UNIVERSITY OF VETERINARY MEDICINE, BUDAPEST

Department of Microbiology and Infectious diseases

The Rabies Epidemic in Sri Lanka

A Review of Literature and Data over a 5-Year Period (2011-2015)

Written by:

Shamithri Ranasinghe

Supervisor:

Prof. Fodor László, Ph.D.

Budapest, Hungary

March 2017

Table of Content

List of Abbreviations

ARV Anti Rabies Vaccination

CNVR Catch, Neuter, Vaccinate, Release

DAPH Department of animal Production and Health

DEPO Depo-Provera

ERIG Equine Rabies Immunoglobulin

FAO Food and Agriculture Organization

FAT Fluorescent Antibody Test

HRIG Human Rabies Immunoglobulin

ICU Internal Care Unit

ID Intradermal

IM Intramuscular

KAP Knowledge, Attitudes and Practices

MIT Mouse Inoculation Test

MP Milwaukee Protocol

MRI Medical Research Institute

NMDA N-methyl D-aspartate

OHE Ovariohysterectomy

OIE World Organization for Animal Health

PCEC Purified Chick Embryo Cell culture vaccine

PEP Post-exposure Prophylaxis

PHVS Public Health Veterinary Services

PVRV Purified Vero cell Rabies Vaccine

REA Rabies Elimination Act

RIG Rabies Immunoglobulin

SAARC South Asian Association for Regional Cooperation

WHO World Health Organization

1. Introduction

Rabies is one of the oldest and deadliest zoonotic diseases known to man. It is an acute progressive encephalomyelitis that irrevocably ends in death and yet is almost entirely preventable by vaccination (Shantavasinkul *et al*, 2010).

Today, an estimated 59,000 deaths occur annually (Hampson *et al*, 2015). The majority is concentrated in Asia and Africa (Matibag *et al*, 2008). Southeast Asia alone is responsible for approx. 23,000 human cases each year (Gongal *et al*, 2011). According to the Public Health Veterinary Services (PHVS), approx. 20-30 deaths occur in Sri Lanka. Loss of mortality and economic productivity are the primary consequences (Hampson *et al*, 2015).

Sri Lanka has been battling this disease since colonial times as evidenced by the Rabies Ordinance of 1893. Human and canine rabies were declared notifiable in 1971 and 2012 respectively (Harischandra *et al,* 2016). Control measures against the disease were established at a national level in 1975.

The dog is the principle reservoir of human exposure in Sri Lanka. Over 95% of infection is the consequence of bites from unvaccinated dogs (Nanayakkara *et al*, 2003). Non-vaccination of dogs, a relatively stable stray dog population and suboptimal post-exposure prophylaxis (PEP) are the primary reasons for the continuous endemic status of rabies in Sri Lanka. Although there has been a general decline of human cases, it still remains a significant matter of public health (Kularatne *et al*, 2016).

Rabies is a classic 'One Health' disease (Wallace *et al*, 2017) and eradication must be implemented at the veterinary-human medicine interface (Lapiz *et al*, 2012). The public, private and animal welfare sectors in Sri Lanka have been cooperating to eradicate rabies from the island by prioritizing the following:

- Dog population control with focus on dog vaccination, female sterilization and adoption programs
- Free of charge and island wide PEP access in all government healthcare establishments for bite victims
- Mass surveillance and public awareness campaigns

In 2016, the World Health Organization (WHO), the World Organization for Animal Health (OIE) and Food and Agriculture Organization (FAO) proposed an initiative of ‘zero deaths by 2030’ to globally eradicate canine rabies (Wallace *et al*, 2017). Sri Lanka was the first country in Southeast Asia to enact a national strategy to eliminate the disease by 2020 (Harischandra *et al,* 2016). This target seems attainable with only 5 human deaths in the first half of 2016 compared to 24 in the whole of 2015 (Harischandra *et al,* 2016).

This review aims to:

- Focus on the current progress and limitations of the national rabies eradication program in Sri Lanka
- Compare available data over a five-year period of 2011-2015 with emphasis on PEP, dog vaccination and dog sterilization

2. Materials and method

This is a critical appraisal based on:

- Scholarly publications on the topic in question

  I used a virtual private network to connect with the library network at the University of Veterinary Medicine, Budapest and was able to utilize the library resources. I researched scientific articles on different databases i.e. Pubmed, Google Scholar, Science Direct, VetFusion and CAB Abstract.

- Data of the annual 'Rabies Statistical Bulletin' reports of 2011-2015 presented by PHVS, Sri Lanka on their official website

  I focused on the following data over the 5-year period:

  - Laboratory diagnosis of positive cases (animal brain tissue samples)
  - Rabies-related human mortality
  - Human anti-rabies vaccination (ARV) consumption
  - Dog/cat vaccination
  - Dog sterilization (surgical and chemical)

3. Results

3.1 The pathogen

The rabies virus belongs to the lyssavirus genus of the Rhabdoviridae family. It is a single stranded RNA virus that is distinctively bullet shaped and enveloped with spike-like projections (Kaur *et al*, 2015). The virus is fragile and can be easily destroyed by UV light, heat and detergents.

The Asian rabies virus is made up of 6 lineages that do not share a common ancestry (Arai *et al*, 2001). 3 of the 6 lineages (Phillipines, Indonesia and Vietnam) originated from a single country while the remaining 3 (Sri Lanka/India, Thailand/Laos, Pakistan/India/Nepal) emerged from geographically proximate countries (Nanayakkara *et al*, 2003). The Sri Lankan virus comprises a single lineage that is distantly linked to the strain found in Madras, south-India (Arai *et al*, 2001). The rabies virus is the only lyssavirus that has been documented in Sri Lanka and has been identified as a genotype 1 lyssavirus (Nanayakkara *et al*, 2003).

3.2 Epizootiology

Rabies can occur worldwide and epidemiologically the virus exists in urban, sylvatic and bat forms. The urban form is prevalent in developing countries while the sylvatic form is dominant in Europe (Torcio, 1996). All warm-blooded animals are susceptible to the disease with spillover between species (Gongal *et al*, 2011). Dogs and red foxes are significant reservoirs in the terrestrial cycle. Bat rabies on the other hand consists of an independent transmission cycle (Krebs *et al*, 1995). Terrestrial spillover of bat lyssavirus is infrequent but is most typically seen via vampire bats in America.

The domestic dog is the primary source of human rabies in developing countries (Gongal *et al*, 2011). Dog rabies has been eliminated from many developed countries by effective pet vaccination programs (Krebs *et al*, 1995). The disease is enzootic in Asia and Africa, especially in rural, poverty-stricken regions with less access to anti-rabies resources (Lapiz *et al*, 2012).

3.2.1 Rabies distribution in Sri Lanka

Sri Lanka is a tropical island of rich biodiversity, located in the Indian Ocean, 35 km south of the Indian peninsula. It encompasses an estimated area of 62,000km^2 made up of 9 provinces and 25 districts. The population is approx. 20 million; the urban, rural and estate populations constitute 18.3%, 77.3% and 4.4% respectively (Karunanayaka *et al*, 2014).

The epidemiology of rabies in the country has been influenced by rapid population growth, urbanization and infrastructure expansion (Karunanayaka *et al*, 2014). Although Sri Lanka is in close proximity to India, there has been no introduction of rabies by translocation or outside introduction (Nanayakkara *et al*, 2003). While dog rabies is the primary form, rabies in wildlife has also been documented. Gene typing of the virus so far has not shown a wildlife reservoir independent of the dog strain (Nanayakkara *et al*, 2003).

Rabies is spread throughout the country with most cases reported from the western province (PHVS, 2011-2015). The districts of Mannar, Kegalle, Nuwaraeliya, Hambatota and Ampara have been rabies free since 2012 (WHO, 2016). As Sri Lanka is an island, it has the advantage of minimal cross-border importation of the virus once eradicated (Kumarapeli and Awerbuch-Friedlander, 2009).

Based on the data reviewed, a total of 150 deaths occurred within the 5-year period of 2011-2015. Overall, the mortality dropped from 41 deaths in 2011 to 24 in 2015. The lowest value was recorded in 2014 (19).

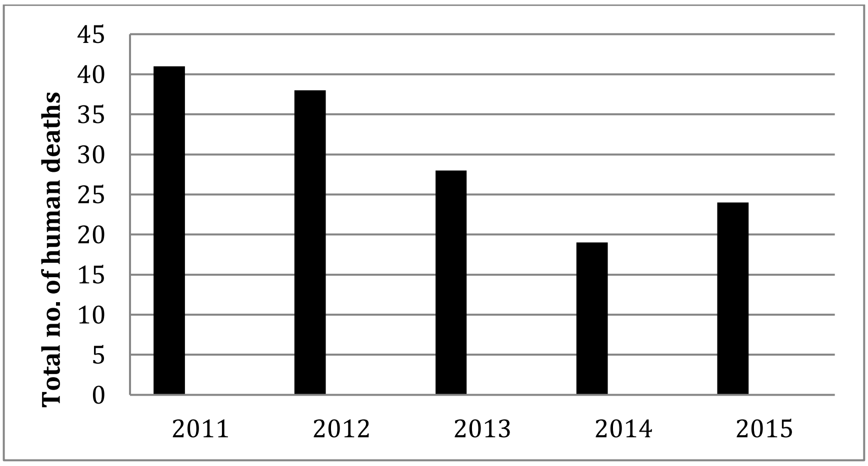

Figure 1. Total no. of rabies-related human fatalities (2011-2015)

From a geographical standpoint, the majority of deaths in the 5 years were reported from the western (35/150), northwestern (28) and eastern (25) regions. The central province accounted for the lowest number (4). Deaths in the eastern province significantly dropped from 11 in 2011 to only 1 in 2015. Comparing 2014 and 2015, fatalities in the northwestern and uva provinces had a 2.23% and 1.33% increase respectively, resulting in a combined 12/24 deaths for 2015.

