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Key words

Rabies, Liberia, diagnostic, phylogenetics, SARE tool, GDREP tool

Abstract

Despite declaration as a national priority disease, dog rabies remains endemic in Liberia, with surveillance systems and disease control activities still developing. The objective of these initial efforts was to establish animal rabies diagnostics, foster collaboration between all rabies control stakeholders, and develop a short-term action plan with estimated costs for rabies control and elimination in Liberia.

Four rabies diagnostic tests, the direct fluorescent antibody (DFA) test, the direct immunohistochemical test (dRIT), the reverse transcriptase polymerase chain reaction (RT-PCR) assay and the rapid immunochromatographic diagnostic test (RIDT), were implemented at the Central Veterinary Laboratory (CVL) in Monrovia between July 2017 and February 2018. Seven samples (n=7) out of eight suspected animals were confirmed positive for *rabies lyssavirus*, and molecular analyses revealed that all isolates belonged to the Africa 2 lineage, subgroup H. During a comprehensive in-country One Health rabies

stakeholder meeting in 2018, a practical workplan, a short-term action plan and an accurately costed mass dog vaccination strategy were developed. Liberia is currently at stage 1.5/5 of the Stepwise Approach towards Rabies Elimination (SARE) tool, which corresponds with countries that are scaling up local-level interventions (e.g. dog vaccination campaigns) to the national level. Overall an estimated 5.3 – 8 million USD invested over 13 years is needed to eliminate rabies in Liberia by 2030.

Liberia still has a long road to become free from dog-rabies. However, the dialogue between all relevant stakeholders took place, and disease surveillance considerably improved through implementing rabies diagnosis at the CVL. The joint efforts of diverse national and international stakeholders laid important foundations to achieve the goal of zero dog-mediated human rabies deaths by 2030.

1. Introduction

Rabies elimination succeeded in much of the western world but remains a huge challenge in resource limited countries. Despite being a preventable viral disease which can be controlled through effective vaccination and population management in the reservoir species, an estimated 59,000 people still die each year and roughly 3 million remain at risk. Of these deaths, the majority occur in children in rural communities in Asia (60%) and Africa (36%), where domestic dogs are the main reservoir species (Hampson et al., 2015; WHO, 2018a). In these regions, the disease is mainly caused through the canine associated classical *rabies lyssavirus* (RABV) in the genus *Lyssavirus* of the family *Rhabdoviridae.* It is a single strand negative-sense RNA virus with five genes (N-, P-, M-, G- and L-gene) (ICTV, 2018). In Africa, four different lineages (Africa 1-4) are known, with the Africa-2 clade the dominant lineage in West- and Central Africa (De Benedictis et al., 2010; Kissi et al., 1995; Talbi et al., 2009; Troupin et al., 2016).

Rabies surveillance methods are often ineffective in resource-limited countries due to lack of laboratory diagnosis, poor disease awareness with bite victims not seeking medical attention, and disease misdiagnosis by clinical staff resulting in massive underreporting of human and animal cases. These factors contribute to a cycle of neglect and lead to under-representation of the true disease burden, preventing decision makers from allocating funds for disease control measures (Cleaveland et al., 2002; Mallewa et al., 2007; Nel, 2013a, 2013b; Weyer and Blumberg, 2007; WHO, 2018a).

