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Review

The Middle East and Eastern Europe rabies Expert Bureau (MEEREB) third meeting: Lyon–France (7–8 April, 2015)

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ABSTRACT

MEEREB is an inter-regional network of countries from North Africa, Europe, the Middle East and Central Asia that work together with the aim of improving rabies control and prevention at local, regional and global level. MEEREB members met for the third time in 2015 in France (Lyon) to review the current rabies situation within the network and to discuss the way forward the prospect of a One Health approach against rabies. Dogs were the main vector of transmission in all MEEREB countries except for Croatia and Serbia where foxes represented the primary source. The number of rabies animal cases reported in 2014 varied substantially between countries with Ukraine reporting the highest number of animal cases. Human cases still occur in North Africa and all Middle East and Eurasian countries while no cases of human rabies were reported in Croatia, Serbia and Romania, although cases of rabies were identified in both dogs and foxes in 2014. Participants concluded that MEEREB can act as a think-tank where countries can share data, information, experiences and best practices to jointly address challenges in rabies control and prevention. They called for elimination of dog-transmitted rabies through vaccine and rabies immunoglobulin stockpiles and implementation of a One Health approach to achieve rabies's eradication.

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Introduction

The Middle East and Eastern Europe rabies Expert Bureau (MEEREB) is a network of rabies enzootic countries that work together with the aim of improving rabies control and prevention at local, regional and global level.

Fig. 1 represents the evolution of MEEREB network overtime. The group met for the first time in June 2010 with representatives from 7 countries to evaluate the feasibility of establishing a regional rabies network [1]. At the end of the meeting, participants agreed to establish an informal regional network—the MEEREB—that can complement the Asian Rabies Expert Bureau (AREB) and the African Rabies Expert Bureau (AfroREB) network established in 2004 and 2008 respectively [1].

In 2012, the group met for the second time with the participation of two more countries, i.e. Romania and Kazakhstan, to review the rabies situation at country and global level [2]. Currently, MEEREB is considered as an inter-regional network of countries from North Africa, Europe, the Middle East and Central Asia.

The three networks, MEEREB, AREB and AfroREB, have played an important role in defining the best practices at regional and local levels through shared experiences, advocacy and implementation of state-of-the-art knowledge in practice [3], survey on rabies notifiability [4], the mapping of centres for the treatment of animal bite [5], and the re-evaluation of the global burden of endemic canine rabies [6]. Due to their increasing role in rabies control and further to the recommendation by the World Health Organization (WHO) that rabies expert bureau (REBs) should be independent from the industry, it was decided that AREB and AfroREB would be under the leadership of the Global Alliance for Rabies Control (GARC), while MEEREB would include North African countries and be coordinated by Fondation Mérieux. The latter is an independent family foundation established in 1967 by Doctor Charles Mérieux with the aim of strengthening local capacities of developing countries to reduce the impact of infectious diseases.

The present report provides an update on the overall rabies situation in participating countries at the third meeting, and a proposed way forward the prospect of a One Health approach against rabies.

Methods

The third meeting of MEEREB (Lyon-France, April 2015) gathered representatives from 12 members among 16 affiliated MEEREB countries, the Pasteur Institute, the WHO, the World Organization for Animal Health (OIE, for Office international des Epizooties), the Food and Agriculture Organization (FAO), and Sanofi Pasteur.

Results

Rabies prevention and control in MEEREB countries

Rabies is a notifiable disease in all MEEREB countries present at the third meeting. Beyond dog vaccination, prevention and control of human rabies in these countries is based on pre-(PrEP) and post-exposure prophylaxis (PEP), by means of vaccination and administration of antirabies immunoglobulin in case of indication, as recommended by the WHO. Except Algeria where nerve tissue vaccines (NTVs) are still used, all other MEEREB countries have fully switched to concentrated and purified cell-culture and embryonated egg-based vaccines (CCVs). PEP regimens consist of either a 4-dose 'Zagreb' or a 5-dose or 6-dose (Ukraine, Kazakhstan and Tajikistan) 'Essen' schedules (Table 2). With the exception of Tajikistan, PEP is free of charge in all MEEREB countries present at the meeting. PrEP is recommended by the WHO for people at risk due to their occupation (e.g. veterinarians, animal holders, medical staff), and travellers to rabies endemic countries [7]. In all participating countries, PrEP is financially covered by governments or institutions for at risk professionals. In Tajikistan, in addition to the government, PrEP expenses is also supported by foreign institutions (WHO, FAO, GRAG, etc.).

