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Zero by 2030 and OneHealth: The multidisciplinary challenges of rabies control and elimination

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Rabies, caused by a negative strand RNA-virus belonging to the genus Lyssavirus (family *Rhabdoviridae* of the order Mononegavirales), remains of global concern [1]. This vaccine-preventable viral zoonotic disease is present in more than 150 countries and territories [2]. According to the World Health Organization (WHO), rabies is estimated to cause ~59,000 human deaths annually, with 95% of cases occurring in Africa and Asia [3,4]. However, rabies still occurs in other regions, such as Latin America and the Caribbean [5–8], Central Asia and the Middle East [9,10]. Whilst a number of animals can host the rabies virus, dogs are the main source of human rabies deaths, contributing up to 99% of all rabies transmissions to humans. Dog-mediated rabies has been eliminated from Western Europe, Canada, the United States of America (USA), Japan and some Latin American countries [11]. Nevertheless, the risk of reintroduction and disease among travellers to risk areas is a matter of concern [12–15]. As occurred with many other communicable and non-communicable diseases, the 2020–2022 COVID-19 pandemic negatively impacted the efforts of control and reemergence of rabies in certain countries [7,16,17]. Post-pandemic challenges to enhance control and prevention are multiple and need urgent actions to achieve the goal in eight years by 2030 [16].

In this complex context, the international community has called for the world to be canine rabies-free by 2030 (Zero by 30); specifically, no indigenously acquired dog-mediated rabies cases among humans are to be achieved by the end of this decade [18]. The Global Strategic Plan to End Human Deaths from Dog-mediated Rabies by 2030, launched in June 2018, targets the disease at the dog reservoir and aligns efforts to prevent human rabies and strengthen animal and human health systems. By implementing the Strategic Plan, affected countries will move a step closer to Sustainable Development Goal (SDG) 3.3, "By 2030, end the epidemics of neglected tropical diseases", and make progress towards achieving SDG 3.8 on universal health coverage [18–21]. As with all zoonotic diseases, a One human, animal and environmental health (One Health) approach with cross-continental multi-disciplinary collaborations will be central to achieving the aims of this strategy [22]. The efforts against rabies should comprehensively consider the need for a multidisciplinary OneHealth response [23–27] at multiple levels, which enable a better understanding amongst complex interactions between human and animal health with the shared environment [28], not only the integration of actions between the WHO, the World Organization for Animal Health (WOAH/OIE) and the Food and Agriculture Organization of the United Nations (FAO), that set the target for global dog-mediated human rabies elimination by 2030 [29]; but at community levels by multidisciplinary teams in the control and prevention of disease in humans and animals. This OneHealth approach is essential to strengthen collaboration, communication, capacity building and coordination equally across all sectors responsible for addressing health concerns at the human–animal–environment interface. Therefore, multisectoral engagement and approach are critical under the umbrella of OneHealth collaboration, including community education, awareness program, and vaccination campaigns [1,30]. Unfortunately, in some countries, e.g. Panama and Venezuela, mandatory rabies vaccination is not regularly performed, although in these territories studies about rabies have also demonstrated their circulation also in chiropterans such as *Desmodus rotundus* [31–33].

The strategies to reach "Zero By 30" condense the societal changes into three objectives: i. To effectively use vaccines, medicines, tools, and technologies; ii. To generate, innovate, and measure impact, through authentic sustainable collaborative partnerships between different scientific disciplines and more sophisticated techniques [28]; and iii. To sustain commitment and resources (Fig. 1) [18]. For example, interrupting transmission is feasible through the mass vaccination of dogs [34]. However, since the cornerstone of rabies eradication are mass vaccination campaigns in dogs, these should be reinforced by verifying the seroconversion of animals [34–36]. Any failure of vaccination or seroconversion should be investigated to trace potential errors in the protocol. Additionally, immediate, thorough wound washing with soap and water after contact with a suspect rabid animal is crucial and can save lives [37]. Also, in certain countries, physicians in areas with

