as the proximate source of dangerous coronaviruses.

In South Asia specifically, a further cluster of zoonotic and vector-borne infections (Table 3) imposes a persistent, under-recognised burden. Japanese encephalitis, maintained in a cycle involving pigs as amplifying hosts, waterbirds and Culex mosquitoes, remains a leading cause of viral encephalitis among children across the region. Crimean–Congo haemorrhagic fever and the related, India-specific Kyasanur Forest disease are tick-borne viral threats linked to livestock and forest exposure. Bacterial zoonoses—leptospirosis, contracted from water contaminated by rodent and livestock urine; brucellosis, acquired from infected animals and unpasteurised dairy products; and anthrax, associated with handling diseased livestock—cause substantial illness in farming and pastoralist communities and frequently go undiagnosed. The common thread running through this entire catalogue—animal reservoirs, environmental and agricultural drivers, and the need for intersectoral control—reinforces the central contention of this review: emerging infections are best understood not as a series of isolated emergencies but as recurring expressions of a single underlying ecology.

***One Health: the unifying solution***

The recurring lesson of every preceding section is that neither an ancient zoonosis nor a novel one can be controlled from within a single discipline. One Health is the formal articulation of this insight. As defined by the One Health High-Level Expert Panel that advises the international agencies, it is an integrated, unifying approach that seeks to sustainably balance and optimise the health of people, animals and ecosystems, recognising that these domains are closely linked and interdependent, and it is organised around the pillars of communication, collaboration, coordination and capacity building (Adisasmito et al., 2022). Institutionally, the approach is now carried by the Quadripartite—the World Health Organization, the World Organisation for Animal Health, the Food and Agriculture Organization and the United Nations Environment Programme—which together promote multisectoral action at the human–animal–ecosystem interface.

Rabies elimination is, in effect, a working proof of concept for One Health. It simply cannot succeed without veterinarians vaccinating and managing dog populations, physicians delivering post-exposure prophylaxis, public-health teams running surveillance and integrated bite-case management, laboratories confirming cases, and communities engaged in responsible animal ownership and prompt reporting. The very same architecture—shared surveillance across sectors, joint outbreak investigation, pre-positioned vaccine and antiviral stockpiles, and the protection of habitats that reduces contact with reservoir species—is precisely what is required to detect and contain the next avian influenza or Nipah event before it escalates. One Health also encompasses the silent, slow-moving emergency of antimicrobial resistance, which likewise spans human, animal and environmental compartments and demands the same coordinated response. Reducing the risk of spillover at its ecological source, rather than merely reacting to outbreaks once they occur, is increasingly recognised as the most cost-effective long-term strategy of all.

Within this framework, veterinarians occupy a uniquely strategic position. They are frequently the first professionals to detect unusual disease or mortality in animals, they hold the technical skills for mass vaccination, herd-health management and laboratory diagnosis, and they routinely move between the worlds of farm, clinic, market and wildlife. Strengthening veterinary services, diagnostic infrastructure and the channels of communication between the animal- and human-health sectors is therefore not a narrow professional interest but a direct and substantial investment in human pandemic preparedness.

One Health also embraces threats that move more slowly than an outbreak but are no less serious.

Antimicrobial resistance is the foremost example: the use of antimicrobials in human medicine, in livestock and aquaculture, and their release into the environment together select for resistant organisms that circulate across all three compartments, eroding the foundations of modern medicine and veterinary practice alike. Tackling resistance demands precisely the coordinated stewardship across human, animal and environmental sectors that the One Health framework is built to deliver, and it sits alongside zoonotic disease as a defining challenge for which veterinary leadership is essential.

**Barriers and the way forward**

Translating the strategies described in this review into results faces a familiar set of obstacles. Surveillance remains the weakest link: in the very regions where rabies and emerging zoonoses are most prevalent, cases go unreported, laboratory confirmation is scarce, and animal- and human-health data are seldom integrated, so that the true burden—and therefore the urgency—is chronically underestimated (Hampson et al., 2015; Thangaraj et al., 2025). Funding is insecure, because diseases of the rural poor struggle to command sustained political and financial commitment. Operationally, the sheer scale of free-roaming dog populations, the logistics of achieving and maintaining seventy per cent vaccination coverage, the cost and supply constraints around vaccines and immunoglobulins, and the difficulty of genuine coordination between sectors that have historically worked in isolation all impede progress.