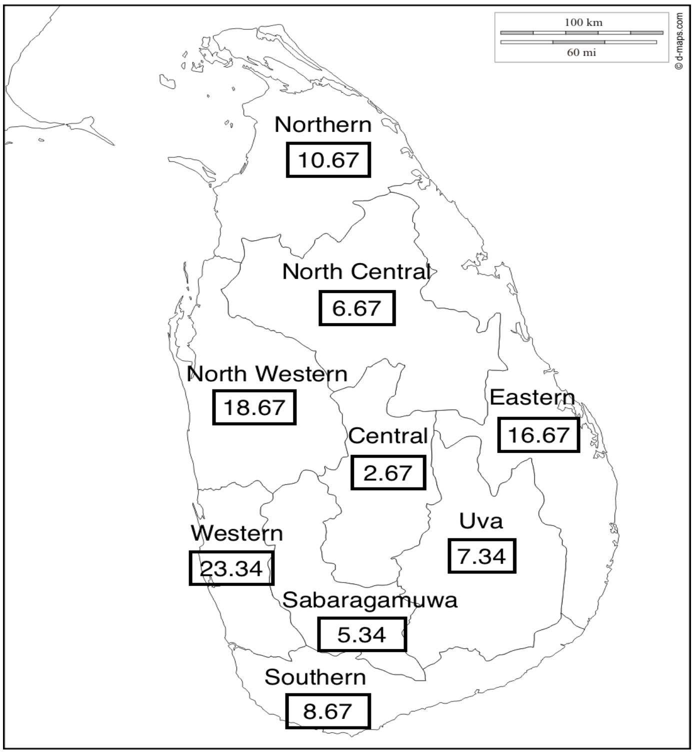

Figure 2. Total no. of human deaths as a percentage by province (2011-2015)

3.3 Transmission

All age groups are susceptible to rabies but children are the most affected worldwide, especially ones below 15 years of age (WHO, 2010a). However, older individuals have also become more susceptible to risk of infection in Sri Lanka (Matsumoto *et al*, 2013).

The virus infects humans predominantly via dog bites or to a lesser extent, scratches, containing virus-laden saliva (Kularatne *et al*, 2016). Aerogenous and organ transplant transmission are rare (Krebs *et al*, 1995). Transmission by raw meat consumption has not yet been documented (WHO, 2010a).

The incubation period of the virus can vary between <1 week to >1 year but is frequently 1-3 months (WHO, 2010a). The virus is neuro-invasive and spreads via retrograde axonal transport (Torcio, 1996). It first replicates in neurons and then spreads i.e. to acinar cells of salivary glands (Morimoto *et al*, 2000; WHO, 2010a). The virus is able to evade the immune system of the host during a majority of its pathogenesis due to its intra-neural location (Torcio, 1996). There is no haematogenous spread between animals.

3.4 Clinical aspect and diagnosis

Death is inevitable following clinical onset (Hampson *et al*, 2015). The animal/human usually dies within a week (Torcio, 1996). Fever and parathesia of wound site are followed by progressive central nervous system disturbances (Krebs *et al*, 1995).

There are two clinical manifestations (Krebs *et al*, 1995); the aggressive 'furious form' (classic mad dog syndrome) is characterized by behavioral changes, excessive salivation and paralysis while the 'silent form' is characterized only by paralysis. Hydrophobia and/or aerophobia are rabies-specific signs in humans during the former (Kularatne *et al*, 2016). While the paralytic form accounts for only 30% of human cases, both forms are ultimately fatal (Krebs *et al*, 1995).

Clinical diagnosis in humans is difficult unless rabies-specific signs are present (Kularatne *et al*, 2016). Misdiagnosis is frequent, especially in malaria endemic regions (Hampson *et al*, 2015) or in the case of paralytic rabies (Gongal *et al*, 2011). Lab confirmation of brain tissue is necessary for definitive diagnosis. Fluorescent Antibody Test (FAT) is the WHO-preferred method of rabies diagnosis in humans and animals (Kularatne *et al*, 2016). Histopathologically, Negri bodies are 100% diagnostic for rabies although found in only 80% of cases (Karunanayake *et al*, 2014). Mouse Inoculation Test (MIT) has been recommended as an adjacent to FAT for early and reliable diagnosis of human rabies (Webster *et al*, 1976).

In Sri Lanka, the Department of Rabies Diagnosis and Research of the Medical Research Institute (MRI) provides the diagnostic and surveillance capacity at a national level (Harischandra *et al*, 2016). The department is subdivided into the National Reference

Laboratory for rabies diagnosis and research and the National Control Laboratory for vaccine quality control. FAT is the most commonly used diagnostic test (Karunanayake *et al*, 2014).

A total 6860 animal brains were tested within the 5-year period, with 50.36% confirmed positive for rabies. 83.97% of the positive samples belonged to the dog (2901) with the rest confirmed in cats (427) and other/wild animals (127) respectively.

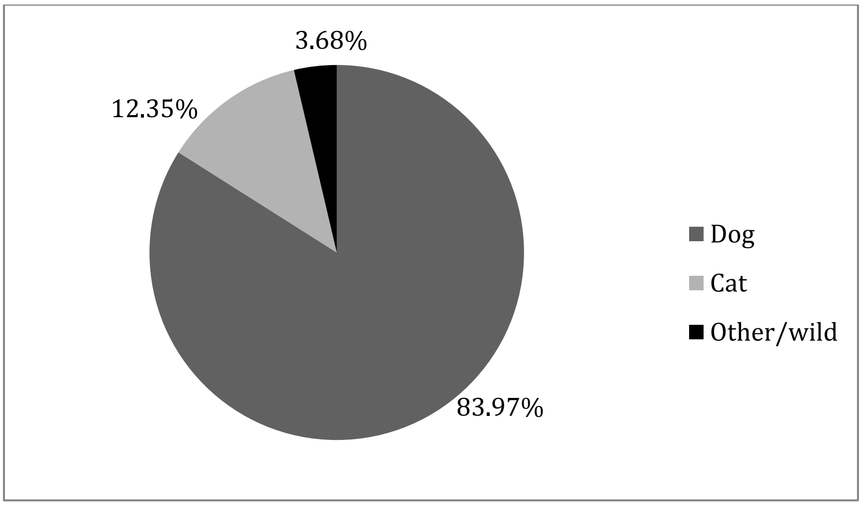

Figure 3. Rabies spread by animal type (2011-2015)

Overall, the dog was the primary infectious source but dropped by 16.5% within the 5 years (548/622 positive dog samples in 2011 vs. 471/607 in 2015). Concurrently, positive feline and other/wild animal samples recorded an 8.35% and 5.24% spike respectively.

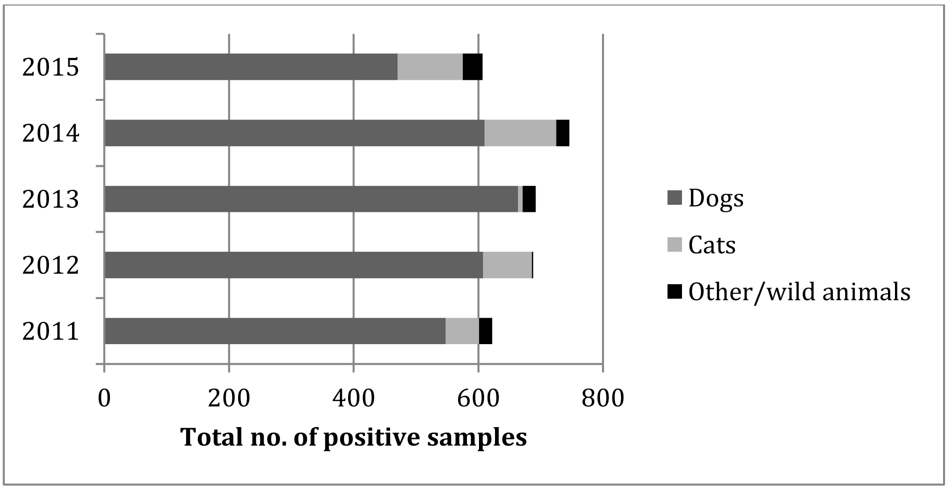

Figure 4. Total no. of rabies positive samples by animal (2011-2015)

Excluding dogs and cats, positive confirmations were predominantly reported in livestock (i.e. cows at 1.56%), mongoose (0.52%) and squirrels (0.43%).

