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Meeting report

Towards rabies elimination in the Asia-Pacific region: From theory to practice

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ABSTRACT

Rabies is a major neglected zoonotic disease and causes a substantial burden in the Asian region. Currently, Pacific Oceania is free of rabies but enzootic areas throughout southeast Asia represent a major risk of disease introduction to this region. On September 25–26, 2019, researchers, government officials and related stakeholders met at an IABS conference in Bangkok, Thailand to engage on the topic of human rabies mediated by dogs. The objective of the meeting was focused upon snowballing efforts towards achieving substantial progress in rabies prevention, control and elimination within Asia by 2030, and thereby to safeguard the Pacific region. Individual sessions focused upon domestic animal, wildlife and human vaccination; the production and evaluation of quality, safety and efficacy of existing rabies biologics; and the future development of new products. Participants reviewed the progress to date in eliminating canine rabies by mass vaccination, described supportive methods to parenteral administration by oral vaccine application, considered updated global and local approaches at human prophylaxis and discussed the considerable challenges ahead. Such opportunities provide continuous engagement on disease management among professionals at a trans-disciplinary level and promote new applied research collaborations in a modern One Health context.

1. Introduction

Rabies is an acute, progressive encephalitis [1]. The causative agents are RNA viruses in the Family Rhabdoviridae, Genus Lyssavirus. This neglected viral zoonosis has the highest case-fatality of any infectious disease, responsible for tens of thousands of human deaths annually, widely distributed but affecting mainly lesser developed countries (LDC) in Africa and Asia. Although all mammals are susceptible to lyssavirus infection, domestic dogs are the most important global reservoir. Currently, the greater Pacific region is free of canine rabies, but at risk of infection from enzootic areas throughout Asia. Sensitive and specific diagnostic tests for laboratory-based surveillance and modern pure, potent, safe and efficacious human and veterinary vaccines form the basis of disease management.

Given the high burden of rabies in southeast Asia, this IABS conference took place strategically in Bangkok, Thailand, during 25–26 September 2019. The meeting focused upon snowballing efforts towards achieving substantial progress in rabies management in the Asia-Pacific region over the next decade. As a key focus was placed on canine rabies, the conference sought to be an important contribution to the initiative of the United Against Rabies (UAR) collaboration of the World Health Organization (WHO), the World Organization for Animal Health (OIE), the Food and Agriculture Organization of the United Nations (FAO), and the Global Alliance for Rabies Control (GARC), at ending human dog-mediated rabies by 2030 (AKA 'Zero by Thirty' or ZBT). Recognized global and local experts gave insights into state-of-the art trans-disciplinary One Health approaches, standards, available tools and guidelines developed by international organizations and institutions and provided best-practice regional examples on how to prevent human rabies by eliminating disease at its animal source. As such, the meeting provided a solid platform for health and veterinary services, managers of national and local rabies elimination programs, researchers and other professionals interested in advancing knowledge of rabies surveillance, prevention and control, to meet one another, to share their experiences and to discuss challenges to overcome. The conference was a strong starting point for a continuous professional exchange on the way towards creating and maintaining a canine rabies-free Asia-Pacific region.

1.1. Canine rabies prevention and control

This session was co-chaired by Drs. Gowri Yale and Karoon Chanachai. A variety of global, regional and local examples demonstrated the critical role of canine vaccination as the single most important facet for cost-effective, long-term disease elimination.

Professor Louis Nel from GARC talked about a Global Strategic Plan for the elimination of dog-mediated human rabies. Specifically, the Association of Southeast Asian Nations (ASEAN) Rabies Elimination Strategy (ARES) was established during 2014 and the ARES action plan during 2015. This was a comprehensive, phased-approach built around four inter-related pillars: Socio-Cultural, Technical, Organizational & One Health and Policy (dubbed STOP rabies, STOP-R) and legislation. The ARES concept of STOP-R was then more widely adopted and became integral to a global framework for the elimination of dog-mediated human rabies, which was developed during 2015 - 16 by the tripartite of FAO, OIE and WHO and GARC. From this global framework followed the UAR global strategic plan. The UAR is essentially a global catalytic initiative to achieve a common global goal of zero human deaths from dog-transmitted rabies (i.e., ZBT) by 2030 [2].

This ZBT goal focuses not only upon the details of the strategy and operational plan (available on the websites of the FAO, OIE, WHO and GARC since 28 September 2018), but also on a reflective comparison with other global disease programs (and in particular where those strategies were successful in elimination). For example, there are

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Abbreviations

APP	Application program
ARACON	Asian Rabies Control Network
ARES	Asian Rabies Elimination Strategy
ASEAN	Association of Southeast Asian Nations
BI	Boehringer-Ingelheim
CCTV	Closed circuit television camera systems
CDC	U.S. Centers for Disease Control and Prevention
CPV	Central point vaccination
CVR	Capture-vaccinate-release
DLD	Thai Division of Livestock Development
ERIG	Equine rabies immune globulin
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FDA	Thai Food and Drug Administration
GARC	Global Alliance for Rabies Control
GDP	Good distribution practice
GDREP	Global Dog Rabies Elimination Pathway
GIS	Global information system
GPS	Global positioning system
HCT	Hand-catching team
HDCV	Human diploid cell rabies vaccine
HRH	Her Royal Highness
HRIG	Human rabies immune globulin
IABS	International Alliance for Biological Standardization
IBCM	Integrated bite case management
ID	Intradermal
IM	Intramuscular
IPC	Institut Pasteur Cambodia
INGO	International non-governmental organization
KAP	Knowledge, attitude and practices survey
LDC	Lesser developed countries
MAbs	Monoclonal antibodies
MERACON	Middle East and Eastern Europe Rabies Control Network
MIC	Middle income countries
MR	Mission Rabies
MUMS	Minor Use in Minor Species Policy
NCT	Net-catching team
NGO	Non-governmental organization
OIE	World Organization for Animal Health
ORV	Oral rabies vaccination
OVD	Oral vaccination of dogs
PARACON	Pan-African Rabies Control Network
PCEC	Purified chick embryo cell vaccine
PEP	Postexposure prophylaxis
PLLAV	Plasmid-Launched Live-Attenuated Vaccine
POI	Point of interest
PrEP	Preexposure prophylaxis
PVRV	Purified Vero cell rabies vaccine
RACE	Rabies Action Centre of Excellence
RFFIT	Rapid fluorescent focus inhibition test
RIG	Rabies immune globulin
RITA	Rabies in the Americas Conference
RP	Reference points
SAARC	South Asian Association for Regional Cooperation
SARE	Stepwise Approach to Rabies Elimination
SMS	Short message service
SP	Sanofi Pasteur
STOP-R	Socio-Cultural, Technical, Organizational & One Health and Policy on Rabies
TRC	Thai Red Cross
UAR	United Against Rabies
VB	Vaccine bank
VNA	Virus neutralizing antibodies
WHO	World Health Organization
WRD	World Rabies Day
WTP	Willingness to pay survey
ZBT	Zero by Thirty

recognizable differences between rabies (i.e., an animal disease but with human impact) and smallpox (i.e., a highly contagious human disease significantly affecting the entire global population), as well as with rinderpest (i.e., an animal disease of momentous economic significance), as reflected on the chronic social and veterinary neglect of dogs throughout the ages and from all parts of the world. Notable examples from Europe were traced to some of the earliest works ranging from Desiderius Erasmus Roterodamus to William Shakespeare.

Stakeholders sought to identify critical success factors that could be elevated beyond disease specifics and to examine the status of these critical factors within the UAR Global Strategy. Five common critical factors were identified from the scientific literature and a brief consideration of these factors as they related to progress in the UAR Strategy included:

1. Feasibility, International Coordination & Strategy: The feasibility of human rabies elimination through the vaccination of dogs is well established. In comparison to the cases of smallpox (i.e., via WHO) and rinderpest (i.e., via OIE, FAO), the UAR offered a new level of international coordination among the tripartite (FAO, OIE, WHO) and GARC (civil society). New 'rabies control networks' that included PARACON (i.e., pan-African), ARACON (i.e., in Asia), MERACON (i.e., in the Middle East and Eastern Europe) and RITA (Rabies in the Americas Conference) are important platforms not only for coordination, but also for advancing other critical elements, *vide infra.*
2. National governments: Although the UAR strategy is country-centric, much progress is needed to assure the 'buy-in' from governments. For example, smallpox eradication was funded primarily by national governments. Applied research suggests that the same is possible for most rabies-endemic nations (e.g., the Stepwise Approach to Rabies Elimination [SARE]; Global Dog Rabies Elimination Pathway [GDREP]; etc.) [3].
3. Communities: The role of communities was critical to the success of the smallpox and rinderpest eradication campaigns. The UAR plan recognizes the importance of community involvement and has a strong educational component.