Recently there has been a global drive to eliminate canine-mediated human rabies by 2030, in line with the United Nations Sustainable Development Goals (UN SDGs). The Food and Agriculture Organization (FAO), the World Organisation for Animal Health (OIE), the World Health Organization (WHO) and Global Alliance for Rabies Control (GARC) launched the United Against Rabies (UAR) initiative in 2018 (Lembo et al., 2011; Minghui et al., 2018). To reach zero dog-transmitted human deaths by 2030, the UAR is the leading global coordination for the implementation of rabies control programmes. In addition, FAO, GARC, US Centers for Disease Control and Prevention (US CDC) and other partners have joined efforts to develop tools, guidelines and initiatives to assist countries in achieving the global goal. Several rabies-dedicated regional networks were established in dog-rabies endemic regions, including the Pan-African Rabies Control Network (PARACON) in 2014 under the secretariat of GARC. Its mission is to provide countries with a platform for sharing knowledge, the dissemination of tools, and advocacy to prioritise rabies and facilitate elimination of dog-mediated human rabies in sub-Saharan Africa by 2030 (Scott et al., 2015). For effective disease control, it is fundamentally important that all rabies control activities are planned and carried out with close collaboration between the animal and human health sectors. This 'One Health' concept should be adapted to specific local settings, based on the human-animal relationship as governed by cultural and religious context. A One Health approach further facilitates better disease surveillance and communication and results in health benefits and financial savings. However, such collaboration often does not exist in low- and middle-income countries (LMICs) (Léchenne et al., 2015; Scott et al., 2015; WHO 2018a; Zinsstag et al., 2015, 2005). Within PARACON, collaboration amongst African countries is highly promoted. Representatives from the partner countries frequently meet for meetings and workshops. A widely used tool within rabies networks like PARACON is the 'Stepwise Approach towards Rabies Elimination' (SARE) tool. The SARE evaluates a country's current situation in relation to dog-mediated rabies control and elimination efforts and facilitates the development and implementation of an effective national control programme (Coetzer et al., 2016). The tool consists of two components, the SARE component and the Practical Workplan component. The SARE component evaluates the country's situation by generating a comprehensive list of accomplished and pending activities, resulting in a SARE score, ranging from 'endemic for dog-mediated rabies' to 'freedom from dog-mediated rabies', based on progression. While the accomplished activities are useful for advocacy and resource mobilisation, the pending activities help countries focus their efforts toward continued implementation of disease intervention initiatives. The Practical Workplan component uses the country's SARE assessment output to automatically create a workplan populated with existing objectives/priority actions, outcomes, responsible authorities, timeframes (including Gantt charts), and deliverables for each of the pending activities. Each activity in the workplan is automatically populated with content based on recommendations from a global panel of experts. Although pre-populated, all content can be modified by the users, customising the workplan into a detailed, country-centred technical document. Countries can easily develop effective, actionable workplans based on sound monitoring and evaluation approaches and principles in a relatively short timeframe (Coetzer et al., 2018, 2016; FAO and GARC, 2012; Scott et al., 2017, 2015). The Global Dog Rabies Elimination Pathway (GDREP) was developed by the US CDC in 2017, to complement the SARE tool. GDREP is a user-friendly Microsoft® Excel-based budgeting tool to produce cost estimates for national mass dog vaccination programmes, based on data gathered from rabies vaccination campaigns in Haiti, Ethiopia, the United States (USA), Vietnam and Latin America (Undurraga et al., 2017; Wallace et al., 2017). The GDREP tool requires information on the size of the human and dog population in the country, current dog rabies vaccination coverage, available workforce and dog vaccination rate. With the user-provided information - gathered prior to and during the SARE workshop - the tool generates a phased framework specifying how many years remain for a specific country to progress to freedom from dog-mediated rabies, coupled with the estimated costs required as both annual and phased sums.

Evaluating the true burden of rabies in dogs is required to understand the current disease situation and to develop strong control strategies. Efficient surveillance programmes, where samples from suspect and biting animals are sent to Central Veterinary Laboratories (CVLs) for RABV detection, analysis and reporting, are crucial. Therefore, elimination in endemic countries also relies on availability of fully functioning and accurate diagnostic facilities. As of 2018, the direct fluorescent antibody (DFA) test and the direct immunohistochemical test (dRIT) - antibody-based protocols for detection of viral antigen - and conventional or real-time-polymerase chain reaction (RT-PCR) assays - molecular investigations for detection of viral RNA - are the diagnostic assays recommended for post-mortem rabies diagnosis by the OIE (OIE, 2018). Having different techniques ready to perform rabies diagnostics offers flexibility to overcome major limitations, for example, from lack of equipment, maintenance, or reagent supply. Although the DFA is an accurate and easy test, it is often challenging to implement in LMICs. The dRIT has several advantages over the DFA and is currently promoted through GARC in PARACON partner countries. The dRIT requires only a basic light microscope, whereas the DFA needs a fluorescence microscope. The dRIT is also easier to interpret in degraded or archived samples, and preserving samples in glycerol seems to influence DFA more than dRIT (Coetzer et al., 2017; Dürr et al., 2008; Scott et al., 2015). However, Lembo et al. (2006) reported that storage in glycerol did not seem to influence the DFA, and they and Prabhu et al. (2018) demonstrated full corroboration in detection of virus from field samples between DFA and dRIT. Advantages of DFA over dRIT are the following: less chemicals are used, which is particularly important in countries where waste disposal is not well regulated; several commercialised rabies conjugated antibodies are marketed; and the test protocol is much simpler with fewer steps. The third OIE-recommended assay is the RT-PCR approach, which is the only recommended technique to detect rabies in decomposed samples (Markotter et al., 2015; McElhinney et al., 2014; Prabhu et al., 2018). Molecular detection by RT-PCR is the only technique available in some veterinary laboratories in Africa, particularly those recently equipped for rapid diagnosis of avian influenza and other transboundary diseases. Nevertheless, implementing a molecular based technique to detect RABV requires great care to prevent sample cross-contamination, so a validated disinfection protocol and good laboratory practice is fundamental (Aiello et al., 2016). Ideally, reliable efficient rabies diagnosis would be through the availability of an antibody based protocol, either DFA or dRIT, and a molecular protocol for diagnostic confirmation. But proper application of the recommended tests in developing countries often remains limited, due to poorly equipped laboratories, challenges maintaining reagent cold chains, appropriate sample transportation, and lack of quality control systems. Existing surveillance data often reflects only the rabies situation of the urban areas near CVLs. In this context, recently developed rapid immunochromatographic diagnostic tests (RIDTs) based on the lateral flow principle, which do not rely on a functional laboratory or adequate cold chain, offer new opportunities for decentralised rabies diagnosis in remote areas where the majority of animal bites cases are reported to occur. Although the sensitivity of RIDTs has been under debate, it has been demonstrated that applying a modified protocol of the Bionote kit results in an increased sensitivity and specificity, ranging from 93% to 98% and from 95% to 99% when compared to DFA, respectively (Léchenne et al., 2016; Mauti et al., 2020; Yale et al., 2019). To reach a higher detection performance, it is necessary to omit the 1:10 dilution of the original sample in phosphate buffered saline (PBS), although the dilution is still recommended by the manufacturer. Nevertheless, RIDTs can now be considered as a practical field tool for initial surveillance purposes. However, confirmation of rabies cases can only be achived by means of one of the gold standard techniques (Duong et al. 2016; Eggerbauer et al., 2016; Léchenne et al., 2016; OIE, 2018; WHO, 2018b).