The cost of rabies prevention and control in enzootic countries has been estimated by modelling and countries were classified into clusters based on their rabies epidemiological situation [6]. The economic burden of rabies in MEEREB countries derived from data collected by Hampson et al. [6] is represented in Fig. 2. Direct cost of PEP, productivity losses from premature death and lost income while pursuing PEP were the most important economic burden in MEEREB countries, though their weight was country-dependent.

Rabies situation in MEEREB countries

Table 1 represents a summary of animal rabies epidemiology and prevention in participating countries. Dogs were the main vector of transmission in all MEEREB countries except for Croatia and Serbia where foxes represented the primary source. Animal rabies is a notifiable disease since decades in the large majority of MEEREB countries present at the meeting. The number of rabies animal cases reported in 2014 varied substantially between countries with Ukraine reporting the highest number of animal cases. Vaccine coverage in dogs was the lowest in Morocco and the highest in Tunisia. The incidence of dog bite exposure per 100,000 populations in MEEREB countries is shown in Fig. 3. We observed high heterogeneity across MEEREB countries with the highest incidence in Georgia and the lowest in Serbia.

The human rabies situation in participating countries is summarised in Table 2. Human cases still occur in North Africa and all

Table 1
Epidemiology and management of **animal rabies** in countries presented at the third MEEREB meeting (Lyon-2015).

	Eastern Europe			North Africa			Middle East/Eurasia					
	Croatia	Serbia	Romania	Algeria	Morocco	Tunisia	Ukraine	Georgia	Kazakhstan	Tajikistan	Iran	Iraq
Main vector	Red fox	Red fox	Dog, fox	Dog	Dog	Dog	Dog & wild animals	Dog, cat (jackal, wolf, Cattle)	Wild & domestic animals	Dog, wolf, jackal	Dog, wild animals	
Animal rabies notifiable? (year)	Yes (1977)	Yes (1928)	Yes	Yes	Yes (1977)	Yes (1985)	Yes (2002)	Yes	Yes (1992)	Yes	Yes (1955)	Yes
Number of diagnostic laboratories for animals	5	4	NA	5	7	1	26	1	16	6	1	NA
Number of animals tested (2014)	692	823	NA	NA	310 (2013)	1148	11,421	407	994	239	468	NA
Number of notified animal cases (2014)	1	3 foxes	142	NA	NA	476	1289	119	163	100	319	NA
Number of animal/dogs rabies cases (2014)	0	3	142/41	NA	NA	NA	1072/217	119/62	163/140	NA	319	NA
Vaccine coverage in dogs (%) ^a	47	47	47	24	14	48	47	21	21	15	18	18

NA: Data not available.

^a Data from Hampson et al. [6].**Table 2**
Epidemiology and management of **human rabies** in countries presented at the third MEEREB meeting (Lyon-2015).

