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Review

An overview of rabies - History, epidemiology, control and possible elimination

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Rabies remains the most important zoonotic disease in many countries. Public concern and fears are most focused on dogs as the source of rabies infection to humans and other domestic animals. Several bat species are reservoir hosts of rabies and therefore can be a public health hazard. The possibility of a carrier state or asymptomatic form of rabies deserves serious evaluation. Rabies in most countries was successfully controlled through mass vaccination of dogs, long before the recognition of bat and other wildlife rabies and the availability of modern vaccines. Though, the epidemiology, virology, transmission, pathology, clinical manifestations, diagnosis, treatment and control of rabies infection have been described extensively, the incidence is increasingly on the high side. However, experts have recognized for decades that rabies is wholly eradicable from all species except bats through targeted mass immunization, and the chief obstacle to eradicating rabies especially in bats is that no one has developed an aerosolized vaccine that could be sprayed into otherwise inaccessible caves and tree trunks. Inventing such a vaccine is considered difficult but possible. Forestalling this problem will require active epidemiological surveillance of wild and domestic animals with a wide range of modern molecular and ancillary epidemiological tools. This also demands government and private sector intervention, funding and collaboration of professionals in human and veterinary medicine with those in the environmental sciences. Recently, the heroic recovery of an unvaccinated teenager from clinical rabies offers hope of future specific therapy. While post-exposure vaccination is essential and should be continued with improvement to achieve consistently positive results, progress toward eliminating rabies has been markedly faster in nations that have emphasized preventive vaccination of animals.

Key words: Control, epidemiology, history, mass vaccination, surveillance, zoonotic disease.

INTRODUCTION

Rabies infection in humans is still a major public health problem all over the world. Rabies kills an estimated 35,000 per year, mostly in Africa, Asia and Latin America (Beard, 2001). It is a viral disease of CNS leading to death of affected animal in most cases. Rabies is mainly a disease of animals. It is also a disease of all warm blooded animals. Its occurrence in man and domestic animals is well known but the importance of wild animals in its spread has not been determined (Umoh and Belino, 2008). Usually humans contract rabies through rabid animal bite. However, human-to-human transmission of

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rabies virus occurred through organ transplantations. Furthermore, the virus is usually transmitted through the bite of an infected animal; corneal transplantation from an infected donor and viral inhalation however, may also result in infection (Takayama, 2005).

Rabies is found all over the world except in some countries where there is strict quarantine system, rigorous eradication or natural barrier like mountains and rivers. By 1995 the world estimate was about 70,000 deaths in humans per year worldwide. However, there are only about 35,000 notifications per year (CDC, 2004). Rabies remains the most important zoonotic disease in many countries. Public concern and fears are most focused on dogs as the source of rabies (Suzuki et al., 2008a, b). Though, the epidemiology, virology, transmission, pathology, clinical manifestations, diagnosis, treatment and control of rabies infection have been described extensively by many authors, the incidence of rabies is increasingly on the high side. This review therefore reports on the overview of rabies - history, epidemiology and control.

HISTORY OF RABIES

Rabies originated about 3000 B.C from the word 'rabha' meaning violence. Rabies is one of the most typical zoonosis that has been well known since ages and has been known for more than 4300 years (Takayama, 2005, 2008). Rabies is a public health problem of significant importance in the majority of Southern and Eastern Mediterranean and Middle Eastern countries. In some of these countries, there is a considerable death rate due to rabies.

Africa

Since 1912 when rabies was first confirmed in Kenya, the disease has largely existed in varied degrees of occurrence. Spatial and temporal distribution of cases of animal rabies are well documented (Borus, 1996). The rabies problem in Kenya has been greatest in Machakos district where the disease has persisted endemically for over 40 years (Kitala et al., 2000). In Kenya, records of human cases have not been as detailed as the veterinary cases. Except in 1960s, rabies outbreaks had occurred in the Kenya for most part of the century (Borus, 1996). The principal animal reservoir for rabies has been dog. The 1980's witnessed a dramatic upward swing in the number of cases reported annually. Over the years an enzootic pattern that covered most parts of the country emerged. In 1996, Borus reviewed available data that showed rabies as an emerging microbial threat in Kenya (Borus, 1996).

Mongoose rabies in South Africa was recognized in 1932 which differs from classic dog rabies (Swanepoel, 2004). Although, an inadequately characterized lyssavirus was isolated from a bat trapped in a survey in 1963, before the existence of rabies-related viruses was known. Awareness of lyssaviruses other than rabies viruses dates from the identification of DUVV in 1970 and was followed by detection of LBV and MOKV in South Africa (Swanepoel, 2004; Cohen et al., 2007). Since the 1970s, most human rabies cases in South Africa have occurred in KwaZulu-Natal Province, where the major animal vector is the domestic dog (Cohen et al., 2007). Before the report of Cohen et al. (2007), the most recent 2 laboratory-confirmed human rabies cases in Limpopo Province occurred in 1980 and 1981. DUVV was discovered in 1970 when it caused fatal rabieslike disease in a person bitten by an unidentified insectivorous bat ≈150 km northwest of Johannesburg, South Africa (Paweska et al., 2006). In 1981, the virus was isolated from what is believed to have been a *Miniopterus schreibersi* insectivorous bat caught in daylight by a cat in Makhado town (formerly Louis Trichardt) in Limpopo Province, South Africa, and in 1986 the virus was recovered from an insectivorous bat, *Nycteris thebaica*, trapped in a survey in Zimbabwe (Paweska et al., 2006).