From FAO, Dr. Katinka de Balogh provided an overview of the fundamental principles of successful canine vaccination and the challenges that create setbacks. In most rabies endemic countries, dog-bites are the main route of transmission of rabies virus to humans. Hence, vaccination of dogs remains the most cost-effective way to prevent rabies in humans. When examining the risk dogs pose in contracting and transmitting rabies virus, restrained dogs and those kept in enclosed areas pose a lower public health risk for viral transmission. Other categories, such as feral dogs or dogs that are not known to community members, have a higher risk to contract rabies. However, community members generally avoid such animals. Dogs that are owned but allowed temporarily to roam freely, as well as more wide-ranging community dogs (i.e., those very common in most Asian countries, where the community members feed but do not specifically take individual responsibility for the dogs) pose the highest risks for transmitting rabies virus to humans. They are known to the community, commonly fed, but often not vaccinated against rabies. These community dogs are exposed to rabid dogs and subsequently when infected, bite community

members, especially children. Understanding the bond that exists between people and their dogs provides useful insights into understanding the best way of engaging communities in control strategies. The need for social scientists is therefore advocated for inclusion in rabies management as part of a One Health approach to address the multi-dimensional aspects of rabies prevention and control.

Globally, there are numerous examples of countries that have been able to prevent human rabies through vaccination of dogs. A vaccination of ~70% of the dog population is targeted during such campaigns. However, reaching this target is especially important for dogs posing the highest public health risk, such as free-roaming owned and community dogs. In addition, the use of high quality vaccines, inducing long-lasting immunity, a functioning cold chain and the correct application of the vaccines are essential for attaining satisfactory herd immunity. Overall, rabies prevention and control require the engagement of both the animal and human health sectors, in addition to (local) government/municipalities and communities.

The estimation of the dog population remains one of the greatest challenges when planning effective vaccination campaigns and the subsequent calculation of the vaccination coverage. Although there are various methods, there are still shortcomings for identifying the number of free-roaming dogs, that are not readily visible. The possibility of using video-surveillance cameras (i.e., CCTV) that can be found in many urban areas could be further explored.

Overall, a thorough understanding of the characteristics of the dog population and the linkages between them and humans yield valuable information on how to foster responsible dog-keeping practices, and a more appropriate design of vaccination campaigns (e.g., a central point or door-to-door scheme; on weekends or school holidays, when the target are young boys to bring the dogs for vaccination; etc.). The accessibility of dogs for vaccination varies in different societies and is often dependent on prevailing socio-cultural characteristics. Dog ecology studies provide valuable insights and should be conducted as part of strategic planning.

Also, over the years the development of downloadable computer applications or 'apps' has been very useful in the planning and evaluation of vaccination campaigns. One constraint is an inexpensive and durable marking of vaccinated dogs, by collars or coloring. This may remain a challenge for oral rabies vaccination (ORV), where there is no direct contact with the vaccinated animal.

Community engagement is key. For example, since its inception during 2007, World Rabies Day (WRD) has contributed to increased awareness among professionals as well as the general public. The WRD 2019 slogan was on "vaccinate to eliminate". Furthermore, having the global target for the elimination of dog-mediated human rabies target by 2030 (i.e., ZBT) has enhanced individual country attention and commitment. Significantly, a meeting organized by the FAO/OIE/WHO tripartite together with ASEAN representatives during December 2018 in Hanoi, Vietnam, and the South Asian Association for Regional Cooperation (SAARC) in Kathmandu during June 2019 fostered the commitment of the countries in Southeast and South Asia towards this goal.

As one illustration of community engagement, an FAO project to support rabies control in Bali focused on the development of integrated bite case management (IBCM) alongside the creation of teams consisting of young persons trained to strategically capture dogs with nets, vaccinating and collaring them [4]. At present, the FAO is fostering the concept of a Rabies Action Centre of Excellence (RACE), to assist the region with the development and implementation of rabies control strategies, including the training of dog capture and vaccination teams.

Clearly, a basic understanding of the dog population is key for many facets, including dog numbers, relative accessibility for vaccination, appropriate application of quality vaccine by well trained and equipped staff, for the success of dog rabies vaccination campaigns [5]. The continuous evaluation and realignment of control strategies based on lessons learned and availability of new tools should be further promoted. As rabies is not a disease that can be eliminated within a short period, high level political engagement and long-term commitment (funding) at central and local levels are required to reach ZBT.

Dr. Victor Del Rio Vilas continued with this theme and shared the regional experiences on canine rabies prevention and control in the Americas, where major focused efforts began during 1983 [6]. In retrospect, rabies elimination is a reality as evident in multiple settings, even at large geographical scales such as in Latin America, given the efficacy of available interventions, mostly focused on dog and human biologics. Whether this reality is feasible in the remaining endemic country settings, where social and organizational complexities may not be properly understood or addressed, is a question of major strategic relevance.

Regardless of this concern, in theory the ZBT is a well-crafted global strategy with clear narratives that will hopefully help to 'nudge' countries into action. How this action is executed by the many actors across geographies and domains, with divergent risk preferences and capacities, is a multi-dimensional challenge that will require specific approaches to address both the technical and organizational complexities ahead. Too often, researchers fail to pay proper tribute to the latter and forget the deliberate consideration of the impact of organizational politics, domain-specific agendas and values on the investment decisions regarding the political economy of rabies prevention, control and elimination efforts. This requires identification and characterisation of the value attributes for all relevant stakeholders. While saving lives remains a long-term passion of most workers in the rabies field, other stakeholders' short-term needs and appetites (stemming from organizational and social tensions), also require consideration, but are often overlooked. Only by understanding such non-technical stressors will long term sustainability be more reasonably ensured.

In hindsight, although social and organizational issues are mentioned at rabies conferences, the reality is that such concerns remain secondary to more technical discussions (e.g. on the development of ever more refined diagnostic tests and vaccines). This tendency overlooks the central role that these social and organizational aspects play in the execution of strategies. While technical capabilities define the possibility of rabies elimination, by providing assurances that interventions and surveillance are sufficiently developed to that effect, social and organizational aspects determine program feasibility, and as part, the certainty around goal setting and resource demands. Given the large uncertainties and unpredictability of long-term goals, the ZBT strategies should consider plausible scenarios of failure, with description of future resource demand and build-up plans, as was desirable in the Americas over several decades [7]. A comprehensive baseline capability assessment is a bare minimum to start informing such scenarios, which must also factor in the common biases affecting goal setting, at any geographical scale. Both outcome (i.e., the tendency to measure decision quality based on the outcome rather on the robustness of the processes that led to that outcome) and hindsight biases (i.e., the tendency to forget past hurdles and exaggerate the probability of success when the outcome was achieved) can alter perception of programme performance. These can trick one into thinking that past successes, normally on a set of somewhat 'easy' challenges, will repeat themselves with equal ease on those that remain, normally of much greater complexity. Clearly, the picking of such lower-hanging fruit is not an ideal predictor of the ease or length of harvest of the entire tree. In addition, outcome bias does little to support robust monitoring of processes. Consequently, this may hamper the learning of possibly valuable exchangeable lessons.

Rabies programmes track cases, objectively when possible, but rarely compile the evidence that led to their decline (or increase). As in prior attempts within Latin America, the cascade of failures is rarely published and the opportunity to learn is negated. Robust knowledge management, mechanisms and implementation of decision quality frameworks would work towards more sustained enlightenment. The systematic implementation of these governance elements would

support identification of organizational benchmarks which, if properly adjusted for contextual variables, merit widely and regular dissemination to promote greater conformity [8]. Note that such an enterprise would work across scales (i.e., from local to global) and diverse stakeholders. Such efforts would allow informed comparisons among rabies management approaches (e.g., those promoting across various domain collaborations). For example, throughout Latin America, efforts display an almost monopolistic approach in the predominant role of the Ministries of Health in the delivery of rabies programmes across the region. Although such an exclusive operational model could have simplified the deployment of rabies programmes, it could have also prevented the innovation that comes from the enhanced scrutiny and competition of a more multi-sectoral setting. Further, the combination of outcome and hindsight biases generally lead to risk aversions, which can also hamper innovation (e.g., ORV). Innovation acquires greater relevance during the frustrating 'last mile' of a program, when the declining slopes of case counts in the control phase turn into stubborn, nearly flat lines with an occasional spike [6].