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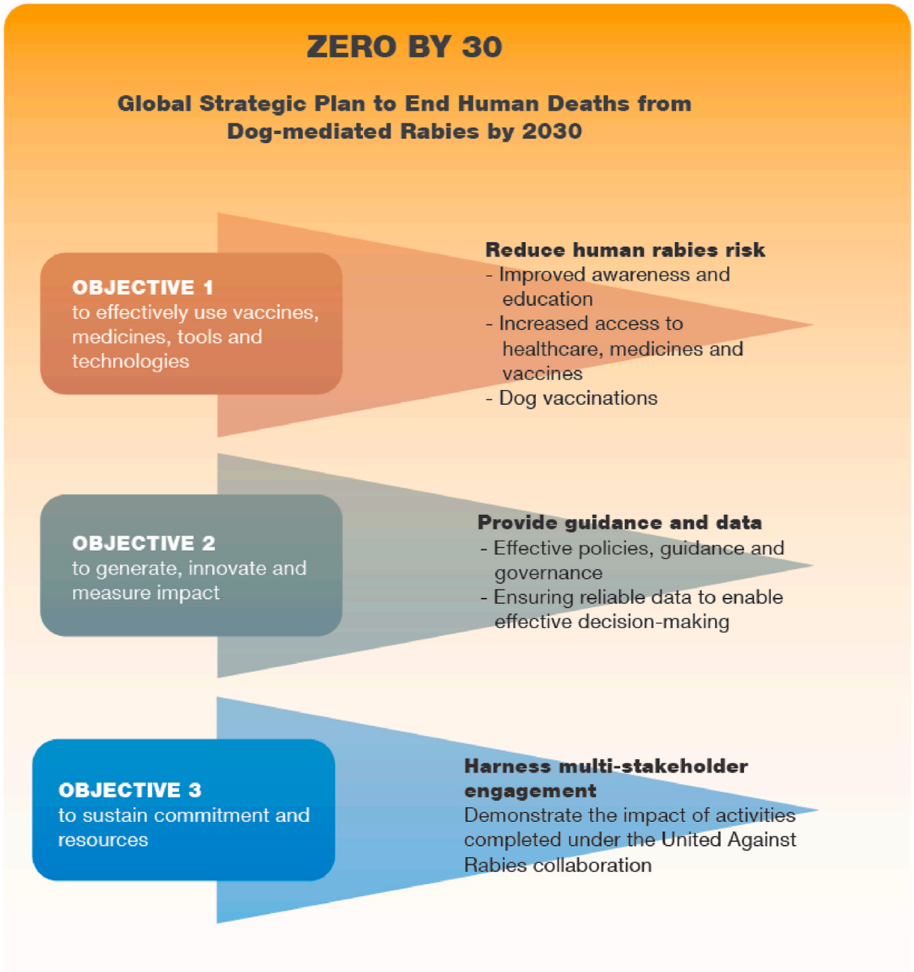

Fig. 1. Global strategic plan to end human deaths from dog-mediated rabies by 2030, WHO [46].