Table 1. Categories of animals as an infection source (2011-2015)

Type of animal	Total no. of animals in the 5-year period	Percentage (%)
Dog	2901	83.97
Cat	427	12.35
Mongoose	18	0.52
Cow	54	1.56
Buffalo	5	0.14
Goat	12	0.35
Pig	5	0.14
Squirrel	15	0.43
Monkey	1	0.03
Pole cat	4	0.12
Jackal	1	0.03
Grey mongoose	6	0.17
Rock squirrel	5	0.14
Rabbit	1	0.03

3.5 Treatment and prevention

Human rabies is 100% fatal but almost completely preventable by vaccination (Shantavasinkul *et al*, 2010; Hampson *et al*, 2015). Canine rabies free countries maintain their free status by imposing strict importation restrictions for dogs and cats over a 6-month period (WHO, 2005). In rabies endemic regions, management is mostly two-fold; namely dog population control and PEP accessibility. The ultimate target is to achieve zero human deaths (Harischandra *et al*, 2016).

In 1975, PHVS of Sri Lanka, together with WHO, launched an island wide rabies eradication program. Emulating 'One Health' governance, a multi-sector rabies advisory committee was established, with health service staff involved at a provincial, district and community level together with vaccinators, dogcatchers and public health inspectors. The 2005 Rabies Elimination Act (REA) formed the legal framework (Matibag *et al*, 2009) while a constantly updated national rabies registry was established in 2016 to survey PEP.

The progress made to date in Sri Lanka could be explained by a high literacy rate and social-welfare oriented state policy (Matibag *et al*, 2009). A decentralized health system allows urban vs. rural inadequacies to be minimized. Government hospitals provide free healthcare for bite victims while the public veterinary sector provides free animal control measures.

3.5.1 Post-exposure prophylaxis

PEP includes prompt wound cleaning, passive immunization with rabies immunoglobulin (RIG) and active immunization with anti-rabies vaccine (ARV). The inactivated vaccine can reduce mortality from 100% to zero if administered on time, that is before the onset of clinical signs. Pregnancy and infancy are not contraindications for inoculation (Chutivongse *et al*, 1995). The OIE vaccination bank is invaluable in efficient delivery of high quality, internationally approved vaccines at a minimal cost. OIE has so far provided about 3.7million doses of rabies vaccines in Asia (WHO, 2016).

Developing countries largely use cost-effective intradermal (ID)-PEP over intramuscular (IM)-PEP (Gongal *et al*, 2011). ID-PEP is superior because skin cells have a faster immune-reactivity than those in muscles (WHO, 2013; Hampson *et al*, 2015). The multi site technique also triggers a higher immune response at a lower dose (Shantavasinkul *et al*, 2010). In short, the urgency of PEP is better compensated by ID treatment. ID-PEP is contraindicated in immunocompromised patients so IM-PEP is used instead (Warrell *et al*, 2008).

When necessary, treatment may be initiated irrespective of 10-day observation period or vaccination history of animal in endemic regions (Harischandra *et al*, 2016). PEP is then discontinued if the animal is declared healthy once the observation period is over or laboratory confirmation is negative (WHO, 2010b).

In Sri Lanka, tissue culture vaccines replaced nerve tissue vaccines in 1995 (WHO, n.d). ID-PEP usage in Sri Lanka is over 90% (Kularatne *et al*, 2014). PEP is free and easily accessible in all Sri Lankan government hospitals.

A total of 1,376,614 vaccination vials were distributed island wide in 2011-2015. It peaked to 317,782 vials in 2013 against 205,645 in 2011 but then dropped to a total 274,405 vial consumptions in 2015.

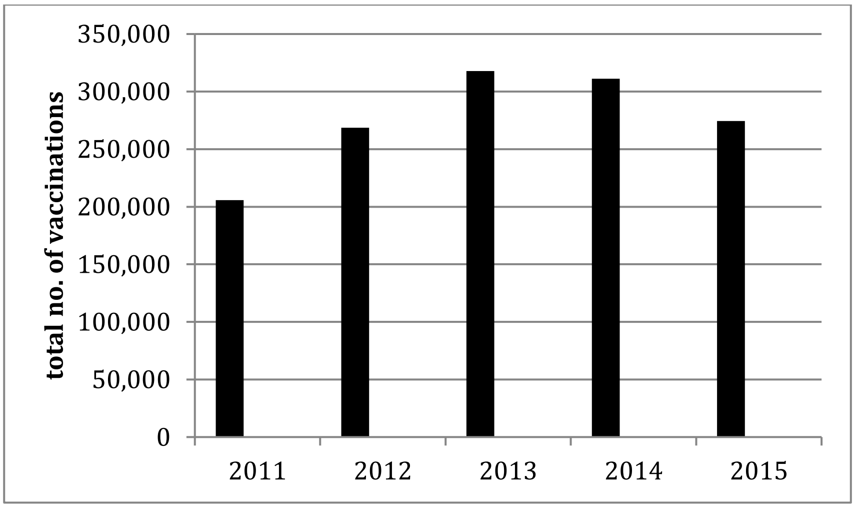

Figure 5. Human ARV vial distribution (2011-2015)

Of the 9 provinces, 20.7% of the total value (285,830 vials) was delivered to the western province, with an additional 10% average distribution to 7 others. The central province recorded the lowest distribution at 6.4%.

3.5.2 Milwaukee protocol

Recovery of clinical rabies in humans is associated with a high level of neutralizing antibody in the blood and cerebrospinal fluid, but is almost always accompanied by severe neurological deficits (Warrell, 2016). Thus far, there are only 13 reported cases of rabies survivors worldwide (Manoj *et al*, 2016).

The only treatment that has been applied with success in clinical rabies to date is the Milwaukee protocol (MP) conceived in 2004. MP involves a drug induced coma and N-methyl D-aspartate (NMDA) receptor antagonist therapy of Ketamine, Amantadine and

Ribavirin (Zeiler and Jackson, 2016). There is debate on the efficacy of MP and it is considered ineffective overall, with approx. 31 failures documented so far (Zeiler and Jackson, 2016). MP does not have any scientific backing but there is no alternative therapy either. Potential treatments include antiviral drug therapy (Zeiler and Jackson, 2016) or injection of an attenuated rabies virus (Warrell, 2016) but further investigation of this is necessary.

3.5.3 Dog immunization

As the dog is the primary source of human exposure, mass dog vaccination is crucial to breaking the transmission cycle (Lapiz *et al*, 2012); (Hampson *et al*, 2015). This in turn correlates to fewer or ideally zero human death (WHO, n.d). A long-term sustainable herd immunity status is vital. Successful rabies elimination is indicated by vaccination coverage of over 70% of the total dog population by three successive inoculation rounds (WHO, 2016). Both parenteral and oral vaccines are available for greater vaccination coverage (WHO, 2007).

Rabies was previously managed in Sri Lanka by culling stray animals but proved unsuccessful, without any decline in statistics. Vaccination was considered a better alternative to controlling rabies at the source (WHO, 2015). In addition to parenteral application, oral vaccines have been delivered to stray dogs in Sri Lanka via a bait delivery system since 1998. A new 'auto-vaccinator' device has also been used for parenteral vaccination of stray animals at a distance (PHVS, 2009). The dog rabies vaccine is provided free of charge by the government, either through mobile clinics or selected vaccine centers (WHO, 2016). All dogs over 3 months must also be legally registered by order of the REA (Matibag *et al*, 2009).

A total 7, 098,936 animals (domestic dogs, stray dogs and cats) were vaccinated within the 5-year period, with a general upsurge by 11.32% (1,086,948 in 2011 vs. 1,890,541 in 2015).

Of the total 1,237,851 vaccinations in 2012, 10,757 cats were inoculated against rabies for the first time (0.85%). The rest was distributed between domestic and stray dogs (88.76%

and 10.45% respectively). Domestic dogs received 68.47% of the total vaccinations in 2015 (1,890,541) while stray dogs received only 8.06%. The total cat vaccinations extended to 43,608 by 2015.

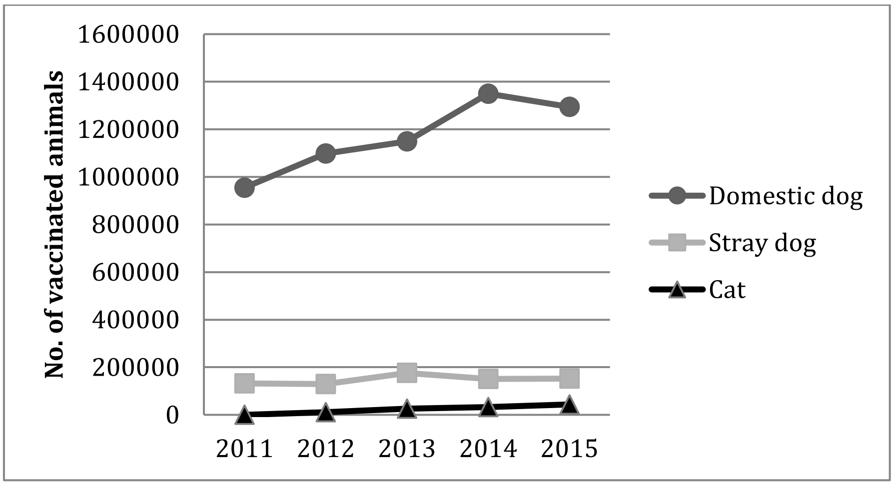

Figure 6. Total no. of vaccinated dogs and cats (2011-2015)

3.5.4 Dog sterilization

In Sri Lanka, the REA gives the local authorities permission to approve the type of population control method within their area of jurisdiction (Matibag *et al*, 2009). A no kill policy was brought into effect for stray dogs in 2006. Instead, a 'capture, neuter, vaccinate and release' (CNVR) policy was adapted. This method is more socially acceptable in the predominantly Buddhist country (Matibag *et al*, 2009). Dogs are captured humanely, neutered and vaccinated. This is recorded by a tattoo on the dog's right ear. After recovery they are released to the initially captured location.