No single epidemiological or modelling output will be able to address the above biases. They will, at best, facilitate identification and characterisation (e.g. the variables of the where, when, how, etc.) of artefacts in deployment of interventions that, most likely, stem from social and organizational tensions. An understanding of the prime cause of why vaccination coverage is not reached, or surveillance is not endorsed by the relevant stakeholders, can only be achieved through social science research [9]. Attempts to address these critical questions cannot be limited to the one-off knowledge, attitude and practices (KAP) survey or the isolated small community-based, semi-qualitative study, mostly research-driven and project-based at its heart. While commendable, the deployment of social and organizational interventions must follow the same planning process as surveillance or vaccination and be funded to the level required to provide actionable evidence to inform the programme.

Rabies remains neglected in many ways, with the lack of robust epidemiological and capacity related data being manifestations of this neglect. Still, such affirmation requires some knowledge of the extent of our collective ignorance (i.e., paraphrasing the economist Thomas Sowell), and reflects ongoing efforts to improve the evidence base. Such a repository of evidence however remains remarkably empty of social and organizational results to vaguely inform the extent of one's ignorance. Recent efforts have shown the occurrence of cognitive biases, namely loss aversion and probability weighing, in decisions pertaining to rabies surveillance investments [10]. These investigators quantified the willingness-to-pay (WTP) for such investments and elicited the study subjects' reference points (RP) that describe their baseline position, from which they asses the attractiveness of risky bets, such as investments in surveillance. The occurrence of such items highlights the need to incorporate adequate frameworks to identify and quantify such biases, prior to surveillance investment decisions. Failing to do so, by ignoring the occurrence of risk aversion, could return biased estimates of the effectiveness of new surveillance streams, as standard cost-effectiveness analyses assume a risk neutral position by default. In addition, knowledge of the surveillance stakeholders' WTP and RP are critical for targeted communication efforts, by informing the framing of messages and the level of possible incentives to encourage surveillance engagement. With the increasing demands for accountability and efficiency, in particular during the daunting 'last mile' towards elimination within the Americas and elsewhere, finer-tuned comparisons between competing interventions, taking into account inherent biases, are a must.

Dr. Ryan Wallace from CDC discussed modern tools for eliminating dog-mediated human rabies through mass canine vaccination campaigns, using Haiti as a relevant LDC example in the region of the Americas [11]. Clearly, use of electronic tools to manage rabies program activities are becoming more common, replacing or appending long-standing pen-and-paper systems. Several published evaluations of these tools have shown net-positive outcomes, as compared to the increased technical capacity needed to operate these programs [12]. A concern among some in the rabies community is that reliance upon so-called "rabies apps" will distract from the core principles of rabies control that must be enacted prior to selection of appropriate electronic tools. Rabies program success depends on adoption and implementation of appropriate protocols for surveillance, diagnostics, vaccinations and animal welfare. A fine tool will not make a bad program any better. Before selecting a tool, a program should first select an appropriate and effective protocol (or strategy). Once a strategy is selected, a tool that facilitates implementation of this protocol should be chosen.

Haiti's current rabies program was built on a strong foundation of advocacy and laboratory-based surveillance. The GDREP and SARE tools were used to provide a pathway and argument that the goal of elimination is cost-effective for Haiti and other countries [3,11]. Dog vaccination programs underwent extensive evaluation, first utilizing paper-based tools, which resulted in poor data quality and inadequate timeliness. Second-generation evaluations utilized Point of Interest (POI) GPS devices to evaluate vaccinations, but these also fell short of the program's data needs in terms of quantity and timeliness [13]. Third-generation evaluations, implemented during 2017, utilized app-based tools, which have enabled Haiti's programs to enact more precise and effective vaccination protocols. These evaluations, conducted from 2014 to 2019, found that campaigns utilizing only the central point vaccination (CPV) method routinely under-vaccinated the target dog population due to numerous societal and dog-specific factors. Alternative methods of ORV and capture-vaccinate-release (CVR) were found to overcome these barriers and achieve > 70% coverage, but Haiti lacked the logistical and financial means to scale these methods to national levels. Mixed-methods approaches, which combined CPV, door to door, and CVR, were designed. A mobile phone App was used to coordinate and monitor these mixed-methods vaccination activities for the national vaccination campaign during 2017–2018. Over 330,000 dogs were vaccinated, which achieved 76% coverage among the target population and an 80% reduction in reported human cases over the following year. Based on the experience of Haiti, the following approach and tools were integral to implementing a successful large-scale dog vaccination program:

- Stage 1: Evaluating the economic costs and health benefits of rabies elimination (i.e., GDREP tool, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5300989/)
- Stage 2: Characterization of the dog population and vaccination capacities, first via paper-based and POI, later by a Mission Rabies (MR) app (https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0200942)
- Stage 3: Planning cost effective vaccination campaigns using a GIS-based prioritization process (i.e., the 'Vax-PLAN' tool, https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-015-1320-2; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6805755/)
- Stage 4: Large-scale implementation using a Vaccinate-Assess-Move method, managed and tracked using the MR app

'App-based' tools are extremely flexible and low-cost investment to create. One may anticipate that numerous app-based tools will continue to be developed as fit-for-purpose needs are identified. Discouraging tool development is unlikely to be a fruitful effort. International agencies should instead focus efforts on ensuring that there is clear guidance as to which protocols are most appropriate under certain settings, and the criteria by which new tools should comply, to be consistent with global recommendations. In general, CPV is the least expensive vaccination method. When CPV alone reaches adequate vaccination levels, it should be continued. When CPV fails to control rabies at a national or sub-national level, mixed methods approaches should be urgently explored and implemented. Haiti, being a donor-driven program, often adopts programs that reflect the perspectives and goals of the donor.

Consequently, frequent changes in donor organizations have led to difficulties in maintaining a consistent protocol for surveillance and vaccination (i.e., for both humans and dogs). Inconsistent funding also jeopardizes future success of elimination.

Additionally, the co-recognition of programs and tools should consider “economies of scale”. There are numerous dog-endemic countries that have managed to develop large-scale vaccination programs. However, these programs are rarely evaluated, published or promoted. For example, Thailand currently vaccinates over 8 million dogs and cats per year and has a national electronic case reporting system that has logged tens-of-thousands of bite events and rabid animals [14]. Significantly, during 2017, South Korea formally declared that they had eliminated canine rabies [15]. Moreover, Vietnam vaccinates over 4 million dogs each year [16]. Yet, the seeming ‘flagship’ programs repeatedly receiving accolades are far smaller in scale than such prior examples. A balance must be struck in the global conversation, in which country programs, such as in the Americas, that have achieved large-scale rabies vaccination practices, are encouraged to evaluate and disseminate their program findings. Programs such as CDC's project in Haiti, MR's projects in Goa and Malawi, the University of Glasgow in Tanzania and GARC in the Philippines have very important lessons that can help improve global practices [11–13]. However, these programs are dwarfed in scale compared to what many countries are already achieving (e.g., Mexico, Brazil, Thailand, etc.) [7]. Perhaps the greatest hurdle for highly endemic rabies-affected countries is the transition from successful pilot projects to large-scale, government-supported, routine rabies control activities. Programs that have recently achieved this hurdle should be given a platform to share their experiences and guide endemic countries with similar scale-up barriers. Lastly, a widespread platform to recognize the excellent work being done by many programs needs to be built, and international agencies should invest resources to assist these countries in evaluating and promoting their own accomplishments.

In contrast to the Americas, Dr Abdul Rahman turned to the Old World and reviewed the situation in India, where the rabies burden is considered to be the highest, based upon estimated human fatalities [17]. Vastly improved availability and accessibility of modern tissue culture vaccines, rabies immune globulins (RIG) and monoclonal antibodies (MAbs), intradermal (ID) vaccination, tools for sero-monitoring of rabies virus-neutralizing antibodies (VNA) and overall socio-economic improvements have led to better rabies awareness and reduction of human rabies deaths. However, constraints remain. Rabies is not a notifiable disease in India. No comprehensive rabies control program exists. There is lack of burden data. More NGOs and INGOs are involved but confined to limited areas. The Government has prepared a “Rabies Action Workplan” for completion over the next 3 years. A National Task Force for rabies elimination has been formed and protocols for handling of probable/confirmed animal rabies cases and animal bite management in other animals have been formulated. Developing of a functional animal rabies surveillance system and strengthening mass dog vaccination campaigns has been envisaged. The ORV concept is considered a potential complementary measure to parenteral mass dog vaccination campaigns. Promising future opportunities and considerable current challenges wait for engagement on the sub-continent.

