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Rabies mortality and morbidity associated with animal bites in Africa: A case for Integrated Rabies Diseases Surveillance, Prevention and Control - A Scoping review

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Abstract

Objective

The objective of this scoping review was to map the current situation and available evidence and gaps on rabies morbidity, mortality, integrated rabies surveillance programs, and existing prevention and control strategies in Africa.

Methods

We conducted a systematic scoping review following the Joanna Briggs methodology and PRISMA-ScR checklist. Medline, EMBASE, Cinahl (EBSCOHost), Scopus, Web of Science and rabies web conferences were used to search for pee-reviewed publications between January 1946-May 2020. Two researchers reviewed the studies and extracted data based on author (year) and region, study design and data collection duration, Participants / Comparators, Interventions and Control Conditions / Exposures, outcomes (rabies mortality and morbidity) and Key Findings / Gaps / Challenges. The results were reported narratively using Arksey methodological framework.

Results

Electronic search yielded 2775 records, of which 43 studies were included. A total of 543,714 bite victims were censored through the included studies. Most of the victims were less than 15 years of age. The studies included, rabies morbidity (21) and mortality (15) fluctuating in space and time across Africa depending on countries rabies prevention and control practices (16). Others were surveillance (nine studies), surveillance and prevention (five studies), management and control (seven studies) and surveillance, prevention and control (six studies). We found challenges in

rabies reporting, existing dog vaccination programs and post-exposure prophylaxis availability or compliance.

Conclusion

This study found challenges for dog rabies control and elimination in Africa and the need for a policy to drive the goal of zero dog-transmitted human rabies by 2030.

Key words: One-Health; rabies; mortality; morbidity; surveillance; zoonosis; neglected tropical disease; Africa

Strengths and limitations of this study

- We conducted an extensive search of published and grey literature to identify studies to include in the scoping review
- Pulling together data from both published and grey literature gave us an opportunity to understand the breadth of rabies epidemiology and how surveillance would be a critical tool in implementing effective control of rabies across Africa
- We conducted screening of identified articles and extraction of data in duplicate
- We reported the results narratively as it was not possible to combine data from different studies conducted using different study designs, and different population groups.

1. Background

The natural history of rabies disease in Africa is not well known, but it is well accepted that the disease must have been present in northern Africa for hundreds of years, particularly as an urban dog disease and also associated with cycles in the Middle East [1]. European colonization influenced the spread of dog rabies in Western and Central Africa [2]. In many sub-Saharan African countries, rabies has become epizootic only in the nineteenth and twentieth centuries involved domestic dogs and free-ranging wildlife species [1-3]. Historically, isolation and epidemiological analysis of these viruses has primarily been associated with research studies and was strongly dependent on available laboratory diagnostic capacity and research group interest [3-4]. A thorough study of the phylogeographic structure of the African lineage-2 revealed strong population subdivisions at country level, with minimal transmission of virus between localities [5]. The molecular epidemiology of rabies virus (RABV) in Africa identified three phylogenetic RABV lines: Africa 1, 2 and 3 [6]. RABV strains from Central and North Africa clustered into Africa 1a and 4 lineages, while those from Southern African countries clustered in Africa 1b and 3 clades [5]. However, all RABV variants were homogeneous and closely related (99 per cent sequence homology), indicating a shared common origin distinct from the out-of-group group [5-7]. The divergence was assumed to represent different progenitor viruses. Africa 1 and 2 lineages were isolated from dogs or humans bitten by feral dogs, while Africa 3 lineages were found to be associated with mongoose species, primarily yellow mongoose (*Cynictis penicillata*) from the Republic of South Africa [6]. The Africa 1 lineage was subdivided into two subgroups: 1a, limited to North and West Africa; and 1b, limited to South East Africa. In general, the Africa 1 lineage was the most similar to the current Eurasian RABV lineage, indicating its recent introduction to Africa [6-8]. The Africa 2 lineage contains wild-type strains originating from many Central and

Eastern African countries and is phylogenetically ancestral to the Eurasian and African 1 RABV clusters [6]. The ancestry of Africa 3, of mongoose origin, is distant from all variants of the dog RABV [6].

Dog rabies predominates throughout most of Africa; the domestic dog is the principal reservoir host as well as the most important source of infection for people [9]. In addition, there are many other lyssaviruses (also referred to as rabies-related viruses) reported from African countries. Most of these rabies-related viruses have been associated with obscure hosts including specific bat species and shrews, partly attribute to the difficulty in bio-surveillance of these viruses. RABV however, spreads in terrestrial mammalian hosts in Africa and has not been associated with bat infections as it is the case in the Americas. While all mammals (domestic and wild) are susceptible to RABV infection, some are able to retain those virus variants adapted to their species whilst others are only reported as dead-end hosts [10]. Rabies has been reported in both domesticated species and wildlife. These are sometimes diagnosed with rabies virus infection in Zambia, South Africa, Ethiopia, Kenya, Tanzania, Zimbabwe and Egypt [10-16].

Most reported cases of rabies in wild carnivorous species included yellow mongoose (*Cynictis penicillata*) and bat-eared fox (*Otocyon megalotis*) [17] as well as critically endangered wild dogs (*Lycaon pictus*) [18-21]. In Ethiopia, rabies outbreaks were described in the endangered Ethiopian wolf (*Canis Simensis*) population [22-23]. In 2014 and 2015, RABV infection was also observed in two wild dogs and a spotted hyaena (*Crocuta crocuta*) in the Madikwe Game Reserve, North West Province of South Africa, in Ethiopia and in Nigeria [16,21,24], monkeys and jackals (*Canis adustus* and *Canis mesomelas*) [11,12, 15-16]. The review of twenty studies across Africa has revealed that bite victims account for 91.9% (48092 dog bites), cat bite for 2.9%, jackal bite for

0.8% and 4.41% others (monkey, donkey, horse, rat, pig, rabbit, Honey badger, kudu, goat, cattle, eland and hyena) [25-44].

More than 59 000 people die of rabies worldwide every year [45-46], 99% of them in African and Asian countries where dog rabies is endemic [45, 47-51]. Due to the lack of laboratory confirmation, sporadic epidemiologic surveillance, and unreported clinical cases in developing countries, current mortality estimates almost certainly under-represent the true incidence of human rabies deaths [45, 49-51]. Rabies is responsible for an estimated 21,000-25,000 death annually in Africa [45, 52-53]. Figure 1 shows a map illustrating rabies distribution in thirty-two African countries considering rabies outbreaks in animals, cases and deaths in humans [54]. In 2011, a total of 33 African countries reported 1,607 outbreaks of rabies, 2,779 cases and 1,524 deaths [54]. Data shows that rabies accounts for 7.2% of all animal disease outbreaks reported making it the disease with the highest number of outbreak reports in Africa in 2011 [54]. Algeria, Namibia, Eswatini (former Swaziland), Tunisia, Uganda, Zambia and Zimbabwe reported high morbidity and mortality with 563 cases (33.9% deaths), 269 (94% deaths), 62 cases (88.7% deaths), 91 cases (90% deaths), 466 cases (40.9%), 207 cases (32.8% deaths) and 114 cases (80.7% deaths) respectively [54].

Mass vaccination of dogs as a key component of national rabies elimination programs has been successful in eliminating dog-transmitted rabies in Europe, North and Latin America, and Japan [55-57]. By far, the most significant public health threat comes from RABV, and over 99% of all globally reported human cases are caused by exposure to unvaccinated dogs infected with canine RABV variant, mostly in Asia and Africa [58].

In most of Africa, and specifically western and central African countries, notification of rabies disease is not mandatory, so epidemiological data are scarce [60]. Human rabies could be prevented by the immediate administration of post-exposure prophylaxis (PEP) following exposure to rabid animals [46, 60]. However, people in low-income countries often do not receive these life-saving treatments because either PEP treatment is costly and not readily available, or because of lack of rabies awareness, people might not go to hospital for treatment [46, 50, 61]. The lack of effective educational outreach at community level had led to gaps in knowledge as to the best way to avoid animal bites and administer first aid following bites or other potential rabies exposures [62]. A recent study has shown considerable in-country variability in the availability of rabies vaccines and immunoglobulins vaccine supply system, administration route (IM versus SC), cost of vaccine and rabies immunoglobulin (RIG). In a global survey conducted in rabies endemic countries, 49 of the 54 African countries were rated as moderate to high risk for human rabies, whilst 16 of the 23 countries that responded to the survey had inadequate surveillance systems [53, 63].

One major barrier is the difficulty of consistently achieving the required coverage of 70% of the dog population across the hard-to-reach landscapes that characterize much of sub-Saharan Africa [64-66]. Reviewing dog vaccination coverage in African countries, only South Africa, Tanzania, Algeria, Morocco and Egypt had the dog vaccination coverage of 63%, 37.24%, 23.7%, 25% and 23.7% respectively [67,68]. In all other African countries dog vaccination coverage was below 18% with further below 5% in some cases [67]. The analysis of the above data and the consideration of the framework for the elimination of dog rabies suggested by Wallace 2017 and others stipulated the existing coverage of dog rabies vaccination, was directly associated with the number of years it would take to achieve rabies elimination [69]. Theoretically, Global Dog Rabies

Elimination Route (GDREP) consisting of a 13-year timeframe would be ample time for even the least developed rabies prevention systems to achieve elimination by 2030 if completely committed to this achievement [69]. This system divided countries into three categories: (1) Phase I: preparation (dog vaccination > 18%), (2) Phase II: vaccination of dogs (dog vaccination: < 18% and > 70%) and (3) Phase III: 70% continued vaccination of dogs. African countries have been categorized into phase I, II, III but with no data on dog vaccination [70]. The available data indicate that most African countries were still at the preparation phase since "zero rabies by 2020" was initiated five years ago. Although the feasibility of reaching 70% dog vaccination coverage has been shown through pilot projects in a wide range of settings. African countries still struggle to achieve a 70% yearly dog vaccination rate [9, 51]. In Africa, dog mass vaccination systems have demonstrated some effectiveness as proof of principle, as in KwaZulu-Natal, South Africa [55-71], Serengeti, Tanzania [55,72-73], Malawi [55,75] and Chad [61, 76-78].

Inadequate education for veterinarians and physicians, insufficient resources for proper confirmatory diagnosis and risk assessment, and the lack of effective communication channels between ministries of health and agriculture frequently have led to failures of prophylactic intervention, even in regions where vaccines and immunoglobulins were available [62]. A recent study conducted in Africa and Asia revealed that rabies immunoglobulins were found to be less available than the vaccine, with access restricted in almost two-thirds of the countries surveyed [79]. Eleven (11) African countries had comprehensive access to RIG. Of the seven countries with broad access to vaccines, 6 of them had a national rabies prevention program or policy. Two of the countries had only a monitoring program / strategy in place [79]. This is worrisome as it exposes a huge absence of surveillance and prevention policies in most African countries. The absence of a robust monitoring process is mostly attributed to the lack of rabies in national

communicable disease plans and reporting systems at national level in Africa [80]. Therefore, widespread underreporting is likely to occur in many affected countries due to lack of health information, civil registration and vital statistical systems, and inaccessibility of clinical care and diagnostic confirmation [80] as symptoms of the disease may be non-specific and similar to other encephalitic infections. Even where data exist in Africa, the lack of communication and exchange of data between the animal and human health sectors also hinders the collection, storage and reporting of coherent data to international data bases [80]. The World Health Organization (WHO) meeting in Geneva in 2018 on "Moving Progress towards Rabies Elimination" pointed out that political engagement is a key factor with governments providing leadership role in the coordination of elimination strategies [53]. The global collection of data on deaths from any neglected disease is a huge challenge, and early attempts to collate data for human deaths from canine rabies were no exception [81]. Due to the lack of regular reporting of rabies cases to the WHO from many member states, the RabNet database was closed down in 2011[82]. Therefore, rabies is not reportable in many African countries, which restricts data collection by structured surveillance systems [80]. One Health evolved from the recognition that an interdisciplinary approach is required to understand complex health problems, and that the health of humans and animals is inextricably linked [83]. Rabies requires a comprehensive, strategic, and targeted control and prevention approach with collaboration from human, animal, and environmental health disciplines at local, national, and global levels to achieve more effective control [84]. The review of literature reveals that most of African countries lack a One Health approach to prevent human rabies deaths.

The WHO, the World Organization for Animal Health (OIE), the Food and Agriculture Organization (FAO) and the Global Alliance for Rabies Control (GARC) have developed a strategic global plan to end human canine-mediated rabies by 2030 [48, 53, 85]. This initiative

provides a concerted approach to the prevention of rabies, combined with the strengthening of human and veterinary health systems. These would enable reaching out to the most underserved communities in the world by engaging, encouraging and supporting all countries to lead and improve elimination efforts [80]. This scoping review was therefore designed to map the evidence on rabies morbidity, mortality, integrated rabies surveillance, prevention and control in African countries. Its objectives were: (1) to assess the extent of available research on the morbidity and mortality of rabies due to animal bites conducted in Africa, (2) to identify research gaps in the literature on the impact of rabies in Africa so as to effectively plan public health intervention, (3) to ascertain the current level of rabies disease surveillance, prevention and control that exists in African countries, (4) to assess the published adverse events and complications associated with rabies vaccination in African countries, (5) to assess the different types of vaccines used and the effectiveness of locally produced and imported vaccines in treating rabies in different parts of Africa, (6) to assess rabies morbidity and mortality associated with dog and livestock bites in humans and animals' population.

2. Methodology

2.1. Study design

This paper used the PRISMA-ScR checklist [86] and The Joanna Briggs Institute guidelines [87] as a norm for reporting scoping review. The analysis was conducted in accordance with the structure suggested by [88], further developed by [89].

2.2. Eligibility criteria

The search was conducted from 1 January 1946 until 30 May 2020. A PICO (Population-Interventions-Comparisons-Outcomes) search framework was set, where P (Humans infected with rabies in African countries), I (Integrated rabies disease surveillance, prevention and control), C (little or no integrated rabies disease surveillance, prevention and control) and O (reduced human morbidity and mortality of rabies associated with animal bites) were chosen. The included studies are described in Table 1.

2.3. Electronic search

We conducted a systematic search of the electronic databases Medline (OVID), EMBASE (OVID), Cinahl (EBSCOHost), Scopus (Elsevier), Web of Science and Conference (*rabiesalliance.org, www.who-rabies-bulletin.org and www.oie.org*). The search techniques were limited to English. The main search strategy was listed in supplementary material 1. EndNote X9 reference manager was used to remove duplicates. JLT reviewed all the papers identified by title in order to pick those that were potentially appropriate, with a clear bias towards retention. The abstracts of all the studies chosen on the basis of their titles were independently reviewed by two reviewers (PSN and JTL) and any variations were preserved in the study.

2.4. Data charting process

For all studies selected at the abstract level, data were extracted and plotted in the table, covering author (year) and region, study design and data collection duration, Participants / Comparators, Interventions and Control Conditions / Exposures, outcomes (rabies mortality and morbidity) and Key Findings / Gaps / Challenges. The final decision to include studies was taken on the basis of this data extraction and whether it met the inclusion / exclusion requirements, based on an

independent review by two authors (PSN and JLT) and a discussion of any differences; the third author (RT) was available for consultation if consensus could not be reached. Our inclusion criteria were: rabies occurrence or mortality rates, all ages included, only studies performed in Africa, studies in which at least one intervention included monitoring, prevention and control of rabies, and then only quantitative studies were included in this study.

A data extraction sheet has been developed and used to extract data from included papers. The data collection sheet included: author, region, year, study design, level of evidence, sample size description, interventions or exposures, results and key findings / Gaps / Challenges. Two reviewers (PSN & JLT) worked separately at all levels of the study. The results were then compared and any variations were addressed and resolved by PSN and JLT. The third author (RT), who also summarized the findings, was consulted when a discrepancy could not be resolved. The evaluation of the probability of bias, the methodological standard of the included studies was not assessed due to the scoping review of the study [88].

2.5. Data items

Seven items were listed in the data collection chart table. We included the first author, the year of publication of the study and the country (item 1). Study design and period of data collection (item 2). The sample size, mean or median age and gender (item 3). The intervention and control conditions / exposures included surveillance, prevention and control of rabies and any other form of intervention used in human rabies (item 4). The number or rate of human rabies morbidity included annually or during the study period (item 5). Human rabies mortality recorded the death or mortality rate annually or during the study period (item 6). Main findings / gaps / challenges

included other outcomes such as data gaps found, available research evidence as well as PEP or vaccine adverse events (item 7).

2.6. Critical appraisal of individual sources of evidence

Methodological quality of included studies was not evaluated due to the scoping nature of the review [84].

2.7. Synthesis of results

Studies were summarized based on author (year) and country, study designs, participants and comparator, interventions and control conditions/exposures, key outcomes, gaps, findings and challenges. Interventions were subdivided into rabies prevention, surveillance, control and management. Table, computed morbidity and mortality rates in case there were not clearly provided and then we reported the results narratively, as recommended in scoping review were methodological framework [88].

3. Results

3.1. Study selection

The searches from the five electronic databases hit a total of 2775 records (Medline: 696, Embase: 952, CINAHL: 289, Scopus: 431 and Web of science: 407) that led to a total of 1127 titles and abstracts that were screened after the removal of duplicates. We retained 111 of these based on their title and abstract screening. The full-text screening's stage led to 43 potential articles relevant to our scoping review. The scoping review flow chart was described in Figure 2.