Interrupting virus transmission requires at least 70% vaccination coverage of the affected dog population (Coleman and Dye, 1996; WHO, 2018a). Several studies demonstrate that mass dog vaccination is the only cost-effective and sustainable control measure (Hampson et al., 2015; Mindekem et al., 2017; Zinsstag et al., 2009). But it is crucial to know more about the target dog population and existing human-dog relationship before planning and implementing dog rabies vaccination programmes (Mauti et al., 2017; Mindekem et al., 2005; WHO, 2018a). In N'Djamena, the capital city of Chad in Central Africa, canine rabies transmission was interrupted after two consecutive vaccination campaigns with sufficient vaccination coverages. However, rabies reappeared earlier than predicted. Based on phylogenetic and phylodynamic analysis, Zinsstag et al. (2017) hypothesised that reintroduction may have been due to influx of infected dogs from neighbouring areas, underlining the importance of including neighbouring settings for rabies control. Domestic dogs are tied to humans, so the role of humans and the precise mechanisms governing rabies diffusion should be further investigated. In some areas, long-distance transport of infected dogs is a known risk for rabies introduction or reintroduction. However, additional analysis of rabies genetics in combination with landscape features from new areas will further clarify disease spread (Bourhy et al., 2016; Brunker et al., 2012; Cori et al., 2018; Dellicour et al., 2017).

In Liberia, dog rabies is endemic and surveillance systems and disease control activities are still in the early phase. However, rabies vaccination in humans has been documented since 1949 (Poindexter, 1953), but following civil war from 1989-2003 and the devastating Ebola outbreak in 2014-2015, health care services and infrastructure were substantially weakened (National Transitional Government of Liberia, 2004; The Lancet, 2014). Large areas of the country still do not have electricity. A few studies have described rabies prevalence, the molecular characterisation of circulating rabies virus isolates and estimated post-exposure prophylaxis (PEP) demand based on dog bites (Jomah et al., 2013; Monson, 1985; Olarinmoye et al., 2019). During 2008-2012, 488 dog bite cases were registered at several county hospitals, with children under 10 years of age the most affected group (Jomah et al., 2013). In the 2018 annual report, the National Public Health Institute (NPHIL) registered 1,645 bite cases and 10 related deaths (Unpublished report, NPHIL, 2018). However, data on the biting animals is poorly captured on the veterinary side. Olarinmoye et al. (2017) applied a decision tree model to human bite data for Monrovia, the capital city of Liberia, estimating 155 human rabies deaths annually and high demand for PEP. However, the actual burden of rabies in Liberia remains unknown. PEP in Liberia is based on wound washing and post-exposure vaccination of exposed persons, since rabies immunoglobulin (RIG) is not available. Rabies vaccine is limited to major cities, with remote and marginalised communities having no access to life-saving treatment. Usually, health facilities in these areas lack continuous power supply to store rabies vaccines, thus limiting possibilities for the adequate supply of vaccine to these remote areas. Collaboration between the public health and veterinary service is minimal, and functional rabies surveillance remains a substantial challenge. However, a One Health Coordination Platform was created in 2017 to coordinate zoonotic disease activities between sectors. The first rabies case was diagnosed by DFA at the CVL in Liberia. Rabies was subsequently declared a priority disease and is currently the focus of a working group which promotes joint disease surveillance systems between the veterinary and human sectors. Whereas dog owners normally have to pay for dog vaccination, free small scale dog vaccination campaigns were conducted between 2012 and 2018. About 1500 dogs, mostly from Monrovia, were vaccinated against rabies during the World Rabies Day (WRD) activities (personal communication). Within the Global Health Security Agenda (GHSA) programme, FAO is committed to improve Liberian national animal health services to assist country compliance with International Health Regulations (IHR, 2005). The technical reorientation of the USAID-funded FAO Emerging Pandemic Threats (EPT-2) led FAO Emergency Centre for Transboundary Animal Diseases (ECTAD) teams to develop work plans supporting implementation of the GHSA against four Action Packages, including Zoonotic Diseases (ZD), Biosafety and Biosecurity (BB), Laboratory Systems (LS) and Workforce Development (WD). Under the ZD Action Package, GHSA countries are expected to conduct a national zoonotic disease prioritisation process using the CDC One Health Zoonotic Disease Prioritisation Tool (OHZDPT). Rabies was deemed a top five priority zoonotic disease in all FAO GHSA countries, including Liberia. Lastly, Liberia was part of a larger study, led by the Swiss Tropical and Public Health Institute (Swiss TPH), to estimate the burden of rabies in Ivory Coast, Mali, Chad and Liberia. The aims for Liberia were to establish diagnostic capacity for animal rabies and collect laboratory data on rabies cases. The research aim coincided with FAO and GARC plans and to avoid overlap of activities close collaboration was sought.