In Nigeria, it dated back to the 1950s. Lagos bat virus (LBV) was also isolated from frugivorous bats (*Eidolon helvum*) on Lagos Island in Nigeria in 1956 (Kemp et al., 1972; MMWR, 1983). Mokola virus (MOKV) was first isolated from shrews (*Crodidua* spp.) in Nigeria in 1968 (Kemp et al., 1972; MMWR, 1983). Mokola virus (MOKV) was believed to have caused rabieslike disease in 2 persons in Nigeria in 1969 and 1971, shortly after its initial discovery in shrews in 1968, but no cases of human infection have subsequently been recognized (Familusi and Moore, 1972; Familusi et al., 1972; Paweska et al., 2006).

With the exception of MOKV, all lyssavirus genotypes (gts) and putative gts have been isolated exclusively or most frequently from chiropteran species. MOKV has never been isolated from these species, but only from terrestrial mammals (Sabeta et al., 2007). The first MOKV was isolated from shrews (*Crocidura* sp.) in Nigeria in 1968. Since then, $\geq$ 20 isolates of this lyssavirus have been found throughout Africa (Cameroon, Central African Republic, Ethiopia, South Africa, and Zimbabwe) (Kemp et al., 1972; Familusi et al., 1972; Sabeta et al., 2007).

America

Rabies in dogs was unknown in the Americas before the arrival of the Spanish "Conquistadores". Until the mid-1980s rabies in animals and, in turn in humans, changed little from year to year, with the number of dog vaccinations reported annually rarely reaching one million (Lucas et al., 2008). Rabies continues to pose major public health concerns in Canada and the United States

(NTHSS, 2005; Blanton et al., 2008; Sterner et al., 2009). In 2007, a total of 6,776 cases in wildlife were reported for the contiguous United States (Blanton et al., 2008).

From July 1st 1987 to December 31st 1988, a total of 317 animals (91% of which were dogs) were confirmed to have rabies in Hermosillo, Mexico (Eng et al., 1993). From 1990 through 2005, a total of 173 cases of rabies were reported in *Cerdocyon thous* (crab-eating fox), 25 in *Callithrix. j. jacchus* (common marmoset) and 6 in *Procyon cancrivorous* (crab-eating raccoon). During this period, in 13 of 40 human cases reported in Ceará, wildlife was the source of infection (Favoretto et al., 2006). According to Favoretto et al. (2006), in 1996, because of this new epidemiologic situation, public health authorities launched an educational program and no human cases due to wildlife were recorded in 1999, despite 84 cases in wildlife registered that year. Favoretto et al. (2006) studied 22 samples, from dogs, cattle, wildlife and humans in Ceará, obtained from 1997 to 2003. This was to elucidate some of the epidemiologic events involved in rabies emergence among wildlife in Ceará.

Twenty one cases of bat-associated rabies occurred in the United States during 1980 - 1999, 12 (57%) occurred in persons with apparent bat contact but no detectable bites (Abazeed and Cinti, 2007). In 1989, five EBLV1-infected serotine bats were found dead during a survey of natural colonies in Huelva (Andalusia) in southern Spain (Vázquez-Morón et al., 2008). In 1990 there were 16,464 reported cases of canine rabies in Latin America. In 1998 that was reduced to 2,608 (Clifton, 2007). During 1988 - 1994, a canine-variant of rabies described in Mexico was confirmed in 163 domestic dogs and 296 coyotes from 18 counties in southern Texas (Velasco-Villa et al., 2005; Sterner et al., 2009). During 1988 - 1994, a total of 283 gray foxes (*Urocyon cinereoargenteus*) and 241 other domestic and wild animals in west-central Texas were confirmed positive for a unique rabies variant typically found in gray foxes (Sidwa et al., 2005; Sterner et al., 2009).

The spread of raccoon rabies epizootic into New York occurred in the 1990s. A raccoon-variant epizootic in New York State began in 1991 (Sterner et al., 2009). In Maryland, for example, 97 cases of animal rabies occurred in 1997. In 2007, new cases of gray fox rabies occurred northwest ward along the Pecos River and in west-central Texas. The arctic variant of rabies virus has been present in red fox (*Vulpes vulpes*) populations in Ontario, Canada, since the mid-1950s (Rosatte et al., 2007). During 1954 - 2006, more than 57,000 rabid animals were reported in Ontario (CFIA, 2006; Rosatte et al., 2006; 2007). During 1999 - 2000, the raccoon variant of rabies was confirmed near Brockville, Ontario (Sterner et al., 2009). In metropolitan Toronto, rabies was cyclic from the 1960s to the 1980s; outbreaks in red foxes and striped skunks (*Mephitis mephitis*) occurred every 2 to 5 years (Rosatte et al., 2007). Greater metropolitan Toronto has been free of reported cases of rabies in red foxes for a decade (1997 - 2006) and is a notable success for the Ontario ministry of natural resources rabies control programs (Rosatte et al., 2007).

Asia

The record of rabies in Chinese history dates back to 556 B.C in Master Zuo's tradition of the spring and autumn annals (Wu et al., 2009). However, robust scientific investigation of the disease began only after 1885, with Louis Pasteur's discovery of post-exposure vaccination against rabies (Wu et al., 2009). In China, at least 108,412 persons died of rabies from 1950 through 2004 (Meng et al., 2007). In the 1930s, a rabies virus (RABV) 3aG strain was isolated in Beijing and was eventually developed into a vaccine for human immunization (Wu et al., 2009). In the 1950s, another RABV strain (CTN) was isolated in Shandong Province and was characterized and attenuated as a vaccine for humans (Wu et al., 2009). A rabies epidemic occurs every 10 years in China (Zhang et al., 2005; Wu et al., 2009).