Dr. Pranee Panichabhongse continued the focus upon the Asian region and shared Thailand's experience in controlling canine and human rabies (Fig. 1). Before 1992, each Thai organization worked separately on dog vaccination, laboratory diagnosis and dog population management. During 1992, the Rabies Act was launched under responsibility of the Department of Livestock Development (DLD),

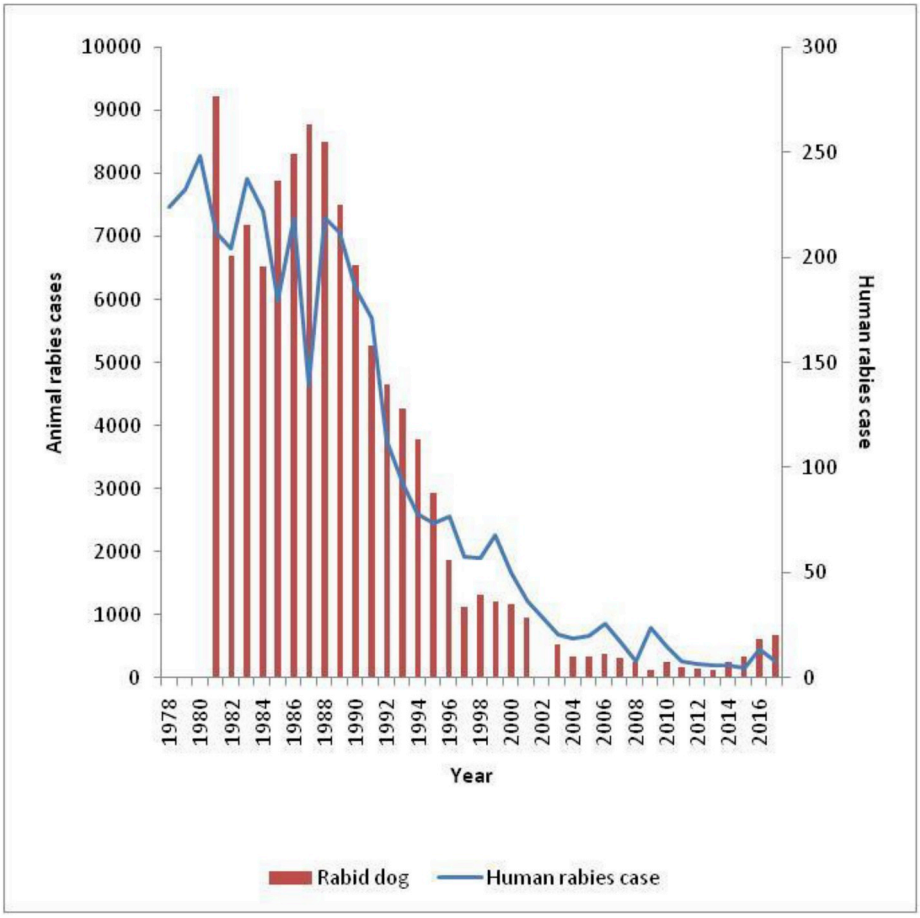


Fig. 1. Cases of rabies in humans and dogs, Thailand 1978–2018.

Ministry of Agriculture and Cooperatives. The DLD also started an activity on dog population control. During 1995, there was an integration of activity among the DLD and the Department of Disease Control Ministry of Public Health. During 2010, the Department of Local Administration, Ministry of the Interior, cooperated on rabies control by providing animal rabies vaccines. During 2016, Professor Dr. Her Royal Highness (HRH) Princess Sawangkawat launched the "Saving Animals and Human Lives from Rabies" Project, following the determination of Professor Dr. HRH Princess Chulabhorn Mahidol, consisting of 8 strategies: surveillance, prevention and control of rabies in animals; management of animal shelters; surveillance, prevention and control of rabies in humans; propulsion on rabies activities in the rural area; Public Relations and integration and management of data related to rabies; project monitoring and evaluation; development of innovations; and technology transfer by integration of 6 ministers. The DLD Rabies control activities were responsible at different levels, by the Provincial Livestock offices, District Livestock offices, Sub-district Livestock offices and village volunteers. Thereafter, disease investigations were focused on: human health and animal health; case verification and investigation; animal quarantine and movement controls; ring vaccination for 3–5 km around an index case; dog and cat population management; and concentrated laboratory-based surveillance for 6 months. In addition, the Thai Rabies Net Program was developed for data collection throughout the country.

1.2. The ORV of wildlife and dogs

This session was co-chaired by Drs. Katinka de Balogh and Ryan Wallace. Clearly, ORV is an essential strategy for disease management in free-ranging animals, as exemplified by the six speakers.

Dr. Thomas Muller gave an overview on the historical concept and application of the ORV of wildlife [18]. Such methodology is a powerful and effective tool for eliminating wildlife-mediated rabies. Despite notable regional successes in eliminating wildlife rabies, as exceptionally exemplified in Europe and North America, the complete elimination of rabies in mesocarnivores is far from becoming a reality [19–21]. A future direction of wildlife rabies control using ORV lies in identifying practical solutions in a wide range of potential reservoirs, including vaccine and bait specific issues as well as effective bait delivery and distribution systems and large-scale vaccine strategies with an increased cost-benefit-ratio. Despite diverse complexities and challenges in applying ORV to control wildlife rabies, such methodology has the potential to become a powerful supplementary measure to control rabies in dogs [22].

Dr. Ad Vos shared his thoughts on why the ORV of dogs is an important component of the UAR global elimination program. Essentially, a large proportion of the dog population in countries with endemic dog rabies is (partially) free-roaming and this subpopulation plays a key role in the transmission of rabies virus among dogs. Hence, a suitable vaccination coverage for this high-risk group is essential to eliminate canine rabies. Unfortunately, in many countries it is sometimes not possible to capture and restrain such dogs for vaccination (or only after intensified efforts). Alternatively, the oral vaccination of dogs (OVD) offers a possibility to vaccinate these inaccessible animals without direct contact (Fig. 2). The OVD therefore increases the efficiency of mass dog vaccination campaigns by reducing time and efforts required to vaccinate such free-roaming dogs. Besides this qualitative effect, more free-roaming dogs can be reached by incorporating OVD in the dog vaccination campaigns than only using traditional vaccination by the parenteral route. Hence, OVD as a complementary tool to parenteral vaccination can increase herd immunity, especially among free-roaming dogs, to levels required to interrupt the rabies virus transmission cycle and consequently eliminate dog-mediated rabies [23].

Dr. Jakava-Viljanen detailed specific aspects on considerations for the use of oral vaccines for dogs and other species, from the perspective of the European Medicine Agency. On the scientific evaluation of the marketing authorization applications and monitoring and control of oral vaccines, it is important to consider the unique aspects of the vaccine on quality, safety and efficacy and specific methods of administration, to ensure that their benefits outweigh their risks. In Europe, there are two oral vaccines centrally authorized for foxes and raccoon dogs (e.g., Rabigen, rabies virus strain SAG2 and Rabitec, rabies virus strain SPBN GASGAS) and many oral candidate vaccines for dogs, however these vaccines are frequently used off-label. Also, there several others with a national license in selected EU Member States (e.g., most recently, Bioveta licensed another ORV product, Rabadrop). In general, a vaccine is presented in a bait attractive to the target species, with a suspension inside filled in a container containing a live attenuated or genetically-modified virus as active substance. The bait protects the vaccine virus and it may contain a biomarker. The vaccine is distributed within a bait in the habitat of the target species, therefore further testing is needed to mimic environmental conditions. The vaccine virus