Both surgical and chemical contraceptive methods, ovariohysterectomy (OHE) and Depo-provera injection (DEPO) respectively, have been used since 2007. A circular was presented in late 2009 to cease male castration and focus only on female spaying as a more effective way of stray dog management (PHVS, 2009).

A total 801,042 dogs were sterilized in the five years (635,469 spays and 165,573 DEPO injections). It peaked in 2013 with 182,809 sterilizations against 158,417 in 2011, but subsequently dropped to 141,444 in 2015. In general, surgical sterilization has been favored over chemical sterilization (4:1 ratio).

There has been a general drop in DEPO. It accounted for only 1% of birth control in 2015 compared to 6.67% in 2011 (8017 injections in 2015 vs. 53,419 in 2011). On the other hand, surgical sterilization increased by 1.27% over the 5-year period (104,998 in 2011 vs. 133,427 in 2015).

Provincially, northwest and north central recorded the most sterilizations overall, with a total of 132,584 and 144,406 within the 5 years respectively.

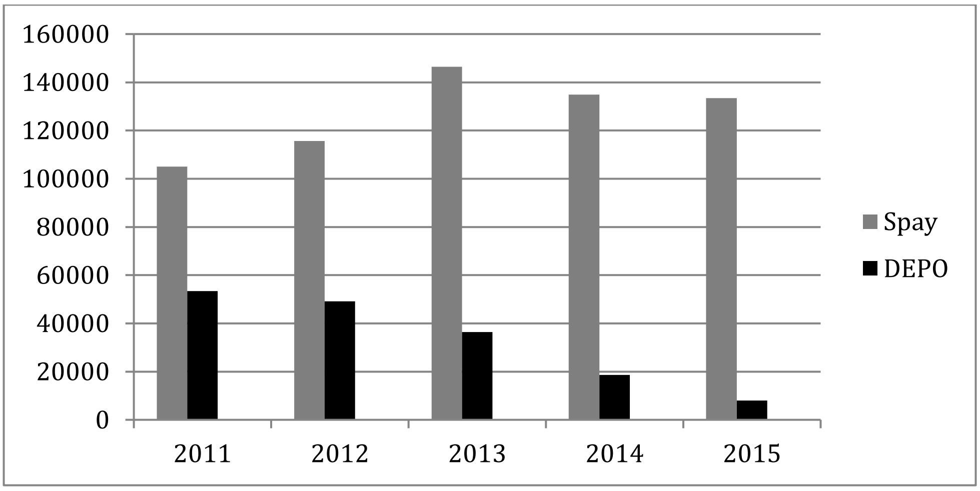

Figure 7. Total no. of surgical and chemical sterilizations in dogs (2011-2015)

3.5.5 Public co-operation

Community awareness is critical for successful elimination and the media should be utilized as a tool for knowledge sharing. Disease control leads to an improved quality of life and can be assessed by quality of life metrics (Häsler *et al*, 2014). An understanding of bite wound first aid, PEP, dog ownership and dog vaccination recordkeeping are points that need attention. Information should be provided at a school level in addition to community-based education (Lapiz *et al*, 2012).

Rabies control in Sri Lanka is feasible in part, due to public support (WHO, 2016). Misconception on virus transmission is relatively low compared to other endemic nations but the unsupervised roaming of pets must be addressed (Matibag *et al*, 2009). Sri Lankans are supportive of control measures in general and have assisted public health workers in CNVR of stray dogs (WHO, 2016).

Conclusively, there has been a decline in human mortality over the 5-year period of 2011-2015. This could be attributed to wider PEP treatment and dog vaccination programs as displayed in figure 8.

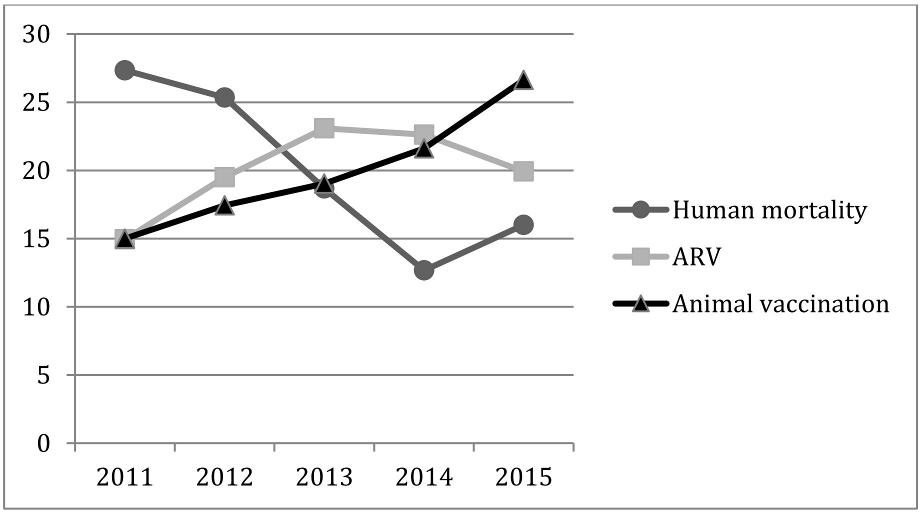

Figure 8. Correlation between human mortality, ARV and dog vaccinations (2011-2015)

3.6 Annual expenditure

Globally, US$583.5 million is spent on rabies treatment each year, out of which US$563 million is borne by Asia on account of a greater demand for PEP (Matibag *et al*, 2008).

Of the budget allowance for drugs and vaccines in Sri Lanka, an annual estimated US$4.6 million (10%) is spent on anti-rabies resources (Matibag *et al*, 2008). The cost of PEP is five times greater than that of animal control measures (Matibag *et al*, 2008). The average cost of rabies PEP per patient is around US$173-177 (Kularatne *et al*, 2016).

As PEP and dog control expenses are borne by the Sri Lankan government the cost to the patient is usually due to income loss as a result of absence from work or transport price to seek PEP (Häsler *et al*, 2014).

The approx. allocation of the budget for the human vs. animal component of rabies is demonstrated in table 2.

Table 2. Major expenditure by the government of Sri Lanka (2013)
(Source: PHVS, 2013)

Item	**Cost in LKR (Sri Lankan rupee)**	**Cost in approx. USD (USA dollar)**
Import of dog rabies vaccine	31,000,000	203,800
Dog sterilization	125,000,000	821,800
Human ARV	231,000,000	1,518.700
Human rabies immunoglobulin	74,000,000	486.500
Horse rabies immunoglobulin	45,000,000	295,900
Total	506,000,000	3,326,800

4. Discussion

Regardless of a national eradication program, rabies remains a significant public health concern in Sri Lanka. The highest mortality was recorded in 1973 (377) at 20/million population (Matibag *et al*, 2009), but has declined overall to 24 in 2015. By July 2016, only 5 deaths had been reported (Harischandra *et al*, 2016). This has largely been a result of a) wider accessibility to PEP and b) mass dog vaccination and sterilization programs. Most residual deaths have been recorded in children (Kularatne *et al*, 2016) and adult men, especially those who evade PEP (Harischandra *et al*, 2016).

4.1. Post-exposure prophylaxis

Prompt PEP has been critical in lowering the number of human cases (Lapiz *et al*, 2012) with almost 1.4million PEP treatments recorded in the 5 years. According to PHVS, the wound must be washed thoroughly for 10-15 minutes with water and soap before seeking immediate PEP at a healthcare facility. The wound is disinfected with 70% ethanol before ARV is administered. In Sri Lanka, PEP is initiated after the patient and animal have been screened as per guidelines of table 3 (Kularatne *et al*, 2016).