3.2. Study characteristics

The review reported only quantitative studies on rabies surveillance, prevention and control. Thirty-two quantitative studies were retrospective cohort with 8 month to 14 years of study duration [16, 25-27, 29, 30, 32,34-42, 44, 90-104], three studies were mixed designs (retrospective and cross-sectional study) [43,105,106], three prospective cohort studies [28,31, 107], two Cross-sectional studies [108,109], one case control [33], one clinical trial [110] and a randomized control trial [111].

We grouped the included studies into five categories based on rabies interventions, namely 1) prevention and control, 2) surveillance, 3) surveillance and prevention, 4) treatment and control, and 5) surveillance, prevention and control. Figure 3 showed the distribution of studies according to the intervention in nineteen African countries. We also summarized all studies included in the final analyses in Table 1 which included seven parts in line with the specified frameworks for data synthesis: (1) rabies morbidity, (2) rabies mortality, (3) interventions for rabies control, (4) rabies disease surveillance, prevention and control, (5) available research evidence, (6) research gaps identified and (7) adverse events and complications associated with rabies vaccination.

3.3. Patient characteristics

A total of 543,714 bite victims were recorded in included studies. Age and sex-specific distribution revealed that the most fatal cases belonged to age groups 0-14 year [25, 29, 31, 34, 39, 41, 42, 44, 90, 97, 98, 100,102, 106, 108]. Other studies identified rabies victims of 15 and above [26, 34, 35, 38, 42, 90, 101, 102, 106, 109]. The median age was 18 years in most of the studies and ranged

from one to 95 years. Most of the children were males [41, 42, 100, 102]. However, other study has indicated that females have more animal-related bites than males [25]. Young children are at higher risk of contracting rabies in the absence of treatment due to the location of the bites they receive [108]. Based on the extent and depth of injury, 1, 567 victims were recorded. Extent and depth of injury was classified as skin broken (11.1 %), scratch (9.25 %), superficial (loss of epidermis only) (36.38 %), deep (27.31 %) and simple (affect only one tissue) (12.38 %) [25,27,107,109]. Further 10, 006 bites were described in regard of the site of exposure among which the head/neck/face (5.08%), leg/feet (61.06%), arm/hand (23.23 %), buttocks/trunk (10.32 %) or multiple (0.31%) [25-29, 38, 43, 99, 101, 105, 108].

Individuals suspected to have rabies were clinically managed by the chief doctor pediatricians and nurses [28, 32, 33, 36, 90, 100, 105, 109]. The main treatments were wound management, antibiotics, prophylaxis against tetanus and rabies. Reports were collected in hospitals, treatment and health centres, health clinics, pharmacies and veterinary clinics [109].

3.4. Study outcomes

3.4.1. Rabies morbidity

Twenty-one studies reported rabies human morbidity in Africa (Table 2) [26, 30-35, 37, 39, 42, 44, 90, 92, 94-98, 103, 105-107, 109]. Among them, five studies were undertaken in Tanzania, the first study estimated an average annual incidence per 100,000 bites of 37.1, 11.3 and 33.5 in human population district of Ulanga (193280 inhabitants), Kilombero (321611 inhabitants) and Serengeti (176057 inhabitants) respectively [95]. The second study found that the incidence of bite patients seeking PEP declined substantially (>50%) from 2011 to 2015 [96]. The third study

estimated an annual incidence of ~58 cases per 100,000 [37], the fourth study reported a mean incidence of 74 bites considered at risk of rabies transmission per 100,000 persons per year [103] and the last study conducted in Tanzania revealed an average of 75.6 and 19.3 probable rabies exposures per 100,000 persons per year [105]. Three studies conducted in Ghana reported 54 dog-bite victims bitten by rabies-positive dogs within three years [90], 13 cases of human rabies in a 6-year retrospective records review [34] and an annual incidence of rabies cases of 172 per 100,000 population [44]. Four studies reported rabies morbidity in Ethiopia. Yizengaw et al. 2018 reported a high incidence rate of rabies exposure during spring (360, 39%) and summer (244, 26.4%) seasons and a total of 924 human rabies exposure cases received the anti-rabies post-exposure prophylaxis from September 2015 to August 2017 [106]. The incidence of human rabies exposure was reported to be 40 per 100,000 population in Ethiopia [29], annual estimated rabies incidence of 2.33 cases per 100,000 in humans [107] and the incidence of human rabies exposure cases calculated per 100,000 populations was 35.8, 63.0, 89.8 and 73.1 in 2012, 2013, 2014 and 2015, respectively [99]. A study conducted in Zimbabwe found among rabies-suspect, 42 (73.7%) were positive [35]. In Madagascar, nine of the 11 suspected human cases tested from 2005 to 2010 with a laboratory confirmed for rabies [92]. In Uganda, a total of 208,720 patients with animal bite injuries were treated at health facilities across the country [94]. Ivory Coast reported 50 cases of human rabies with annual incidence of 0.06−0.08 per 100,000 [31]. Human animal-bite injuries incidence was 289 per 100,000 persons with the highest incidence reported at 302 per 100,000 and lowest at 121 per 100,000 persons in Kenya [29]. Another undertaken in Malawi reported 14 paediatric rabies cases during the study period [98]. A six-year retrospective study revealed 31 positive cases of human rabies in Madagascar [42]. In Democratic Republic of Congo, a five year retrospective study found 29 positive to rabies in a total of 5,053 dog bites recorded in the

veterinary clinics [30] and Frey 2013 estimated an annual incidence of bites from suspected rabid animals of 12.9/100 000 and an incidence of 0.7 human rabies deaths/ 100,000 in Chad [109]. Namibia reported above 16 cases per year from 2011 until 2015 with a maximum of 23 cases observed in 2015 with an incidence of 1.0 and 2.4 per 100,000 inhabitants and per year on average [39].

Table 2: Mapping human rabies morbidity rate

Country (region, district and town)	Human rabies morbidity rate	Study duration
Chad (N'Djamena)	An annual incidence of bites from suspected rabid animals of 12.9/100 000 [109]	Seven months [109]
Democratic Republic of Congo (Kinshasa)	29 positive to rabies in 5,053 dog bites recorded in the veterinary clinics [30].	Five years [30]
Ethiopia (National level; Ababa and outside of Addis Ababa; North Gondar administrative zone)	A total of 924 human rabies reported [107] The incidence of human rabies exposure was reported to be 40 per 100,000 population in Ethiopia [29] Annual estimated rabies incidence of 2.33 cases per 100,000 in humans [107] The incidence of human rabies exposure cases calculated per 100,000 populations was 35.8, 63.0, 89.8 and 73.1 every year [97]	One year [29]; Two years [106]; three years [97]; Eleven months [107]
Ghana (Techiman Municipality; Eastern Region of Ghana)	54 dog-bite victims bitten by rabies-positive dogs [90] 13 cases of human [34] An annual incidence of rabies cases of 172 per a population of 100,000 [44]	Three years [90]; Six years [34]; Two years [44]

Ivory Coast (National level)	Annual incidence of 0.06−0.08 per 100,000 [31]	Two years [31]
Kenya (Machakos and Kitui counties in lower eastern region; Kisumu County in Lake Victoria basin; Nandi County in Central rift valley and Kilifi coastal region).	Human animal-bite injuries incidence of 289 per 100,000 persons [26]	Five years [26]
Madagascar (National level)	Nine of the 11 suspected human cases tested with a laboratory confirmed for rabies [92]. 31 positive cases of human rabies reported [42].	Five years [92]; Six years [42]
Malawi (Blantyre)	14 paediatric rabies cases reported [98].	Six years [98]
Namibia (Kavango)	An incidence of 1.0 and 2.4 per 100,000 inhabitants and per year on average [39]	Six years [39]
Tanzania (Mwanza region; Tabora; Shinyanga; Mara; Ulanga; Kilombero; Serengeti; Dodoma Region; Ngorongoro districts in northern Tanzania and in the 11 districts in southern)	Average annual incidence per 100,000 bites of 37.1, 11.3 and 33.5 in Human population [95] An incidence of bite patients seeking PEP declined substantially (>50%) [96]. An annual incidence of 58 cases per 100,000 [37] Mean incidence of 74 bites considered at risk of rabies transmission per 100,000 persons per year [103]. An average of 75.6 and 19.3 probable rabies exposures per 100,000 persons per year [105]	Five years [37]; Four years [95-96]; Seven years [103]; Five years [105]
Uganda (National level)	208,720 patients with animal bite injuries treated at across the country [94].	Fourteen years[94]

Zimbabwe (National level)	Among rabies-suspect, 42 (73.7%) were positive [35].	Eleven years [35]

3.4.2. Rabies mortality

Sixteen studies reported rabies related mortality in Africa (Table 3) [16, 27, 33, 36, 38, 40, 41, 91, 93-95, 104, 105,107-109]. Ethiopia reported three studies among which 320 people, diagnosed clinically, died of rabies in a 5-year retrospective study conducted in the national level [16], 386 human rabies fatality were reported in a 8-year retrospective study with annual range of 35 to 58 deaths in Addis Ababa and outside of Addis Ababa [41]. There were also 32 cases in human rabies recorded from which three humans ended with fatality in North Gondar administrative zone [107]. Four studies assessed rabies mortality in Tanzania from which Ulanga, Kilombero and Serengeti districts reported human rabies mortality rates of 2.4; 0.8 and 1.4/100,000 per year respectively [95]. Sixteen human deaths (1,291 victims bite) due to rabies were reported within the Integrated Bite Case Management (IBCM) study across 20 districts in 4 regions in Southern, Central, and Northern Tanzania [104]. Other studies reported twenty-eight deaths from suspected rabies cases during the five-year period in the two districts, an average of 1.5/100,000 per year in Serengeti and 2.3/100,000 in Ngorongoro [40]. Fourteen (14) among 1005 victim bites died showing clinical signs of rabies within 5 years [105]. Three (3) studies identified rabies mortality in Uganda. Among them, were592 (95% CI 345–920) deaths [108], 1 dose of PET was sufficient for protection following a rabid animal bite. Another research estimated a total of 371 deaths of rabies with a cumulative total of 117,085 rabies cases in nine years [93] and a 14-year retrospective study revealed a total of 486 suspected human rabies deaths among 208,720 patients with animal bite injuries treated at health facilities across the country [94]. A study undertaken in Moramanga

district (Madagascar) recorded an annual incidence of 42–110 rabies exposures and 1–3 deaths per 100,000 persons [27]. An estimated 7 rabies deaths (95% confidence interval 4–10 deaths) per year was recorded in N'Djamena (Chad) [107]. A study conducted in Algeria excluding Sahara region found an annual average of 20.6 human rabies deaths [91]. A total of 14 cases of fatal rabies with 12 death reported in Maputo City is the capital of Mozambique [33]. An average annualized rabies attack rate of 136 rabies cases per 100 000 dog-bite injuries (7/5 139) with 6/7 deaths were reported in South Africa [38]. There were patients with furious rabies manifestations and the case-fatality rate of 100% in a study conducted in Kinshasa (DRC) [36].

Table 3: Mapping human rabies mortality rate

Country (region, district and town)	Morbidity rate	Study duration
Algeria (National level excluding Sahara region)	An annual average of 20.6 human rabies deaths [91]	Thirteen years [91]
Chad (N'Djamena)	An estimated 7 rabies deaths (95% confidence interval 4–10 deaths) per year [109]	Seven months [109]
Democratic Republic of Congo (Kinshasa)	Case-fatality rate of 100% [36]	Eight months [36]
Ethiopia (National level, Ababa and outside of Addis Ababa, North Gondar administrative zone)	320 people died of rabies in a 5-year [16]. 386 humans rabies fatality were reported with annual range of 35 to 58 deaths [41] 32 cases in human rabies recorded [107].	Five years [16]; Eight years [41]; Eleven months [107]
Madagascar (Moramanga district)	An annual incidence of 42–110 rabies exposures and 1–3 deaths per 100,000 persons [27]	One year [27]
Mozambique (Maputo city)	A total of 14 cases of fatal rabies with 12 deaths [33]	Three months [33]
South Africa (Uthungulu District of Kwazulu-Natal province)	An average annualized rabies attack rate of 136 rabies cases	Three years [38]

	per 100 000 dog-bite injuries (7/5 139) with 6/7 [38]	
Tanzania (Ulanga, Kilombero and Serengeti districts; 20 districts in 4 regions in Southern, Central, and Northern Tanzania; Serengeti and Ngorongoro)	Human rabies mortality rates of 2.4; 0.8 and 1.4/100,000 per year respectively [95]. Sixteen human deaths (1,291 victims bite) due to rabies were reported [105]. Twenty-eight deaths from suspected rabies cases during the five-year period in the two districts, an average of 1.5/100,000 per year and 2.3/100,000 [40] Fourteen (14) among 1005 victim bites died showing clinical signs of rabies within 5 years [105].	Five years [40]; Four years [95]; Five years [105]
Uganda (National level; ten district)	592 (95% CI 345–920) deaths [108] An estimated a total of 371 deaths of rabies with a cumulative total of 117,085 rabies cases in nine years [93] A total of 486 suspected human rabies deaths among 208,720 patients in fourteen years[94]	Eight years [93]; Fourteen years[94]; Three months [108]

3.4.3. Rabies disease surveillance, prevention and control

3.4.3.1. Rabies prevention and control

The review summarized rabies prevention and control in point of view rabies exposure status, PEP, dog vaccination and seasonality. Among 36,741 bite victims recorded in studies reporting PEP

[25, 37, 41, 90, 97, 98, 103], the PEP was initiated based on WHO grade of exposure [112]. We found 505 bites in grade 1 (8.78%), 2050 in grade 2 (35.63%) and 3199 in grade 3 (55.59%) [28, 29, 38, 101, 102]. The overall PEP course among bite victims varied between 24% to 99% [25, 90]. We reported 2,652 bites victims in studies reporting PEP and mass dog vaccination [29, 34, 35, 91, 106]. Dog vaccination coverage varied from 14.1% to 68.78% [29,91]. Other study found that the dog vaccination decreased significantly across the study and also the health status of most dogs involved in biting was unknown [35,106]. Rabies prevention and control also depended on the seasonality. In Ethiopia, two studies reported season wise rabies exposure. The first study reported rabies exposure during spring (360/924, 39%) and summer (244/924, 26.4%) seasons [106]. The second study that found the highest human rabies exposures were reported in spring (April to June) followed by winter (January to March) while the lowest distribution of human rabies exposure was recorded in autumn (October to December) [29]. In Nigeria, Osaghae et al. reported the prevalence of dog bite was highest, 41/81 (50.6%), during the hot season (April– June) and low, 14/81 (17.3%), during the wet season (July–October) [99]. Another study conducted in Nigeria recorded the highest number of dog bites with two peaks in April and October 2008 [43]. However, the number of dog bite cases was lowest. For all years the numbers of dog bite cases recorded were lowest at the beginning of the year and dog bites increased during the last 3 months (October-December) of the year 2006 [43]. Animal-to-human rabies transmission was highest during the dry months of July to November in Zimbabwe [35]. In DRC, a study found there was no seasonal difference observed for rabies occurrence either for clinical cases or confirmed cases throughout the study period [30]. In Tanzania, each year, the majority of rabies cases were recorded during the period June to October [37]. In the dry season, significantly fewer rabies positive cases were reported than in the rainy season in Namibia [39]. In Chad, more rabies records per month

were collected during the hot, dry season months (March and April), than during the dry season months (September–February) [109]. In Senegal, dig bite victims were higher in dry season (Nov-May) than rainy season (June-Oct) [28]. Besides, bite victims in rural areas took longer, on average, to receive PEP than those in urban areas [95,103,106]. Probable human rabies cases were higher in rural than urban areas [29,31]

3.4.3.2. Rabies surveillance, prevention and control

The findings revealed that 39,802 bites victims were recorded in rabies surveillance and prevention interventions. The studies included laboratory, database and network surveillances [30, 32, 38, 42, 96]. The rabies prevention included PEP and dog vaccination. Laboratory surveillance has improved rabies diagnostic [30, 32, 38, 42, 96] and database and network surveillances improved mortality and morbidity records [32,38,96] and allowed better estimates of the true rabies burden [32] Further, Compliance with PEP regimens was significantly higher, rating from 83.7% to 93% in two studies [38,96]. In contrast, dog vaccination remained low (10%-12.6%) [32, 42].

We found five studies including rabies diseases surveillance, prevention and control [27, 28, 33, 40,104, 105]. Among them, three studies [28, 33, 40] have reported significantly improved rabies morbidity and mortality and also PEP uptake. The PEP uptake was 71% and it dramatically reduced the risk of developing rabies [40]. Another study did not report any death with high number of patients receiving PEP [28].

A combined strategy of mass dog vaccination, enhanced surveillance, and expanded access to PEP reduced the annual incidence of rabies exposures and deaths annually in Madagascar [27]. Strict measures such as vaccination of dogs in the neighborhoods where human rabies cases had

occurred, mass vaccination campaign of dogs, participation of private veterinary clinics in animal vaccination, collection of stray dogs in selected neighborhoods and community education regarding prevention and control measures had drastically reduced rabies cases in human to 14 during the study period in Mozambique [33].