	Eastern Europe			North Africa			Middle East/Eurasia					
	Croatia	Serbia	Romania	Algeria	Morocco	Tunisia	Ukraine	Georgia	Kazakhstan	Tajikistan	Iran	Iraq
Human population (in million) in 2014	4.2	7.1	20.0	39.1	33.3	11.0	42.9	4.8	17.3	8.3	77.4	35.1
Number of diagnostic laboratories for human rabies	5	1	NA	1	1	1	1	1	1	2	1	NA
Number of human rabies cases (2014)	0	0	0	8	20	3	4	4	3	7	5	10
Human rabies death incidence per million (2014)	0	0	0	0.2	0.6	0.27	0.09	0.8	0.17	0.8	0.05	0.3
PEP vaccination regimen	IM 4-dose Zagreb & Essen	IM 4-dose Essen	IM 4-dose Zagreb	IM Zagreb & Essen	IM 4-doses Zagreb	IM 4/5-dose Zagreb & Essen	IM 6-dose Essen	IM 5-dose Essen	IM 6-dose Essen	IM 6-dose Essen	IM 5-dose Essen	IM 5-dose Essen
PEP coverage in bitten people (%)	27.6%	6.4%	78.6%	100%	86.5%	100%	24.4%	89.1%	99%	60%	100%	100%
PEP incidence per 100,000 population (2014)	33.2	11.6	31.1	298	153	482	54.5	1052.6	361.2	105	195	45
Number of PrEP (2014)	185	60	NA	NA	NA	NA	50	NA	61	0	2674 (2013)	NA

Data on human population were extracted from population reference bureau (<http://www.prb.org/pdf14/2014-world-population-data-sheet.eng.pdf>).

NA: Data not available; IM: intramuscular.



Fig. 1. Evolution of the MEEREB network overtime.

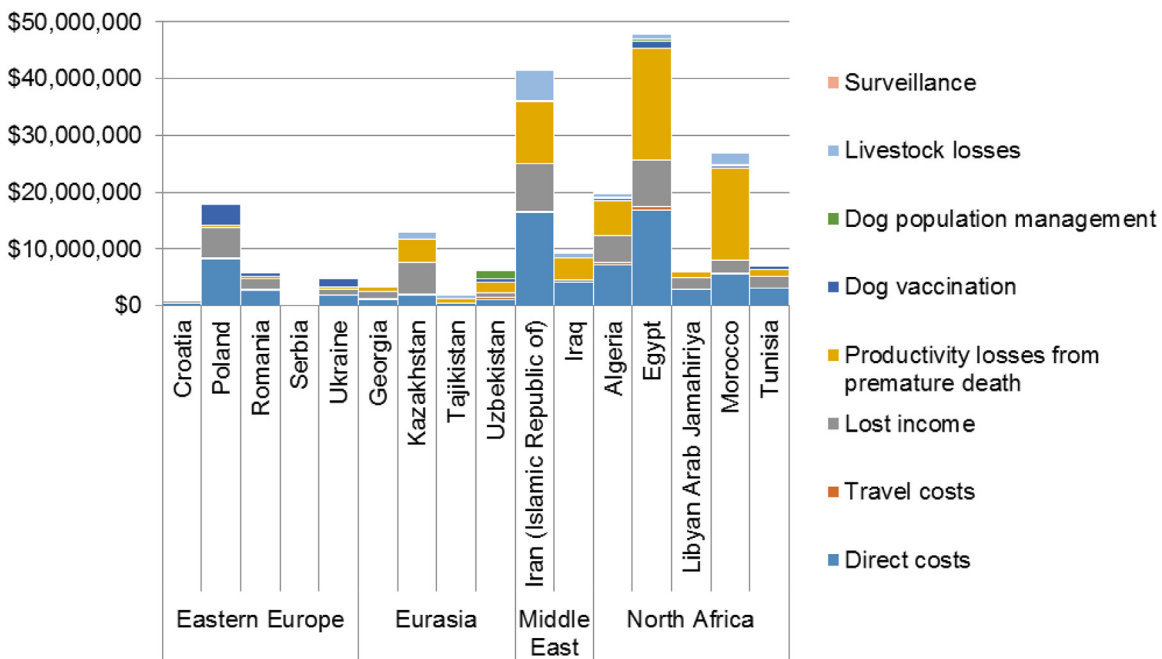


Fig. 2. Economic burden of rabies in MEEREB countries.

Data extracted from Hampson et al. [6].

Middle East and Eurasian countries while no cases of human rabies were reported in Croatia, Serbia and Romania, although cases of rabies were identified in both dogs and foxes in 2014. Croatia will soon become a rabies-free country due to the absence of human cases since 1964 and very few notified cases of infected animals. Indeed, only one fox out of 4488 examined in 2014 was proved to be rabid. Campaigns of oral rabies vaccination of foxes and compulsory vaccination of dogs supported by the European Union (EU) could explain the absence of human cases in Croatia.