The aim of the present work was to establish animal rabies diagnostics at the CVL, to foster collaboration between all stakeholders involved in rabies control in Liberia *inter alia* through a comprehensive in-country rabies stakeholder workshop in Margibi County and to develop a short-term action plan for rabies control and elimination in Liberia.

2. Material and methods

2.1. Study area

Liberia is located in West Africa and has never been colonised. It is bordered by Guinea to the north, Côte d'Ivoire to the east, the Atlantic Ocean to the south and Sierra Leone to the west. The country is divided into 15 counties, covering 111,369 km^2. The estimated population of Liberia was approximately 4.9 million inhabitants in 2018. The capital city Monrovia forms one district, which is a subunit of Montserrado County. Phylogenetic analyses (see point 2.4.) were performed on rabies strains originating from three counties, urban Monsterrado and Margibi and rural Lofa. Montserrado County is in the northwest of Liberia, with a population of around 1.1 million people. Margibi County borders Montserrado to the west and has around 199,689 inhabitants. Lofa is in the north, with 276,863 inhabitants (Central Intelligence Agency, USA. 2018) (Figure 1).

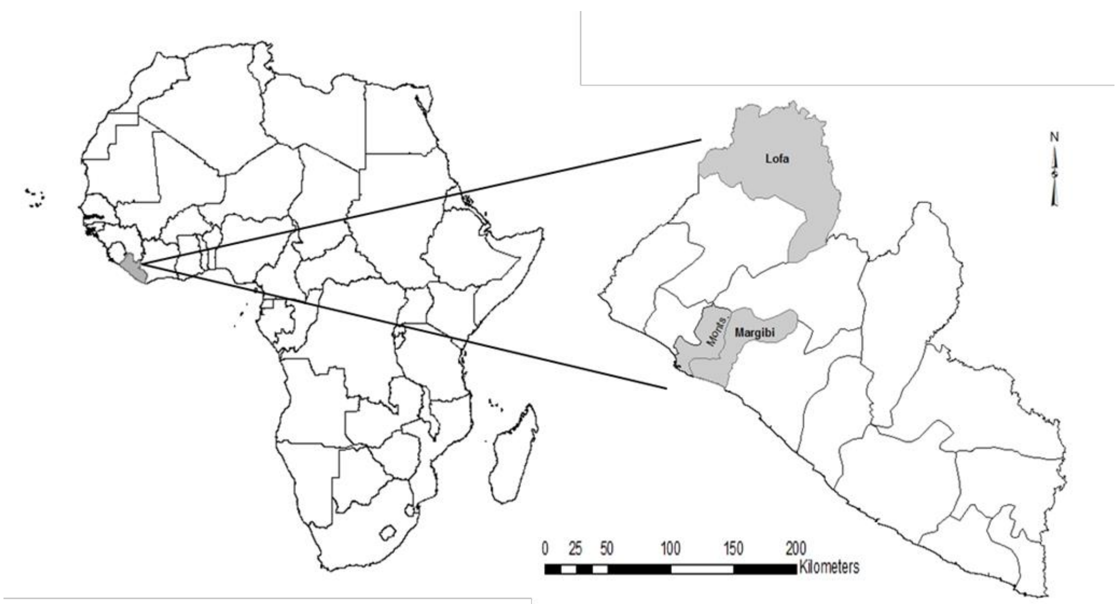

Figure 1: County map of Liberia (study areas in grey)