3.4.3.3. Post exposure management

We found seven studies on rabies management and control. Among them, six studies addressed wound management and PEP [36, 43, 99, 100, 101, 109]. Wound severity was graded as follows, 0 = no apparent injury seen, 1 = skin scratch with no bleeding, 2 = minor wound with some bleeding, 3 = deep or multiple injury [101]. The reported severity of the wound was classified as deep wound, lacerated wound, superficial wound or scratch [109]. The severity of the injury was determined using the WHO dog bite injury grading system [112]. Soap, water, wound dressing, tetanus prophylaxis, anti-rabies vaccination, intravenous fluids, diazepam and antibiotics were also part of the management. The overall review reported 5754 bites managed according to the WHO dog bite injury grading system, 3199 (55.59%) were grade 3; 2050 (35.63%) were grade 2; and 505 (8.78%) were grade 1. In 52 cases (7%), grade of bite was not recorded [26, 27, 36, 99, 102].

3.4.4. Available research evidence on human rabies

Rabies cases in various committees emphasize the need for active surveillance by following up of people bitten by animals and mass dog vaccinations to alleviate the zoonotic threat of the virus [93]. Strengthening rabies surveillance, controlling rabies in dogs, proper post exposure management, increasing the awareness of the community and ensuring availability of post exposure prophylaxis at lower health facilities are the best approach of eliminating rabies [94, 98,

107]. Other studies have demonstrated that reinforcements of rabies surveillance system can improve rabies reporting, which ultimately allows for better estimates of the true rabies burden in the countries [31, 32, 38, 96]. Compliance with PEP regimens was significantly higher for patients following the implementation of automated reminders in comparison to patients attending normal clinics [38, 96]. Other studies concluded that preventing dog bites would most effectively reduce bite injuries by improving public health education among children below 15 years [38]. Public health education is also enhanced by encouraging early PEP initiation and completion, development and implementation of responsible dog ownership, animal behaviour educational programmes as well as improving human and veterinary health linkages [26, 38]. Evidence also showed that no rabies victim in Mozambique received full post-exposure vaccination and the factors significantly associated with human rabies were: age <15 years ($p = 0.05$), bite by stray dog ($p = 0.002$), deep wound ($p = 0.02$), bite in the head ($p = 0.001$), bite by unimmunized dog ($p = 0.01$), no use of soap and water ($p = 0.001$), and no PEP ($p = 0.01$) [35]. Studies have shown that all the rabies vaccines including suckling mouse brain virus (SMBV), fetal bovine kidney virus (FBKV), purified chicken embryo cell rabies vaccine, purified vero cell rabies vaccine, sheep brain anti- rabies vaccine, human diploid-cell vaccine and Purified equine rabies immunoglobulin) and RIG were efficacious. However, the WHO contraindicated SMBV and FBKV [25, 27, 28, 32, 41, 42, 108,110, 111]. Furthermore, a clinical trial with a purified chicken embryo cell rabies vaccine dose used intramuscularly every two years generated ineffective immune response to rabies virus [110] as the Zagreb protocol (2 intradermal injections of 0.1 mL at two sites, deltoids and/or thighs, on days 0, 3, 7 and 28) was not applied. Even though a randomized control trial showed antibody response 26.7% of SMBV recipients and 28.6% of FBKV recipients within a week, both SMBV and FBKV were equally efficacious and well

tolerated [111], however those vaccines are contraindicated by WHO because of its association with neurological adverse reactions (severe allergic encephalomyelitis), further these vaccines are inferior to modern vaccine in terms of potency and immunogenicity [113]. The table 4 described available research evidence on human rabies in Africa.

Table 4: Mapping human rabies evidence identified in Africa

Evidence map	Studies	Impacts/Outcomes
Strengthening rabies surveillance	[31,32,38,93,94,96,98,107]	Reinforcements of rabies surveillance system can improve rabies reporting and increasing the awareness of the community and ensuring availability of post exposure prophylaxis at lower health facilities are the best approach of eliminating rabies.
Automated SMS reminders and telephone contacts	[38,40, 96,104,105]	Compliance with PEP regimens was significantly higher for patients following the implementation of automated SMS reminders and telephone contacts.
Public health education (PEP initiation and completion, responsible dog ownership, behaviour educational programmes and veterinary health linkages)	[26,38,43,94,98,107]	Lack of enforcement of regulations for licensing of dogs and rabies vaccination increased human rabies morbidity and mortality.
Accurate rabies diagnostic	[27,31,32,34,35,42,92,105]	The diagnosis of dog bite and rabies was clinical and laboratory-based. This improved accurate rabies cases reporting.
Mass dog vaccination	[35,91,98]	Even though the 70% coverage was not achieved, there was an inverse relationship between dog vaccination coverage and dog

		rabies cases during the study period.
SMBV, FBKV, purified chicken embryo cell rabies vaccine, purified vero cell rabies vaccine, sheep brain anti- rabies vaccine, human diploid-cell vaccine and Purified equine rabies immunoglobulin (Zagreb protocol)	[25,27,28,32,42,108,110,111]	Studies have shown that all the rabies vaccines and RIG were efficacious and well tolerated. However, the WHO contraindicated SMBV and FBKV.
Effective rabies control and management	[32, 38, 91, 98]	PEP, mass dog vaccination, and WHO dog bite injury-grading system
Integrated bites case management/ Rabies Diseases Surveillance, Prevention and Control	[27,28, 33,40,104,105]	Studies have shown the importance of coordinated surveillance, prevention and control in the eradication of rabies.

3.4.5. Adverse events and complications associated with rabies vaccination

Adverse events and complications associated with rabies vaccination were reported based on SMBV, FBKV, purified chicken embryo cell rabies vaccine, purified vero cell rabies vaccine, sheep brain anti- rabies vaccine, human diploid-cell vaccine and purified equine rabies immunoglobulin. All the 4-dose or Zagreb regimen was reported in all the RIG [114]. Among the studies reporting rabies vaccination, only one study using a purified vero cell rabies vaccine at D0 (2 doses), D7 (one dose) and D21 (one dose) study found that adverse events occurred in 6% of the patients with two doses and after the third dose 3% developed adverse event However, most of the adverse events were minor and associated with headache fever and pain at the injection site that occurred simultaneously on the same day of the vaccine injection [28]. Other studies did not

report any adverse events and complications associated with rabies vaccination [25, 27, 32, 41, 42,108, 110, 111].

3.4.6. Research gaps identified

In this review, we identified 66.67% African countries reporting poor rabies diagnostic capacity, 50 % reported the lack of coordinated surveillance, 50% showed the lack of PEP course completion, 22.22% had insufficient rabies control, and 77.78% had low dog vaccination coverage. Insufficient knowledge and practice on rabies prevention was also identified as a gap. However, we did not find enough studies to evaluate this gap in Africa (Table 5).

The recorded data available so far has showed the underestimation of rabies diagnosis, post exposure prophylaxis and fatal human cases and could be attributed to poor diagnostic capacity and the absence of national rabies surveillance system. In African countries, rabies diagnostic is mostly clinical [16, 26, 28-30, 33, 36, 38, 39, 41, 44, 93-95, 98-100, 103, 108, 109] Among eleven studies including human rabies surveillance, only four reported adequate and successful surveillances [31,32,38,96], twelve studies reported lack of accurate data or non-existing surveillance data [26,30,33,38,39,42,44,92-94,108,109] (Table 5). Other studies reported that dog-bite victims did not complete the post exposure anti human rabies vaccine course and were not likely to be postexposure prophylaxis [27, 28, 31, 37, 38, 40, 90, 95, 100, 103, 105] (Table 5). The exposure victims considered to be at risk of rabies either did not receive any PEP or did not receive all PEP vaccinations due to unavailability, shortage, cost barriers, insufficient knowledge about prompt PEP, category 1 exposure injury or misadvise [32, 36, 38, 40, 43, 44, 101, 104, 105]. A study has reported that the lack of PEP was the cause of 100% fatality rate in Democratic Republic of Congo [36]. There was significant difference between rural and urban exposure cases in respect to the time of arrival to the hospital and living in rural area was statistically associated with loss to

follow up after the first dose [30, 43, 103, 106]. There was also high human rabies exposure rate in children and in the rural community [27, 30,103,106]. Insufficient knowledge about rabies dangers and prevention, particularly prompt PEP, but also wound management, was the main cause of rabies deaths [40]. A higher proportion of human rabies exposures was caused by unprovoked dogs and of these, the majority were unvaccinated [29, 43]. Dog vaccination remains an urgent intervention gap. Among eighteen studies conducted in nine countries, none of them reported the target of 70% of dog vaccination (Table 5). The highest dog vaccination rate was reported in Algeria (67.3%) [91] and the lowest in Madagascar (10%) [42].

Table 5: Mapping research gaps in Africa

African countries	Research gaps identified					
	Diagnostic capacity	Coordinated surveillance	Lack of PEP course completion /PEP unavailable	Inefficient control	Insufficient knowledge and practice on rabies prevention	Low dog vaccination coverage(<70 %
Algeria	N/A	N/A	N/A	√ [91]	N/A	X [91]
Cameroon	√ [32]	√ [32]	X [32]	√ [32]	N/A	X [32]
Chad	X [109]	X [109]	X [109]	X [109]	N/A	X [109]
Democratic Republic of Congo	X [30,36]	X [30]	X [30,36]	X [30,38]	N/A	X [38]
Ethiopia	X [16,29,41]	N/A	X [97]	X [29,97,107]	X [107]	X [29,97,107]
Ghana	X [44]	X [44]	X [44,90]	X [34,44,90]	N/A	X [34,90]
Ivory Coast	√	√ [31]	X [31]	X [31]	N/A	X [31]

	[31]					
Kenya	X [26]	X [26]	X [26]	X [26]	N/A	N/A
Madagascar	√ [27,42,92]	X [42,92]	X [27,42]	X [27,42,92]	N/A	X [27,42]
Malawi	X [98]	√ [98]	√ [98]	√ [98]	N/A	N/A
Mozambique	X [33]	X [33]	X [33]	X [33]	N/A	X [33]
Namibia	X [39]	X [39]	N/A	X [39]	N/A	N/A
Nigeria	X [99,100]	N/A	X [43,99-101]	X [43,99-101]	N/A	X [43]
Senegal	X [28]	√ [28]	X [28]	X [28]	√ [28]	X [28]
Tanzania	X [95,103]	√ [95,103]	X [37,40,95,103,105]	X [37,40,95,103,105]	X [40]	N/A
Uganda	X [93,94,108]	X [93,94,108]	X [108]	X [93,94,108]	N/A	X [93,108]
South Africa	√ [38]	√ [38]	X [38,102]	√ [38]	N/A	N/A
Zimbabwe	√ [35]	√ [35]	N/A	X [35]	N/A	X [35]

Footnote: "X: research gaps identified in different included studies; √: research strengths identified in different studies; N/A: Not applicable"

4. Discussion

This is to our knowledge, the first scoping review synthesizing publically available data on rabies in Africa and to weigh such data in support of the global goal of 'zero human rabies deaths by 2030'. The purpose of this scoping analysis was to provide a summary of evidence on rabies morbidity, mortality, integrated rabies surveillance, prevention and control in Africa. Overall, studies have shown that African countries face a range of problems from the point of view of rabies surveillance, prevention and control that have a negative effect on rabies mortality and morbidity. Reviewing rabies morbidity and mortality rates across Africa, data obtained fluctuated largely over time and space in various countries, as well as in different regions or districts across the same area. While some countries may have shown significant improvement in rabies morbidity and mortality data, the morbidity and mortality rates in Africa generally remain high. Included studies showed no standardization in reporting human rabies outcomes, human rabies morbidity and mortality rates were reported in term of annual incidence and number of infected human rabies and deaths related to rabies. Moreover, small-scale studies may not reflect the national or regional human rabies morbidity and mortality rates. Then this was difficult to have an accurate picture per country and assess human rabies situation between African countries.

These are the consequences of lack of laboratory rabies confirmation, epidemiological surveillance, inadequate mass dog vaccination and PEP policy, and unreported clinical cases in African countries. Lack of monitoring data on rabies or low data quality is problematic, resulting in rabies being poorly addressed in most African countries. Results have also shown that, of the eleven countries in which rabies surveillance has been applied, only four studies reported that surveillance decreased rabies morbidity and mortality [31, 32, 38, 96]. Comparing old and new data (before and after the “zero rabies by 2030” target), rabies diagnostic and surveillance has not improved in most of the African countries. As a result, well-structured rabies surveillance

enhanced the reporting of morbidity and mortality and also has a visible impact on rabies elimination strategy in Africa. While strategies have been subdivided into surveillance, prevention, control and management of rabies (see table of included studies), only three studies have shown the efficacy of the combination of surveillance, prevention and control of rabies [28, 33, 40]. However, passive surveillance has shown its limitations in rabies elimination because cases are reported clinically with or without laboratory-based strategies, inducing inaccurate diagnostic, scarcity of laboratory confirmation and poor reporting system [26, 39, 42, 93, 94, 108]. This is why both passive and active surveillance are preferable to strengthen rabies monitoring and reporting in African countries [115]. Strengthening rabies surveillance also is the foundation of the provision of actionable data for efficient management of wildlife diseases [116]. Besides, the review has shown that strengthening surveillance, prevention and management of rabies has shown good evidence in three separate studies [28, 33, 40]. Coordination of surveillance, prevention and control of rabies can play an important role in the eradication of rabies in Africa. It is worth noting that specific awareness of when and where disease occurs is essential to the formulation of prevention, control and elimination strategies [116].

As seen above, the implementation of different rabies interventions at national level has never been reached in African countries. It is vital that African countries achieve the 2030 target of eliminating human rabies by providing readily accessible and affordable PEP in all countries in the continent where rabies infection is endemic. The exposure victims considered to be at risk of rabies either did not receive any PEP or did not receive complete PEP vaccinations due to unavailability, shortage, cost barriers, insufficient knowledge about prompt PEP or misadvise [32,36,40,44,101,104,105]. This could be emulated from Thailand, which has significantly reduced human deaths from rabies to fewer than 10 cases per year by educating the public and

health workers and delivering PEP free of charge across the country before mass dog vaccination achieved the minimum 70 per cent coverage [117,118]. When provided correctly and in a timely manner, rabies PEP is almost 100% effective in the prevention of disease [79,119]. The findings of the review revealed that the dog victims found to be at risk of rabies either did not receive PEP or did not receive all the PEP vaccines due to unavailability, shortages, cost barriers, long distance travel to the hospital or misadvise [27,28,31,32,36,37,40,44,90,95,100,101,103-105]. It is important to remember that PEP combined with other treatments such as soap, water, wound dressing, antibiotics, tetanus prophylaxis and anti-rabies vaccination has been shown to be beneficial for dog bite victims. Two studies have shown that compliance with PEP regimens was substantially higher for patients who did not receive PEP after automated reminders [38, 96]. Taken together, our results point to a sub-optimal system requiring specific improvements to achieve prompt provision of rabies PEP for persons exposed to rabies [118].

Statistical modeling studies show that the annual vaccination of 70% of the canine population would induce adequate herd immunity to effectively eradicate canine rabies and subsequent human exposure [40, 51]. The lowest and highest reviewed dog vaccination rate was 10% and 67.3% respectively [42, 51] and no reliable data on dog vaccination were reported in most of the studies. This is because many campaigns, if conducted, struggle to achieve a 70% vaccination rate [9, 51]. This is due to husbandry practices, rabies knowledge, geographical area/location, and the ages of dogs [120]. Evidence has shown the dog mass vaccination systems have demonstrated some effectiveness in reducing human rabies morbidity and mortality in countries such as KwaZulu-Natal, South Africa [55, 71], Serengeti, Tanzania [55, 72, 74], Malawi [55, 75] and Chad [76, 77]. However, the Tanzanian study has shown that, if vaccine coverage was not sustained, rabies infection would resurface extremely quickly [40]. Despite effective monitoring of rabies at the

Tanzania study site from 1998 to 2001, vaccine coverage decreased from 2001 to 2003 resulting in a new rabies outbreak, with human exposures increasing by six times in 2003 relative to previous years [40]. Further, free mass dog vaccination intervention has proven to increase dog vaccination coverage. Government and stakeholders work actively to provide a free sustainable dog vaccination.

Besides, the evidence has also illustrated the effectiveness of other strategies, such as mobile phone touch tracing strategies, new rabies vaccines, integrated bite case management, wound management were correlated with PEP and/or mass dog vaccination. Africa is yet to recognize rabies as an immediate public health problem; this may be due to a lack of awareness of the burden of disease and inadequate surveillance. Policies should be put in place to raise awareness of rabies at grassroots level and coordination between the appropriate agencies for improvements of the policies [53, 60].

The World Animal Health Information System (WAHIS) is a well-established global animal disease reporting system that reproduces the data submitted by countries to the OIE, but is also constrained by the under-reporting problems inherent in national reporting systems [121,122]. The need for regional, One Health-oriented reporting network has therefore become apparent [123,124]. The development of rabies-specific regional bulletins has been extremely effective in the Pan-American Health Organization field [122]. The Database such as Advanced Epidemiological Surveillance System (SIEPI) should be applicable in Africa.