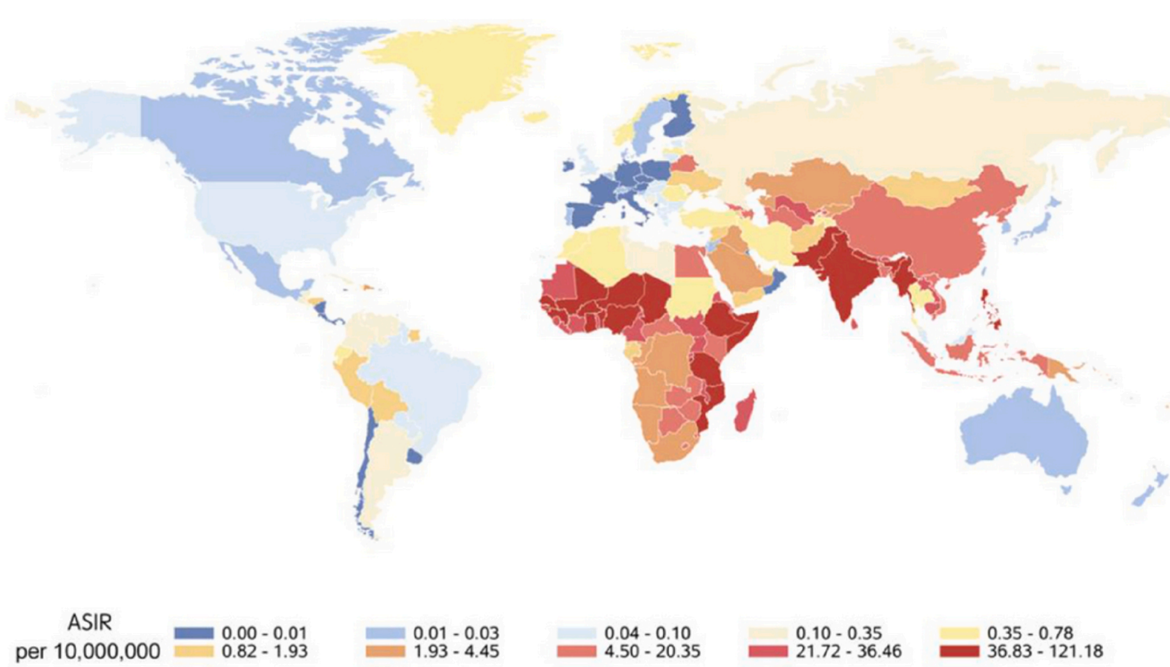

Fig. 2. Age-standardized incidence rate (ASIR) (cases per 10,000,000) in 2019 of rabies in 204 countries and territories [40].

demonstrated rabies circulation in cattle [58], do not consider the importance of cycles where also canids are present, increasing the risk for humans (e.g. Colombia, Guatemala and Panama) [38,39].

Recent estimates from the Global Burden of Disease (GBD) study (Fig. 2) [40] indicated that in 2019, the incident cases of rabies worldwide were 14,075 (95% uncertainty interval, UI: 6,124–21,618), and the number of deaths was 13,743 (95%UI: 6,019–17,938) (for a case fatality rate of 97.6%), both of which were lower than that in 1990. The actual numbers may be higher due to lack of resources for accurate diagnosis, documentation and reporting in rabies endemic developing countries. In addition, data suggested that with the improvement of the socio-demographic Index (SDI), the incident cases, the number of deaths, age-standardized incidence rate (ASIR), age-standardized death rates (ASDR), and disability-adjusted life years (DALYs) of rabies all showed downward trends. Adolescents and adults under 50 represented most rabies cases worldwide [40].

In addition to rabies, in the *Rhabdoviridae* family, at least three genera of animal viruses are included, Lyssavirus, Ephemerovirus, and Vesiculovirus. Lyssavirus has rabies, Lagos bat, Mokola virus, Duvenhage virus, European bat virus 1 & 2 and Australian bat virus (www.cdc.gov) [41,42]. Another animal of emerging importance in transmission of rabies to human is the bat [57]. Rabies can spread to people from bats after minor, seemingly unimportant, or unrecognized bites or scratch. It is worth mentioning that novel related viruses continue to be discovered, predominantly in bat populations, that are of interest purely through their classification within the lyssavirus genus alongside the rabies virus [43]. Although bat rabies accounts for a relatively small proportion of human cases worldwide, it accounts for most human rabies cases in the Americas. In most parts of the continent, haematophagous bats are the primary source of human cases, either by direct transmission or by infection through an intermediate species such as cats, which, given their hunting habits, become a “bridge” between bat rabies and urban areas [44]. Vampire bat rabies is also a significant cause of livestock mortality, affecting subsistence and commercial farmers throughout the geographic range of this bat (from northern Mexico to Argentina and Uruguay) [11,45]. The surveillance and detection of rabies and other pathogens in bats and other sylvatic animals is a complex challenge for public health systems, especially in resource-constrained countries.