2.2. Implementation of rabies diagnostics at the Central Veterinary Laboratory

Implementation of rabies diagnostic tests was a joint effort by Swiss TPH, FAO, Istituto Zooprofilattico Sperimentale delle Venezie (IZSVe – FAO Reference Center for rabies) and GARC. The FAO organised assessment missions for quality assurance (October 2016) and diagnostic techniques (January 2017). Subsequently, in 2017, the FAO renovated the Leon Quedlum Central Veterinary Diagnostic Laboratory (CVL) in Monrovia, supported by the GHSA programme. To design a functional and modern diagnostic laboratory according to biosafety/biosecurity (B/B) and quality assurance (QA) standards (ISO 17025), the initial renovation over several months included full infrastructure restoration, including roof repair, city power grid connection and restructuring of the water supply system. A molecular unit was configured, including an RNA extraction room, a PCR mix room and a “gel” room, in addition to reception and necropsy rooms. Key equipment and required reagents were provided mainly by FAO, with support from Swiss TPH. Between July 2017 and February 2018, the three OIE-recommended rabies tests were implemented: the DFA test (by FAO and the FAO Reference Center (RC), the IZSVe, and Swiss TPH and their Malian study partner, the CVL Bamako), the dRIT (by Swiss TPH and GARC) and the molecular conventional RT-PCR protocol (by FAO and the IZSVe) (De Benedictis et al., 2011). Additionally, the RIDT (Anigen/Bionote Inc.) was introduced by Swiss TPH and the CVL Bamako. Staff were trained on standard protocols in sessions organised by FAO, IZSVe and Swiss TPH. Laboratory staff were instructed on B/B (May 2017), QA, Good Laboratory Practices (GLPs), and the most commonly used molecular methods for animal pathogen diagnosis (reverse transcription (RT), end-point and real time polymerase chain reaction (PCR)) (December 2017) by FAO. The FAO RC invited the CVL to carry out the rabies diagnosis proficiency testing (PT) in November 2018, which provided time to the laboratory staff to practice the implemented techniques. This was an effort to support the government in improving the sector through capacity building.

A PT panel of 10 blind samples including two controls for the exercise were provided. The PT samples consisted of lyophilized material prepared from healthy mammals’ brain homogenates, including 5 samples which were mixed with mice brain experimentally infected with RABV or rabies-related lyssaviruses. The

PT panels were prepared according to the ISO 17043 and were shipped, using a dedicated courier, as dangerous goods. In order to be cost effective, a unique parcel containing the PT panel and the 2 controls (1 positive and 1 negative) along with extra control vials used for the training purposes were shipped on dry ice prior to the training course organized by FAO and IZSVe (on DFA and RT-PCR). The results of this PT programme which included 14 laboratories from Sub-Saharan African countries are presented in the work of Gourlaouen et al. (2019). A high concordance rate was achieved amongst the participants with 87.7% and 98.2% for the DFA and the RT-PCR, respectively (Gourlaouen et al., 2019).

2.3. Sample collection and rabies diagnostics

Sample collection was event driven. After the implementation of rabies diagnostics at CVL, fifteen County Livestock Officers, Health Surveillance Officers and members of the OH platform were asked to contact staff of CVL via mobile phone following a suspected dog bite or identification of suspected animals. CVL staff, trained on proper animal handling, travelled to field sites and transported the animal or carcass by car to the CVL. If a field visit was not possible, the animal head was transported in an icebox to CVL using a local transport company. Sample collection was performed at the CVL and brain samples were tested with the DFA test and RIDT tests. A questionnaire was completed with information on the biting animal, date of examination and origin of the sample. However, the renovation work of the CVL in 2017 interrupted the sample collection process and analysis of suspected rabies samples as there was no electricity and laboratory space to store and analyse suspected samples.

2.4. Confirmatory testing and phylogenetic analysis

Following an agreement with Liberian veterinary services, aliquots of all rabies suspected samples (n=8) were shipped (some in parallel) to IZSVE (n=6) and Institut Pasteur Paris (n=7, RNA samples) between May 2017 and August 2018 for confirmatory testing and molecular characterisation. DFA test, cell culture test and/or molecular techniques (conventional and real-time RT-PCR) were used to re-test the samples in the international reference laboratories as described previously (Dacheux et al., 2016, 2008; De Benedictis et al., 2011; OIE, 2018). Sequencing of the complete N and G gene sequences was performed after amplification as previously described (Bourhy et al., 2008; Fusaro et al., 2013), with specific primers available upon request, or by next-generation sequencing (WHO, 2018c). Using jModelTest2 (Darriba et al., 2012), the best-fit model of nucleotide substitution according to the Bayesian Information Criterion was the general time reversible model plus gamma-distributed rate heterogeneity (GTR+G), which was further confirmed using Smart Model Selection in PhyML (Lefort et al., 2017). A maximum-likelihood phylogenetic tree was constructed using subtree-pruning-regrafting branch-swapping and PhyML version 3.0 (Guindon and Gascuel, 2003). The robustness of individual nodes on the phylogeny was estimated using 1000 bootstrap replicates with aBayes branch supports. In addition to the Liberian sequences, sequences from West and Central African countries were included in the analysis.