Indeed, the elimination of rabies is not feasible without African cooperation. No single country will retain rabies-free status unless it is brought under control in neighboring countries [124]. Regionally organized efforts are required to eradicate human rabies, taking into account country-

specific needs and socio-cultural acceptability [124]. This study has highlighted evidence required for rabies surveillance, prevention and control in Africa. The literature has shown that such evidence has eliminated dog-mediated rabies in countries such as Singapore and Malaysia [124]. The probability of meeting the 2030 goal without African and international solidarity is low, as more than two-thirds of countries are in the low-level human development community [125]. Leading countries should serve as role models, sharing their knowledge and skills so that no nation is left behind. African unification with international support will enable, the common goal of zero human rabies deaths to be achieved by 2030 [125]. Therefore, regional networks support, channel and pool efforts, support monitoring platforms will help make much progress [126]. Partnerships are important to the achievement of an objective and the last mile is going to be the most demanding [126]. In addition, contact and collaboration between human health and veterinary systems is also critical for the follow-up of both human and animal cases [127]. Data collected on alleged cases of human rabies, human exposures and rabid animals must be constantly reviewed and effectively disseminated [127]. Communication between the various national levels of healthcare administration is a crucial means of disseminating outcomes [127]. Finally, stakeholders need to be engaged in the long term to ensure that surveillance is effective [127]. Knowing that the Global Strategic Plan is catalytic and not intended to replace the strategies and commitments of individual countries [126], African countries should emphasize gaps, challenges, barriers and evidence applicable in the various districts, countries and regions as indicated in this present study. One Health interventions is provided by approaches to the prevention of human rabies deaths [128]. Human rabies is 100% preventable through two complementary measures: first, PEP, which involves administration of rabies immunoglobulin and a multi-dose course of rabies vaccination to people bitten by suspected rabid animals; second, mass vaccination of animal

reservoirs (primarily domestic dogs, the reservoir in the vast majority of human cases), which reduces the risk of human exposure and can ultimately result in rabies virus elimination [128].

New rabies control tests and technologies have been developed, such as oral rabies vaccine (ORV), which is effective for instance in skunks, red foxes and raccoons, and lessons have been learned from recent outbreaks [129]. Oral recombinant vaccinia virus expressing the immunizing rabies glycoprotein has been used in in Switzerland years ago [130]. It has been demonstrated to be effective for the oral immunization of foxes, some of them being competitors for long baits year consumption. Switzerland eradicated wild rabies since 1985 [127] V-RG is effective at inducing immunity in red foxes through intradermal, subcutaneous and oral routes [131,132]. Adult foxes were completely covered against rabies virus challenge 12 and 18 months after oral administration of Glycoprotein Recombinant Virus (V-RG) [133]. Seroconversion was also observed in 44.4% of vaccinated jackals on day 150 post-vaccination and 77.7% vaccinated jackals survived the rabies challenge that killed all 10 controls [132,133]. A single oral dose of V-RG administered in an experimental sponge bait shape protected raccoons from rabies virus challenge, with 100% survival at 28 days post-vaccination and 80% survival at 205 days [132,134]. Since 2004, ORV campaigns have been conducted annually around Israel. After several years of ORV, the vast majority of Israel (90%) is actually free of carnivorous rabies virus variants. Wildlife rabies is managed in Canada in the same way as in the USA by reservoir population management and ORV distribution [132,135].

These were associated with a less robust and inadequate supply system for rabies biologicals operated separately to that used by routine vaccines and the use of the intramuscular route for PEP

administration as opposed to the dose-saving intradermal route with high cost of rabies PEP and rabies immunoglobulin (RIG) to bite patients [118].

5. Conclusion

This comprehensive scoping review is of crucial importance in assessing various evidence of human rabies morbidity, mortality, monitoring, prevention and management. Rabies control strategies and case effects, available studies establishment to address various gaps are also important in the management of rabies in Africa. The analysis included past, existing and future viewpoints that are important for African countries to achieve zero dog-transmitted human rabies by 2030. The findings of forty-three studies included thirty-two quantitative retrospective studies, three mixed designs (retrospective and cross-sectional studies), three prospective cohort studies, two cross-sectional studies, one case control, one clinical trial and one randomized control study. Mapping the outcomes, the review included rabies morbidity (21 studies), mortality (15 studies), rabies prevention and control (16 studies), surveillance (9 studies), surveillance and prevention (5 studies), management and control (7 studies), surveillance, prevention and control (6 studies), strong research evidence (14 studies), rabies vaccination or PEP adverse events (4 studies) and research gaps were identified (41 studies).

Evidence has shown that human rabies morbidity and mortality remain high compared to rabies globally, and human rabies morbidity and mortality fluctuate in time and space across different African countries. In order to better understand this, the review has shown that monitoring, prevention and control of rabies diseases is inadequate and insufficient in most African countries. This is attributable to a variety of gaps and challenges across African countries. In addition, this study found insufficient and ineffective surveillance of rabies, unavailability of PEP, high cost,

lack of information on prevention of rabies, and poor or non-existent data on dog vaccination. However, few studies have shown a thorough design of rabies measures such as enhanced surveillance of rabies, regulation of rabies in dogs, proper post-exposure treatment, improved community awareness and availability of PEP in all rural areas, use of cell phone intervention to enhance surveillance of rabies, prevention and control of enhanced rabies morbidity, and more. In addition, African countries can learn about different community-based obstacles that can interfere with surveillance, prevention and control of rabies diseases. This is important to point out that no single country will preserve rabies-free status unless it is brought under control in neighboring countries [120]. That is why African countries should build a forum for rabies that may be significant to exchange data and experience on rabies. Finally, African countries can also look at futuristic rabies innovations such as ORV.

6. Patients and public involvement

No patients or the public were involved in this scoping review.

7. List of abbreviations

FBKV: Fetal Bovine Kidney Virus; FAO: Food and Agriculture Organization of the United Nations; GARC: Global Alliance for Rabies Control; JBI: Joanna Briggs Institute; OIE: World Organization for Animal Health; ORV: Oral Rabies Vaccine; PEP: Post-Exposure Prophylaxis; PICO: Population-Interventions-Comparisons-Outcomes; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RABV: Rabies virus; RIG: Rabies Immunoglobulin; SMBV: Suckling Mouse Brain Virus; SIEPI: Specialized Epidemiological Surveillance System; WAHIS: World Animal Health Information System; V-RG: Vaccinia-rabies Glycoprotein Recombinant Virus; WHO: World Health Organization;

8. Footnotes

Author Contributions: PSN initiated the study project. PSN and JLT conducted the data extraction. Both authors wrote the review in consultation with JW, RT, AM, SVN, TB, JLT, LN, NEN, GKH, MTG, AA, SD, LB, RB and CD. All the authors reviewed and approved the final version of the manuscript.

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Ethics Approval: Since this is a scoping review, there is no institutional requirement to obtain ethical clearance from the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences, Stellenbosch University. We used data from open source and publicly available accessed on different databases as described in the methods.

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Table 1: Extracting and charting data table

Rabies mortality and morbidity associated with animal bites in Africa: A case for Integrated Rabies Diseases Surveillance, Prevention and Control - A Scoping review

Author(year) and country	Study designs	Participants/Comparators	Interventions and Control conditions/Exposures	Outcomes	Key findings/Gaps/Challenges
Rabies prevention and control					
Harry 1984 Nigeria	Randomized control trial	136 patients aged three to 74 years.	Controlled treatment of dog-bite victims with suckling mouse brain (SMBV) versus fetal bovine kidney (FBKV) rabies vaccines.	By day 7, 26.7% of SMBV recipients and 28.6% of FBKV recipients showed antibody response These percentages increased to 95.1 and 81.1, respectively, by day 14, and by day 20 (for SMBV recipients) or day 30 (FBKV recipients) the response was 100%. Titres dropped by day 90, but in no case to below 1 EU ml^{-1}.	We have concluded that both vaccines are equally efficacious and well tolerated.
Tefera 2002 Ethiopia	5-year retrospective study	15,940 people dog bite victims	post exposure anti-rabies prophylaxis treatment	320 people were reported to have died of rabies.	The result supports the hypothesis that there is a lack of appropriate reporting system on prevalence of rabies and its impact on humans.

Deressa 2010 Ethiopia	8-year retrospective study	17,204 people received post exposure treatment	Post Exposure Prophylaxis 5% suspension of phenolized sheep brain tissue.	The fatal human cases were 386 humans with annual range of 35 to 58. The age and sex specific distribution showed that the most fatal cases were 42% from the age group 0-14 category. According to this record 66.66% of deaths were males and 33.33% were females.	PEP against rabies varies from 35.96% to 64.4% across the study. The recorded data showed the underestimate of rabies diagnosis, post exposure prophylaxis and fatal human cases, which could be attributed due to the absence of national rabies surveillance system.
Olugasa 2010 Nigeria	Clinical trial	Of these 70 healthy individuals, 29 (41.4%) consisting of 15 zoological garden workers (75.0%), 13 veterinarians (65.0%) and 1 veterinary student (3.3%)	A purified chicken-embryo cell rabies vaccine One dose (1 ml of ≥ 2.5 IU/ml vaccine potency) was administered intramuscularly every two years immune to rabies virus (antibody titre >0.5 equivalent units per ml), while 41 (58.6%) were not immune.	Overall, antibody levels increased from 1-5 years to 10-30 years on the job.	Almost all those who had spent at least 10 years on the job had higher levels of rabies vaccination compliance and were immune.
Mazigo 2010 Tanzania	A 5-year retrospective study	A total of 767 bite injuries inflicted by rabies-suspected animals were reported.	Adherence to post-exposure prophylaxis (PEP) regimen	mean annual incidence of ~58 cases per 100,000 (52.5% males, 47.5% females)	Only 28% of the victims completed the vaccination regime.
Jemberu 2013 Ethiopia	Cross-sectional and year prospective cohort study	120 selected dog owners 5 traditional healers in North Gondar zone, Ethiopia.	clinical observation A questionnaire on rabies people's knowledge and practices	Annual estimated rabies incidence of 2.33 cases per 100,000 in humans. During the follow up period, a total of 32 in humans were recorded	Vaccination of dogs, proper post exposure management, and increasing the awareness of the community are suggested to reduce the disease burden.

				from which 3 humans ended with fatality.	
Edward 2014 Ghana	3-year retrospective study	546 dog-bite victims were reported; 295 (54%) were children < 15 years, 169 (31%) were between 15-59 years and 82 (13%) were above 60 years.	Post-exposure prophylaxis	54 dog-bite victims bitten by rabies-positive dogs were reported.	24% of dog-bite victims did not complete the post exposure anti human rabies vaccine course and were not likely to be postexposure prophylaxis.
Ramos 2015 Ethiopia	A retrospective, registry-based study	A total of 683 persons (51.1% females, 73% children) with animal- related bites.	All the patients received an anti-rabies nervous-tissue vaccine.	No important complications were reported.	99% of whom completed the vaccination course.
Kardjadj 2019 Algeria	A 13- year retrospective study	Annual average of PEP cases: 96,203 people	post-exposure prophylaxis and dog vaccination	Annual average of 20.6 human rabies deaths	Overall dog rabies vaccination coverage rate of 68.78%.
Pfukenyi 2009 Zimbabwe	A retrospective study	A total of 57 rabies-suspect human samples were examined and The 15–19 year age group had the highest number of cases.	Dog vaccination coverage	Among rabies-suspect, 42 (73.7%) were positive.	During the study period, there was an inverse relationship between dog vaccination coverage and dog rabies cases. Dog vaccination coverage decreased across the study from 100% to 50%.
Punguyire 2017 Ghana	6-year retrospective records review	680 dog victims, the median age of rabies victims was 30 (range 3-80 years).	Post-exposure prophylaxis of rabies Dog rabies vaccination	13 cases of human rabies were recorded.	Less than 35% of the suspected rabies dogs that bit people over the period were vaccinated. About 20% of the offending dogs had unknown vaccination status.
Teklu 2017 Ethiopia	A Four-Year Retrospective Study	In total, 2180 human rabies exposure cases were registered and followed for their PEP. the greatest exposed age group was >=15 years in all the study years	Prior to PEP administration for humans. Dog vaccination	The incidence of human rabies exposure cases calculated per 100,000 populations was 35.8, 63.0, 89.8 and 73.1 in 2012, 2013, 2014 and 2015, respectively.	The total annually allocated PEP to the region, nearly 60% was utilized.

					Data on the coverage of preventive dog vaccination and demography were not evident in the study area.
De Nardo 2018 Tanzania	6-year retrospective study	14,624 patients attended the clinics because of animal's bites. Eighty-three per cent (12,098) individuals came from Dodoma Region.	The adherence to post-exposure prophylaxis (PEP)	Mean incidence of 74 bites considered at risk of rabies transmission per 100,000 persons per year.	Overall, 46.0% of the total number of individuals exposed to potentially rabid animals completed the PEP course, while 6.5% (698) did not receive any dose. Living in rural area was statistically associated with loss to follow up after the first dose ($p<0.001$) or after the second dose ($p<0.001$) Females were more likely to be lost after the first dose ($p = 0.006$).
Yizengaw 2018 Ethiopia	2-year retrospective cross-sectional study	A total of 924 human rabies exposure cases received the anti-rabies post-exposure prophylaxis. Of these, males accounted 55.2% and the median age was 18 year (ranges: 1–80 years).	anti-rabies post exposure prophylaxis A structured data collection questionnaire	High incidence rate of rabies exposure was reported during spring (339%) and summer (26.4%) seasons.	There was significant difference between rural and urban exposure cases ($p = 0.001$) in respect to the time of arrival to the hospital. There was high human rabies exposure rate in children and in the rural community. The health status of most dogs (67.3%) involved in biting was unknown (they were stray dogs) and 28.8% were sick: develop the signs of rabid animal within ten days follow up.
Gebru 2019 Ethiopia	One year retrospective study	368 human rabies exposure cases. Age group of 5 to 14 years old.	Recommendation to start PEP immediately after exposure, depending on the type of exposure.	Incidence of human rabies exposure was 40 per 100,000 populations.	A higher proportion of human rabies exposures was caused by unprovoked dogs (96.5%; 95% CI, 94.0–98.0), and of these, the majority were

			Dog vaccination 14.1%		unvaccinated (85.9%; 95% CI, 81.9–89.1).
Zimmer 2019 Malawi	6-year Retrospective study	Children victims of dog bite. The average age was seven years (range 3–11).	Pre and post a comprehensive canine vaccine campaign	14 paediatric rabies cases were found during the study period. More males than females were affected (males: 10 (71%); females: 4 (29%)).	The study shows the importance of eliminating human rabies through canine rabies vaccination.
Rabies surveillance					
Fevre 2005 Uganda	Cross-sectional study	A total of 517 patients were interviewed in 10 randomly selected districts in Uganda in the 3 months of the study.	Passive surveillance Survey of dog bite injuries and rabies post-exposure treatment activities in treatment centres supplied with rabies vaccine.	Death in absence of post-exposure prophylaxis (PET), 592 (95% CI 345–920) deaths One dose of PET is sufficient for protection following a rabid animal bite, 20 (95% CI 5–50) deaths annually. Complete course of PET is required for protection following a rabid animal bite, up to 210 (95% CI 115–359) deaths would occur, as 41% of patients did not complete their course of PET.	Most patients are bitten by dogs, and that a considerable proportion of these are young children, who are at greater risk of developing rabies in the absence of treatment due to the location of the bites they receive. Active animal bite surveillance studies are required to improve our mortality estimates and determine the true burden of rabies in the Ugandan population
Reynes 2011 Madagascar	6-year retrospective study	11 human samples were tested for rabies.	Laboratory Surveillance of domestic or tame wild terrestrial mammal and dog brains tested.	Nine of the 11 suspected human cases tested were laboratory confirmed for rabies.	Rabies remains endemic in Madagascar. this study has found the lack of epidemiological data in Madagascar

Nyakarahuka 2012 Uganda	9-year retrospective study	Cumulative total of 117,085 rabies cases were reported in 9 years.	Surveillance reports from all the districts.	A total of 371 deaths of rabies were recorded.	Findings emphasize the need for active surveillance; follow up of people bitten by animals and mass dog vaccinations to alleviate this zoonotic threat.
Sambo 2013 Tanzania	Cross-sectional study	Human population (district) Ulanga: 193280 Kilombero: 321611 Serengeti: 176057 The ages of suspect bite victims ranged from 1 to 90 years. The majority of suspect bite victims (51%) were children less than 15 years of age.	Extensive investigative interviews were used to estimate the incidence of human deaths and bite exposures.	Average annual incidence/ 100,000 Bites: 37.1;11.3 and 33.5 respectively Death: 2.4; 0.8 and 1.4 respectively	Ninety-four percent (391/415) of these suspects bite victims reported to health facilities for PEP.
Adomako 2018 Ghana	3-year retrospective study	Overall, 4821 dog victims' bites. Most of the cases were in children aged below 10 years.	The health and veterinary services on issues related to surveillance and data quality.	Annual incidence of rabies cases of 172 per a population of 100,000.	In the 82% of cases where data was available, no postexposure prophylaxis (PEP) was administered. The fatality rate was 100%. The study found gross disparities in the number of reported events and overall impression of underreporting.
Masiira 2018 Uganda	A 14-year retrospective review	A total of 208,720 patients with animal bite injuries were treated at health facilities across the country. Up to 81% were patients >=5 years of age and 19% (n = 9,102) were below 5 years of age.	Epidemiological surveillance data .	A total of 486 suspected human rabies deaths were reported.	Strengthening rabies surveillance, controlling rabies in dogs and ensuring availability of post exposure prophylaxis at lower health facilities are the best approach of eliminating rabies.