Beyond these ecological issues, as a clinical condition, rabies is still challenging, prevention and control remain as key factors, while significant limitations still exist for managing cases. Despite the use of evidence-based approaches, the case fatality rate of rabies is high. Post-exposure prophylaxis (PEP) is critical in its management (Table 1) [46] and should be enhanced in risk areas. Although that, personnel at risk, such as veterinarians and biologists in endemic areas, do not have regular access to prophylaxis in many low and middle-income countries. Even more, in some of these nations, access to vaccine and immunoglobulins is also limited. In the case of travelers there is a high cost for medical evacuation when required, especially if there is no access to vaccines and immunoglobulins. For example, in countries such as Colombia, sometimes rabies affected populations include Afroamerican and Amerindian children, as reported in Choco department, a vulnerable area with rabies outbreaks reported in 2004–2005 [47].

Research on rabies should also be increased, including more assessment of potential antiviral therapies, immunotherapy, and other biological approaches, including more antibodies and vaccines [48–50]. Although pre-exposure and post-exposure treatment options are available, they are efficacious only when initiated before the onset of clinical symptoms. Furthermore, the current rabies vaccine does not cross-protect against the emerging zoonotic phylogroup II lyssaviruses. A requirement for an uninterrupted cold chain and the high cost of the immunoglobulin component of rabies PEP generate an unmet need for developing rabies-specific antivirals [51].

Active and passive surveillance should be enhance in humans and animals [52]. In addition to the intersectoral and multisectoral integration for control of rabies, national evidence-based guidelines should be developed and available periodically for healthcare workers to provide the best available clinical preventive, diagnostic and therapeutic management [53–55].

Table 1
Clinical approach for management of rabies exposure [46].

Exposure	Category	Approach
Intact skin (=no exposure)	I	Washing, but no vaccine
Minor scratches (no bleeding)	II	Washing plus vaccine
Transdermal bite (wounded skin) Multiple wounds	III	Washing plus vaccine plus RIG

Indeed, after the COVID-19 pandemic, multiple challenges remain or even are on recrudescence, including the effective control of rabies in many regions [56]. We are making a call for more research and development to reach globally the “Zero by 30” goal, which will be more feasible if more multi-, inter-, and transdisciplinary work is done, as well as prioritizing the utilization of global health and OneHealth approaches for this zoonotic viral disease. Rabies is preventable. A unified global OneHealth effort is required to make sure that human rabies deaths end by 2030. Investing more into rabies control will build OneHealth solidarity, reduce health inequalities and strengthen core capacities in resource poor regions for tackling fatal zoonotic diseases.

Declaration of competing interest

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D. Katterine Bonilla-Aldana
Research Unit, Universidad Continental, Huancayo, Peru
Committee of Tropical Medicine, Zoonoses and Travel Medicine, Asociación Colombiana de Infectología (ACIN), Bogotá, DC, Colombia

Julian Ruiz-Saenz
Committee of Tropical Medicine, Zoonoses and Travel Medicine, Asociación Colombiana de Infectología (ACIN), Bogotá, DC, Colombia
Grupo de Investigación en Ciencias Animales-GRICA, Universidad Cooperativa de Colombia, Bucaramanga, Colombia

Marlen Martinez-Gutierrez
Committee of Tropical Medicine, Zoonoses and Travel Medicine, Asociación Colombiana de Infectología (ACIN), Bogotá, DC, Colombia
Grupo de Investigación en Microbiología Veterinaria, Escuela de Microbiología, Universidad de Antioquia, Medellín, Colombia

Wilmer Villamil-Gomez
Committee of Tropical Medicine, Zoonoses and Travel Medicine, Asociación Colombiana de Infectología (ACIN), Bogotá, DC, Colombia
Secretaría de Salud de Barranquilla, Barranquilla, Atlántico, Colombia

Hugo Mantilla-Meluk
Colección de Mastozoología y Centro de Estudios de Alta Montaña, Universidad del Quindío, Carrera 15 Calle 12N, Armenia, Quindío, Colombia