The way forward follows directly from these barriers. Surveillance must be strengthened and integrated, with bite-case management linking the animal and human sectors, notifiable-disease reporting enforced, and laboratory and genomic capacity expanded in endemic districts rather than concentrated in a few central institutions (Banyard et al., 2013). Dog vaccination should be scaled up and sustained, supported by humane population management, community engagement and, where appropriate, oral vaccination of hard-to-reach dogs. Access to affordable post-exposure prophylaxis, including monoclonal antibodies and dose-sparing intradermal regimens, must be widened. And for emerging infections more broadly, investment should shift upstream toward prediction and prevention—reducing the ecological drivers of spillover, protecting habitat, regulating the wildlife trade, and embedding One Health coordination into routine governance so that it is not improvised anew in each crisis (Morse et al., 2012; Plowright et al., 2017). None of this is beyond reach; what it requires is the political will to treat animal, human and environmental health as the single, indivisible challenge they truly are.

**Future directions**

Several scientific and programmatic advances promise to reshape both rabies control and the management of emerging infections in the coming decade. In rabies prevention, the maturation of rabies-specific monoclonal antibodies offers a scalable, consistent alternative to scarce immunoglobulin for category III exposures; abbreviated, lower-cost intradermal vaccine regimens improve access and compliance; and the prospect of effective, thermostable oral vaccines for free-roaming dogs could finally bring the success of wildlife oral vaccination to the canine reservoir that drives almost all human deaths (Vos et al., 2025; World Health Organization, 2018). Genomic and molecular tools, already transforming diagnosis through assays such as the pan-lyssavirus LN34 platform, increasingly enable real-time tracing of transmission and rapid characterisation of emerging pathogens (Gigante et al., 2018).

More broadly, the future of emerging-disease preparedness lies in moving upstream—from reaction toward prevention. This means investing in surveillance at the animal–human interface, particularly in the biodiverse, rapidly changing and densely populated regions identified as future spillover hotspots; integrating viral discovery with biodiversity monitoring as species ranges shift under climate change; building laboratory and workforce capacity in the countries most exposed; and embedding One Health coordination into routine governance rather than improvising it during each crisis (Carlson et al., 2022). For a country such as India, which simultaneously bears one of the world's heaviest rabies burdens and sits within a recognised emergence hotspot, the pay-off from building durable, cross-sectoral capacity is doubly large: the same systems that carry the nation toward a rabies-free 2030 will also stand as its first line of defence against the next novel outbreak.

## Conclusion

Rabies and emerging infections bookend the zoonotic challenge. One is ancient, thoroughly understood and entirely preventable, yet still kills tens of thousands of people every year, most of them poor and many of them children. The others are new, unpredictable and capable of spreading across the globe within weeks, as COVID-19 demonstrated with brutal clarity. What they share is decisive: an origin at the animal–human–environment interface, a dependence on human ecological behaviour, and a solution rooted in the One Health philosophy whose seed Pasteur planted in 1885. World Zoonoses Day is a fitting moment to recommit to both fronts at once—to press on toward the elimination of dog-mediated rabies under Zero by 30 and India's NAPRE, and to build the surveillance, the research and the cross-sectoral collaboration that will blunt whatever emerges next. For the veterinary community, the message could hardly be clearer: the same vigilance, the same vaccines and the same partnerships that can finally end the world's oldest zoonosis are also our most reliable safeguard against its newest ones.

**Table 3.** Selected zoonotic and emerging infections of public-health importance.

| Disease | Causative agent | Principal reservoir / host | Main route to humans | Status / burden |
|---|---|---|---|---|
| Rabies | Rabies lyssavirus (Rhabdoviridae) | Domestic dogs; wildlife in some regions | Bite or scratch (saliva) | ~59,000 deaths/yr; ~100% fatal once symptomatic; vaccine-preventable |
| Avian influenza (H5N1) | Influenza A virus, clade 2.3.4.4b | Wild birds, poultry; recently dairy cattle | Contact with infected animals or products | Pandemic potential; cattle spillover in USA, 2024 |
| Nipah virus disease | Nipah virus (Henipavirus) | Pteropus fruit bats | Contaminated fruit/sap; close human contact | CFR up to ~90% in India; no licensed vaccine |
| COVID-19 | SARS-CoV-2 (Coronaviridae) | Bats; wildlife-trade intermediate hosts | Respiratory; emerged via wildlife trade | Caused the 2020 global pandemic |
| Mpox | Monkeypox virus (Poxviridae) | African rodents and wildlife | Animal contact; human-to-human | Global health emergency declared 2022 and 2024 |
| Japanese encephalitis | JE virus (Flaviviridae) | Pigs and waterbirds (mosquito-borne) | Culex mosquito bite | Leading cause of viral encephalitis in children in Asia |

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