Tiembre 2018 Ivory Coast	A 2-year descriptive prospective observational study	2968 weekly reports, all were received by the NIPH Anti-rabies Center. Almost one-half of the human rabies cases were in children <=15 years old.	Human rabies surveillance system in those 28 NIPH local units, with specific goals of improving the infrastructure, training, communication, and government involvement.	50 cases of human rabies (15±18 cases/year; annual incidence = 0.06−0.08per 100,000) and more than 30,000 animal exposures (annual incidence = 41.8−48.0 per 100,000).	The study is the result of enhancing human rabies surveillance in Ivory Coast None of cases had received PEP. Post-exposure prophylaxis with rabies vaccine was administered to all animal exposure victims presenting at the NIPH local units; only about 57% completed the full immunization schedule.
Ngugi 2018 Kenya	5-year retrospective study	Among 7307 records analyzed, 7201 (98.6%) had age recorded. The median age was 22 years	Surveillance of PEP was given and number of PEP doses administered.	Human animal-bite injuries incidence was 289 per 100,000 persons with the highest incidence reported at 302 per 100,000 and lowest at 121 per 100,000 persons.	The study concluded preventing dog bites would most effectively reduce bite injuries by improving public health education among children below 15 years, encouraging early PEP initiation and completion, development and implementation of responsible dog ownership and animal behaviour educational programmes as well as improving human and veterinary health linkages.
Hikufe 2019 Namibia	6-year retrospective study	Of the total number of 113 cases, the majority (67%) were children and teenagers below 16 years of age, peaking at 5–9 years.	Human rabies surveillance data were retrieved from the epidemiological database of the Ministry of Health. Surveillance in animals is based on the reporting of all suspected cases.	Rabies cases have been above 16 cases per year from 2011 until 2015 with a maximum of 23 cases observed in 2015. Incidence: 1.0 and 2.4 per 100,000 inhabitants and per year on average.	Kavango, the region with the highest human rabies incidence was also the region with the lowest animal rabies surveillance intensity.
Rabies surveillance and prevention					

Andriamandimby 2013 La Reunion, Mayotte, and Madagascar	6-year Retrospective study	24 946 patients visited the ARMC at the IPM, of which 97.2% (n = 24 299) received PEP. Males represented 54.3% (n = 13 556) of the cases and ranged in age from one to 97 years (median = 18 years). Children under 15 years old represented 40.5% (n = 10 107) of the consultants.	Laboratory surveillance of rabies Post-exposure prophylaxis of rabies	31 positive cases of human rabies	None of these patients received PEP with the exception of one who started PEP late, 10 days after the suspected bite. Dog vaccination coverage in Madagascar was 10%
Kubheka 2013 South Africa	3-year retrospective study	2 601 patients who were offered rabies PEP. The median age of the people bitten by dogs during the two years was 20 years (with a range from 1- 92 years). The majority (61.3%) were aged 5-29 years old.	human rabies surveillance database the uptake of the rabies PEP and patients telephone contact.	An average annualized rabies attack rate of 136 rabies cases per 100 000 dog-bite injuries (7/5 139). 6/7 died	83.7% [95% confidence interval (CI): 82.4-85.2] completed the PEP treatment.
Sofeu 2018 Cameroon	A one year retrospective study	A total of 1,402 animal exposures were reported in the West region of Cameroon.	The surveillance network consisted of local, regional, and national health and veterinary authorities. PEP and immunizations received prior to the current exposure; and the wound treatment were recorded.	Overall incidence rate of 6.1 exposures per 100,000 people. One was confirmed positive for rabies	Overall, at least 421 (60%) of the exposure victims considered to be at risk of rabies either did not receive any PEP or did not receive all PEP vaccinations. Only 12.6% (117/925) of dogs were reported to have been vaccinated and only 14.4% of the animal exposure cases were followed-up with a visit by a veterinarian No adverse events to PEP were reported.
Mtema 2016 Tanzania	A 5-year retrospective study	Reports recorded bite patients seeking PEP (14,565 records, 49%), detailing visits of approximately 5,800 patients.	Automated SMS (short message service, commonly known as a “text” message)	Human rabies cases (42 reported) reflected issues with PEP supply.	Compliance with PEP regimens was significantly higher for patients following the implementation of automated reminders in comparison

			reminders to patients due for further PEP doses. Mass dog vaccinations Mobile Phones As Surveillance Tools	Incidence of bite patients seeking PEP declined substantially (>50%)	to patients attending clinics prior 7% of patients failed to obtain PEP.
Twabela 2016 DRC	A 5-year retrospective study	A total of 5,053 attacks were recorded in the veterinary clinics.	Laboratory surveillance PEP and immunizations	29 were found positive to rabies.	Rabies cases were three times higher in peri-urban zone than in urban zone. It was observed that among the 5,053 attacks registered, 83 (1.6%) animals were killed and 15 (0.3%) disappeared just after attack without a follow-up or a veterinary observation.
Post exposure management					
Osaghae 2011 Nigeria	A twelve-year retrospective study	105 episodes of human and animal bites Recorded. Comparators: N/A	Wound Management Twenty (%) domestic dogs were vaccinated while 11(%) and six (%) were not vaccinated and without known vaccination status respectively.	A 10-year-old girl had rabies and died on the second day of admission.	The anti-rabies vaccine was not administered to the children bitten by the vaccinated animals.
Alabi 2014 Nigeria	3-year retrospective study and cross-sectional study	Only 195 (50.9%) of the 383 bite victims linked to a positive dog specimen could be traced.	A review of detailed profiles of dog bite victims managed in the clinics.	54% of the victims took complete PEP. For those who did not complete PEP, 93% of the biting dogs were not vaccinated.	It has shown lack of enforcement of regulations for licensing of dogs and rabies vaccination.

		About three quarters (141 (73%)) of the victims were aged <16 years.			
Muyila 2014 DRC	A 8-month retrospective study	21 cases were observed, rather three cases per month. There were 12 boys (57.1%) and 9 girls (42.9%). Biting animal was found to be dog in all cases (100%).	(9.5%) had their wounds treated and received an anti-rabies vaccine (ARV) after the bite incident. Two (9.5%) patients received rabies immunoglobulin (RIG).	100% of patients showed furious rabies manifestations The case-fatality rate was 100%.	The study revealed the dogs were not immunized for rabies.
Frey 2013 Chad	Cross-sectional study	Of 86 people exposed to a suspected rabid animal. The median age was 18 years, with a range between. 2 months and 79 years.	Post-exposure vaccination and wound cleaned.	Estimated annual incidence of bites from suspected rabid animals of 12.9/100 000 and an incidence of 0.7 human rabies deaths/ 100 000, resulting in 7 estimated deaths (95% confidence interval 4–10 deaths) per year.	50% received post-exposure vaccination and a further 8% had their wound cleaned.
Ogundare 2017 Nigeria	A retrospective study	In all, 84 cases of dog bite injuries were managed constituting 0.89% of the total consultations. Most of the victims were aged 6-12 years (60.7%) and majority (71.4%) was boys.	Treatments received in the hospital ranged from washing the bite site with soap and water, to suturing of lacerations and wound dressing, analgesics, tetanus prophylaxis, anti-rabies vaccination (ARV), intravenous fluids and diazepam administration as well as antibiotics administration.	Six (7.1%) of cases had rabies and died.	Although seventy-eight (92.9%) of the victims had post-exposure prophylaxis (PEP) with anti-rabies vaccine, only 45 (53.6%) of them were managed successfully and subsequently discharged after ensuring adequate wound healing and completion of the vaccination regimen. Thirty-three (39.3%) were lost to follow up.
Abubakar 2012 Nigeria	A 10-year	81victims of dog bite injuries. The majority, 45 (55.6%), were	Wound care	Two cases of clinical rabies were seen during the study period.	Prevalence of dog bite was highest, 41 (50.6%), during the hot season (April– June) and low, 14 (17.3%), during the wet season (July–October).

	retrospective study	children less than 18 years while 36 (44.4%) were adults.	PEP and the Immunization schedule		None of the victims was previously immunized against rabies.
Kent 2012 South Africa	A 4-year retrospective study	A total of 821 patients complaining of dog bite. Male children aged 6 - 10 years are most likely to present with dog bites.	Advice only Wound management Give vaccine Give anti-rabies immunoglobulin	Of the 821 bites, 642 (78%) were grade 3; 84 (10%) were grade 2; and 43 (5%) were grade 1. In 52 cases (7%), grade of bite was not recorded. Treatment with rabies vaccine was started in 90% of cases of grade 1 bites, 97% of grade 2 bites and 99% of grade 3 bites. Immunoglobulin was administered for 53% of grade 1 bites, 84% of grade 2 bites and 82% of grade 3 bites.	Males present more frequently than females, and young males (ages 6 - 10) are most likely to present. This trend reverses after the age of 40 years, when females are more likely to present than males. We also showed that 99% of grade 3 bite patients are treated with rabies vaccine, but the rate of treatment with immunoglobulin is lower (82%).
Rabies Diseases Surveillance, Prevention and Control					
Lushasi 2020 Tanzania	Multi-center retrospective study	1,291 victims bite. The study was undertaken across 20 districts in 4 regions in Southern, Central, and Northern Tanzania.	Integrated Bite Case Management (IBCM). We trained government staff to implement IBCM, comprising risk assessments of bite patients by health workers, investigations by livestock field officers to diagnose rabid animals, and use of a mobile phone	Only 63 of these bite patients were referred to other facilities for PEP with 43 assessed as being suspect rabies exposures. Sixteen human deaths due to rabies were reported within the IBCM study districts. Overall bite patient presentations corresponded to an	Throughout the study regions, PEP was unavailable for 74 bite patients (5.7%) upon presentation to a health facility, during the period of IBCM implementation.

			application to support integration.	incidence of 17.4 bites per 100,000 persons per annum.	
Changalucha 2019 Tanzania	5-year retrospective and cross-sectional study	About 36% of patient presentations at health facilities were due to bites from probable rabid dogs (1,878/5,162 patients that sought care) as assessed through contact tracing, with the remainder from healthy animals or animals with unknown status.	Mobile phone-based surveillance records PEP was supplied free-of-charge to hospitals and selected outlying facilities in each district and training was provided to over 300 health workers in use of the updated Thai Red Cross ID regimen (5-dose Essen IM regimen). Qualitative interviews with stakeholders at different levels within the health system to characterize the logistics associated with PEP provision.	We detected an average of 75.6 and 19.3 probable rabies exposures per 100,000 persons per year. Of 1005 individuals identified during contact tracing who received late and/or incomplete postexposure vaccination, 14 died showing clinical signs of rabies.	Upon seeking care a further 15% of probable rabies exposed persons did not obtain PEP due to shortages, cost barriers or misadvice. Of those that initiated PEP, 46% did not complete the course. Decentralized and free PEP increased the probability that patients received PEP and reduced delays in initiating PEP.
Rajeev 2019 Madagascar	One year retrospective study	1019 patients reported to the anti-rabies medical centers (ARMC).	A combined strategy of mass dog vaccination, enhanced surveillance, and expanded access to PEP.	Annual incidence of 42–110 rabies exposures and 1–3 deaths per 100,000 persons annually. Extrapolating an annual burden of 282–745 human rabies deaths with current PEP provisioning averting 1499–3958 deaths each year.	A high proportion of rabies-exposed persons from Moramanga sought (84%) and completed PEP (90% of those that initiated PEP).

Diallo 2019 Senegal	A prospective cohort study was carried out from April 1,2013 to March 31, 2014,	1036 patients sought a consultation at the Pasteur Institute of Dakar for suspicion of rabies exposure.	Post-exposure prophylaxis implementation (consists of injection of four intramuscular doses of a purified vero cell rabies vaccine). Dog rabies vaccination treatment (local treatment of injuries, antibiotics administration, and previous rabies vaccination), knowledge of rabies and attitudes in respect to animal bite.	No death was reported during the study period. Adverse events were reported after the first two doses by 6% of the patients (42/678) (including 5 patients who also received equine RIG at D0), and after the third dose, by 3% (16/493). Most of them were minor: headache (46.5%), fever (31%) and pain at the injection site (22%), and mostly (74%) occurred on the same day of the vaccine injection (up to 7 days).	Out of the patients receiving PEP, 162 (18%) patients received two doses only at D0, 185 (20.5%) three doses at D0 and D7 and 493 (54.5%) completed the full 4-dose schedule.
Hampson 2008 Tanzania	5-year retrospective study	1080 people were traced and interviewed who had been bitten by animals.	Contact tracing was used to gather data on rabies exposures, post-exposure prophylaxis (PEP) delivered and deaths case reports from livestock offices and community based surveillance activities.	Twenty-eight deaths from suspected rabies were recorded during the five-year period in the two districts, an average of 1.5/100,000 per year in Serengeti and 2.3 in Ngorongoro	Insufficient knowledge about rabies dangers and prevention, particularly prompt PEP, but also wound management, was the main cause of rabies deaths. Received PEP: 685 (71%) Attended hospital: 971 (85%) PEP dramatically reduced the risk of developing rabies (OR 17.33, 95% CI 6.39–60.83).

Salomão 2017 Mozambique	A case control study	819 cases of animal bites were registered, of which 64.6% (529/819) were from Maputo City. Same neighborhood close to the human rabies victim's house were used as controls (case: control ratio of 1:4).	Affixing posters in health units regarding treatment of animal bites and post-exposure prophylaxis. Delivery of additional quantities of anti-rabies vaccine to the Prophylaxis. Decentralization of post-exposure prophylaxis. Vaccination of dogs in the neighborhoods where human rabies cases had occurred. Mass vaccination campaign of dogs. Participation of private veterinary clinics in animal vaccination. Collection of stray dogs in selected neighborhoods. Community education regarding prevention and control measures.	A total of 14 cases of fatal rabies, Among them 12 died.	No rabies victim received full post-exposure vaccination Factors significantly associated with human rabies were: age <15 years ($p = 0.05$), bite by stray dog ($p = 0.002$), deep wound ($p = 0.02$), bite in the head ($p = 0.001$), bite by unimmunized dog ($p = 0.01$), no use of soap and water ($p = 0.001$), and no post-exposure prophylaxis ($p = 0.01$).

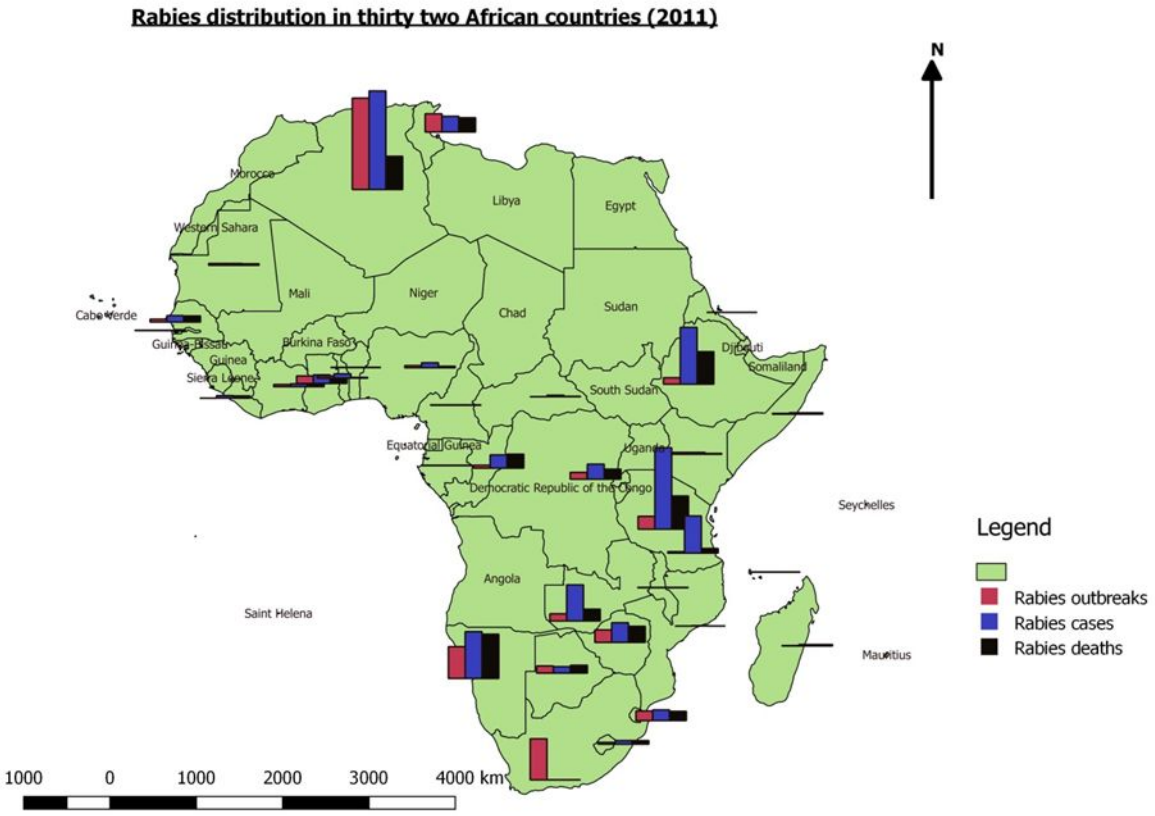

Figure 1: Human rabies distribution in thirty-two African countries (2011)