Although no rabies case has been reported since 1957 in Japan, there are many areas where rabies is yet endemic or epidemic (Takayama, 2005; Tamashiro et al., 2007). The evolutionary mechanisms underlying the phylogenetic patterns and observations made in Canada throughout the 20th century (Nadin-Davis et al., 2006) have documented frequent movement of the arctic rabies lineage from northern regions to the south, by transmission among populations of red and arctic foxes (Nadin-Davis et al., 2007). Similarly, this lineage could have moved southward from Siberia or other northern latitudes of the former Soviet Union into Nepal, India and other Asian countries by means of a species jump from the fox to the dog at some point during this spread (Nadin-Davis et al., 2007).

Europe

Since 1946 there have been fox rabies arrivals in northeast Germany; in 1947 from the other side of the Odra River in Poland, and the disease rapidly moved westwards into West Germany (Müller et al., 2005). In 1951, the infection spread to foxes in south eastern Bavaria bordering Austria and what was then Czechoslovakia (Müller et al., 2005). In subsequent years there was dramatic progression of the disease in many parts of Europe, and rabies spread all over Germany (Müller et al., 2004). Consequently, from 1953, the number of reported rabies cases steadily increased until 1968 (Müller et al., 2005). Twenty cases of rabies in England and Wales have all been traced to infection abroad (Beard, 2001). The last instance of rabies in a native French animal was reported in 1998.

HOSTS AND VIRUS PHYLOGENY

Rabies is one of the better known encephalitis viruses of the family *Rhabdoviridae* and genus *Lyssavirus*. In the sylvatic cycle, this infection is maintained as an enzootic disease in several species, such as foxes, raccoons and bats (Salmón-Mulanovich et al., 2009). Rabies remains a zoonotic viral disease that affects humans, domestic and wild animals. Two types of rabies exist, this include sylvatic and urban. It is an acute, highly contagious and fatal disease caused by rabies virus (RABV), a bullet-shaped, enveloped RNA virus 75-180 nm with projections and helical nucleocapsid known as Lyssavirus type 1 in the family Rhabdoviride and marked by a long and variable incubation period (Awoyomi et al., 2007).

The prototype lyssavirus genotype and species, rabies virus (RABV), has a single, continuous, negative-strand RNA of ≈12,000 nt that codes for 5 proteins: nucleoprotein, matrix protein, phosphoprotein, glycoprotein and polymerase. It is very sensitive to some environmental factors and is rapidly destroyed by direct sunlight, U.V irradiation, heat at 60% for five minutes lipid solvent (70% alcohol and ether), sodium deoxycholate, trypsin and common detergents (Awoyomi et al., 2007).

RABV is highly neurotropic and functionally conservative. It is transmitted to animals and humans through close contact with saliva from infected animals (Awoyomi et al., 2007). It is transmitted mainly through animal bites, although rare non-bite exposure routes have been reported. Because of this characteristic, the dissemination of rabies is relatively slow (Wu et al., 2009). Once symptoms of the disease develop, rabies is fatal to both animals and humans (Awoyomi et al., 2007). The spread of the disease needs a minimum threshold support of host population density. Therefore, the frontline of waves of rabies infections gathers little public attention (Wu et al., 2009).

The *Lyssavirus* genus was created after isolation of several viruses in Africa and Europe that were related to, but serologically distinct from, RABV (Markotter et al., 2006a). The genus *Lyssavirus* currently includes rabies virus (RABV) (genotype 1) and 6 rabies-related viruses consisting of 6 genotypes (gts) or species: 3 from Africa; Lagos bat virus (LBV) (genotype 2), Mokola virus (MOKV) (genotype 3) and Duvenhage virus (DUVV) (genotype 4) which have been found only in Africa (Markotter et al., 2006a); European bat lyssaviruses 1 and 2 (EBLV1 and 2) (genotypes 5 and 6) and Australian bat lyssavirus (ABLV) (genotype 7) (Fauquet et al., 2004; Markotter et al., 2006a; Paweska et al., 2006), and diversity may expand with the addition of new isolates from Eurasia (Kuzmin et al., 2005), which are tentative species in the *Lyssavirus* genus (Markotter et al., 2006a). Other viruses in this genus are Kotonkan and Obodhiang. Strains of RABV (genotype 1) undergo genetic adaptation to particular animal hosts so that within specific areas the disease is manifested and transmitted predominantly by 1 host species. The canid or dog, biotype of RABV is the most widely distributed in the world (Paweska et al., 2006; Markotter et al., 2006a). Some novel lyssaviruses identified in bat species in the former Soviet Union are considered putative genotypes (gts) within this genus (Fauquet et al., 2004; Sabeta et al., 2007).