Table 3. Screening of human victim and dog after bite wound
(Source: PHVS, 2009)

Exposure type in human	Animal	PEP
Major exposure (Category I according to WHO Expert Consultation on Rabies, 2013)	Apparently healthy and observable with >2 ARV less than 2 years apart + last vaccination within 1 year of incident	PEP can be delayed while observing animal for 14 days
	Suspicious or sick but observable	PEP is initiated while observing animal and discontinued if animal is declared healthy
	Rabid (definitive diagnosis) or unobservable	Full course of PEP is continued

Minor exposure (Category II)	Apparently healthy and observable with >1 ARV within 1 year of incident at age >3 months OR incident within 1 month after the vaccination	PEP can be delayed while observing animal for 14 days
	Suspicious or sick but observable	PEP is initiated while observing animal and discontinued if animal is declared healthy
	Rabid (definitive diagnosis) or unobservable	Full course of PEP is continued

In case of a major exposure, RIG is administered prior to the ARV course, preferably on the same day, but at a different injection site. Following a minor exposure, only the ARV course is applied (Kularatne *et al*, 2016). All treated patients are given a document containing the date and type of vaccination used.

4.1.1 Rabies Immunoglobulin

Sri Lanka uses human and equine RIG for passive immunization (HRIG and ERIG respectively). RIG can be injected up to a maximum of 7 days from date of first ARV (WHO, 2010b). After this time it will suppress the body's antibody production. Sensitivity testing is suggested for ERIG due to possible anaphylaxis but is not backed by scientific evidence (WHO, 2010b; Sudarshan *et al*, 2011).

RIG is infiltrated in and all around the wound. The remaining volume is injected into the anterior thigh (IM). Deltoids are spared for ARV. If RIG dose is insufficient it be diluted 2-3 fold with saline for thorough infiltration. Supposing RIG scarcity in the market, it can successfully be applied locally at the wound without systemic IM use (Bharti *et al*, 2015).

Cost-effective ERIG is preferred in Sri Lanka (Harischandra *et al*, 2016). ERIG and HRIG cost per vial is approx. US$13 (2,000LKR) and US$50 (7,000LKR) respectively (Fazlulhaq and Wickremasekara, 2012).

HRIG can be substituted in case of ERIG sensitivity. If HRIG is unavailable, ERIG can used with adrenaline and antihistamine in an ICU setting to manage anaphylaxis (WHO, 2013). In Sri Lanka,

- RIG is replaced by modified 4-site ID-ARV if the animal is apparently health and observable. Once the animal is declared healthy, 4-site ARV is completed without RIG.
- If the animal is reported as sick or dead during the first 7 days of ARV initiation, ERIG is used with adrenaline/antihistamine. This is followed up by a fresh 2-site ID-ARV course.

4.1.2 Human anti-rabies vaccination

There are two types of ARV used for active immunization in Sri Lanka → purified chick embryo cell culture vaccine (PCEC) and purified Vero cell rabies vaccine (PVRV).

ID-ARV is the preferred regimen (Gongal *et al*, 2011). IM-ARV is used in hospitals with less than five bite patients a day or in case of immunosuppressive state i.e. chloroquine drug use (Warrell *et al*, 2008; WHO, 2013). Usually the deltoid muscle is injected while the gluteus is avoided due to poor absorption.

Two different IM dose schedules are applied as follows:

- Major exposure → 5 dose schedule of one dose each on day 0,3,7,14 and 30 (Essen regimen) + RIG
- Minor exposure→ 4 dose schedule of two doses on day 0 and one dose each on day 7 and 21 (Zagreb regimen)

0.1ml dosage (=one dose) is recommended per site for both PCEC and PVRV ID-PEP. The reconstituted vaccine has a short shelf life of 6 hours and must be kept at 2-8°C (WHO, 2013).

ID-PEP is as follows:

- 2-site ID-ARV (Updated Thai Red Cross regimen) is the standard schedule used in Sri Lankan government hospitals. One dose each is given to 2 sites (deltoid muscle of each arm) on day 0, 3, 7 and 30.
- The modified 4-site ID schedule includes one dose each to 4 different sites on day 0 (usually deltoids and lateral thighs), followed by one dose on 2 sites on days 3,7 and 30.

Table 4. PEP schedule used in Sri Lanka
(Source: PHVS, 2009)

Vaccination schedule	No. of doses					
	Day 0	Day 3	Day 7	Day 14	Day 21	Day 30
5-dose IM	1	1	1	1	0	1
4-dose IM	2	0	1	0	1	0
2-site ID	2	2	2	0	0	2
4-site ID	4	2	2	0	0	0

The advantages of 4-site vs. 2-site ID-PEP are being investigated. 4-site treatment requires one less clinical visit and the course is completed within a week (Shantavasinkul *et al*, 2010). This reduces the dropout in case the patient forgoes subsequent vaccinations for any reason i.e. inability to travel from a remote location. It has a wider safety margin because the vial is divided between 4 sites on the 1st day (Warrell *et al*, 2008).

The efficacy of 4-site PEP with or without RIG has also been demonstrated (Warrell *et al*, 2008); (Shantavasinkul *et al*, 2010). It is also economical as evidential by the pooling technique of Himachal as fewer vaccines are required for the same number of patients at a clinic (Bharti *et al*, 2015). In other words, if two or more patients are treated on the same day, vials can be shared during later visits (Warrell *et al*, 2008)

4.1.3 Re-exposure after previous treatment

According to PHVS, if a patient is re-exposed to rabies having previously completing treatment, PEP can be delayed during the 10-day observation period if the animal is apparently healthy and observable.

If the animal is suspected of being infected by rabies:

- <6 months after last ARV dose→ PEP is not indicated
- 6 months-5 years→ 2-site ID (2 doses each on day 0 and 3), IM (one dose each on day 0 and 3) or 4-site ID (4 doses on day 0) is given. RIG is not indicated up to five years
- >5 years→ full ARV course with or without RIG

In case of incomplete PEP:

- <30 days after last dose→ original course is continued
- 1-6 months→ 2-site ID (2 doses each on day 0 and 3), IM (one dose each on day 0 and 3)
- 6 months-5 years→ full course of 2-site ID-ARV or IM-ARV
- >5 years→ full ARV course with or without RIG

4.2 Pre-exposure therapy

Pre exposure therapy is recommended for high-risk personnel by PHVS and the schedule is IM-PEP of one dose each on day 0, 7 and 28 followed by a booster a year later. Additional boosters are given once every 5 years. RIG is contraindicated in pre-exposure therapy (WHO, 2013). Following a major exposure, IM-PEP of one dose is given on day 0 and 3 as boosters.

4.3 Animal control measures

Managing the canine source in Sri Lanka is two-fold, that is by vaccination and population control. The number of rabid dogs has remained relatively stable (Harischandra *et al*, 2016). The dog to human population ratio was 1:6 in 2012 (Fazlulhaq and

Wickremasekara, 2012) and 1:6.7 in 2016 (Satisraja, 2016). By October 2016, approx. half a million stray dogs had been reported on the roads (Satisraja, 2016).

Evidenced by data of the 5-year period, approx. 1.5million dogs had been vaccinated in 2015 compared to only 1million in 2011. The Ministry of Health forecasts an increase of up to 2.4 million dog vaccinations by 2020 (Harischandra *et al*, 2016). Vaccination coverage depends on the dog population turnover (WHO, 2016). If the turnover is high, a single vaccination campaign is pointless. Therefore sustainability of vaccination is a critical factor to be considered (Hampson *et al*, 2015). A vaccination program usually takes one year to cover an area so newborns maybe overlooked in the process (WHO, 2016). This has a negative effect on herd immunity. Herd immunity is achieved when over 80% vaccination coverage is observed in a specific area over a 3-month period (WHO, 2016).

While all dogs over 6 weeks must be vaccinated as per the REA, immunization before 6 weeks is recommended (Matibag *et al*, 2009). The vaccination schedule for dogs and cats in Sri Lanka is explained in Table 5.

Table 5. Vaccination protocol in Sri Lanka
(Source: Department of animal Production and Health [DAPH], 2013)

Dam immunity	1st inoculation (age)	1st booster (age)	Revaccination (age)
DOMESTIC DOG			
Immunized	6th week	14th week	Annually
Not immunized	At time of presentation (after opening eyes)	14th week	Annually
STRAY DOG			
	At time of presentation	>10th week	Annually
CAT			
	6th week	14th week	Annually

In case of rabies PEP for dogs, a booster is given if the victim has been properly immunized (DAPH, 2013). If the immunization is incomplete, the animal is revaccinated after a 6-month observation period (DAPH, 2013).

Cats are becoming increasingly responsible for bites and have accounted for 24% of all bites vs. 71% of dog bites (Kularatne *et al*, 2016). It is therefore recommended that cats be included as much as possible in vaccination campaigns to increase coverage (Harischandra *et al*, 2016). This was demonstrated with approx. 40,000 cat inoculations in 2015.

The dynamics of the dog population are categorized by six parameters; population size, sex ratio, age structure, annual population turnover, levels of dog supervision and accessibility of dogs (WHO, 2007). Disturbances will change the stability of the population i.e. the presence of a female dog in estrus or invasion by a dog in the early clinical stage of rabies (Kumarapeli and Awerbuch-Friedlander, 2009). This in turn will increase dog interactions and risk of rabies transmission. In Sri Lanka, the estimated dog population density is 108dogs/km^2 and is much higher than the threshold value of 4.5dogs/km^2 necessary for persistent rabies (Kularatne *et al*, 2016).