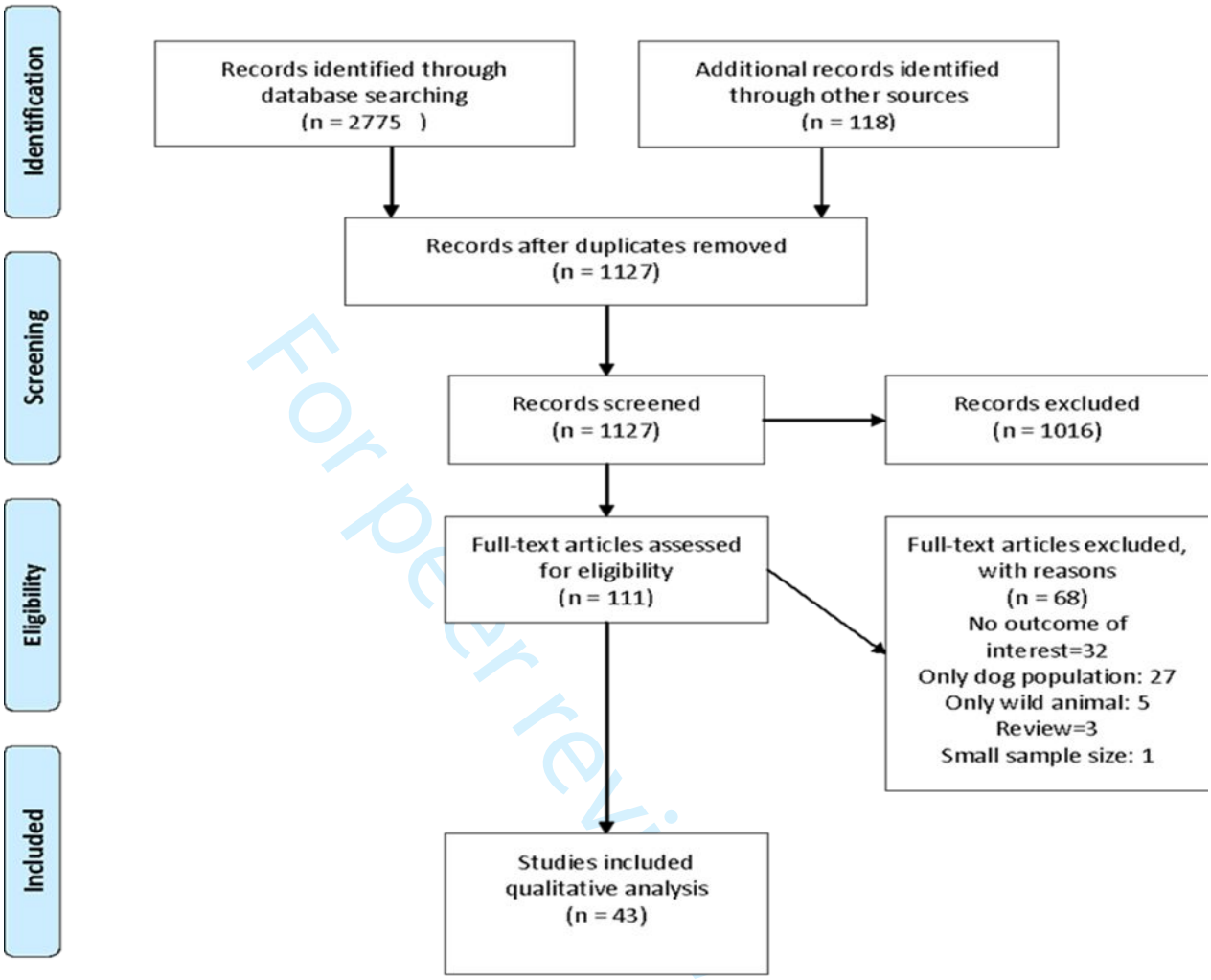

Figure 2: Flow diagram of human rabies mortality and morbidity associated with animal bites in Africa. Note From PRISMA: www.prisma-statement.org [86]

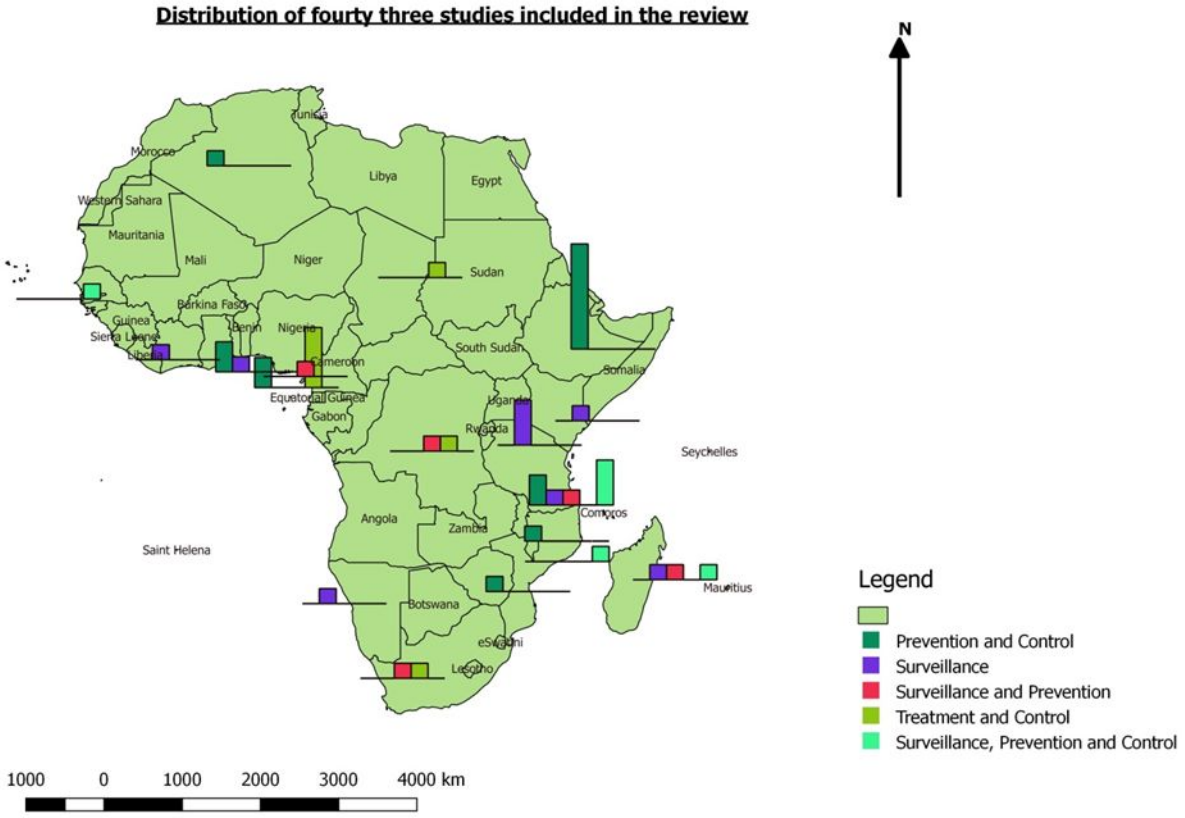

Figure 3: Distribution of forty-three studies in African countries.

Supplementary material 1

Search Strategy:

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to May 25, 2020>

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1 exp rabies/ or exp Rabies virus/ or rabies.mp.

2 africa*.mp. or exp Africa/

3 (Algeria or Angola or Benin or Botswana or Burkina Faso or Burundi or Cameroon or Cape Verde or "Central African republic" or Chad or Comoros or Congo or "Democratic Republic of Congo" or DRC or Djibouti or Equatorial guinea or Egypt or Eritrea or Ethiopia or Gabon or Gambia or Ghana or Guinea or Bissau or Ivory coast or "“Cote d ivoire" or Jamahiriya or Kenya or Lesotho or Liberia or Libya or Madagascar or Malawi or Mali or Mauritania or Mauritius or Mayotte or Morocco or Mozambique or Namibia or Niger or Nigeria or Principe or Reunion or Rhodesia or Rwanda or "Sao Tome" or Senegal or Seychelles or "Sierra Leone" or Somalia or "South Africa" or "St Helena" or Sudan or Swaziland or Tanzania or Togo or Tunisia or Uganda or Zaire or Zambia or Zimbabwe or "Central Africa" or "West Africa" or "East Africa" or "Southern Africa" or South Africa).mp.

4 2 or 3

5 1 and 4

6 mortality/ or mortality.mp.

7 fatality.mp.

8 morbidity.mp. or Morbidity/

9 surveillance.mp. or Population Surveillance/

10 (vaccine or vaccines).mp. or Vaccination/

11 6 or 7 or 8 or 9 or 10

12 Rabies Vaccines/

13 5 and 11

14 4 and 12

15 13 or 14

16 limit 15 to english language

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	Page 1; Lines 1-2
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	Page 3-4; Lines 32-54
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	Page 6-12; Lines 76-226
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	Page 12; Lines 218-226
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	Not applicable
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	Page 13; Lines 232-238
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	Page 13; Lines 239-242
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Page 13; Line 243
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Page 13; Lines 244-247
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	Page 13-14; Lines 248-266
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	Page 14; Lines 267-276
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe	Page 15; Lines 277-279

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
		the methods used and how this information was used in any data synthesis (if appropriate).	
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	Page 15; Lines 280-286
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Page 15; Line 293
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Page 16; Lines 295-309
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Not applicable
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	page 62-75
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Page 17-32; Lines 328-542
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	Page 33-37; Lines 546-603
Limitations	20	Discuss the limitations of the scoping review process.	Page 5; 33; Lines 66-74; 554-559
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	Page 39-40; Lines 684-714
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	Page 41; Line 731

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

BMJ Open

Rabies mortality and morbidity associated with animal bites in Africa: A case for Integrated Rabies Diseases Surveillance, Prevention, and Control - A Scoping review

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Rabies mortality and morbidity associated with animal bites in Africa: A case for Integrated Rabies Diseases Surveillance, Prevention and Control - A Scoping review

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Abstract

Objective

The objective of this scoping review was to map the current situation and available evidence and gaps on rabies morbidity, mortality, integrated rabies surveillance programs, and existing prevention and control strategies in Africa.

Methods

We conducted a systematic scoping review following the Joanna Briggs methodology and PRISMA-ScR checklist. Medline, EMBASE, Cinahl (EBSCOHost), Scopus, Web of Science and rabies web conferences were used to search for peer-reviewed publications between January 1946-May 2020. Two researchers reviewed the studies and extracted data based on author (year) and region, study design and data collection duration, Participants / Comparators, Interventions and Control Conditions / Exposures, outcomes (rabies mortality and morbidity) and Key Findings / Gaps / Challenges. The results were reported narratively using Arksey methodological framework.

Results

Electronic search yielded 2775 records, of which 43 studies were included. A total of 543,714 bite victims were censored through the included studies. Most of the victims were less than 15 years of age. The studies included, rabies morbidity (21) and mortality (15) fluctuating in space and time across Africa depending on countries rabies prevention and control practices (16). Others were surveillance (nine studies), surveillance and prevention (five studies), management and control (seven studies) and surveillance, prevention and control (six studies). We found challenges in

rabies reporting, existing dog vaccination programs and post-exposure prophylaxis availability or compliance.

Conclusion

This study found challenges for dog rabies control and elimination in Africa and the need for a policy to drive the goal of zero dog-transmitted human rabies by 2030.

Key words: One-Health; rabies; mortality; morbidity; surveillance; zoonosis; neglected tropical disease; Africa

Strengths and limitations of this study

- We conducted an extensive search of published and grey literature to identify studies to include in the scoping review
- Pulling together data from both published and grey literature from the Ministries of Health gave us an opportunity to understand the breadth of rabies epidemiology and how surveillance, prevention and control would be a critical tool in implementing effective control of rabies across Africa
- We conducted screening of identified articles and extraction of data in duplicate
- We reported the results narratively as it was not possible to combine data from different studies conducted using different study designs, and different population groups.

1. Background

The natural history of rabies disease in Africa is not well known, but it is well accepted that the disease must have been present in northern Africa for hundreds of years, particularly as an urban dog disease and also associated with cycles in the Middle East [1]. European colonization influenced the spread of dog rabies in Western and Central Africa [2]. In many sub-Saharan African countries, rabies has become epizootic only in the nineteenth and twentieth centuries involved domestic dogs and free-ranging wildlife species [1-3].

More than 59 000 people die of rabies worldwide every year [4-5], 99% of them in African and Asian countries where dog rabies is endemic [4, 6-10]. Due to the lack of laboratory confirmation, sporadic epidemiologic surveillance, and unreported clinical cases in developing countries, current mortality estimates almost certainly under-represent the true incidence of human rabies deaths [4, 8-10]. Rabies is responsible for an estimated 21,000-25,000 death annually in Africa [4, 11-12]. Figure 1 shows a map illustrating rabies distribution in thirty-two African countries considering rabies outbreaks in animals, cases and deaths in humans [13]. In 2011, a total of 33 African countries reported 1,607 outbreaks of rabies, 2,779 cases and 1,524 deaths [13]. Data shows that rabies accounts for 7.2% of all animal disease outbreaks reported making it the disease with the highest number of outbreak reports in Africa in 2011 [13]. Algeria, Namibia, Eswatini (former Swaziland), Tunisia, Uganda, Zambia and Zimbabwe reported high morbidity and mortality with 563 cases (33.9% deaths), 269 (94% deaths), 62 cases (88.7% deaths), 91 cases (90% deaths), 466 cases (40.9%), 207 cases (32.8% deaths) and 114 cases (80.7% deaths) respectively [13].

Dog rabies predominates throughout most of Africa; the domestic dog is the principal reservoir host as well as the most important source of infection for people [14]. In addition, there are many

other lyssaviruses (also referred to as rabies-related viruses) reported from African countries. Most of these rabies-related viruses have been associated with obscure hosts including specific bat species and shrews, partly attribute to the difficulty in bio-surveillance of these viruses. RABV however, spreads in terrestrial mammalian hosts in Africa and has not been associated with bat infections as it is the case in the Americas. While all mammals (domestic and wild) are susceptible to RABV infection, some are able to retain those virus variants adapted to their species whilst others are only reported as dead-end hosts [15]. Rabies has been reported in both domesticated species and wildlife. These are sometimes diagnosed with rabies virus infection in Zambia, South Africa, Ethiopia, Kenya, Tanzania, Zimbabwe and Egypt [15-21].

Most reported cases of rabies in wild carnivorous species included yellow mongoose (*Cynictis penicillata*) and bat-eared fox (*Otocyon megalotis*) [22] as well as critically endangered wild dogs (*Lycaon pictus*) [23-26]. In Ethiopia, rabies outbreaks were described in the endangered Ethiopian wolf (*Canis Simensis*) population [27-28]. In 2014 and 2015, RABV infection was also observed in two wild dogs and a spotted hyaena (*Crocuta crocuta*) in the Madikwe Game Reserve, North West Province of South Africa, in Ethiopia and in Nigeria [21,26,29], monkeys and jackals (*Canis adustus* and *Canis mesomelas*) [16,17, 20-21]. The review of twenty studies across Africa has revealed that bite victims account for 91.9% (48092 dog bites), cat bite for 2.9%, jackal bite for 0.8% and 4.41% others (monkey, donkey, horse, rat, pig, rabbit, Honey badger, kudu, goat, cattle, eland and hyena) [30-49].

Mass vaccination of dogs as a key component of national rabies elimination programs has been successful in eliminating dog-transmitted rabies in Europe, North and Latin America, and Japan [50-52]. By far, the most significant public health threat comes from RABV, and over 99% of all

globally reported human cases are caused by exposure to unvaccinated dogs infected with canine RABV variant, mostly in Asia and Africa [53].

In most of Africa, and specifically western and central African countries, notification of rabies disease is not mandatory, so epidemiological data are scarce [54]. Human rabies could be prevented by the immediate administration of post-exposure prophylaxis (PEP) following exposure to rabid animals [5, 46]. However, people in low-income countries often do not receive these life-saving treatments because either PEP treatment is costly and not readily available, or because of lack of rabies awareness, people might not go to hospital for treatment [5, 9, 55]. The lack of effective educational outreach at community level had led to gaps in knowledge as to the best way to avoid animal bites and administer first aid following bites or other potential rabies exposures [56]. A recent study has shown considerable in-country variability in the availability of rabies vaccines and immunoglobulins vaccine supply system, administration route (IM versus SC), cost of vaccine and rabies immunoglobulin (RIG). In a global survey conducted in rabies endemic countries, 49 of the 54 African countries were rated as moderate to high risk for human rabies, whilst 16 of the 23 countries that responded to the survey had inadequate surveillance systems [12, 57].