The incidence of human rabies deaths varied across countries, ranging from zero to 0.8 cases per million inhabitants. In North Africa, the highest incidence were in Morocco (0.63/1,000,000 inhabitants). In all these countries, dog vaccination programmes are organised but reach from 25% to 60% of the dog population, which is insufficient to break the transmission chain in dogs [7] and can explain the persistence of human rabies. The high incidence

rates of human cases observed in Morocco compared to Algeria and Tunisia could be explained by low dog vaccination coverage, low rabies awareness in the Moroccan population and incomplete PEP. Indeed, rabies is still a persistent public health concern in Morocco despite a national programme that was established in 1986 and revised in 2003 and the availability of vaccine at no cost for patients in rabies prevention centres. All Middle East and Eurasian countries represented at the meeting reported human rabies deaths, the highest rate being in Georgia and Tajikistan (0.8/1,000,000 inhabitants). In Georgia, admission to special care centres after exposure or suspected exposure to potentially rabid animal showed an increased rate of 4.2% in 2014 compared to 2013. To assist improvement of PEP policy and practice and to enhance priorities for national rabies control and surveillance in Georgia, new guidelines and protocols (standard case definitions, case registration, notification, reporting requirements, case/outbreak investigation and response, protocols

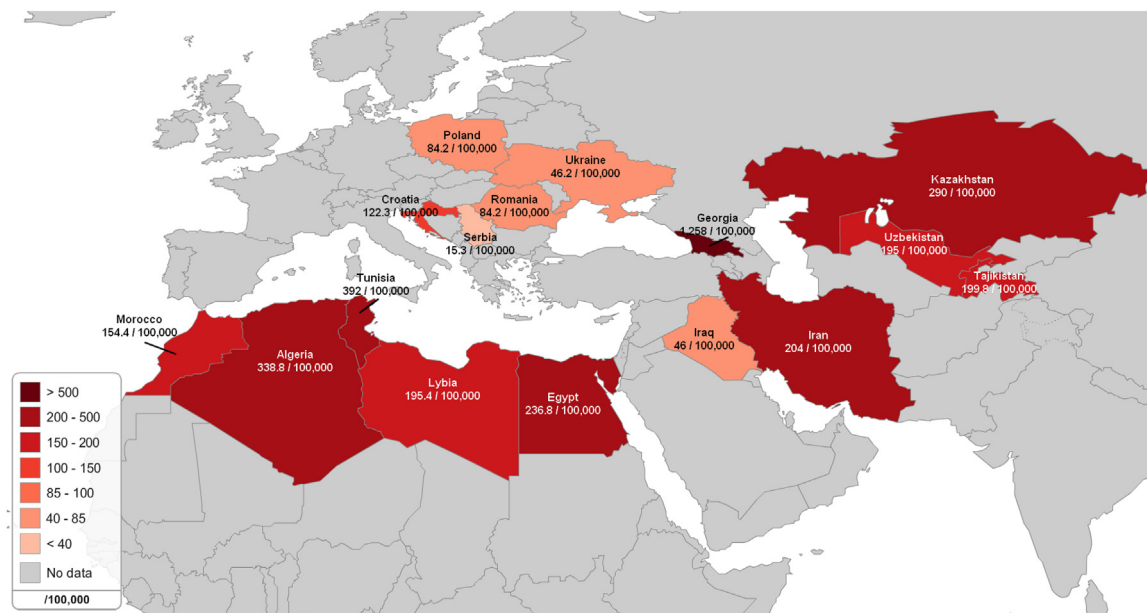


Fig. 3. Incidence of dog bite exposures (per 100,000) in MEEREB countries.

Data came from MEEREB experts (Algeria, Croatia, Georgia, Iran, Serbia, Tunisia). For other countries, data were extracted from Hampson et al. [6].

for sample collection and storage and surveillance activities) were developed based on WHO recommendations and subsequently approved by the ministry of health.