From literatures, several bat species are reservoir hosts of zoonotic viruses and therefore can be a public health hazard. Lyssaviruses of different genotypes have emerged from bats in America (Genotype 1 rabies virus; RABV), Europe (European bat lyssavirus; EBLV) and Australia (Australian bat lyssavirus; ABLV), whereas Nipah virus is the most important recent zoonosis of bat origin in Asia. Furthermore, some insectivorous bat species may be important reservoirs of SARS coronavirus, whereas Ebola virus has been detected in some megachiropteran fruit bats (van der Poel et al., 2006; Markotter et al., 2006a). Thus far, European bat lyssavirus (EBLV) is the only zoonotic virus that has been detected in bats in Europe and Australian bat lyssavirus (gt7) has only been identified in Australia (Markotter et al., 2006a). New zoonotic viruses may emerge from bat reservoirs and known ones may spread to a wider geographical range (van der Poel et al., 2006). Although gt1 viruses have a global distribution, gt5 and gt6 viruses are restricted to Europe and gt7 viruses are limited to Australia. Natural infections with gt2, gt3,and gt4 viruses have been found only in Africa (Sabeta et al., 2007).

Recognized lyssavirus genotypes are divided into 2 serologically, pathogenically and genetically distinct phylogroups (Markotter et al., 2006a). One phylogroup consists of Mokola virus and LBV (group II), while all other genotypes are in group I. Members of phylogroup I are reported to be pathogenic for mice when introduced intramuscularly and intracerebrally. In contrast, members of phylogroup II are believed to be pathogenic in mice only when introduced by the intracerebral (i.c.) route (Markotter et al., 2006a). Commercial vaccine strains belong to gt1 (RABV) phylogroup 1 and these vaccines provide protection against RABV and all the other members of phylogroup I. However, laboratory data suggest that these vaccines (gt1 based) will not offer protection against lyssaviruses in the phylogroup II cluster (Nel, 2005; Hanlon et al., 2005; Markotter et al., 2006a). On the basis of criteria proposed for lyssavirus phylogroups, West Caucasian bat virus could be considered an independent phylogroup III because of genetic distance and absence of serologic cross-reactivity with phylogroup I and II viruses (Hanlon et al., 2005; Markotter et al., 2006a).

In a study by Salmón-Mulanovich et al. (2009), bats from the genus *Carollia* were collected more frequently from natural, non-disturbed refuges (e.g., creeks, caves), while other insectivorous, frugivorous and vampire bats were found in more visibly disturbed or modified foraging areas (e.g., plantations, cattle farms) ($p < 0.001$). Seventeen bats were antibody positive to rabies virus

(cut-off value 0.5 IU), of an antibody prevalence of 10.3% (95% confidence interval 6.1 - 16.0). Antibody prevalence was similar (p = 1.000) among vampire bats (1/7, 14%), *Carollia* spp. (12/125, 10%), and other non-vampire bat genera (*Uroderma*, *Sturnira*, *Platyrhinus*, and *Artibeus*) (4/33, 12%) (Salmón-Mulanovich et al., 2009). Haematophagous bats, including *D. rotundus*, are usually the species associated with sylvatic bat rabies outbreaks in South America, but little is known about the role of nonhematophagous bats (Salmón-Mulanovich et al., 2009).

The different distribution of bat species may be related to food availability, which would explain why *D. rotundus* bats were found near cattle farms and the more ubiquitous distribution of *Carollia perspicillata* bats, which feed primarily on fruit in addition to pollen and insects (Salmón-Mulanovich et al., 2009). The bat species collected in a study by Salmón-Mulanovich et al. (2009) have been previously found in areas at similar altitudes in Peru; therefore, their distribution in this area follows a regular pattern (Salmón-Mulanovich et al., 2009).

In addition, RABV isolates from dogs on all continents are grouped into genotype 1 (Wu et al., 2009). Phylogeny analyses reinforce the perspective that vaccine matching in most country is redundant. In a rabies-epidemic region such as China and Nigeria, rabies in wildlife may result from spill over from dogs (Wu et al., 2009). Without proper investigation of animal population density and characterization of the RABV isolates, wildlife rabies in any country can be elucidated only after dog rabies is well controlled (Wu et al., 2009).

PREVENTION, MANAGEMENT, TREATMENT AND CONTROL

Rabies is a fatal disease in humans, and, to date, the only survivors of the disease have received rabies vaccine before the onset of illness. The approach to management of the rabies normally should be palliative (Jackson et al., 2003). In unusual circumstances, a decision may be made to use an aggressive approach to therapy for patients who present at an early stage of clinical disease. According to Jackson et al. (2003), no single therapeutic agent is likely to be effective, but a combination of specific therapies could be considered, including rabies vaccine, rabies immunoglobulin, monoclonal antibodies, ribavirin, interferon-alpha, and ketamine. Corticosteroids should not be used. As research advances, new agents may become available in the future for the treatment of human rabies (Jackson et al., 2003).

Rabies has the highest case-to-fatality ratio of any infectious disease, and no spontaneous recoveries are reported. With rare exception, comfort care, sedation, and life support measures may prolong life, but do not prevent death. Thus, in most situations, use of the term treatment is a misnomer and usually refers to medical aid related to animal bite and disease prevention by postexposure prophylaxis (Rupprecht, 2007). More than 12 million humans annually are exposed and may undergo antirabies prophylaxis, but in excess of an estimated 50,000 to 100,000 die, primarily from the bite of an infected dog. Public health expenditures have been poorly quantified. Regional epidemiologic surveillance and knowledge of viral pathogenesis development of vaccination algorithms, and communication of risk to different occupational groups can significantly reduce human morbidity from inappropriate prophylaxis and lyssavirus mortality (Lyles and Rupprecht, 2007). Eliminating primary exposure to rabid animals is a fundamental means of rabies prevention. Human rabies deaths are infrequent in regions with controlled canine rabies. Nevertheless, tens of thousands of potential exposure cases are treated annually in Europe and North America because of enzootic wildlife rabies (Hanlon et al., 1999a).