One major barrier is the difficulty of consistently achieving the required coverage of 70% of the dog population across the hard-to-reach landscapes that characterize much of sub-Saharan Africa [58-60]. Reviewing dog vaccination coverage in African countries, only South Africa, Tanzania, Algeria, Morocco and Egypt had the dog vaccination coverage of 63%, 37.24%, 23.7%, 25% and 23.7% respectively [61,62]. In all other African countries dog vaccination coverage was below 18% with further below 5% in some cases [61]. The analysis of the above data and the

consideration of the framework for the elimination of dog rabies suggested by Wallace 2017 and others stipulated the existing coverage of dog rabies vaccination, was directly associated with the number of years it would take to achieve rabies elimination [63]. Theoretically, Global Dog Rabies Elimination Route (GDREP) consisting of a 13-year timeframe would be ample time for even the least developed rabies prevention systems to achieve elimination by 2030 if completely committed to this achievement [63]. This system divided countries into three categories: (1) Phase I: preparation (dog vaccination > 18%), (2) Phase II: vaccination of dogs (dog vaccination: < 18% and > 70%) and (3) Phase III: 70% continued vaccination of dogs. African countries have been categorized into phase I, II, III but with no data on dog vaccination [64]. The available data indicate that most African countries were still at the preparation phase since "zero rabies by 2020" was initiated five years ago. Although the feasibility of reaching 70% dog vaccination coverage has been shown through pilot projects in a wide range of settings. African countries still struggle to achieve a 70% yearly dog vaccination rate [10, 14]. In Africa, dog mass vaccination systems have demonstrated some effectiveness as proof of principle in countries such as South Africa [50-65], Tanzania [50, 66-68], Malawi [50,69] and Chad [55, 70-72].

Inadequate education for veterinarians and physicians, insufficient resources for proper confirmatory diagnosis and risk assessment, and the lack of effective communication channels between ministries of health and agriculture frequently have led to failures of prophylactic intervention, even in regions where vaccines and immunoglobulins were available [56]. A recent study conducted in Africa and Asia revealed that rabies immunoglobulins were found to be less available than the vaccine, with access restricted in almost two-thirds of the countries surveyed [73]. Eleven (11) African countries had comprehensive access to RIG. Of the seven countries with broad access to vaccines, 6 of them had a national rabies prevention program or policy. Two of

the countries had only a monitoring program / strategy in place [73]. This is worrisome as it exposes a huge absence of surveillance and prevention policies in most African countries. The absence of a robust monitoring process is mostly attributed to the lack of rabies in national communicable disease plans and reporting systems at national level in Africa [74]. Therefore, widespread underreporting is likely to occur in many affected countries due to lack of health information, civil registration and vital statistical systems, and inaccessibility of clinical care and diagnostic confirmation [74] as symptoms of the disease may be non-specific and similar to other encephalitic infections. Even where data exist in Africa, the lack of communication and exchange of data between the animal and human health sectors also hinders the collection, storage and reporting of coherent data to international data bases [74]. The World Health Organization (WHO) meeting in Geneva in 2018 on "Moving Progress towards Rabies Elimination" pointed out that political engagement is a key factor with governments providing leadership role in the coordination of elimination strategies [12]. The global collection of data on deaths from any neglected disease is a huge challenge, and early attempts to collate data for human deaths from canine rabies were no exception [75]. Due to the lack of regular reporting of rabies cases to the WHO from many member states, the RabNet database was closed down in 2011[76]. Therefore, rabies is not reportable in many African countries, which restricts data collection by structured surveillance systems [74]. One Health evolved from the recognition that an interdisciplinary approach is required to understand complex health problems, and that the health of humans and animals is inextricably linked [77]. Rabies requires a comprehensive, strategic, and targeted control and prevention approach with collaboration from human, animal, and environmental health disciplines at local, national, and global levels to achieve more effective control [78]. In fact, most of African countries lack a One Health approach to prevent human rabies deaths [79].

The WHO, the World Organization for Animal Health (OIE), the Food and Agriculture Organization (FAO) and the Global Alliance for Rabies Control (GARC) have developed a strategic global plan to end human canine-mediated rabies by 2030 [7, 12, 80]. This initiative provides a concerted approach to the prevention of rabies, combined with the strengthening of human and veterinary health systems. These would enable reaching out to the most underserved communities in the world by engaging, encouraging and supporting all countries to lead and improve elimination efforts [74]. This scoping review was therefore designed to map the evidence on rabies morbidity, mortality, integrated rabies surveillance, prevention and control in African countries. Its objectives were: (1) to assess the extent of available research on the morbidity and mortality of rabies due to animal bites conducted in Africa, (2) to identify research gaps in the literature on the impact of rabies in Africa so as to effectively plan public health intervention, (3) to ascertain the current level of rabies disease surveillance, prevention and control that exists in African countries, (4) to assess the published adverse events and complications associated with human rabies vaccination in African countries, (5) to assess the different types of vaccines used and the effectiveness of locally produced and imported vaccines in treating rabies in different parts of Africa, (6) to assess rabies morbidity and mortality associated with dog and contact with an suspect animal in humans.

2. Methodology

2.1. Study design

This paper works' used the PRISMA-ScR checklist [81] and The Joanna Briggs Institute guidelines [82] as a norm for reporting scoping review. The analysis was conducted in accordance with the structure suggested by [83], further developed by [84].

2.2. Eligibility criteria

The search was conducted from 1 January 1946 until 30 May 2020. A PICO (Population-Interventions-Comparisons-Outcomes) search framework was set, where P (Humans infected with rabies in African countries), I (Integrated rabies disease surveillance, prevention and control), C (little or no integrated rabies disease surveillance, prevention and control) and O (reduced human morbidity and mortality of rabies associated with animal bites) were chosen. The included studies are described in Supplementary Table 1.

2.3. Electronic search

We conducted a systematic search of the electronic databases Medline (OVID), EMBASE (OVID), Cinahl (EBSCOHost), Scopus (Elsevier), Web of Science and Conference (*rabiesalliance.org, www.who-rabies-bulletin.org and https://www.oie.int/*). The search techniques were limited to English. The main search strategy was listed in supplementary material 1. EndNote X9 reference manager was used to remove duplicates. JLT reviewed all the papers identified by title in order to pick those that were potentially appropriate, with a clear bias towards retention. The abstracts of all the studies chosen on the basis of their titles were independently reviewed by two reviewers (PSN and JTL) and any variations were preserved in the study.

2.4. Data charting process

For all studies selected at the abstract level, data were extracted and plotted in the table, covering author (year) and region, study design and data collection duration, Participants / Comparators, Interventions and Control Conditions / Exposures, outcomes (rabies mortality and morbidity) and Key Findings / Gaps / Challenges. The final decision to include studies was taken on the basis of this data extraction and whether it met the inclusion / exclusion requirements, based on an independent review by two authors (PSN and JLT) and a discussion of any differences; the third author (RT) was available for consultation if consensus could not be reached. Our inclusion criteria were: rabies occurrence or mortality rates, all ages included, only studies performed in Africa, studies in which at least one intervention included monitoring, prevention and control of rabies, and then only quantitative studies were included in this study.

A data extraction sheet has been developed and used to extract data from included papers. The data collection sheet included: author, region, year, study design, level of evidence, sample size description, interventions or exposures, results and key findings / Gaps / Challenges. Two reviewers (PSN & JLT) worked separately at all levels of the study. The results were then compared and any variations were addressed and resolved by PSN and JLT. The third author (RT), who also summarized the findings, was consulted when a discrepancy could not be resolved. The evaluation of the probability of bias, the methodological standard of the included studies was not assessed due to the scoping review of the study [83].

2.5. Data items

Seven items were listed in the data collection chart table. We included the first author, the year of publication of the study and the country (item 1). Study design and period of data collection (item 2). The sample size, mean or median age and gender (item 3). The intervention and control

conditions / exposures included surveillance, prevention and control of rabies and any other form of intervention used in human rabies (item 4). The number or rate of human rabies morbidity included annually or during the study period (item 5). Human rabies mortality recorded the death or mortality rate annually or during the study period (item 6). Main findings / gaps / challenges included other outcomes such as data gaps found, available research evidence as well as PEP or vaccine adverse events (item 7).

2.6. Critical appraisal of individual sources of evidence

Methodological quality of included studies was not evaluated due to the scoping nature of the review [84].

2.7. Synthesis of results

Studies were summarized based on author (year) and country, study designs, participants and comparator, interventions and control conditions/exposures, key outcomes, gaps, findings and challenges. Interventions were subdivided into rabies prevention, surveillance, control and management. Table, computed morbidity and mortality rates in case there were not clearly provided and then we reported the results narratively, as recommended in scoping review were methodological framework [83].

3. Results

3.1. Study selection

The searches from the five electronic databases hit a total of 2775 records (Medline: 696, Embase: 952, CINAHL: 289, Scopus: 431 and Web of science: 407) that led to a total of 1127 titles and abstracts that were screened after the removal of duplicates. We retained 111 of these based on their title and abstract screening. The full-text screening's stage led to 43 potential articles relevant to our scoping review. The scoping review flow chart was described in Figure 2.

3.2. Study characteristics

The review reported only quantitative studies on rabies surveillance, prevention and control. Thirty-two quantitative studies were retrospective cohort with 8 months to 14 years of study duration [21, 30-32, 34, 35, 37, 39-47, 49, 85-99], three studies were mixed designs (retrospective and cross-sectional study) [48, 100, 101], three prospective cohort studies [33, 36, 102], two Cross-sectional studies [103,104], one case control [38], one clinical trial [105] and a randomized control trial [106].

We grouped the included studies into five categories based on rabies interventions, namely 1) prevention and control, 2) surveillance, 3) surveillance and prevention, 4) treatment and control, and 5) surveillance, prevention and control. Figure 3 showed the distribution of studies according to the intervention in nineteen African countries. We also summarized all studies included in the final analyses in Supplementary Table 1 which included seven parts in line with the specified frameworks for data synthesis: (1) rabies morbidity, (2) rabies mortality, (3) interventions for rabies control, (4) rabies disease surveillance, prevention and control, (5) available research evidence, (6) research gaps identified and (7) adverse events and complications associated with rabies vaccination.

3.3. Patient characteristics

A total of 543,714 bite victims were recorded in included studies. Age and sex-specific distribution revealed that the most fatal cases belonged to age groups 0-14 year [30, 34, 36, 39, 44, 46, 47, 49, 85, 92, 93, 95,97, 101, 103]. Other studies identified rabies victims of 15 and above [31, 39, 40, 43, 47, 85, 96, 97, 101, 104]. The median age was 18 years in most of the studies and ranged from one to 95 years. Most of the children were males [46, 47, 95, 97]. However, other study has indicated that females have more animal-related bites than males [30]. Young children are at higher risk of contracting rabies in the absence of PEP and wound care due to the location of the bites they incur [103]. Based on the extent and depth of injury, 1, 567 victims were recorded. Extent and depth of injury was classified as skin broken (11.1 %), scratch (9.25 %), superficial (loss of epidermis only) (36.38 %), deep (27.31 %) and simple (affect only one tissue) (12.38 %) [30, 32, 102, 104]. Further 10, 006 bites were described in regard of the site of exposure among which the head/neck/face (5.08%), leg/feet (61.06%), arm/hand (23.23 %), buttocks/trunk (10.32 %) or multiple (0.31%) [30-34, 43, 48, 94, 96, 100, 103].

Individuals suspected to have rabies were clinically managed by the chief doctor pediatricians and nurses [33, 37, 38, 41, 85, 95, 100, 104]. The main treatments were wound management, antibiotics, prophylaxis against tetanus and rabies. Nine studies reported wound management as part of PEP [33, 38, 41, 48, 94-97]. Reports were collected in hospitals, treatment and health centres, health clinics and pharmacies [104].

3.4. Study outcomes

3.4.1. Rabies morbidity

Twenty-one studies reported rabies human morbidity in Africa (Table 1) [31, 35-40, 42, 44, 47, 49, 85, 87, 89-93, 98, 100-102, 104]. Among them, five studies were undertaken in Tanzania, the first study estimated an average annual incidence per 100,000 bites of 37.1, 11.3 and 33.5 in human population district of Ulanga (193280 inhabitants), Kilombero (321611 inhabitants) and Serengeti (176057 inhabitants) respectively [90]. The second study found that the incidence of bite patients seeking PEP declined substantially (>50%) from 2011 to 2015 [91]. The third study estimated an annual incidence of ~58 cases per 100,000 [42], the fourth study reported a mean incidence of 74 bites considered at risk of rabies transmission per 100,000 persons per year [98] and the last study conducted in Tanzania revealed an average of 75.6 and 19.3 probable rabies exposures per 100,000 persons per year [100]. Three studies conducted in Ghana reported 54 dog-bite victims bitten by rabies-positive dogs within three years [85], 13 cases of human rabies in a 6-year retrospective records review [39] and an annual incidence of rabies cases of 172 per 100,000 population [49]. Four studies reported rabies morbidity in Ethiopia. Yizengaw et al. 2018 reported a high incidence rate of rabies exposure during spring (360, 39%) and summer (244, 26.4%) seasons and a total of 924 human rabies exposure cases received the anti-rabies post-exposure prophylaxis from September 2015 to August 2017 [101]. The incidence of human rabies exposure was reported to be 40 per 100,000 population in Ethiopia [34], annual estimated rabies incidence of 2.33 cases per 100,000 in humans [102] and the incidence of human rabies exposure cases calculated per 100,000 populations was 35.8, 63.0, 89.8 and 73.1 in 2012, 2013, 2014 and 2015, respectively [94]. A study conducted in Zimbabwe found among rabies-suspect, 42 (73.7%) were positive [40]. In Madagascar, nine of the 11 suspected human cases tested from 2005 to 2010 with a laboratory confirmed for rabies [87]. In Uganda, a total of 208,720 patients with animal bite injuries were

treated at health facilities across the country [89]. Ivory Coast reported 50 cases of human rabies with annual incidence of 0.06−0.08 per 100,000 [36]. Human animal-bite injuries incidence was 289 per 100,000 persons with the highest incidence reported at 302 per 100,000 and lowest at 121 per 100,000 persons in Kenya [39]. Another undertaken in Malawi reported 14 paediatric rabies cases during the study period [93]. A six-year retrospective study revealed 31 positive cases of human rabies in Madagascar [47]. In Democratic Republic of Congo, a five year retrospective study found 29 positive to rabies in a total of 5,053 dog bites recorded in the veterinary clinics [35] and Frey 2013 estimated an annual incidence of bites from suspected rabid animals of 12.9/100 000 and an incidence of 0.7 human rabies deaths/ 100,000 in Chad [104]. Namibia reported above 16 cases per year from 2011 until 2015 with a maximum of 23 cases observed in 2015 with an incidence of 1.0 and 2.4 per 100,000 inhabitants and per year on average [44].

Table 1 : Mapping human rabies morbidity rate

Country (region, district and town)	Human rabies morbidity rate	Study duration
Chad (N'Djamena)	An annual incidence of bites from suspected rabid animals of 12.9/100 000 [104]	Seven months, September 2008 - April 2009 [104]
Democratic Republic of Congo (Kinshasa)	29 positives to rabies in 5,053 dog bites recorded in the veterinary clinics [35]	Five years, 2009-2011 [35]
Ethiopia (National level; Ababa and outside of Addis Ababa; North Gondar administrative zone)	A total of 924 human rabies reported [102]. The incidence of human rabies exposure was reported to be 40 per 100,000 population in Ethiopia [34]; Annual estimated rabies incidence of 2.33 cases per 100,000 in humans [102]; The incidence of human rabies exposure cases calculated per 100,000 populations was 35.8,	One year, January 2016-31 December 2016 [34]; Two years, 2015-2017 [101]; three years, 2012-2015 [92]; Eleven months, April 2009 - March 2010 [102].