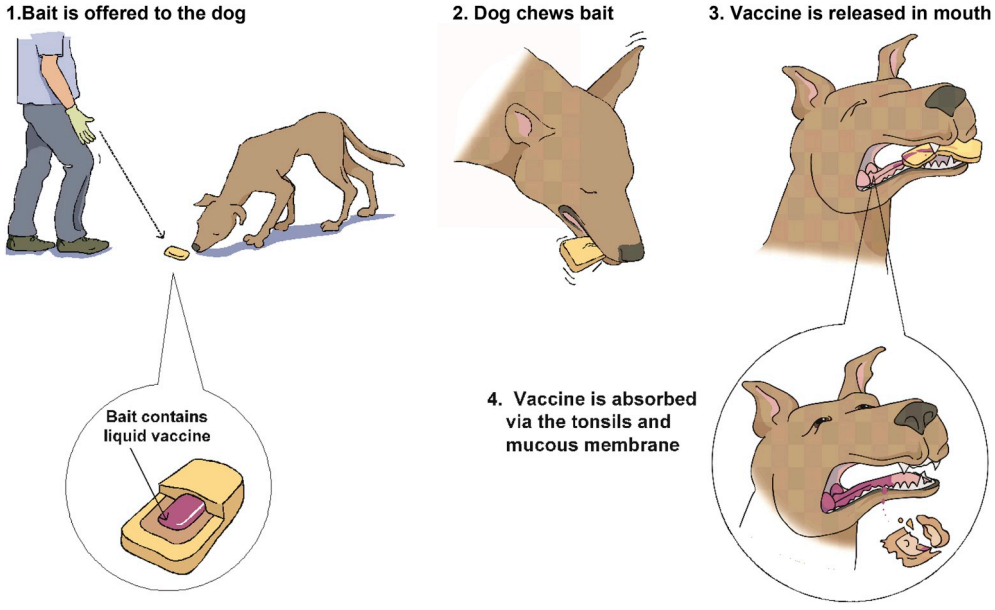


Fig. 2. The basic concept of the oral vaccination of dogs (OVD) against rabies.

needs to have stable genetic markers that discriminates the vaccine virus strain from other rabies viruses. The efficacy of the vaccine should be demonstrated by virulent challenge in each species for which the vaccine is claimed, for at least 6 months after administration of the vaccine bait. Besides effectiveness, the vaccine needs to be evaluated for safety in the target species and major endemic non-target species (including humans), likely to be attracted by the baits, when sufficiently justified. In the EU, the Minor Use in Minor Species (MUMS) policy allows the omission of field trials. Testing that the vaccine potency remains the same in the baits, before and after distribution, provides evidence that the vaccine will induce an adequate immune response. In the EU, quality, safety and efficacy of vaccines need to be demonstrated in compliance with Directive 2001/82/EC, and amongst other the Guideline on requirements for the production and control of immunological veterinary medicinal products (EMA/CVMP/IWP/206555/2010) and the relevant monographs of the European Pharmacopoeia.

Continuing the theme of ORV assessment, Dr. Jesse Blanton supplied background on a model for risk quantification for adverse events related to distribution of modified-live rabies virus vaccines. Inarguably, vaccination of animals is an effective means of protecting human health through the reduction of zoonotic pathogens, protection of agricultural animals and conservation of wildlife species [24]. While programs for the parenteral vaccination of most domestic animals are well established, vaccination of wildlife or free-roaming domestic animals (e.g. free-ranging dogs) by the oral route remains a challenge. The use of baits containing live-virus vaccines has been a successful model for vaccinating different domestic and wildlife species against a variety of diseases, including rabies. However, the presence of live, replication-competent organisms used in these baits continue to raise concerns for their distribution and unsupervised presence in the environment, specifically related to potential human exposures. To help address these concerns and provide a systematic approach for assessing human risk, CDC developed a Markov chain model to estimate the number of severe adverse events resulting from contact with live attenuated vaccines distributed in the environment. The safety profile of several ORV biologics for animals were used to evaluate the model, which found that the risk of severe adverse events in populations approached zero, where third-generation genetically-modified live rabies virus vaccines were used, even after adjusting for sensitivity testing. Overall, the use of this Markov chain model for estimating risk illustrated the safety of third generation rabies vaccines for use, as in the OVD, and exhibited a role for such models to bridge safety profile data, obtained from *in vitro* and *in vivo* studies to estimating community based risk during large scale environmental distribution.

Within this same topic, Dr. Gowri Yale assessed the need for the OVD in India. Basically, throughout the region, a public fear of rabies may continue to divert resources towards human prophylaxis, until canine rabies is eliminated, and the risk of a rabid dog bite is reduced to nil. The only long-term, cost-effective approach to curtail this problem is mass dog vaccination, as free roaming dogs are the primary reservoir of rabies virus in endemic LDC and middle-income countries (MIC), where dogs also live very closely to humans. To reach these dogs, OVD is a solution, but the aerial distribution system model, as predominantly used for wildlife, is not suitable for free-ranging community dogs, as they share the same general environment as humans.

Since 2015, MR has been working in India with the Goa government, vaccinating approximately 100,000 dogs annually, with a coverage of approximately 70% throughout the state. Canine rabies cases were reduced from 78 during 2017 to only 4 during 2019. Detected human rabies cases were reduced from 17 during 2014 to 0 over the last 2 years. A SARE workshop conducted during April 2018, facilitated by Dr. Wallace, CDC, scored Goa at 3.5 on a scale of 5.0, indicating that rabies is under control in Goa and becoming close to elimination.

Currently, one of the best methods to mass vaccinate dogs is by hand catching and net catching, as demonstrated by MR. A hand catching team (HCT) consists of 2 people on a moped or motor bike, going door to door, vaccinating dogs parentrally without using any other tools. This team is successful in vaccinating both owned and some free roaming dogs. A net catching team (NCT) consists of ~4–5 catchers with nets, a vaccinator and a person to carry the vaccine cooler box, a transport vehicle and a driver. Thus, the total NCT consists of ~7–8 people. The NCT is sent into an area after the HCT, to vaccinate any remaining dogs. MR's experience in the field shows that the HCT is vaccinating close to ~50% of dogs. This number can vary across different landscapes and demographic settings but suggests that a majority of dogs can be accessed at a far lower cost. If the HCT can be equipped with OVD as a tool to improve coverage, mass dog vaccination will be far more feasible. To date, MR performed studies to observe specific bait preferences, acceptance and consumption by free roaming dogs and compared the costs of conducting HCT and OVD, through a handout model of baits by the NCT. Studies suggest that an egg bait is the most attractive choice and a handout model costs far less, needing fewer staff as required by the NCT method [23]. For example, to vaccinate 50,000 dogs over 2 weeks (in 1 district), MR would need approximately 560 individuals for the NCT compared to only 146 with the handout method. The handout method of bait delivery to dogs has been specifically designed to minimize non-target vaccine bait contacts, especially to humans.

Within Thailand, Dr. Suwicha Kasemsuwan summarized canine vaccination progress. As elsewhere, parenteral delivery is the recommend route for rabies vaccination in the country. However, rabies vaccine coverage can be increased by using OVD as a supplemental vaccine approach [25]. In preliminary OVD studies, using a third-generation rabies virus (i.e., SPBN GASGAS), dogs developed detectable immune responses from day 14, when compared with day 7 of a parenteral vaccine group, suggesting its utility to safely and effectively enhance herd immunity.

1.3. Human pre- (PrEP) and postexposure prophylaxis (PEP)

This session was co-chaired by Drs. Thomas Müller and Conrad Freuling. Since the time of Pasteur, human rabies vaccines have continued to improve upon safety and efficacy, as illustrated by the four speakers on this highly relevant topic.

On behalf of Dr. Bernadette Abela-Ridder from WHO, Dr. Charles Rupprecht shared an update on human PrEP and PEP [26]. Human rabies deaths are preventable through timely and adequate PrEP and PEP, to people at high risk or comply under WHO category II and III rabies virus exposures. While previously recommended rabies vaccine schedules remain acceptable, WHO also recommends newer, shorter vaccine regimens that reduce costs, quantity of vaccine, and number of clinic visits required for both PEP and PrEP (Table 1). Evidence shows that ID administration of modern intramuscular (IM) rabies vaccines (> 2.5IU/IM dose), for either PEP or PrEP, is comparable to IM

Table 1
Update of World Health Organization position on human rabies immunization.

Topic	2010	2018
PEP regimen duration	3–4 weeks, 4-5 visits	1–2 weeks, 3-4 visits
Vaccine savings during PEP	ID: 0.8 mL IM: 5 vials	ID: 0.6 mL IM: 4 vials
PrEP regimen duration	3 weeks	1 week
RIG infiltration	Wound plus distant IM administration	Wound only ~ 40% RIG vials
RIG prioritization	All category III exposures	Focus on high risk category III exposures - 60 to 90% RIG

*Abbreviations ID = intradermal route. IM = intramuscular route. PEP = postexposure prophylaxis. PrEP = preexposure prophylaxis. RIG = rabies immune globulin.

administration. This cost-effective multi-site ID vaccination is suited for high burden countries. Rabies vaccines and RIG are considered safe to use in pregnant/lactating women and immune-compromised individuals, whether of homologous human (HRIG) of heterologous equine (ERIG) formulations. Vigorous wound washing with soap and copious amounts of water should be performed immediately for all exposures. If a limited amount of RIG is available, its allocation should be prioritized for patients with high risk and category III exposures. Moreover, RIG should be administered only once, preferably at initiation of PEP and not more than 7 days following the first rabies vaccine dose. When the calculated RIG dose is too large to infiltrate around the wound site, WHO no longer recommends IM injection of the remainder at a site distant from the wound.