2.5. Development of a short-term action plan for rabies control and elimination

Following on from establishment of rabies surveillance in Liberia, and to advance rabies control and elimination efforts in general, representatives from all governmental stakeholders and line ministries involved in rabies control participated in a comprehensive in-country One Health rabies stakeholder meeting organized by FAO and GARC. The workshop took place in Liberia from May 28 to June 1, 2018. Three work-streams were completed: undertaking a SARE assessment, developing a practical workplan using the SARE tool’s Practical Workplan component, and estimating costs of mass dog vaccination with the GDREP tool. The cost estimates generated were based on a cost of USD 2.60 per dog vaccinated, which is representative of published values for the region (Kayali et al., 2006).

2.6. Ethical considerations

Research approval was granted by national authorities in Liberia and the Ethics Committee of Northwest and Central Switzerland (EKNZ Basec Req-2017-00495) in July 2017. The research project fulfilled all ethical and scientific standards and posed no health hazards. All involved personnel were vaccinated against rabies following the instructions of the vaccine producer. All data were handled confidentially.

3. Results

3.1. Phylogenetic analysis of the first laboratory-confirmed animal rabies positive cases

Between February 2017 and April 2018, eight suspected animals were submitted to CVL. Seven samples tested by RIDT and DFA were confirmed positive for rabies virus. Details on positive animals are shown in Table 1.

Table 1: Information on positive tested animals

Nr.	Species	Known owners	Sex	Age	Symptoms	Vaccination status	Date of sample collection	Date of examination	Orgin of the sample	Genbank accession numbers
17013LIB_Liberia_2017	dog	yes	male	adult	change in behavior, no food intake	unvaccinated	27.02.2017	25.07.2017	Margibi County	MN049979
18005LIB_Liberia_2017	cat	yes, animal neighbor	male	subadult	change in behavior, no food intake	unknown	05.12.2017	14.02.2018	Montserrado County	MN049983
18007LIB_Liberia_2017	dog	yes, animal of the household	female	puppy	change in behavior, no food intake	unvaccinated	25.09.2017	16.02.2018	Montserrado County	MN049982/MH481712
18008LIB_Liberia_2017	dog	yes, animal of the household	female	adult	change in behavior	unvaccinated	25.03.2018	25.04.2018	Montserrado County	MN049981/MH481711
18009LIB_Liberia_2018	dog	yes	na	na	na	na	na	na	Lofa County	MN049980
18018LIB_Liberia_2017	dog	na	na	na	na	na	na	na	na	MN049984
IZSVe_18RD/666_4_Liberia_2017	na	na	na	na	na	na	na	na	na	MH481713

Full sequences of the genes encoding for viral glycoprotein and nucleoprotein from isolates 17013LIB_Liberia_2017, 18005LIB_Liberia_2017, 18007LIB_Liberia_2017, 18008LIB_Liberia_2017, 18009LIB_Liberia_2018, 18018LIB_Liberia_2017, IZSVe_18RD/666_4_Liberia_2017 were obtained and subsequently published in GenBank (accession numbers MN049979 – MN049984; MH481708 - MH481713). The phylogenetic analyses of the N genes revealed that the RABV detected in Liberia belonged to the Africa 2 lineage subgroup H, which circulates in central and western African canine populations. The Liberian viruses from this study clustered together with viruses circulating in neighbouring countries (Côte d'Ivoire, Mali, Mauritania and Burkina Faso). Isolate 18018LIB_Liberia_2017 had high similarity to isolate 01007CI_Cote_Ivoire_2001 from Côte d'Ivoire (Figure 2).

Figure 2: Maximum-likelihood phylogenetic tree based on 1350-nt nucleoprotein genes of seven rabies virus sequences from Liberia, 2017-2018 and representative sequences from Mali, Côte d'Ivoire, Mauritania, Burkina Faso, Senegal, Nigeria, Chad, Cameroon, Central African Republic, Niger, Benin, Guinea, Sierra Leone, Gambia, Guinea Bissau, Namibia and Madagascar. Subgroups A-H within the Africa-2 lineage are indicated, with Liberian sequences obtained during this study marked by black dots. Bootstrap values (1000 replicates) > 70% are shown next to nodes. Scale bar indicates nucleotide substitutions per site.

3.2. Results from the Stepwise Approach toward Rabies Elimination (SARE) tool – SARE assessment and Practical Workplan component.