To date, no effective medical therapy has been established for overt rabies. The rabies post-exposure prophylaxis (PEP), which is a serial vaccination against rabies starting as soon as possible after the patient was bitten by a suspected rabid animal, is the only way to prevent death (Takayama, 2008). WHO recommends immediate washing of the wound with soap and water, application of human anti-rabies immunoglobulin and administration of tissue-culture rabies vaccine at 0, 3, 7, 14, 30, and 90 days after exposure (Takayama, 2008). Human diploid-cell vaccine and rabies vaccine adsorbed, which stimulate the production of antibodies, and human rabies immune globulin, which provides protective antibodies, are nearly 100% effective in preventing progression from stage I disease. If left untreated, rabies is usually fatal. However, treatment with human diploid-cell vaccine or rabies vaccine adsorbed and with human rabies immune globulin is nearly always curative if initiated early in the incubation period (Frenia et al., 1992).

Preventive and control measures include exposure of vaccinated animal, immediate vaccination, quarantine and investigation for 10 days. Exposed unvaccinated animal should be euthanise immediately. In human, First Aid should be given, and a medical doctor should be consulted immediately. Other control methods include: vaccination, quarantine, pounding and killing stray dogs, wildlife around should be killed during an epidemic, wild animals should not be kept as pets, and then oral vaccines should be given to wild animals through bait. Modern cell culture-based inactivated rabies virus vaccines have been used in control programs (Lucas et al., 2008).

Postexposure prophylaxis in humans includes proper wound care and the administration of rabies vaccine and antirabies immune globulin (WHO, 1992; CDC, 1999c). Although, the inclusion of antirabies serum or immune

globulin in the prophylaxis protocol is not new, it is infrequent (Lyles and Rupprecht, 2007). Most cases of human rabies prophylaxis in Africa, Asia, and Latin America are with vaccine only, often a nervous system tissue vaccine (Lyles and Rupprecht, 2007). Human diploid cell rabies vaccines (HDCV) are used in much of the developed world and form the standard for historical comparison with the Pasteurian neural vaccines from the 19th century, including its later phenolized derivatives (Fermi, Semple, et al., ????) (Lyles and Rupprecht, 2007). Inactivated cell culture vaccines and antirabies immune globulin, which are major improvements over cruder biologicals, decrease the adverse events related to anaphylaxis or serum sickness. HDCV is one of only three vaccines now licensed in the United States (CDC, 1999c) for either pre- or postexposure prophylaxis. Other major rabies vaccines are produced in avian embryo fibroblasts or in rhesus monkey kidney cells, with aluminum phosphate as an adjuvant (CDC, 1988). Production of HDCV is relatively difficult, with limited viral yields, resulting in high production costs. Primary hamster kidney cell vaccines are used in China and other parts of Asia and a purified vero cell vaccine is also widely used. Efficacy trials using reduced doses, different immunization schedules, and alternative routes (e.g., intradermal administration) have been conducted and have demonstrated both high efficacy and safety (Lyles and Rupprecht, 2007).

Control of Rabies in Animals

Rabies is not considered a serious candidate for disease eradication at this time because of numerous and diverse wild reservoirs (CDC, 1999c). The correlation between canine rabies and human fatalities, however, has led to the successful application of domestic animal vaccines, particularly in developed countries (Lyles and Rupprecht, 2007). A comprehensive domestic animal program also requires responsible pet ownership. Such a program entails stray animal management; leash law amendments; humane population curtailment (e.g., early spay and neuter programs); animal importation, translocation, and quarantine regulations; schedules for early preexposure vaccination of companion animals (in light of potential maternal immune inhibition); and rational postexposure management (CDC, 1999c, d). Unlike post-exposure prophylaxis of humans, euthanasia is usually recommended for the naive animal exposed to rabies, but this may eventually change with the development of safe and effective biologicals and protocols (Lyles and Rupprecht, 2007).

Current veterinary vaccines are more potent than earlier attenuated and inactivated vaccines (Lyles and Rupprecht, 2007). Because no vaccine is 100% effective, given poor cross-reactivity with some genotypes (von Teichman et al., 1998), and because correct identification of the properly immunized animal may be confusing, the vaccinated dog or cat is not exempt from confinement and close observation. This strict period of observation of the biting animal applies to dogs, cats, and, in some countries, domestic ferrets (CDC, 1999c). In addition, pet vaccination status does not necessarily alter the need for euthanasia of an offending animal, regardless of vaccine potency or efficacy, if rabies is suspected (Lyles and Rupprecht, 2007).

In the case of free-ranging, nondomestic mammals, population reduction of major rabies reservoirs has been practiced for centuries, but has not been generally regarded as a humane, long-term, cost-effective, or ecologically sound tool to control widespread lyssavirus infection (Hanlon et al., 1999b). Anticoagulants, however, have been used successfully to control hematophagous bats in Latin America. Anticoagulants have been applied topically to bite wounds on cattle, followed by systemic treatment of exposed cattle, and finally topical treatment of vampire bats themselves, exploiting their behavior of mutual grooming at the roost (Lyles and Rupprecht, 2007). These control efforts can avoid the destruction of beneficial nontarget bat species, perhaps some day to be augmented with novel vaccination strategies (Lyles and Rupprecht, 2007).