The proportion of patients bitten by suspected rabid animals who received PEP ranged from less than 7% in Serbia to 100% in Iraq and Iran.

Discussion

Eliminating rabies in dogs

Dog and wild animal vaccination through well planned campaigns would have a significant public health benefit, and would strengthen the control of other zoonosis [2]. Considerable progress has been made in the production of veterinary rabies vaccines during the past two decades with increasing use of continuous cell lines as a substrate and adoption of fermenter technology for antigen production [8]. Vaccination of dogs has reduced the number of human rabies cases in several countries, particularly in Latin America, in some areas in Asia (e.g. Bohol in the Philippines, Bali in Indonesia, Sri Lanka, and Bangladesh) and South Africa (KwaZulu Natal) [8]. Vaccination of at least 70% of dogs in rabies enzootic areas breaks the transmission cycle in dogs, thereby preventing rabies in human. For this purpose, it is necessary to vaccinate puppies and new-born dogs and conduct two vaccination campaigns per year. Conducting mass vaccination campaigns during weekends or school holidays can improve the turnout as children often bring their dog [7].

One Health approach against rabies

Different organisations and professional groups are involved in rabies control and prevention. For at least three decades, the WHO has fought to break the “cycle of neglect” affecting rabies prevention and control, particularly in low- and middle-income countries through advocacy, surveys and research on the use of new tools. The WHO provides international guidelines and standards, recommendations and policies on rabies prophylaxis, rabies control and elimination [8–11]. Besides, the WHO collects, analyses and maps rabies data globally, advocates for rabies prevention and control

and supports the development of regional strategies and initiatives, and coordinates a network of WHO collaborating centres for reference and research on rabies.

The World Organization for Animal Health (OIE) defines the intergovernmental standards (OIE Terrestrial Animal Health Code) for the improvement of animal health and welfare and veterinary public health worldwide [12]. In cooperation with the WHO and Food and Agriculture Organization of the United Nations (FAO), OIE has also established Regional Vaccine Bank for Rabies in Asia (2011) and in Africa (2014), with funding from the European Union, Australia, France, Singapore, and the Swiss Tropical and Public Health Institute. The vaccine bank is a rolling stock of injectable rabies animal vaccines produced when needed and delivered to beneficiary countries by vaccine suppliers that are selected through an international call for tender. Priority is given to providing emergency vaccines to developing countries with the lowest Gross-Domestic-Product (GDP) that do not have immediate access to high quality vaccines.

In response to the identified need to assist member countries in developing their action plans and identifying milestones in the prevention of rabies, partners for rabies prevention (including FAO, GARC, OIE, and WHO) developed a stepwise approach to move from endemic to free human-rabies (Fig. 4).

Rabies control requires, however, collaborative, cross-sectorial coordination and harmonisation of international guidelines and policies and a multidisciplinary approach that considers the complexities of the ecosystem where human and animals co-exist. Preventing and mitigating human rabies require control and, where feasible, elimination of the disease in the animal reservoirs. To address health risks at the human–animal–ecosystem interface (e.g. rabies), WHO, OIE and FAO united to call for a strategic plan for long-terms international collaboration through a One Health approach [13]. FAO–OIE–WHO tripartite strategic alignment promote and implement meaningful collaboration and communication between multiple allied disciplines working locally, nationally, and internationally to manage rabies in the most efficient and effective way. The One Health approach consists of promoting human rabies prevention by combining elimination of rabies in dogs and a wider access to and use of PEP (Fig. 5).