While approx. 800,000 dogs were sterilized within the 5 years of 2011-2015, further legislation and policy making pertaining to population control is vital for the eradication process. All dogs in Sri Lanka over 3 months must be currently registered with the local authority by order of the REA (Matibag *et al*, 2009). The absence of a valid registration certificate can result in an approx. US$46 (5,000LKR) fine.

Ecological changes can impact the population dynamic so environmental controls must be applied and enforced accordingly. Dog movement and commercial breeding are also areas that lack stringent regulation (WHO, 2016). Laws on animal abandonment must be further imposed while the public should be continuously educated on responsible dog ownership and compulsory vaccination.

While PEP management has improved overall, the expected 70% dog vaccination coverage has not been attained yet and therefore a huge cost is still expected for PEP resources (WHO, 2016). The allocation of the budget must be reformed as necessary. For example, the savings of cost-effective ERIG use could be depleted to strengthen the dog component of the program (Harischandra *et al*, 2016).

A greater demand for resources of the dog component is expected if rabies is to be eradicated by 2020. On estimation, more dog vaccinations will be required by 2020 compared to human ARV vials as demonstrated in Table 6.

Table 6. Projected requirement in Sri Lanka (2016-2020)
(Source: Harischandra *et al*, 2016)

No. of vials					
	2016	2017	2018	2019	2020
Human ARV (1ml vial)	310,000	3000,000	290,000	280,000	270,000
HRIG 300IU	15,000	15,000	15,000	15,000	15,000
HRIG 700IU	10,000	10,000	10,000	10,000	10,000
ERIG 1000IU	100,000	90,000	80,000	70,000	60,000
Dog ARV (10ml vial)	1,800,000	2,000,000	2,200,000	2,400,000	2,400,000

4.4 Public awareness

The government conducts mass education programs using multiple sources as part of the eradication process. The knowledge, attitudes and practices (KAP) regarding rabies control are generally high despite inconsistency between pet owners/ non-pet owners and urban/ rural residents (Matibag *et al*, 2007). Most information is communicated through tri-media (radio, newspaper, television), schools and government campaigns respectively (Matibag *et al*, 2009).

A majority of citizens (urban and rural) are aware of the transmission route and free availability of PEP (Häsler *et al*, 2014), but pet owners have a better understanding of the dog component i.e. dog vaccination schedules and records, compared to non-pet owners (Matibag *et al*, 2007). These are all good indicators of the benefits of public engagement so far. Although more dog bites were reported on account of these programs, there was also an increased complacency with regard to PEP once the recommended first aid measures were applied (Matibag *et al*, 2009).

Currently the disconnection between attitude and practice is wide in both urban and rural locations (Matibag *et al*, 2007). While most people feel responsibility towards stray population control (Matibag *et al*, 2009), there is a heightened acceptance of dog roaming in society, especially in rural regions (Häsler *et al*, 2014). This in turn has elevated the risk of disease spread. Rabies elimination has also been hindered by disposal of leftover food in streets, resulting in stray dog population growth (Kularatne *et al*, 2016).

The importance of record keeping and knowledge on the fatality of human rabies must also be regularly stressed upon. Additionally a low rate of submission for lab diagnosis suggests that people should be encouraged to send in more samples, especially in cases of livestock and wild animals (Matibag *et al*, 2009).

While there are awareness programs in place, the evidence suggests that KAP should be continuously reinforced on a larger scope for as long as rabies is endemic in Sri Lanka. The public must be informed on adequate pet care practices that include the procedure in case of suspicion of rabies in an animal and maintenance of dog vaccination schedules i.e. earliest vaccination age. Bite wound first aid and the importance of PEP must also be constantly demonstrated. Psychological trauma associated with rabies has been known to reduce with improved knowledge on rabies (Häsler *et al*, 2014).

Extra focus should be given to non-pet owners and rural residents due to a higher misconception of information (Matibag *et al*, 2007). Further KAP at a school level is also imperative as more cases present in children during school vacation in April, August and December (Kularatne *et al*, 2016). In addition to tri-media, innovative technology could also be used as a supplementary tool for public health communication (Wu *et al*, 2016).

4.5 Diagnostics and surveillance

Due to its rapid progression, victims die before seeking treatment so the actual mortality may be grossly underestimated (Hampson *et al*, 2015). The number of dog cases is also generally under-reported as a majority is handled by private clinics in Sri Lanka (DAPH, 2013). But diagnosis by MRI is an indirect indicator of the dog rabies situation in the country. In 2016, dogs, cats, humans, wild animals and livestock accounted for a total 85.2%, 7%, 9%, 3.8%, 2% and 1% positive samples respectively (Satisraja, 2016). Possible spill over from rabid dogs may have resulted in wild animal and livestock-mediated rabies (Arai *et al*, 2001).

Laboratory confirmation of rabies is always desirable and should be encouraged to reduce data inadequacies. Data evaluation provides patterns to identify possible gaps, thereby allowing for better resource mobilization. It can forecast the spread of infection to other areas (Lapiz *et al*, 2012) and monitor the impact of already placed control efforts (Hampson *et al*, 2015). Positive case surveillance must also be reformed so that an efficient response is possible in case of an outbreak (WHO, 2016). Novel molecular detection methods and wider diagnostic laboratory access are necessary for the advancement of surveillance and diagnosis in Sri Lanka (Karunanayaka *et al*, 2014).

A proper surveillance system on wildlife rabies is also absent as the focus has largely been on the eradication of canine rabies. Unrecognized wild fauna can provide undiscovered reservoirs for the virus. Rabies in livestock accounts for 6% of the US$8.6 billion global economic loss (Hampson *et al*, 2015). Data on the economic significance of rabies in livestock in Sri Lanka is insufficient and must be further developed (WHO, 2016). Farmers should be encouraged to submit livestock samples for lab diagnosis (Karunanayaka *et al*, 2014). Accessibility to diagnostic facilities for animal head submission and animal vaccination must also be developed, especially in rural regions (Matibag *et al*, 2007).

Joint studies on human and dog rabies deaths, PET administration and dog ecology are fundamental in assessing the eradication program. (Kumarapeli and Awerbuch-Friedlander, 2009). Data on non-monetary effects i.e. animal welfare and social acceptability are also invaluable in explaining the overall eradication impact and must be further updated (Häsler *et al*, 2014).

4.6 The ‘SAARC Rabies Elimination Project’

Approx. 31,000 deaths occur in Asia annually (Knobel *et al*, 2001). Most cases occur in remote, poverty-stricken areas of the South Asian Association for Regional Cooperation (SAARC) with suboptimal access to PEP. Rabies is endemic in all SAARC countries excluding Maldives and is considered a priority communicable disease (WHO, 2016). An estimated 4 million people receive PEP in this region every year (Gongal *et al*, 2011).

The ‘SAARC Rabies Elimination Project’ is a regional initiative taken by SAARC Members in 2012 with the cooperation of WHO, OIE and FAO. This is a first step towards cross-border coordination on rabies elimination. It includes a six-step (step 0-5) eradication approach by FAO in which the final step (step 5) is zero dog-dog transmission in 12 consecutive months (WHO, 2016). According to OIE, a country is declared rabies-free if the disease has notifiable status and ongoing surveillance has been in place for at least two years before free status declaration, with no indigenous or imported cases within this time (WHO, 2016). As part of the SAARC initiative, OIE operates a dog rabies vaccination bank that is easily accessible by endemic regions (WHO, 2016).

On a global scale, the Global Alliance for Rabies Control (GARC) launched ‘World Rabies Day’ in 2007 to combat rabies extensively. The ‘rabies blueprint’ was developed as part of this campaign to provide free and easy access to resources on rabies eradication. The theme for 2016, marking the 10^{th} World Rabies Day was ‘Educate, Vaccinate and Eliminate Rabies’.

5. Conclusion

Rabies eradication is a long-term investment involving a multi dimensional control approach. While great headway has been made, if complete eradication of rabies is to be achieved by 2020 in Sri Lanka, a few key areas should be continuously improved upon.

The dog is the primary source of rabies so eradication has to originate here. Dog vaccination and population control programs reduce the consumption of human vaccination and human mortality, thereby reducing the total cost involved (Hampson *et al*, 2015). As dog roaming is limited in certain areas of Sri Lanka while unrestricted in others, movement regulations need to be enforced to manage stray dog population dynamics (Matsumoto *et al*, 2013). Dog sterilization must be extended island wide, especially to remote locations with high-density dog populations (Gongal *et al*, 2011). Dog vaccination coverage should also be expanded upon, with focus on long-term sustainability.

Wider PEP availability must be achieved so that treatment can be distributed to even the farthest, most inaccessible part of the country. Rural neighborhoods should be given priority on account of insufficient access to modern diagnostic and treatment facilities (Matibag *et al*, 2009). Vaccination banks are essential in efficient delivery of anti-rabies treatment. Alternative funding mechanisms to obtain vaccines i.e. Pan American Health Organization (PAHO) revolving fund, should be considered if necessary (WHO, 2015).

The general public should be educated on the importance of seeking out and completing the PEP course while the advantages of using 4-site ID-PEP must be further investigated in order to reduce non-compliance and drop out rate in patients. Private funding is essential for a wider dispersion of human resources and the investment in rabies eradication can be made attractive to donors by focusing on its social impact.