In contrast to PEP, PrEP should only be considered for persons at high risk of rabies virus exposure, such as veterinary staff, diagnostic workers, dog vaccinators, bat handlers and other animal health workers in endemic areas. The PrEP schedules that are now recommended for people in all age groups are (a) 2-site ID on days 0 and 7, or (b) 1-site IM on days 0 and 7. The PEP vaccine schedules for immunologically naïve individuals for all age groups include 2-site ID on days 0, 3 and 7 or (b) 1-site IM on days 0, 3, 7 and a final dose between days 14–28. These schedules are considered to have advantages of reducing time, cost, improving adherence/compliance, as well as decreasing the total volume of patients visiting health care facilities over several dates. Along with partners, WHO is invested in future research on rabies prevention using internationally standardized questionnaires and surveillance to improve cost-effectiveness, programmatic feasibility and acceptability to patients and clinicians.

Focusing attention locally, Dr. Onphirul Yurachai described the R36, a web-based PEP reporting system in Thailand. While human rabies is a notifiable condition in Thailand, rabies virus exposures are not reportable. The primary function of the R36 system is to improve patient adherence to recommended PEP regimens, through real-time electronic tracking of medical provider recommendations and hospital visits for vaccination The R36 platform collects demographic data on the exposed person, date of exposure, risk factors of the biting animal, severity of the bite, treatment recommended and adherence to the PEP regimen. The R36 can track patient data across any hospital which utilizes the platform. If persons seek care at multiple health centers, their data are linked through a unique patient identification number. However, use of this database is voluntary. Annually, around ~250,000 to 450,000 exposures were reported to the system. The R36 system was analyzed thoroughly, from eight provinces in eastern Thailand, where 46 confirmed and probable human rabies cases were reported, for the time period January 1 – December 31, 2015. As a result, 6,204 suspected rabies virus exposures were reported with a crude exposure rate of 106 reported exposures per 100,000 population. Adherence to either the IM or the ID PEP regimen was low. Given the patient tracking-capacity of the platform and utility for monitoring trends in rabies virus exposures and PEP adherence, more hospitals should consider utilizing R36. Although this system is very useful for tracking patients and for data analysis, comparing to other injury reporting systems that are used in Thailand, the R36 evaluation should be more widely evaluated, to compare the advantages and disadvantages, as regards the practitioner's perception for future improvement.

Thereafter, Dr. Terapong Tantawichien summarized the considerable progress in PrEP and PEP in Thailand [27]. Significantly, the keys to the success of a substantial reduction of human rabies fatalities (e.g., from 370 reported deaths during 1980 to 15 human deaths during 2010), has been because of increasing accessibility to PEP using an ID regimen of improved vaccination, assessing the impact of the vaccination through intensified follow-up of patients exposed to suspected or laboratory-confirmed rabid animals, public education, mass dog vaccination and control of free roaming dogs. One of the most substantial improvements in PEP has been the use of the highly efficacious, safe and economical two-site Thai Red Cross (TRC) ID regimen (2-2-2-0-2-0) with cell-culture vaccine. Any PEP failures after the TRC-ID regimen are exceedingly rare, compared to the millions of successful PEPs that are administered. The safety and cost of PEP are prime concerns. Also, the amount of vaccine and the number of visits, in addition to the adequate immunogenicity produced after the vaccination, should be taken into account when choosing a regimen. From the experience gained in Thailand, a 2-week ID regimen of PEP (ID 2-2-2-2-0) without RIG induced significantly lower rabies VNA titers than the TRC-ID regimen on day 90 after vaccination. In addition, a prospective single-blind study was conducted to compare the level of rabies VNA (i.e., titers measured by the RFFIT) up to day 90 after simulated PEP with the Institut Pasteur Cambodia (IPC)-ID regimen (2-2-2-0-0) with purified ERIG (group I; $n = 30$, age range 25–56 years) compared with the TRC-ID regimen (2-2-2-0-2) with purified ERIG (group II; $n = 29$, age range 22–54 years). The vaccine used was purified Vero cell rabies vaccine (i.e., PVRV, potency 4.7 IU per 0.5 mL). The purified ERIG was manufactured by the Queen Saovabha Memorial Institute (batch number, RF 02118). The overall pattern of VNA response was similar in each study group. It was highest on day 28, then slowly decreased up to day 90. All subjects had VNA levels ≥ 0.5 IU/mL on day 28. The GMTs of VNA in group II (TRC-ID regimen with ERIG) were statistically significantly higher than the GMTs from group I (IPC-ID regimen with ERIG) on day 90 after vaccination ($p < 0.001$). No subjects in Group II, but 5 subjects in group I (16.7%), had VNA levels < 0.5 IU/mL on day 90 after simulated PEP. Thus, until now, the shortened 1- or 2-week ID regimens are not recommended for PEP in Thailand. Also, RIG was administered to ~17% of bite victims attending rabies prevention clinics. Because the maximum benefits of RIG are gained when given directly into the wound, only the amount of RIG infiltrated into and around all wounds are administered, as much as anatomically possible. Two booster doses of rabies vaccine (ID or IM) are recommended on days 0 and 3 or an economic single booster vaccination (four 0.1-mL ID doses of vaccines on day 0) for pre-immunized individuals, who are later exposed to rabies virus. Today, Thai pediatricians recommended that PrEP be proposed as an optional vaccine for children, who are at a higher risk of viral exposure and live in the highest canine rabies endemic areas. To reduce non-medical expenses, PrEP is simplified to the standard with the 2-site ID regimen of vaccine (e.g., PVRV), with 2 visits, on days 0 and the second any time between days 7–21.

Next, Ms. Anna Charinna Amparo provided information about a community-level, digital, IBCM system that the GARC launched in one city in the Philippines [28]. This was part of a Community-Based Rabies Surveillance project, the objectives of which were to: establish a system for early detection of suspect rabid animals and humans with high-risk rabies virus exposures; use the data for rapid and targeted intervention responses; and to track and visualize the progress of rabies elimination efforts to guide program implementation. This system was built within the Rabies Epidemiological Bulletin and is freely available for any interested government in a rabies-endemic country. The IBCM system enables the implementation of active surveillance where the early detection of high-risk events, such as suspect rabid animals and potential exposures in the community, facilitates immediate investigation and response. This is made possible through automated, system-generated alerts via SMS, email and internal system messages to the relevant authorities (i.e., the community health workers, veterinary team, human health team, and laboratory staff). Data regarding the suspect animal, human victims and their PEP, and animal laboratory diagnosis are all linked and can be viewed by the appropriate personnel. The IBCM system also records negative reports that are essential to build an evidence-base for the declaration and certification of a rabies-free area in the future.

Turning attention from human subjects, Dr. Charles Rupprecht introduced the suggested extension of human PEP to the veterinary field. All domestic animals at risk of rabies virus exposure should receive PrEP. However, some animals may be unvaccinated, due in part to age, vaccine label issues, availability of veterinary care, vaccine cost and

other variables. Millions of these animals are euthanized after rabies virus exposure in both developed and LDC. Considering that several mammalian species serve as surrogates for human subjects during preclinical testing and the demonstration of the effectiveness of biologics in these taxa after viral exposure in experimental settings, greater attention should be paid to the potential utilization of PEP for the naïve domestic animal. Pilot programs within North America should be extended elsewhere to further document the utility of this approach within a One Health context [29].

1.4. Production and evaluation of quality, safety and efficacy of human and veterinary rabies vaccines

This session was co-chaired by Drs. Ronello Abila and Richard Hill. The production and oversight of modern biologics is an under-appreciated facet of disease elimination programs, as exemplified by the information from the five presenters.