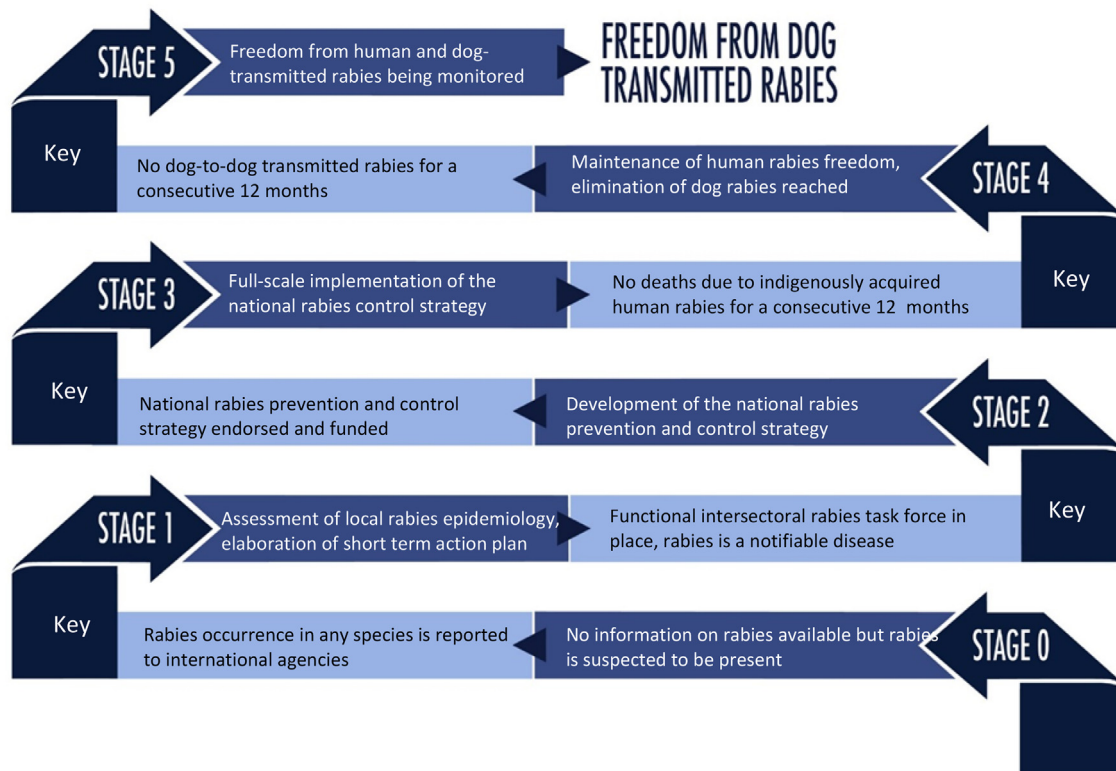


Fig. 4. Stepwise approach towards rabies elimination developed by partners for rabies prevention.