For more than four decades, efforts have been made to protect free-ranging wildlife against virulent street virus by oral consumption of vaccine contained within bait. A vaccinia rabies glycoprotein (V-RG) vaccine was the first recombinant rabies vaccine to be constructed, field tested, and considered for regulation in Europe and North America for wildlife rabies control. This vaccine has been extensively reviewed to ensure safety (tested in >40 species of mammals and birds) and efficacy (proved against severe rabies challenge in target species). Thermostability of the vaccine has been demonstrated under laboratory and field conditions (Lyles and Rupprecht, 2007). Following the success of the V-RG vaccine against fox rabies in Belgium and France, preliminary field trials suggest its potential utility for rabies control in raccoons, foxes, and coyotes in the United States. Other orthopoxviruses have been considered as vectors of lyssavirus antigens, but these have not yet been field tested (Lyles and Rupprecht, 2007). In the past several years, millions of rabies-virus, vaccine-laden baits have been distributed over rural and urban areas in western Europe, eastern Canada, and the United States for wildlife rabies control and a number of attenuated and recombinant rabies vaccines have been developed. Oral vaccines have been successfully developed for red, Arctic, and gray foxes; coyotes, raccoon dogs, raccoons, skunks, and domestic dogs (Lyles and Rupprecht, 2007).

GLOBAL ERADICATION, ELIMINATION AND CONTROL

The recent re-emergence and severe incidence of rabies have attracted the attention of scientists and

administrative authorities in countries like China. However, efforts are distracted by and concerns misleadingly focused on healthy dog carriers, possible rabies in wildlife, vaccine matching, inferior or counterfeit vaccines and seroconversion testing after vaccination (Wu et al., 2009).

Eradication

Eradication is defined as reduction of the worldwide incidence of a disease to zero as a result of deliberate efforts, obviating the necessity for further control measures (MMWR, 1993). Eradication is the permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts; intervention measures are no longer needed (Hinman, 1999). Eradication represents the ultimate in sustainability and social justice (Hinman, 1999). Between the extremes of disease "control" (reduction in incidence and/or prevalence) and "eradication," several intermediate levels of impact on diseases may be described. Even as smallpox was being eradicated, public health authorities recognized that the eradication campaign was possible because of several important characteristics of smallpox and the smallpox vaccine (MMWR, 1993).

According to the original work of (Eisinger and Thulke, 2008), eradication means a negative growth rate of rabies even if the dog or fox population is at the maximum density (the disease-free dog or fox density). In the simulation model by Eisinger and Thulke (2008), they determined eradication of rabies by starting with a fox population at the disease-free density with the desired level of population immunization and 100 infected foxes randomly distributed on the grid. If rabies has a negative growth rate under these conditions, rabies cannot be established in the population. Thus, if rabies is unable to invade the immunized fox population in any of 1000 repetitions of a simulation scenario, they equated this to 100% eradication. With respect to practical management, Eisinger and Thulke (2008) additionally applied a more feasible criterion where the full history of the management was followed up explicitly in the simulation (that is, starting from an epidemic situation) and control was defined successful when, after 4 years of repeated vaccination campaigns, rabies was eradicated with 95% probability.

To date, the only infectious disease that has been eradicated is smallpox. Poliomyelitis is targeted for eradication by the year 2000, and the eradication initiative is well under way, with the Western Hemisphere certified as being polio-free and more than one year having passed since polio cases occurred in the Western Pacific Region of the World Health Organization (Hinman, 1999). Smallpox was epidemiologically vulnerable because it had no natural reservoir in species other than humans; the infection was obvious and usually easily diagnosed; the duration and intensity of infectiousness were limited; persons who recovered were immune for life and often permanently scarred; and its transmission was highly seasonal in many areas. The vaccine was safe, effective even in newborns, inexpensive, easily administered and stable in tropical climates; its effects were long-lasting and vaccinated persons had a recognizable scar (MMWR, 1993).

Elimination

The term "elimination" is sometimes used synonymously with "eradication," but it refers to a single country, continent, or other limited geographic area, rather than global eradication (MMWR, 1993). True eradication usually entails eliminating the microorganism itself or removing it completely from nature, as in the case of smallpox virus, which now exists only in storage in two laboratories (MMWR, 1993). It is also theoretically possible to "eliminate" a disease in humans while the microbe remains at large, as in the case of neonatal tetanus, for which the World Health Organization (WHO) in 1989 declared a goal of global elimination by 1995. Finally, "elimination" can be defined as control of the manifestations of a disease so that the disease is no longer considered "a public health problem," as an arbitrarily defined qualitative or quantitative level of disease control (e.g. WHO's goal of eliminating leprosy by the year 2000, which is defined as reducing its incidence to a level below one case per 10,000 population) (MMWR, 1993).

Control

The term control means to restrain or limit infection, e.g. in expression, occurrence, or rate of increase. Control of animal-borne diseases is a major challenge faced by applied ecologists and public health managers. To improve cost-effectiveness, the effort required to control such pathogens needs to be predicted as accurately as possible (Eisinger and Thulke, 2008). Vaccination with three doses of human diploid cell rabies vaccine was recommended for people living or travelling in enzootic areas who may be exposed to unusual risks, or who undertake particularly long journeys in remote areas where medical treatment may not be immediately available (WHO, 1997).