Mr. Wittawat Viriyabancha provided a perspective from the Thai FDA. This focused on regulatory strategies for rabies vaccine provisions, based on advancing regulatory science implementation programs, turning the present regulatory approach into a product quality management system throughout the product lifecycle. These strategies included: strengthening the registration process by revising the process and laboratory testing requirement; a Good Distribution Practice (GDP) implementation program for ensuring quality products from the factory to patients; a specific rabies vaccine market surveillance program; and a strategy to promote and support domestic research and the development of institutes and industries to develop medicinal products needed for the Thai public health system. The Thai FDA has strengthened the regulatory system not only for ensuring quality, safety, and efficacy of vaccines, but also making the products available in a timely manner for national vaccine security.

Dr. Rick Hill's presentation on regulatory provisions for production of animal rabies biologics highlighted standards and guidelines that have allowed rabies vaccines to serve as one of the most powerful tools in the battle against rabies virus for domestic animals and wildlife. The OIE International Standards provide a framework for the production and testing of rabies vaccines by competent regulatory authorities. Laws, standards, and guidelines for veterinary vaccines from the EU and the United States were highlighted, as examples of successful regulatory control schemes. Under these regulatory control systems, the manufacture and distribution of quality vaccines led to the elimination of canine rabies from several regions and provided a framework for wildlife rabies control in multiple species. Regulatory control systems are essential to provide production and testing standards that facilitate the development and availability of safe and effective animal rabies virus vaccines for use in control programs.

Dr Jacques Léchenet focused upon the quality of veterinary rabies vaccines from the perspective of the producer. He shared his experience on developing an *in vitro* test for replacing the historical potency release test by challenge in mice, as under active assessment for both human and veterinary biologics [30,31]. Highlighting the importance of the built-in quality in vaccine manufacturing, he showed the value of better describing the Boehringer-Ingelheim (BI) inactivated and adjuvanted rabies vaccine through a specific ELISA. Already authorized in the EU, his expectations are that this method, based on a consistency approach, should be used to release BI's vaccines worldwide, saving hundreds of animals as well as highlighting the high quality of these products.

Dr. Guy Houillon commented upon the new WHO human rabies vaccine regimens from a manufacturer's perspective. In essence, if the global rabies market is estimated to be approximately 80–85 million doses per year, only a few vaccines are licensed in a large number of countries. Sanofi Pasteur (SP) contributes to roughly 10% of this global volume with 2 vaccines, human diploid cell vaccine (i.e., HDCV) and a purified Vero cell rabies vaccine (i.e., PVRV), distributed in 20 and more than 80 countries, respectively. The ID administration during PEP is included in the label for PVRV in several Asian countries since 1996, with the recommendation to use the classical TRC regimen, that was documented during several early product development clinical trials. Even if alternate regimens, either for PrEP or PEP, have been studied and published during the past 20 years by many investigators, the need for internal data is required for regulatory purposes. More precisely, the IPC regimen consisting of 0.1 mL administration twice (i.e., on D0, D3, D7) was not documented by studies sponsored by SP. During 2012, a specific trial with PVRV, to document another shortened PEP regimen (i.e., a 0.1mL X 4 on D0, D3, D7) was initiated, including a comparative arm with the TRC regimen. The data generated in the control group for the TRC protocol will also be used to document the safety and immunogenicity of the IPC regimen at D14, that is 7 days after the third dose. The first part of the study has been published [32]. The outcome showed a 98.9% seroconversion rate at D14 for the IPC regimen with concomitant local infiltration of ERIG. The second part, including administration of a one-day booster dose (i.e., a 0.1 mL X4) as recommended by WHO, is expected to be published during the coming months. Regarding PrEP in the short regimen (i.e., D0-D7) by the 2 routes of administration, a second trial is ongoing, including a simulated PEP after one year. These two clinical trials, in addition to the existing product files, will support inclusion of the ID route of PVRV at a global level. In retrospect, even if the WHO decision to modify vaccine regimens was anticipated, the time to generate data and integrate them into a regulatory file that would be accepted by international health authorities requires a significant amount of time and qualified personnel before being implemented worldwide. As a vaccine manufacturer, SP foresees an eventual decrease in the off-label use of rabies biologics and a better forecasting of vaccine needs and use, especially in highly endemic countries.

For veterinary applications, Dr Ronello Abila presented the accomplishments with the OIE rabies vaccine bank (VB), since its launch during 2012 (Table 2). More than 22 million doses have been delivered to countries in Asia and Africa. The VB ensures that countries will have access to high quality veterinary vaccines, compliant with OIE standards [33]. The use of the VB also supports countries to receive vaccines when needed, with limited delay and reduced administrative hurdles. Countries have multiple options to access the VB, either through support from donors or using their own funds. Dr Abila emphasized that one of the biggest constraints in controlling dog-mediated rabies is the lack of organizational ownership in many countries. The Agriculture agencies in such countries do not prioritize rabies, because it is not a disease of animal production. Alternatively, unlike in the Americas, many Health agencies in Africa and Asia do not provide resources for dog rabies vaccines, because their concern is focused upon human vaccination. To succeed towards ZBT, an improved integrated governmental approach is needed to prioritize rabies control and eventual elimination.

Table 2
Canine rabies vaccine delivery in Asia, 2012–2019.

Country	Doses	Remarks
Bangladesh	365,000	200K OIE; 165K CDC
Bhutan	110,000	OIE
Cambodia	50,000	OIE
Indonesia	350,000	OIE
Lao PDR	290,400	OIE
Malaysia	200,000	Paid by the county
Myanmar	650,000	400K OIE; 250K 4PAWS
Nepal	200,000	OIE
Philippines	15,819,750	1.2 M OIE; 14.7 M paid by the country via WHO
Singapore	95,000	Paid by the country
Sri Lanka	300,400	OIE
Vietnam	872,000	OIE
Pakistan	50,000	WHO

1.5. Research and innovation in vaccines and biologics: do we need something better?

This session was co-chaired by Drs. Conrad Freuling and Charles E. Rupprecht. Although current rabies virus vaccines are highly effective, the three speakers in this last portion of the meeting impressed upon the need for ongoing research and development of improved biologics for the UAR and ZBT plans.

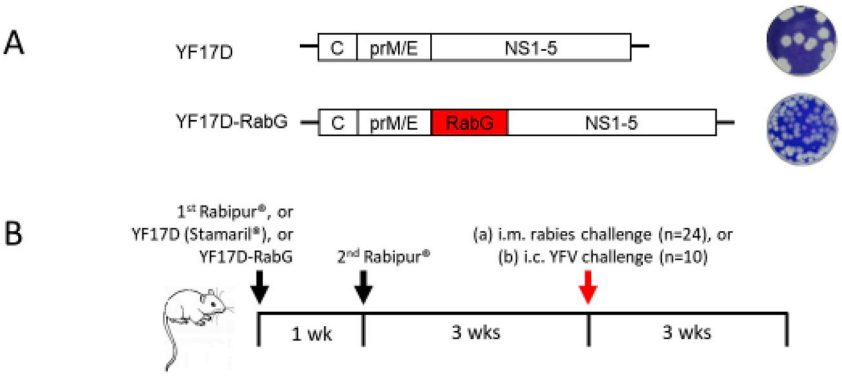
Dr. Hildegund Ertl presented an update on novel rabies vaccines that are undergoing pre-clinical or clinical testing [34]. Current vaccines, although safe and efficacious, are costly and thereby not always used when needed. Furthermore, their expense precludes their widespread use for preventative vaccination in highly endemic areas, which, as was shown in Peru, can reduce the incidence of human rabies. To allow for more cost-effective PrEP of rabies, a vaccine should cost no more than ~$3 USD, taking the need for a booster dose following exposure to a rabid animal into account. Needless to say, any novel, less expensive rabies vaccine would have to be as safe and efficacious as current vaccines. In addition, such a biologic should induce sustained antibody and B cell memory responses after a single dose.

As to new products, three novel rabies vaccines have undergone clinical testing. A mRNA vaccine expressing the rabies virus glycoprotein was tested, but with disappointing results in a phase I trial. Although the vaccine was in general well tolerated, only a fraction of vaccine recipients developed an adequate VNA response or recall responses after a booster dose. In a second example, the so-called Pika vaccine, which consists of a purified chick embryo cell (PCEC) vaccine with a TLR-3 agonist adjuvant, showed in a 3 dose IM regimen higher immunogenicity compared to commercial Rabipur in its usual diluent given 4 times, thus warranting additional trials. Thirdly, a rabies virus glycoprotein nanoparticle vaccine, based on an insect cell-derived rabies virus glycoprotein, has entered a phase III trial indicating that the vaccine is immunogenic. Nevertheless, thus far none of the clinical data have been published for this product. It is unlikely that any of these three vaccines will be cost-effective for wide-spread rabies PrEP.