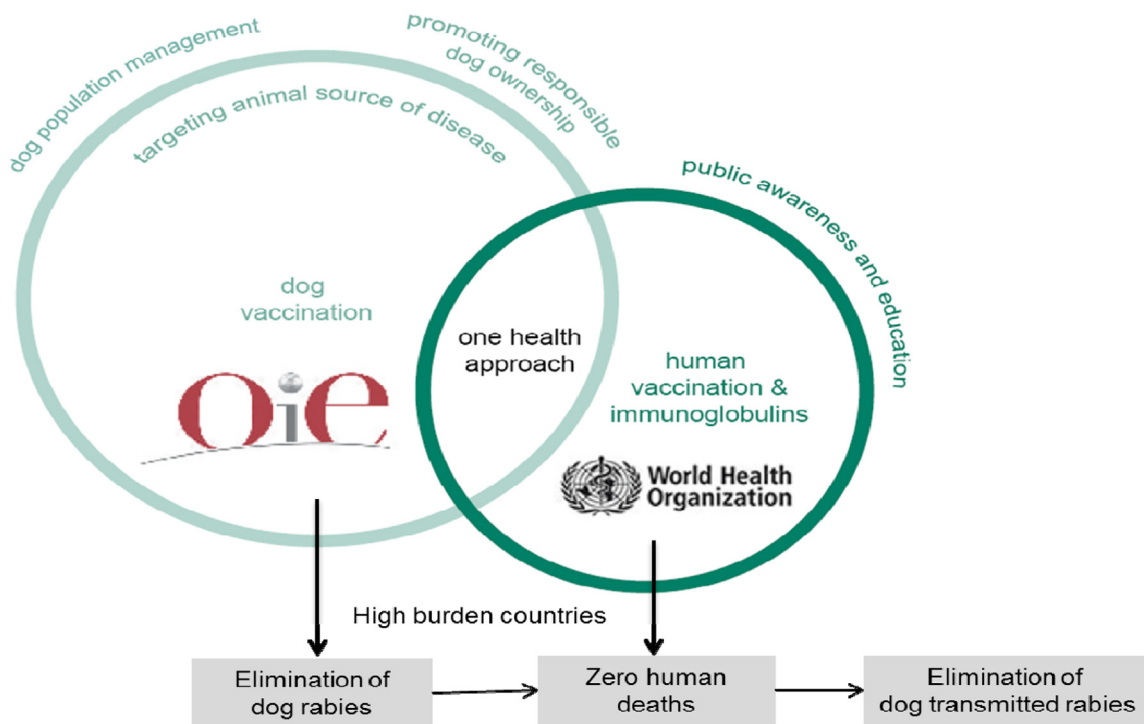


Fig. 5. Schematic presentation of the One Health approach's concept to eliminate rabies.

The strategic methods of the One Health approach are the following:

1. Prevention: by introducing cost-effective public health intervention techniques to improve accessibility, affordability and availability of PEP including mass dog vaccination;
2. Promotion: by improving understanding of rabies through advocacy, awareness, education and operational research;
3. Partnership: by providing coordinated support for anti-rabies drive with the involvement of community, governments and non-governments sectors and international partners.

Next steps

Representatives of MEEREB countries recognised that freedom from dog-mediated rabies is a global public benefit that could be fast-tracked by leveraging collaboration and resources. They called for elimination of dog-transmitted rabies through vaccine and rabies immunoglobulin stockpiles and implementation of a One Health approach to achieve rabies's eradication through fostered collaboration between international partners, ministries of health, nongovernmental organisations, financing bodies, academic and research institutions, civil society and the private sector.

The participants agreed that MEEREB can act as a think-tank where countries can share data, information, experiences and best practices to jointly address challenges in rabies control and prevention through: (1) fostering networking among local actors, country members and international organisations; (2) promoting one health inter-sectorial collaboration and (3) increasing awareness and commitment through knowledge sharing and exchange of experiences between decision-makers, communities and other related local actors. They established a list of activities to be carried out between MEEREB meetings. This included the establishment of a baseline assessment of country situation (questionnaire, country reports, etc.), mapping interventions, identifying gaps and priorities, revising action plans already in place and supporting capacity building for their implementation and promoting dissemination of knowledge and rabies resources (e.g. stepwise approach, educational programmes).

Representatives of Croatia, Serbia and Romania considered that their main efforts should be primarily targeted on rabies control in foxes through oral vaccination and with the aim of being free of terrestrial rabies. In other countries where dog rabies is still present, efforts will be focused on increasing dog vaccination coverage and dog population control. We observed large variation in the PEP coverage ranging from 6% to 100%. Although the causes of this variation are not known, some factors such as be explained by discrepancy between participating countries in the number of PEP centres, logistical issues, education programmes for health care workers and the public could explain, at least partly, the observed discrepancy between participating countries. Currently, there are no guidelines to increase PEP coverage. However, Algeria, Iran, Serbia and Kazakhstan have listed the national recommendations on PEP in accordance with international standards as one of their priorities. Representatives from Algeria stated that elimination of urban animal rabies is the first step of their fight against rabies prevention and control. No commitment was taken to phase-out nerve tissue vaccines in this country.

The key areas of policies and actions identified by participants were: (1) to use the World Rabies Day to advocate social responsibility of animal health sector and to promote weekly vaccination campaigns of dogs rather than all the year around; (2) to advocate rabies elimination as a model for operationalisation of "One Health Approach"; (3) to support rabies enzootic countries through low-cost technology transfer and laboratory twinning and training.

Conflict of interest

AR is employee of Sanofi Pasteur. Other authors declare that they have no conflicts of interest to report.

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