A spectrum of disease control

Although a disease itself may remain, a particularly undesirable clinical manifestation of it may be prevented entirely. Examples of this level of eradication are the use of chemotherapy with ivermectin to eliminate blindness resulting from onchocerciasis and of vitamin A to eliminate xerophthalmia (MMWR, 1993). Eliminating

transmission of a disease may also be considered; as in the case of yaws, the late non-infectious clinical manifestations remained but was not a danger to others. As a tool for international public health, eradication of well-chosen diseases has two advantages:

1.) Eradication is permanent, as are its benefits. In contrast, the costs of control programs continue indefinitely, along with the risks of future exacerbation of the disease following a disaster of natural or human origin. For some diseases, achieving control would require only marginally less effort than that needed to achieve eradication, but control measures would need to be continued indefinitely.
2.) Eradication is the ultimate "sustainable" improvement in public health. The recent re-importation of wild poliovirus into the Western hemisphere more than 18 months since its last known previous occurrence (CDC, 1993a) and the possibility of changes in other pathogens in ways that can make them impervious to once-effective control measures (CDC, 1993b) would not be of concern had successful eradication campaigns taken place. The fear of the consequences of emerging resistance of malarial mosquito vectors and of the parasite itself was partly responsible for the precipitous decision in the 1950s to eradicate malaria.

A time-limited goal of eradication allows mobilization of support for a concentrated effort more readily than does a control program, both within countries where the disease is endemic and internationally. If developed countries have to spend resources to prevent or control importations of the disease (e.g. poliomyelitis, smallpox), such countries have additional incentive to help support an eradication campaign (MMWR, 1993).

Rabies control technologies

Oral rabies vaccination (ORV), trap-vaccinate-release (TVR) and point infection control (PIC) are an evolving rabies control technologies for use in wildlife (Sterner et al., 2009). ORV involves distribution of baits containing orally immunogenic vaccines onto the landscape, thereby targeting wildlife to establish population immunity and prevent spread or eliminate specific rabies variants (Sterner et al., 2009). The first use of ORV sought to control rabies in red foxes (*Vulpes vulpes*) in Switzerland; subsequent programs were reported throughout much of Western Europe (Cliquet and Aubert, 2004). Switzerland, France, Belgium and Luxembourg were deemed free of the red fox variant by 2001 (Cliquet and Aubert, 2004). ORV of wildlife has had positive public health effects. Multiyear campaigns have led to progressive elimination of arctic fox-variant and canine-variant rabies in Ontario and Texas, respectively (Sterner et al., 2009). Trap-vaccinate-release (TVR), point infection control (PIC) and ORV zones have prevented raccoon-variant rabies from becoming established in Ontario (Sterner et al., 2009).

CONSIDERATIONS FOR GLOBAL PUBLIC HEALTH SURVEILLANCE AND CONTROL OF RABIES

Virus infections with zoonotic potential can become serious killers once they are able to establish the necessary adaptations for efficient human-to-human transmission under circumstances sufficient to reach epidemic proportions (Heeney, 2006). The monitoring and early diagnoses of these potential risks are overlapping frontiers of human and veterinary medicine (Heeney, 2006). Indeed, global public health surveillance is critical for the identification and prevention of emerging and re-emerging infectious diseases (Sturtevant et al., 2007). As the pace of emergence and re-emergence of infectious diseases quickens, the International Health Regulations, which have served as the legal and policy framework of epidemic control for over 57 years, were been revised by the World Health Organization (WHO). The review by Plotkin and Kimball (1997), indicated that revision efforts should address 1) the limited scope of disease syndromes (and reporters of these syndromes) now in the regulations and 2) the mismatch between multi-sectoral factors causing disease emergence and the single agency (WHO) administering the regulations. The revised regulations should expand the scope of reporting and simultaneously broaden international agency coordination.

However, the World Health Organization recently released revised International Health Regulations (IHR) that serve as global legislation and provide guidelines for surveillance systems. According to Sturtevant et al. (2007), the IHR aim to identify and prevent spread of these infectious diseases; however, there are some practical challenges that limit the usability of these regulations. IHR requires member states to build necessary infrastructure for global surveillance, which may not be possible in underdeveloped countries. A large degree of freedom is given to each individual government and therefore different levels of reporting are common, with substantial emphasis on passive reporting. The IHR need to be enforceable and enforced without impinging on government autonomy or human rights. Unstable governments and developing countries require increased assistance in setting up and maintaining surveillance systems (Sturtevant et al., 2007).

Costly and politically attractive programs

As long ago as 1973, William Winkler, M.D., of the U.S. Centers for Disease Control and Prevention, warned in the National Academy of Sciences' handbook control of rabies, that "Persistent trapping or poisoning campaigns

as a means to rabies control should be abolished. According to Dr. Winkler, there was no evidence, "that these costly and politically attractive programs reduce either wildlife reservoirs or rabies incidence." Similar language has appeared ever since in the Compendium of Animal Rabies Prevention and Control, an annual publication of the National Association of State Public Health Veterinarians (Clifton, 2007).

Rabies campaigns have been relatively expensive. Sterner et al. (2009) estimated that ≥$130 million (combined Can$ and US$) has been spent on ORV programs in North America during the past 10 years. Programs which have proved lengthy (typically >5 years), have required enhanced surveillance and have often required contingency actions to ensure rabies elimination without reintroduction. Most economic assessments and modeling studies indicate that ORV programs can yield cost savings (Shwiff et al., 2008; Sterner et al., 2009). Regional increases in PEP administrations (and associated public health costs) from 2 - 4/100,000 before to 24/100,000, 45/100,000 or 66/100,000 (Sterner et al., 2009) residents during or after have been documented for nonbat rabies epizootics. Reduced PEP, epizootic-related pet vaccinations, animal diagnostic tests, public education activities and other factors represent costs avoided by ORV programs (Sterner et al., 2009).