Pre-clinically, genetically-modified rabies virus has shown high efficacy, but such a vaccine may not meet public or regulatory approval for human use. A genetically-modified inactivated rabies vaccine that expresses two copies of the rabies virus glycoprotein was shown to have higher immunogenicity compared to the traditional vaccine and may thereby allow for dose-sparing. In the same token, novel delivery systems are being explored by the group Particles for Humanity, that seal the vaccine in a polymer particle allowing for repeated release of vaccine doses at pre-defined time points, which could allow for a single injection rabies vaccine.

By contrast, Dr. Ertl, in collaboration with Dr. Rupprecht, has focused on replication-defective adenovirus vectors of chimpanzee origin expressing the rabies virus glycoprotein, termed AdC68.rab.gp. Preclinical studies showed the vaccine to be immunogenic in mice and nonhuman primates. Animals vaccinated once IM with a modest dose of the AdC68rab.gp vector were protected for over a year against challenge with a virulent dose of rabies virus, which also elicited a robust recall response. This vaccine might be considered for PrEP rather than PEP, because even if given together with RIG, it failed to protect adequately if given after rabies virus challenge. A team at Oxford University, led by Dr. S. Douglas, further modified the AdC68rab.gp vaccine by replacing some of the open reading frames of E4 of the vector backbone with those of human serotype 5 adenovirus, which increases vector production. This modified vaccine, which is expected to be inexpensive, is scheduled for clinical testing by the Oxford team in collaboration with Dr. Ertl during the 1st quarter of 2020.

Considering the issue of viral cross reactivity, Dr. Ashley Banyard summarized current options being investigated to develop a broadly reactive lyssavirus antigen for future vaccine options. Clearly, the immediate focus for lyssavirus prophylaxis is developing a strategy and the required momentum across endemic areas, to reduce and eventually eliminate dog-mediated human rabies. Whilst dog-mediated rabies is the major global issue faced, the threat of rabies virus infection from bats to both human and carnivore populations also exists. Across the New World, bat rabies is problematic with a several bat-associated human rabies cases being reported annually. Certainly, across Latin America, where vampire bat rabies viruses circulate, the impact on humans and livestock is well documented. However, across the Old World, classical rabies virus has never been documented in bats. Instead, a broad range of divergent lyssaviruses exist, generally in bat species. Each of these distinct lyssavirus species cause encephalitis following infection. However, currently these lyssaviruses have only been defined as the cause of human rabies on a handful of occasions. The infection of mesocarnivores with these viruses has also been rare and sporadic with both wild and domesticated carnivores being



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	anti-RABV > 0.5 IU/mL	anti-YFV antibodies	(a) protection from rabies	anti-YFV antibodies	(b) protection from yellow fever
Rabipur® (two doses)	24/24	0/24	100%	absent	0%
Stamaril®	0/24	24/24	0%	present	100%
YF17D-RabG	23/24	24/24	96%	present	100%
Sham	0/24	0/24	0%	absent	0%

Fig. 3. Development of a candidate yellow fever – rabies virus vaccine candidate.
Dual yellow fever-rabies (YF17D-RabG) vaccine candidate developed by the EU H2020 RABYD-VAX consortium. (A) Insertion of the rabies virus glycoprotein (RabG) between the YF17D vaccine envelope (E) and non-structural (NS) 1 proteins (left), and recovery of fully replication competent live-attenuated recombinant YF17D-RabG viruses with a slightly smaller plaque phenotype if compared to wild-type YF17D (right). (B) Set up for experimental vaccine-challenge in Balb/c mice comparing YF17D-RabG head-to-head with licensed human rabies (Rabipur®; two doses) and yellow fever vaccines (YF17D, Stamaril®; single dose). (C) YF17D-RabG conferred dual protection against both, lethal rabies (a) and yellow fever (b) infection.

reported as being infected and dying from rabies caused by different lyssaviruses. The threat from these viruses remains undefined, principally because the ability to detect and genetically type viruses implicated in clinical disease is lacking across much of Africa and Asia. As such, the extent of lyssavirus infection as a current or future threat cannot be readily determined.

The antigenic diversity of these viruses was originally typed by reaction with panels of MAbs known to bind to the rabies virus glycoprotein. A lack of reaction with such Mab panels defined the early antigenic divergence of some isolates. The later evaluation of the ability of antibodies to neutralise these divergent viruses has demonstrated that the VNA response induced by vaccination with standard rabies vaccines is insufficient to neutralise several other lyssaviruses. Genetic characterisation has further confirmed this divergence although a lack of glycoprotein structure has precluded meaningful assessment of amino acid sequence divergence. However, this inability for existing vaccines to cross protect means that, should lyssavirus infection of human or animal populations becomes emergent, novel vaccines would be required.

Dr Banyard overviewed options with this in mind and demonstrated experimental evidence that a high degree of specificity for individual lyssavirus glycoproteins exists, using sera specific for each lyssavirus species. This observation means that a number of distinct viral glycoproteins to generate any pan-lyssavirus vaccine is high. Alternative assessment of chimeric glycoproteins containing antigenic features of divergent viruses may be a suitable way forward [35]. This may be relevant, should more broadly reactive antigens be required for vaccines in a post dog-mediated human rabies environment. Evidence that artificial glycoproteins could induce more broadly reactive VNA is available and the aim to increase the breadth of antigenicity of a single or multiple glycoprotein was presented. Future vaccines to enable protective immunity against these divergent lyssaviruses may require further expansion of this approach, as well as more broadly reactive RIGs and MAbs.

Lastly, Dr. Kai Dallmeier reported on the discovery of a novel human rabies vaccine candidate, that is based on the KU Leuven proprietary Plasmid-Launched Live-Attenuated Vaccine (PLLAV) technology [36]. In brief, a live flavivirus, such as the yellow fever (YF) 17D vaccine, is employed as a viral vector to efficiently deliver and express the rabies virus glycoprotein antigen (i.e., RabG) necessary for immunization. In PLLAV, the entire cDNA of the recombinant YF17D-RabG vaccine is cloned as a stable DNA plasmid, that can be amplified in a simple bacterial fermentation process, amenable to high scale production. Importantly, the resulting vaccine product, PLLAV-YF17D-RabG, is thermostable and does not require a cold chain for vaccine storage, transport and deployment. Data obtained to date provide preclinical proof of concept that the vaccine constructs confer long-term humoral and cellular immunity and protect in animal models of infection against both a rabies virus as well as yellow fever virus challenge, after single vaccination dose only (Fig. 3). Considering the flexibility of PLLAV, similar dual vaccines have been presented that may meet specific regional needs, such as a rabies-Japanese encephalitis vaccine for South East Asia and the Asia Pacific region, or a rabies-Ebola-yellow fever combination for sub-Saharan Africa, as well as others, to be used as multivalent prophylactic vaccines, fitting into pediatric immunization schedules [37].

2. Conclusions

Considering the diverse input of speakers from all of the sessions, Dr. Joris Vandeputte summarized the high points of the meeting. He stressed that although rabies has perpetuated throughout history for millennia, new hope is emerging for combating this neglected zoonosis, bolstered by the evidence as documented during the conference. Clearly, the world is poised towards augmentation of the WHO's ZBT, as exemplified by the Thai experience. The combination of human prophylaxis and mass parenteral canine vaccination forms the basis for this strategy. Besides the Americas, important strides are continuing in the Asian region towards canine rabies elimination as the major safeguard strategy to keeping the Pacific region free of this zoonosis. As realized for ORV of wildlife in Europe and North America, application of OVD would form a substantial and economical implementation of herd immunity among free-ranging dogs. Simplification of PrEP and PEP regimens and dose-sparing strategies have already had a major impact on decreasing human rabies cases as confirmed in the region. Harmonization among producers, regulators and providers are critical to ensure the availability of needed biologics to support the duality of rabies prevention and control programs. Although current human and veterinary biologics are highly safe and efficacious, future research may produce additional candidates to further enhance this commitment towards high quality and cost-effectiveness. Given the extreme burden of animal and human rabies in Asia, future IABS conferences may be considered for the region, considering the productive atmosphere for continued progress and collaboration.

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Declaration of competing interest

Dr. Guy Houillon is an employee of Sanofi Pasteur, Dr. Jacques Léchenet is an employee of Boehringer-Ingelheim and Dr. Ad Vos is an employee of CEVA. The other authors declare no competing interests.

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