Surveillance and diagnostics inadequacies should be rectified and consensus maintained to ensure traceability. A continuously updated data system can monitor the impact of current control measures and provide an action plan in the event of an outbreak. Further attention must also be given to wildlife and livestock surveillance. Coordination between local authorities and the central diagnostic laboratory should be developed and a satellite diagnostic strategy must be considered (Matibag *et al*, 2007).

'One health' management must start at the level of the individual and expand gradually into an inter-sector co-contribution of the government, private and non-profit organizations. Barriers to engaging private sector veterinarians need to be lifted and additional consideration must be given to reforming laws and policies of rabies management. Although legislations are in place, their implementation must be strictly and uniformly enforced.

In conclusion, a global eradication of dog-mediated rabies is within grasp as successfully proven by the Bohol Rabies Project (Lapiz *et al*, 2012). Sri Lanka is a key SAARC country that has made great progress on this front but constant development and implementation of the veterinary-medical interphase is necessary for a 'zero deaths by 2020' target to be achieved.

6. Summary

Rabies is one of the oldest and deadliest zoonotic diseases known to man, accounting for approx. 59,000 human deaths each year. The majority of deaths occur in remote, poverty-laden regions of Asia and Africa. Approx. 20-30 deaths result annually in Sri Lanka. This review evaluates the current progress and limitations of the nationally implemented rabies eradication program in Sri Lanka and compares data of the annual 'Rabies Statistical Bulletin' reports of 2011-2015 presented by the Public Health Veterinary Services of Sri Lanka on their official website.

Canine rabies is endemic in Sri Lanka and accounts for over 95% human cases. Despite a general decline of dog-mediated rabies, it still remains a significant public health concern, in part due to a high stray dog population. Eradication measures in Sri Lanka focus on the veterinary-human medicine interphase. Dog control measures are two-fold; they include mass vaccination campaigns for sustainable herd immunity and sterilization campaigns to manage dog populations. The human component comprises wider accessibility of post-exposure prophylaxis and public awareness.

Human mortality dropped from 41 in 2011 to 24 in 2015. Post-exposure prophylaxis distribution rose from 205,645 vials in 2011 to 274,405 in 2015 but peaked in 2013. Approx. 1.9million dogs and cats received the anti-rabies vaccination in 2015 compared to approx. 1.1million dogs in 2011. Cat inoculation began in 2012. However, there was a drop in birth control during this period, with 141,444 sterilizations in 2015 against 158,417 in 2011. While lab diagnosis was highest in the dog there was an increased submission of cat and other/wild animal samples for lab confirmation over the 5-year period.

Sri Lanka was the first country in Southeast Asia to enact a national strategy to eliminate canine rabies by 2020. This is a first step in the WHO mediated global eradication initiative of 'zero rabies deaths by 2030'. This target is feasible considering the data over the 5-year period of 2011-2015 but further implementation of rabies control is necessary for as long as the disease remains endemic in the country.

Acknowledgements

I would like to first and foremost thank my supervisor, Prof. Fodor László for his guidance, enthusiasm and encouragement with my thesis topic. He was able to provide invaluable expertise and was always willing to answer any question I had regarding the subject.

I must also mention the librarians at the University of Veterinary Medicine, Budapest for their co-operation in resource gathering and referencing. I would like to especially thank Ms. Bikádi Katalin, who went out of her way to help with this process. I truly appreciate her assistance.

Last but not least I'm grateful to my parents, family and friends for being my unconditional support system, not only during this process but also throughout the whole of my veterinary education.

I appreciate this opportunity to walk away with a greater understanding on the current rabies situation both in Sri Lanka and around the world.

Reference List

Arai, Y.T., Takahashi, H., Kameoka, Y., Shiino, T., Wimalaratne, O. and Lodmell, D.L., 2001. Characterization of Sri Lanka rabies virus isolates using nucleotide sequence analysis of nucleoprotein gene. *Acta Virologica*, **45**(5-6), pp.327-333.

Bharti, O.K., Madhusudana, S.N., Kale, A., Gaunta, P.L., Chaudhry, L.S., Kumar, J., Gupta, N. and Shyam, D., 2015. Success Story of a Low Cost Intra-Dermal Rabies Vaccination (IDRV) Clinic-Lessons Learnt over Five Years of 12,000 Patient Vaccinations "Without Failure" at DDU Hospital Shimla, Himachal Pradesh, India. *World*, **5**, pp.129-139.

Chutivongse, S., Wilde, H., Benjavongkulchai, M., Chomchey, P. and Punthawong, S., 1995. Postexposure rabies vaccination during pregnancy: effect on 202 women and their infants. *Clinical Infectious Diseases*, **20**(4), pp.818-820.

DAPH, 2013. Rabies: a major zoonosis. *Veterinary Epidemiological Bulletin*, **6**(2), pp.1-4. [online] URL: http://www.daph.gov.lk/web/images/content_image/news_bulletins/epidemiological/veterinary_epidemiological_bulletin_volume_6_no_2.pdf. [Accessed 18 Mar. 2017].

Fazlulhaq, N, and Wickremasekara, D., 2012. Roaming dogs and rise of rabies. *The Sunday Times* [newspaper] 15 January 2012 URL: http://www.sundaytimes.lk/120115/News/nws_24.html. [Accessed: 4 March 2017].

Gongal, G. and Wright, A.E., 2011. Human rabies in the WHO Southeast Asia Region: forward steps for elimination. *Advances in Preventive Medicine*, 2011, Article ID 383870, pp.1-5.

Hampson, K., Coudeville, L., Lembo, T., Sambo, M., Kieffer, A., Attlan, M., Barrat, J., Blanton, J.D., Briggs, D.J., Cleaveland, S. and Costa, P., 2015. Estimating the global burden of endemic canine rabies. *PLoS Neglected Tropical Diseases*, **9**(4), p.e0003709.

Harischandra, P.L., Gunesekera, A., Janakan, N., Gongal, G. and Abela-Ridder, B., 2016. Sri Lanka takes action towards a target of zero rabies death by 2020. *WHO South East Asia Journal of Public Health*, **5**(2), pp.113-116.

Häsler, B., Hiby, E., Gilbert, W., Obeyesekere, N., Bennani, H. and Rushton, J., 2014. A one health framework for the evaluation of rabies control programmes: a case study from Colombo City, Sri Lanka. *PLoS Neglected Tropical Diseases*, **8**(10), p.e3270.

Karunanayake, D., Matsumoto, T., Wimalaratne, O., Nanayakkara, S., Perera, D., Nishizono, A. and Ahmed, K., 2014. Twelve years of rabies surveillance in Sri Lanka, 1999–2010. *PLoS Negl Trop Dis*, **8**(10), p.e3205.

Kaur, M., Garg, R., Singh, S. and Bhatnagar, R., 2015. Rabies vaccines: where do we stand, where are we heading?. *Expert review of vaccines*, **14**(3), pp.369-381.

Knobel, D.L., Cleaveland, S., Coleman, P.G., Fèvre, E.M., Meltzer, M.I., Miranda, M.E.G., Shaw, A., Zinsstag, J. and Meslin, F.X., 2005. Re-evaluating the burden of rabies in Africa and Asia. *Bulletin of the World health Organization*, **83**(5), pp.360-368.

Krebs, J.W., Wilson, M.L. and Childs, J.E., 1995. Rabies—epidemiology, prevention, and future research. *Journal of Mammalogy*, **76**(3), pp.681-694.

Kularatne, S.A.M., Ralapanawa, D.M.P.U.K., Weerakoon, K., Bokalamulla, U.K. and Abagaspitiya, N., 2016. Pattern of animal bites and post exposure prophylaxis in rabies: A five year study in a tertiary care unit in Sri Lanka. *BMC Infectious*

Diseases, **16**(1), p.62 [online] URL: http://doi.org/10.1186/s12879-016-1394-5. [Accessed: 3 March 2017].

Kumarapeli, V. and Awerbuch-Friedlander, T., 2009. Human rabies focusing on dog ecology—A challenge to public health in Sri Lanka. *Acta Tropica*, **112**(1), pp.33-37.

Lapiz, S.M.D., Miranda, M.E.G., Garcia, R.G., Daguro, L.I., Paman, M.D., Madrinan, F.P., Rances, P.A. and Briggs, D.J., 2012. Implementation of an intersectoral program to eliminate human and canine rabies: the Bohol Rabies Prevention and Elimination Project. *PLoS Neglected Tropical Diseases*, **6**(12), p.e1891.

Manoj, S., Mukherjee, A., Johri, S. and Kumar, K.H., 2016. Recovery from rabies, a universally fatal disease. *Military Medical Research*, **3**(1), p.21.

Matibag, G.C., Kamigaki, T., Kumarasiri, P.V., Wijewardana, T.G., Kalupahana, A.W., Dissanayake, D.A., De Silva, D.N., Gunawardena, G.P.D.S., Obayashi, Y., Kanda, K. and Tamashiro, H., 2007. Knowledge, attitudes, and practices survey of rabies in a community in Sri Lanka. *Environmental Health and Preventive Medicine*, **12**(2), pp.84-89.