Based on the SARE assessment undertaken during the in-country workshop, Liberia achieved a nationally-endorsed SARE score of 1.5/5, indicating it is in the process of scaling up intervention campaigns based on existing data. To help Liberia progress up the SARE ladder to freedom from dog-mediated human rabies, national stakeholders developed a practical workplan utilising the SARE tool. Based on consensual agreement amongst participants, only remaining content from workplan Stage 0 and Stage 1 activities (all relating to core, fundamental programmatic activities like small-scale vaccination campaigns and local-level dog population estimates) were finalised to ensure a solid foundation before scaling-up to nationwide control efforts. The workplan, focussing primarily on fundamental activities at the local level, was used to populate a short-term rabies action plan to be actioned by government personnel for the next three years (2019 – 2021). The short-term rabies action plan can be used to ensure programmatic implementation at the local-level and advocate for additional funding necessary for disease intervention initiatives to continue and expand in waves.

3.3. Results from the Global Dog Rabies Elimination Pathway (GDREP)

Based on the information provided for Liberia and information gathered prior to and during the workshop, the GDREP tool estimated that dog-mediated human rabies deaths could be eliminated by 2025 and dog rabies could be completely eliminated by 2028, followed by self-declaration of freedom from dog rabies by 2030. These estimates are based on a three-phase approach where total cost of the proposed elimination programme (through mass dog vaccination) will scale up over the three phases. During phase I (years 1-3), an additional 75,000 USD per year is required in addition to the estimated 1,000 USD now spent annually on in-country rabies control efforts. For phase 1, a total of 228,000 USD is needed over the initial three years to strengthen capacity for surveillance and vaccination and to implement demonstration projects (e.g. small-scale mass dog vaccination events at pre-selected local areas). These activities will generate data to support scale-up of activities and raise disease awareness. In phase II (years 4-6), additional funds needed increase from an estimated 75,000 USD per year to 662,000 USD per year. This three-year phase focusses on increasing the national dog vaccination coverage from <18% to the required 70% coverage. Phase III (years 7-13) is considered the maintenance phase and is the most critical phase with regards to mobilisation of funds and sustainable governmental commitment. Phase III focusses on maintenance of adequate vaccination coverage to ensure dog rabies elimination. To accomplish this, Liberia requires an estimated additional 746,000 USD per year to eliminate dog rabies and undertake the self-declaration process for freedom from dog-mediated rabies. In total, it is predicted that Liberia requires an investment of 5.3 – 8 million USD over the next 13 years to successfully implement and maintain dog vaccination coverage to end disease transmission and eliminate canine rabies in the country.

4. Discussion

Controlling and eliminating dog-mediated rabies in Liberia is a complex undertaking. However, a diverse set of stakeholders recently joined together to achieve this goal. A major initial hurdle was overcome through implementation of effective rabies diagnosis in the country, resulting in the first laboratory-confirmed animal rabies cases being diagnosed and reported. Documentation of the disease within the country enabled government authorities to begin planning for control and elimination of canine rabies in Liberia. A practical workplan and short-term action plan were developed using the SARE tool and an accurately costed mass dog vaccination strategy produced using the GDREP tool at a 2018 rabies stakeholder meeting. Liberia is currently at stage 1.5 of the SARE tool, signifying the country is preparing for local-level intervention dog vaccination campaigns, and needs investment of 5.3 – 8 million USD over the next 13 years for successful elimination of rabies by 2030.

There are still no accurate estimates of the 'true' national rabies burden in Liberia, so future research activities should focus on developing a well-functioning 'One Health' rabies surveillance system. This can be achieved through timely confirmation of suspect rabies samples at the Monrovia CVL using the recently established DFA test, and through decentralisation of rabies diagnosis using dRIT or RIDT. The latter test is especially useful in areas lacking electricity, as it does not require a microscope and can be stored at room temperature (Léchenne et al., 2016). Some challenges were experienced during implementation of the dRIT test. A break in cold chain seemingly influenced the viability of the diagnostic reagents, and it was difficult to locally source some required test reagents. However, these challenges should not influence implementation of the test in Liberia or other resource-limited countries, because the test has many advantages. Regarding molecular detection of rabies, further commitment is needed to ensure successful accurate diagnosis. In addition to laboratory confirmation of rabies cases, improvement of rabies awareness for the community and health care personnel is also crucial for effective disease surveillance. Exposed people need to have timely access to PEP, which consists of effective wound washing, rabies vaccination and, under certain circumstances, administration of RIG, to reach the goal of zero human deaths by 2025 as projected by the GDREP. Approval from the responsible authorities to use RIG thoughout the country should be prioritised to ensure feasibility to reach the goal.