German Arrieta
Committee of Tropical Medicine, Zoonoses and Travel Medicine, Asociación Colombiana de Infectología ACIN, Bogotá, DC, Colombia
Universidad de Córdoba, Instituto de Investigaciones Biológicas del Trópico, Clínica Salud Social Sincelejo, Corporación Universitaria del Caribe: CECAR, Sucre, Colombia

Darwin A. León-Figueroa
Facultad de Medicina Humana, Universidad de San Martín de Porres, Chiclayo, Peru
Unidad de Revisiones Sistemáticas y Meta-Análisis, Tau-Relaped Group, Trujillo, Peru

Vicente Benites-Zapata
Unidad de Investigación para la Generación y Síntesis de Evidencias en Salud, Universidad San Ignacio de Loyola, Lima, Peru

Joshuan J. Barboza
Vicerrectorado de Investigación, Universidad Norbert Wiener, Lima, Peru

Agueda Muñoz-Del-Carpio-Toia
Escuela de Postgrado, Vicerrectorado de Investigación, Universidad Católica de Santa María, Arequipa, Peru

Oscar H. Franco
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands

Maritza Cabrera
Centro de Investigación de Estudios Avanzados del Maule CIEAM, Universidad Católica del Maule, Talca, 3480094, Chile
Facultad Ciencias de la Salud, Universidad Católica del Maule, Talca, 3480094, Chile

Ranjit Sah
Tribhuvan University Teaching Hospital, Institute of Medicine, Kathmandu, Nepal
Research Scholar, Harvard Medical School, Boston, MA, USA
Dr. D.Y Patil Medical College, Hospital and Research Centre, Dr. D.Y. Patil Vidyapeeth, Pune, Maharashtra, India

Jaffar A. Al-Tawfiq
Specialty Internal Medicine and Quality Department, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia
Infectious Diseases Division, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA
Infectious Diseases Division, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Ziad A. Memish
Al-Faisal University, Riyadh, Saudi Arabia
King Saud Medical City, Ministry of Health, Riyadh, Saudi Arabia
Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA

Fatma A. Amer
Medical Microbiology and Immunology Department, Faculty of Medicine, Zagazig, Egypt
Chair of Viral Infection Working Group, and Executive Committee Member, International Society for Antimicrobial Chemotherapy VIWG/ISAC, Egypt

José Antonio Suárez
Instituto Conmemorativo Gorgas de Estudios de la Salud, Investigator 1 of the SNI, Senacyt, Panama City, Panama

Andres F. Henao-Martinez
Division of Infectious Diseases, School of Medicine, University of Colorado Anschutz Medical Campus, 12700 E. 19th Avenue, Mail Stop B168, Aurora, CO, 80045, USA

Carlos Franco-Paredes
Hospital Infantil de México, Federico Gómez, México City, Mexico
Department of Microbiology, Immunology, and Pathology, Colorado State University, Fort Collins, CO, USA

Alimuddin Zumla
Division of Infection and Immunity, University College London, London, UK
NIHR Biomedical Research Centre, University College London Hospitals, London, UK

Alfonso J. Rodriguez-Morales*
Committee of Tropical Medicine, Zoonoses and Travel Medicine, Asociación Colombiana de Infectología ACIN, Bogotá, DC, Colombia
Gilbert and Rose-Marie Chagoury School of Medicine, Lebanese American University, Beirut, Lebanon
Master of Clinical Epidemiology and Biostatistics, Universidad Científica del Sur, Lima, 4861, Peru
Grupo de Investigación Biomedicina, Faculty of Medicine, Fundación Universitaria Autónoma de las Américas - Institución Universitaria Visión de las Américas, 660003, Pereira, Risaralda, Colombia
Editor-in-Chief, Travel Medicine and Infectious Diseases

* Corresponding author. Committee of Tropical Medicine, Zoonoses and Travel Medicine, Asociación Colombiana de Infectología ACIN, Bogotá, DC, Colombia.
E-mail address: arodriguezmo@cientifica.edu.pe (A.J. Rodriguez-Morales).