Matibag, G.C., Kamigaki, T. and Wijewardana, T.G., 2008. Rabies related risk factors and animal ownership in a community in Sri Lanka. *Journal of Epidemiology*, **6**(1), pp.56-61.

Matibag, G.C., Ohbayashi, Y., Kanda, K., Yamashina, H., Kumara, W.B., Perera, I.G., De Silva, D.N., Gunawardena, G.P.D.S., Jayasinghe, A., Ditangco, R.A. and Tamashiro, H., 2009. A pilot study on the usefulness of information and education campaign materials in enhancing the knowledge, attitude and practice on rabies in rural Sri Lanka. *The Journal of Infection in Developing Countries*, **3**(01), pp.055-064.

Matsumoto, T., Ahmed, K., Karunanayake, D., Wimalaratne, O., Nanayakkara, S., Perera, D., Kobayashi, Y. and Nishizono, A., 2013. Molecular epidemiology of human rabies viruses in Sri Lanka. *Infection, Genetics and Evolution*, **18**, pp.160-167.

Morimoto, K., Foley, H.D., McGettigan, J.P., Schnell, M.J. and Dietzschold, B., 2000. Reinvestigation of the role of the rabies virus glycoprotein in viral pathogenesis using a reverse genetics approach. *Journal of Neurovirology*, **6**(5), pp.373-381.

Morters, M.K., McNabb, S., Horton, D.L., Fooks, A.R., Schoeman, J.P., Whay, H.R., Wood, J.L. and Cleaveland, S., 2015. Effective vaccination against rabies in puppies in rabies endemic regions. *Veterinary Record*, pp.vetrec-2014 [online] URL: http://veterinaryrecord.bmj.com/content/early/2015/06/24/vr.102975.citation-tools. [Accessed: 6 March 2017].

Nanayakkara, S., Smith, J.S. and Rupprecht, C.E., 2003. Rabies in Sri Lanka: splendid isolation. *Emerging Infectious Diseases*, **9**(3), pp.368-371.

PHVS, 2009. *Public Health Veterinary Services, Ministry of Health* [online] URL: http://www.rabies.gov.lk. [Accessed: 4 March 2017].

PHVS, 2011. *Rabies Statistical Bulletin 2011* [online] URL: http://www.rabies.gov.lk/download/Annal_statistics_2011.pdf. [Accessed: 25 February 2017].

PHVS, 2012. *Rabies Statistical Bulletin 2012* [online] URL: http://www.rabies.gov.lk/download/anual_rabies_statistic_2012.pdf. [Accessed: 25 February 2017].

PHVS, 2013. *Rabies Statistical Bulletin 2013* [online] URL: http://www.rabies.gov.lk/download/Annual%20Report%20PHVS%202013.pdf. [Accessed: 25 February 2017].

PHVS, 2014. *Rabies Statistical Bulletin 2014* [online] URL:

http://www.rabies.gov.lk/download/Annual%20Report%202014.pdf. [Accessed: 25 February 2017].

PHVS, 2015. *Rabies Statistical Bulletin 2015* [online] URL: http://www.rabies.gov.lk/download/Stasistics%20%202015.pdf. [Accessed: 25 February 2017].

Satisraja, A., 2016. Huge stray dog numbers neuter rabies fight. *The Sunday Times* [newspaper] 2 October 2016 URL: https://www.pressreader.com/sri-lanka/sunday-times-sri-lanka/20161002/281827168261141. [Accessed: 17 March 2017].

Shantavasinkul, P., Tantawichien, T., Wilde, H., Sawangvaree, A., Kumchat, A., Ruksaket, N., Lohsoonthorn, V., Khawplod, P. and Tantawichien, T., 2010. Postexposure rabies prophylaxis completed in 1 week: preliminary study. *Clinical Infectious Diseases*, **50**(1), pp.56-60.

Sudarshan, M.K., Narayana, D.H. and Ravish, H.S, 2011. Is the skin sensitivity test required for administering equine rabies immunoglobulin. *The National Medical Journal of India*, **24**(2) pp.80-82.

Torcio, N., 1996. Characteristics and molecular biology of the rabies virus. In F. X. Meslin et al., ed. *Laboratory techniques in rabies*, **4**. Switzerland, Geneva, World Health Organization, pp.28 URL: http://bvs1.panaftosa.org.br/local/File/textoc/WHO_LabTec_cap3_Characteristics_rabies.pdf. [Accessed: 6 March 2017].

Wallace, R.M., Undurraga, E.A., Blanton, J.D., Cleaton, J. and Franka, R., 2017. Elimination of Dog-Mediated human rabies Deaths by 2030: needs assessment and alternatives for Progress Based on Dog Vaccination. *Frontiers in Veterinary Science*, **4**(9) [online] URL: http://doi.org/10.3389/fvets.2017.00009. [Accessed: 27 Feb 2017].

Wandeler, A.I., Matter, H.C., Kappeler, A. and Budde, A., 1993. The ecology of dogs and canine rabies: a selective review. *Revue scientifique et technique (International Office of Epizootics)*, **12**(1), pp. 51-71 [online] URL: http://www.oie.int/doc/ged/D8704.PDF. [Accessed: 16 March 2017].

Warrell, M.J., 2016. The dilemma of managing human rabies encephalitis. *Tropical Medicine & International Health*, **21**(4) pp. 456–457.

Warrell, M.J., Riddell, A., Yu, L.M., Phipps, J., Diggle, L., Bourhy, H., Deeks, J.J., Fooks, A.R., Audry, L., Brookes, S.M. and Meslin, F.X., 2008. A simplified 4-site economical intradermal post-exposure rabies vaccine regimen: a randomised controlled comparison with standard methods. *PLoS Neglected Tropical Diseases,* **2**(4), p.e224.

Webster, W. A., Casey, G. A., & Charlton, K. M., 1976. The mouse inoculation test in rabies diagnosis: early diagnosis in mice during the incubation period. *Canadian Journal of Comparative Medicine*, **40**(3) pp. 322–325.

WHO, 2005. WHO expert consultation on rabies: first report. *WHO technical report*, series 931, Chapter 10, pp.73-74 [online] URL: http://apps.who.int/iris/bitstream/10665/43262/1/WHO_TRS_931_eng.pdf. [Accessed: 20 March 2017].

WHO, 2007. *Oral vaccination of dogs against rabies: Guidance for research on oral rabies vaccines and Field application of oral vaccination of dogs against rabies* [online] URL: http://www.who.int/rabies/resources/guidelines%20for%20oral%20vaccination%20of%20dogs%20against%20rabies_with%20cover.pdf. [Accessed: 14 March 2017].

WHO, 2010a. Rabies vaccines: WHO position paper. *Weekly Epidemiological Record*, 6

August 2010, No. 32, 85, pp.309-320 [online] URL: http://www.cdc.gov.tw/uploads/files/0d884cda-2128-4990-8432-2ff865d7e8c6.pdf. [Accessed: 1 March 2017].

WHO, 2010b. *WHO GUIDE for Rabies Pre and Post-exposure Prophylaxis in Humans (revised 15 June 2010)* [online] URL: http://www.who.int/rabies/PEP_prophylaxis_guidelines_June10.pdf. [Accessed: 12 March 2017].

WHO, 2013. *FAQs Frequently asked questions on rabies* [online] URL: http://www.who.int/rabies/resources/SEA_CD_278_FAQs_Rabies.pdf. [Accessed: 5 March 2017].

WHO, 2015. *Global elimination of dog-mediated human rabies: report of the rabies global conference, 10-11 December 2015, Geneva, Switzerland* [online] URL:http://apps.who.int/iris/bitstream/10665/204621/1/WHO_HTM_NTD_NZD_2016.02_eng.pdf?ua=1&ua=1. [Accessed: 18 March 2017].

WHO, 2016. *Prevention and Control of Rabies in SAARC Countries: Report of the workshop 11-13 August 2015, Colombo, Sri Lanka* [online] URL: http://apps.who.int/iris/handle/10665/206500. [Accessed 18 March 2017].

WHO, n.d.. *Rabies in the South-East Asia Region* [online] URL: http://www.searo.who.int/about/administration_structure/cds/CDS_rabies.pdf.pdf. [Accessed: 1 March 2017].

Wu, H., Chen, J., Zou, L., Zheng, L., Zhang, W., Meng, Z., Magalhaes, R.J.S., Wang, Y., Kang, J. and Sun, X., 2016. Community-based interventions to enhance knowledge, protective attitudes and behaviors towards canine rabies: results from a health communication intervention study in Guangxi, China. *BMC Infectious Diseases*, **16**(1), p.701.

Zeiler, F.A. and Jackson, A.C., 2016. Critical appraisal of the Milwaukee protocol for rabies: this failed approach should be abandoned. *Canadian Journal of Neurological Sciences/Journal Canadien des Sciences Neurologiques*, **43**(01), pp.44-51 [online] URL: https://www.cambridge.org/core/services/aop-cambridge-core/content/view/S0317167115003315 [Accessed: 20 March 2017].