Molecular characterisation of the RABV-positive samples improved the resolution of the surveillance network and revealed that the seven laboratory-diagnosed and sequenced samples all belong to subgroup H of the lineage Africa-2. This result is not surprising, as the Africa 2 lineage is widely distributed in central and western Africa with subgroup H being prevalent in Côte d'Ivoire, Mauritania, Mali and Burkina Faso (Talbi et al., 2009). This demonstrates the transboundary nature of rabies (Coetzer et al., 2017; Hayman et al., 2011) and has implications for its control in Liberia. One Liberian isolate was similar to an isolate from Côte d'Ivoire and suggests a wide distribution of this subgroup over a large area including at least Liberia and Côte d'Ivoire. The recently published study of Olarinmoye et al. (2019) detected the Africa-2 lineage as well as the China lineage 2 and Africa lineage 3 in Liberia, but these results are still being debated by the wider scientific community. Based on this discrepancy among studies, more information is required to better understand the current rabies situation in Liberia through improved molecular epidemiological studies – possible through well established collaborations fostered during this study and through regional rabies networks such as PARACON. With such studies, it would be possible to identify rabies hotspots and areas of concern for rabies transmission, enabling more strategic targeted mass dog vaccinations with a more cost-effective approach. Dogs are inevitably linked to humans and thus to human-mediated transportation within the region, and future rabies control efforts must take this into account (Bourhy et al., 2016; Brunker et al., 2012; Dellicour et al., 2017; Talbi et al., 2010). For better resolution of virus circulation patterns in Liberia and the neighbouring countries, a broader range of samples orginating from neighbouring areas should be included in future analyses.

While improved burden estimates are important for disease prioritisation and elimation, improving active and passive surveillance programmes are long-term activities that require considerable resources and time. In an effort to ensure short-term progress and maintain governmental support, the SARE tool was used to identify additional activities that need to be accomplished to contribute to rabies elimination. By accomplishing the activities, Liberia can advocate for further operational and financial support from both domestic and international donors and stakeholders to ensure that the national strategy for rabies elimination remains adequately resourced throughout the 13 year time period. As evidenced by the GDREP tool, an estimated total cost of 7,436,000 USD is required over 13 years to achieve elimination through mass dog vaccination, re-emphasising the need for continued, long-term and stable investment. The estimates generated by the GDREP tool were based on a cost of USD 2.60 per dog vaccinated, which is representative of published values in the region (Kayali et al., 2006). However, as there is limited data available for Liberia due to the limited number of vaccination campaigns undertaken in the country, these estimates should be refined further with efforts made to reduce these costs. Additionally, detailed information on the size and structure of the dog population should be studied in future research projects. By obtaining a more accurate cost per dog vaccinated and reducing costs where feasible, the costs towards dog-rabies elimination by mass dog vaccination can be dramatically reduced. The full benefit of the GDREP tool not only accurately estimates costs of dog vaccination campaigns, but also generates realistic, evidence-based figures for stakeholders to create long-term resource mobilisation plans and implement effective strategies for timely resource mobilisation.

Important questions remain on who pays for rabies control and how necessary funds may be secured up front. One interesting possibility is development impact bonds (DIB) (Anyiam et al. 2017), a performance-based investment instrument, where costs of rabies control efforts are shared between the government, private investors and outcome funders. With such an approach, the investment risk is shared, securing resources over a longer-term and mobilising current resources to drive intervention campaigns. With clear objectives, deliverables and timelines and the short-term action plan for Liberia developed using the SARE tool's Practical Workplan component, the investment impact and outcomes are more easily measured and quantified. Other non-financial resources are also available to facilitate country efforts towards achieving elimination. Mass dog vaccination is key to achieving rabies elimination, so procurement and delivery of dog vaccine remains vital. Through utilisation of resources such as the OIE rabies vaccine bank, which provides high-quality vaccine at an affordable price in a timely manner, Liberia can reduce associated costs and immediately initiate planned local-level intervention strategies, as detailed in the short-term action plan. This, and the many other available resources, can help Liberia scale up efforts towards nationwide intervention programmes.

5. Conclusion

This study in Liberia illustrates the difficulties of rabies control and elimination in LMICs in Africa. Liberia still has a long road to become free of dog-rabies. However, the dialogue between all relevant stakeholders occurred and preparations for small-scale intervention campaigns began. Following implementation of rabies diagnosis at the CVL, which improved disease surveillance, improved communication between the animal and human health sector remains of utmost importance. RIG, which is not currently available in the country, should be made immediately available so adequate treatment of category III exposed individuals and category II immune-compromised persons is possible. Through implementation of accurate laboratory diagnosis, initiation of molecular epidemiological analyses, improved rabies surveillance, formation of a One Health taskforce and development and implementation of a detailed, accurate workplan and short-term action strategy, Liberia and its partners laid the foundation towards achieving the goal of zero dog-mediated human rabies deaths by 2030. The results obtained from the above described project activities in Liberia pave the way to developing rabies control strategies in other African countries and beyond.

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Disclaimer

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