Inequality

Although inequality is often measured through three critical indicators - education, income and life expectancy-health-related differences are also essential elements for explaining levels of equality or inequality in modern societies (Lazcano-Ponce et al., 2005). Investment and investigation in health also involve inequalities at the global level, and this includes insufficient North-South transfer of funds, technology and expertise in the health field, including the specific area of communicable diseases (Lazcano-Ponce et al., 2005).

Global capacity

Globally, epidemics and outbreaks in any geographic region can represent international public health emergencies and this type of threat requires a global response. Therefore, given the need to strengthen the global capacity for dealing with threats of infectious diseases, a framework is needed for collaboration on alerting the world to epidemics and responding to public health emergencies. This is necessary to guarantee a high level of security against the dissemination of communicable diseases in an ever more globalized world (Lazcano-Ponce et al., 2005).

Devastating impact on international trade

Emerging diseases such as rabies could have a devastating impact on international trade unless there is a change in the traditional approach to disease control and new holistic prevention and control strategies are adopted (Thiermann, 2004). The impact that emerging diseases will have on international trade will depend on several factors, such as the nature of the pathogen, the degree of co-ordination and integration between veterinary services and public health authorities, the ability to rapidly detect and respond to a disease appearance and the existing trade relationship between countries (Thiermann, 2004).

CONCLUSIONS

In the 1920s, long before the recognition of bat and other wildlife rabies and the availability of modern vaccines, rabies in Japan was successfully controlled through mass vaccination of dogs (Wu et al., 2009). The alliance for rabies control strongly favors post-exposure immunization, as well as prophylactic vaccination, but points out that post-exposure immunization is not a rabies suppression strategy because it does not neutralize the host reservoir (Clifton, 2007). The potential partnership between the normative function of the food and agriculture organization (FAO) in developing and promoting emergency preparedness and the implementation of improved national and regional disease surveillance by pan-African programme for the control of epizootics (PACE) and other partners could witness the commencement of more progressive control of epidemic diseases in Africa and greater self-reliance by African countries in coping with transboundary animal disease emergencies (Roeder et al., 1999).

Welte and Vargas-Terán (2004) briefly described FAO emergency prevention-system for transboundary animal and plant pests and diseases (EMPRES) Livestock, its vision, mission and activities to assist FAO developing member countries and regions in improving the ability of veterinary services to reduce the risks of introduction and/or dissemination of transboundary animal disease, by preventing, controlling and eradicating those diseases, assisting countries in building their own surveillance/early warning systems, establishing contingency plans and establishing a global information system for disease monitoring.

In response to these needs (inequality and global capacity), international health agencies have put a number of strategies into practice in order to contribute to the control of communicable diseases in poor countries. According to Lazcano-Ponce et al. (2005), the principle strategies include:

1) implementation of mechanisms for international epidemiologic surveillance;

2) use of international law to support the control of communicable diseases;
3) international cooperation on health matters;
4) strategies to strengthen primary care services and health systems in general;
5) promotion of the transfer of resources for research and development from the North to the South. To reduce risk for emerging zoonoses, the public should be educated about the risks associated with wildlife, bushmeat and exotic pet trades; and proper surveillance systems should be implemented (Chomel et al., 2007).

Forestalling of these problems (emerging zoonosis, rabies) will require active epidemiological surveillance of wild and domestic animals with a wide range of modern molecular and ancillary epidemiological tools (Cabello and Cabello, 2008). This also demands government and private sector (that is, animal husbandry) intervention, funding and the collaboration of professionals in human and veterinary medicine with those in the environmental sciences including ecology, climatology and oceanography (Cabello and Cabello, 2008).

The critical lesson to impart to policymakers is that extortion does not raise the resources that the humane community needs to do the work it can do best. Neither does impatience help small charities to grow into doing big jobs. Few if any humane societies in the developing world (or anywhere) have built sterilization programs faster than Animal Help, of Ahmedabad, India, but Animal Help built capacity for six years before it sterilized and vaccinated 50,000 dogs in 2006. Founder Rahul Sehgal frankly acknowledges that the time and practice was essential to subsequent success (Clifton, 2007). Again, particularly for countries with limited resources, we must ask whether it is cost-saving to the public health sector to prevent human rabies by vaccinating dogs. Bögel and Meslin showed that over 15 years in areas where the virus still circulates in the dog population, dog vaccination combined with post-exposure treatment of dog-bite patients is more cost-effective than post-exposure prophylaxis alone (Zinsstag et al., 2007).

However, experts have recognized for decades that rabies is wholly eradicable from all species except bats through targeted mass immunization and the chief obstacle to eradicating rabies especially in bats is that no one has developed an aerosolized vaccine that could be sprayed into otherwise inaccessible caves and tree trunks. Inventing such a vaccine is considered difficult but possible (Clifton, 2007). Recently, the heroic recovery of an unvaccinated teenager from clinical rabies offers hope of future specific therapy (Rupprecht et al., 2006). According to Clifton (2007), while post-exposure vaccination is essential and should be continued with improvement to achieve consistently positive results, progress toward eliminating rabies has been markedly faster in nations that have emphasized preventively vaccinating animals and humans.

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