	63.0, 89.8 and 73.1 every year [92]	
Ghana (Techiman Municipality; Eastern Region of Ghana)	54 dog-bite victims bitten by rabies-positive dogs [85]; 13 cases of human [39]; An annual incidence of rabies cases of 172 per a population of 100,000 [49]	Four years, 2009-2012 [85]; Six years, 2011-2016 [39]; Two years, 2013–2015 [49]
Ivory Coast (National level)	Annual incidence of 0.06−0.08 per 100,000 [36]	Three years, 2014-2016 [36]
Kenya (Machakos and Kitui counties in lower eastern region; Kisumu County in Lake Victoria basin; Nandi County in Central rift valley and Kilifi coastal region).	Human animal-bite injuries incidence of 289 per 100,000 persons [31]	Six years, 2011- 2016 [31]
Madagascar (National level)	Nine of the 11 suspected human cases tested with a laboratory confirmed for rabies [87]. 31 positive cases of human rabies reported [47].	Six years, 2006-2011 [87]; Six years, 2005-2010 [47]
Malawi (Blantyre)	14 paediatric rabies cases reported [93].	Six years, 2012-2017 [93]
Namibia (Kavango)	An incidence of 1.0 and 2.4 per 100,000 inhabitants and per year on average [44]	Seven years, 2011-2017 [44]
Tanzania (Mwanza region; Tabora; Shinyanga; Mara; Ulanga; Kilombero; Serengeti; Dodoma Region; Ngorongoro districts in northern Tanzania and in the 11 districts in southern)	Average annual incidence per 100,000 bites of 37.1, 11.3 and 33.5 in Human population [90] An incidence of bite patients seeking PEP declined substantially (>50%) [96]. An annual incidence of 58 cases per 100,000 [42] Mean incidence of 74 bites considered at risk of rabies transmission per 100,000 persons per year [98]. An average of 75.6 and 19.3 probable rabies exposures per 100,000 persons per year [100]	Five years, 2002-2006 [42]; Four years, 2002-2006; [90]; January 2011 to January 2013 [91]; Seven years, 2008-2014 [98]; 2002–2017; 2011–2017; 2011–2016 [100]
Uganda (National level)	208,720 patients with animal bite injuries treated at across the country [89].	Fourteen years, 2001-2015 [89]
Zimbabwe (National level)	Among rabies-suspect, 42 (73.7%) were positive [40].	Eleven years, 1992-2003 [40]

3.4.2. Rabies mortality

Sixteen studies reported rabies related mortality in Africa (Table 2) [21, 32, 38, 41, 43, 45, 46, 86, 88-90, 99, 100,102-104]. Ethiopia reported three studies among which 320 people, diagnosed clinically, died of rabies in a 5-year retrospective study conducted in the national level [21], 386 human rabies fatality were reported in a 8-year retrospective study with annual range of 35 to 58 deaths in Addis Ababa and outside of Addis Ababa [46]. There were also 32 cases in human rabies recorded from which three humans ended with fatality in North Gondar administrative zone [102]. Four studies assessed rabies mortality in Tanzania from which Ulanga, Kilombero and Serengeti districts reported human rabies mortality rates of 2.4; 0.8 and 1.4/100,000 per year respectively [90]. Sixteen human deaths (1,291 victims bite) due to rabies were reported within the Integrated Bite Case Management (IBCM) study across 20 districts in 4 regions in Southern, Central, and Northern Tanzania [99]. Other studies reported twenty-eight deaths from suspected rabies cases during the five-year period in the two districts, an average of 1.5/100,000 per year in Serengeti and 2.3/100,000 in Ngorongoro [45]. Fourteen (14) among 1005 victim bites died showing clinical signs of rabies within 5 years [100]. Three (3) studies identified rabies mortality in Uganda. Among them, were592 (95% CI 345–920) deaths [103], 1 dose of PET was sufficient for protection following a rabid animal bite. Another research estimated a total of 371 deaths of rabies with a cumulative total of 117,085 rabies cases in nine years [88] and a 14-year retrospective study revealed a total of 486 suspected human rabies deaths among 208,720 patients with animal bite injuries treated at health facilities across the country [89]. A study undertaken in Moramanga district (Madagascar) recorded an annual incidence of 42–110 rabies exposures and 1–3 deaths per 100,000 persons [32]. An estimated 7 rabies deaths (95% confidence interval 4–10 deaths) per year was recorded in N'Djamena (Chad) [102]. A study conducted in Algeria excluding Sahara

region found an annual average of 20.6 human rabies deaths [91]. A total of 14 cases of fatal rabies with 12 death reported in Maputo City is the capital of Mozambique [38]. An average annualized rabies attack rate of 136 rabies cases per 100 000 dog-bite injuries (7/5 139) with 6/7 deaths were reported in South Africa [43]. There were patients with furious rabies manifestations and the case-fatality rate of 100% in a study conducted in Kinshasa (DRC) [41].

Table 2: Mapping human rabies mortality rate

Country (region, district and town)	Morbidity rate	Study duration
Algeria (National level excluding Sahara region)	An annual average of 20.6 human rabies deaths [86]	Thirteen years, 2006-2018 [86]
Chad (N'Djamena)	An estimated 7 rabies deaths (95% confidence interval 4–10 deaths) per year [104]	Eight months, September 2008 to April 2009 [104]
Democratic Republic of Congo (Kinshasa)	Case-fatality rate of 100% [41]	Eight months, December 2008 and July 2009 [41]
Ethiopia (National level, Ababa and outside of Addis Ababa, North Gondar administrative zone)	320 people died of rabies in a 5-year [21]. 386 humans rabies fatality were reported with annual range of 35 to 58 deaths [46] 32 cases in human rabies recorded [102].	Five years, 1997-2001, [21]; Eight years, 2001-2009 [46]; Eleven months, April 2009 - March 2010 [102] One year, January 2016 - 31 December 2016 [34]; Two years, 2015-2017 [101]; three years, 2012-2015 [92]; Eleven months, April 2009 - March 2010 [102]
Madagascar (Moramanga district)	An annual incidence of 42–110 rabies exposures and 1–3 deaths per 100,000 persons [32]	One year, 2016-2017 [32]
Mozambique (Maputo city)	A total of 14 cases of fatal rabies with 12 deaths [35]	Three months, April - July 2014 [35]
South Africa (Uthungulu District of Kwazulu-Natal province)	An average annualized rabies attack rate of 136 rabies cases per 100 000 dog-bite injuries (7/5 139) with 6/7 [43]	Three years, 2008-2009 [43]
Tanzania (Ulanga, Kilombero and Serengeti districts; 20 districts in 4 regions in	Human rabies mortality rates of 2.4; 0.8 and 1.4/100,000 per year respectively [90].	Five years, 2002 - 2006 [45]; Three years, 2006-2008 [90];

Southern, Central, and Northern Tanzania; Serengeti and Ngorongoro)	Sixteen human deaths (1,291 victims bite) due to rabies were reported [100]. Twenty-eight deaths from suspected rabies cases during the five-year period in the two districts, an average of 1.5/100,000 per year and 2.3/100,000 [45] Fourteen (14) among 1005 victim bites died showing clinical signs of rabies within 5 years [100].	2002–2017; 2011–2017; 2011–2016 [100]
Uganda (National level; ten district)	592 (95% CI 345–920) deaths [103] An estimated a total of 371 deaths of rabies with a cumulative total of 117,085 rabies cases in nine years [88] A total of 486 suspected human rabies deaths among 208,720 patients in fourteen years[89]	Eight years, 2001 – 2009 [88]; Fourteen years, 2001–2015 [89]; Three months [103]

3.4.3. Rabies disease surveillance, prevention and control

3.4.3.1. Rabies prevention and control

The review summarized rabies prevention and control in point of view rabies exposure status, PEP, dog vaccination and seasonality. Among 36,741 bite victims recorded in studies reporting PEP [30, 42, 46, 85, 92, 93, 98], the PEP was initiated based on WHO grade of exposure [107]. We found 505 bites in grade 1 (8.78%), 2050 in grade 2 (35.63%) and 3199 in grade 3 (55.59%) [33,

34, 43, 96, 97]. The overall PEP course among bite victims varied between 24% to 99% [30, 85]. We reported 2,652 bites victims in studies reporting PEP and mass dog vaccination [34, 39, 40, 86, 101]. Dog vaccination coverage varied from 14.1% to 68.78% [34,86]. In Ethiopia and Zimbabwe, the dog vaccination decreased significantly across the study and also the health status of most dogs involved in biting was unknown [40,101]. Rabies prevention and control also depended on the seasonality. In Ethiopia, two studies reported season wise rabies exposure. The first study reported rabies exposure during spring (360/924, 39%) and summer (244/924, 26.4%) seasons [101]. The second study that found the highest human rabies exposures were reported in spring (April to June) followed by winter (January to March) while the lowest distribution of human rabies exposure was recorded in autumn (October to December) [34]. In Nigeria, Osaghae et al. reported the prevalence of dog bite was highest, 41/81 (50.6%), during the hot season (April–June) and low, 14/81 (17.3%), during the wet season (July–October) [94]. Another study conducted in Nigeria recorded the highest number of dog bites with two peaks in April and October 2008 [48]. However, the number of dog bite cases was lowest. For all years the numbers of dog bite cases recorded were lowest at the beginning of the year and dog bites increased during the last 3 months (October-December) of the year 2006 [48]. Animal-to-human rabies transmission was highest during the dry months of July to November in Zimbabwe [40]. In DRC, a study found there was no seasonal difference observed for rabies occurrence either for clinical cases or confirmed cases throughout the study period [35]. In Tanzania, each year, the majority of rabies cases were recorded during the period June to October [42]. In the dry season, significantly fewer rabies positive cases were reported than in the rainy season in Namibia [44]. In Chad, more rabies records per month were collected during the hot, dry season months (March and April), than during the dry season months (September–February) [104]. In Senegal, dig bite victims were higher in

dry season (Nov-May) than rainy season (June-Oct) [33]. Besides, bite victims in rural areas took longer, on average, to receive PEP than those in urban areas [90, 98, 101]. Probable human rabies cases were higher in rural than urban areas [34,36].

3.4.3.2. Rabies surveillance, prevention and control

The findings revealed that 39,802 bites victims were recorded in rabies surveillance and prevention interventions. The studies included laboratory, database and network surveillances [35, 37, 43, 47, 91]. The rabies prevention included PEP and dog vaccination. Laboratory surveillance has improved rabies diagnostic [35, 37, 43, 47, 91] and database and network surveillances improved mortality and morbidity records [36, 43, 91] and allowed better estimates of the true rabies burden [37] Further, Compliance with PEP regimens was significantly higher, rating from 83.7% to 93% in two studies [43, 91]. In contrast, dog vaccination remained low (10%-12.6%) [37, 47].

We found five studies including rabies diseases surveillance, prevention and control [32, 33, 38, 45, 99, 100]. Among them, three studies [33, 38, 45] have reported significantly improved rabies morbidity and mortality and also PEP uptake. The PEP uptake was 71% and it dramatically reduced the risk of developing rabies [40]. Another study did not report any death with high number of patients receiving PEP [33].

A combined strategy of mass dog vaccination, enhanced surveillance, and expanded access to PEP reduced the annual incidence of rabies exposures and deaths annually in Madagascar [32]. Strict measures such as vaccination of dogs in the neighborhoods where human rabies cases had occurred, mass vaccination campaign of dogs, participation of private veterinary clinics in animal vaccination, collection of stray dogs in selected neighborhoods and community education

regarding prevention and control measures had drastically reduced rabies cases in human to 14 during the study period in Mozambique [38].

3.4.3.3. Post exposure management

We found seven studies on rabies management and control. Among them, six studies addressed wound management and PEP [41, 48, 94, 95, 96, 104]. Wound severity was graded as follows, 0 = no apparent injury seen, 1 = skin scratch with no bleeding, 2 = minor wound with some bleeding, 3 = deep or multiple injury [96]. The reported severity of the wound was classified as deep wound, lacerated wound, superficial wound or scratch [104]. The severity of the injury was determined using the WHO dog bite injury grading system [107]. Soap, water, wound dressing, tetanus prophylaxis, anti-rabies vaccination, intravenous fluids, diazepam and antibiotics were also part of the management. The overall review reported 5754 bites managed according to the WHO dog bite injury grading system, 3199 (55.59%) were grade 3; 2050 (35.63%) were grade 2; and 505 (8.78%) were grade 1. In 52 cases (7%), grade of bite was not recorded [31, 32, 41, 94, 98].

3.4.4. Available research evidence on human rabies

Rabies cases in various committees emphasize the need for active surveillance by following up of people bitten by animals and mass dog vaccinations to alleviate the zoonotic threat of the virus [88]. Strengthening rabies surveillance, controlling rabies in dogs, proper post exposure management, increasing the awareness of the community and ensuring availability of post exposure prophylaxis at lower health facilities are the best approach of eliminating rabies [89, 93, 102]. Other studies have demonstrated that reinforcements of rabies surveillance system can improve rabies reporting, which ultimately allows for better estimates of the true

rabies burden in the countries [35, 37, 43, 91]. Compliance with PEP regimens was significantly higher for patients following the implementation of automated reminders in comparison to patients attending normal clinics [43, 91]. Other studies concluded that preventing dog bites would most effectively reduce bite injuries by improving public health education among children below 15 years [43]. Public health education is also enhanced by encouraging early PEP initiation and completion, development and implementation of responsible dog ownership, animal behaviour educational programmes as well as improving human and veterinary health linkages [31, 43]. Evidence also showed that no rabies victim in Mozambique received full post-exposure vaccination and the factors significantly associated with human rabies were: age <15 years ($p = 0.05$), bite by stray dog ($p = 0.002$), deep wound ($p = 0.02$), bite in the head ($p = 0.001$), bite by unimmunized dog ($p = 0.01$), no use of soap and water ($p = 0.001$), and no PEP ($p = 0.01$) [40]. Studies have shown that all the rabies vaccines including suckling mouse brain virus (SMBV), fetal bovine kidney virus (FBKV), purified chicken embryo cell rabies vaccine, purified vero cell rabies vaccine, sheep brain anti- rabies vaccine, human diploid-cell vaccine and Purified equine rabies immunoglobulin) and RIG were efficacious. However, the WHO and OIE contraindicated SMBV and FBKV in both animals and humans [30, 32, 33, 37, 46, 47, 103, 105, 106]. Furthermore, a clinical trial with a purified chicken embryo cell rabies vaccine dose used intramuscularly every two years generated ineffective immune response to rabies virus [105] as the Zagreb protocol (2 intradermal injections of 0.1 mL at two sites, deltoids and/or thighs, on days 0, 3, 7 and 28) was not applied. Even though a randomized control trial showed antibody response 26.7% of SMBV recipients and 28.6% of FBKV recipients within a week, both SMBV and FBKV were equally efficacious and well tolerated [106], however those vaccines are contraindicated by WHO because of its association with neurological adverse reactions (severe allergic

encephalomyelitis), further these vaccines are inferior to modern vaccine in terms of potency and immunogenicity [108]. The table 3 describes available research evidence on human rabies in Africa.

Table 3: Mapping human rabies evidence identified in Africa

Evidence map	Studies	Impacts/Outcomes
Strengthening rabies surveillance	[36,37,43,88,89,91,93,102]	Reinforcements of rabies surveillance system can improve rabies reporting and increasing the awareness of the community and ensuring availability of post exposure prophylaxis at lower health facilities are the best approach of eliminating rabies.
Automated SMS reminders and telephone contacts	[43,45, 91,99,100]	Compliance with PEP regimens was significantly higher for patients following the implementation of automated SMS reminders and telephone contacts.
Public health education (PEP initiation and completion, responsible dog ownership, behaviour educational programmes and veterinary health linkages)	[31,43,48,89,93,102]	Lack of enforcement of regulations for licensing of dogs and rabies vaccination increased human rabies morbidity and mortality.
Accurate rabies diagnostic	[32,36,37,39,40,47,87,100]	The diagnosis of dog bite and rabies was clinical and laboratory-based. This improved accurate rabies cases reporting.
Mass dog vaccination	[40,86,93]	Even though the 70% coverage was not achieved, there was an inverse relationship between dog vaccination coverage and dog rabies cases during the study period.

SMBV, FBKV, purified chicken embryo cell rabies vaccine, purified vero cell rabies vaccine, sheep brain anti- rabies vaccine, human diploid-cell vaccine and Purified equine rabies immunoglobulin (Zagreb protocol)	[30,32,33,36,47,103,105,106]	Studies have shown that all the rabies vaccines and RIG were efficacious and well tolerated. However, the WHO contraindicated SMBV and FBKV.
Effective rabies control and management	[37, 43, 86, 93]	PEP, mass dog vaccination, and WHO dog bite injury-grading system
Integrated bites case management/ Rabies Diseases Surveillance, Prevention and Control	[32,33, 38,45,99,100]	Studies have shown the importance of coordinated surveillance, prevention and control in the eradication of rabies.

3.4.5. Adverse events and complications associated with rabies vaccination

Adverse events and complications associated with rabies vaccination were reported based on SMBV, FBKV, purified chicken embryo cell rabies vaccine, purified vero cell rabies vaccine, sheep brain anti- rabies vaccine, human diploid-cell vaccine and purified equine rabies immunoglobulin. All the 4-dose or Zagreb regimen was reported in all the RIG [109]. Among the studies reporting rabies vaccination, only one study using a purified vero cell rabies vaccine at D0 (2 doses), D7 (one dose) and D21 (one dose) study found that adverse events occurred in 6% of the patients with two doses and after the third dose 3% developed adverse event However, most of the adverse events were minor and associated with headache fever and pain at the injection site that occurred simultaneously on the same day of the vaccine injection [33]. Other studies did not report any adverse events and complications associated with rabies vaccination [30, 32, 37, 46, 47,103, 105, 106].

3.4.6. Research gaps identified

In this review, we identified 66.67% African countries reporting poor rabies diagnostic capacity, 50 % reported the lack of coordinated surveillance, 50% showed the lack of PEP course completion, 22.22% had insufficient rabies control, and 77.78% had low dog vaccination coverage. Insufficient knowledge and practice on rabies prevention was also identified as a gap. However, we did not find enough studies to evaluate this gap in Africa (Table 4).

The recorded data available so far has showed the underestimation of rabies diagnosis, post exposure prophylaxis and fatal human cases and could be attributed to poor diagnostic capacity and the absence of national rabies surveillance system. In African countries, rabies diagnostic is mostly clinical [21, 31, 33-35, 38, 41, 43, 44, 46, 49, 88-90, 93-95, 98, 103, 104] Among eleven studies including human rabies surveillance, only four reported adequate and successful surveillances [36,37,43,91], twelve studies reported lack of accurate data or non-existing surveillance data [31, 35, 38, 43, 44, 47, 49, 87-89,103,104] (Table 4). Other studies reported that dog-bite victims did not complete the post exposure anti human rabies vaccine course and were not likely to be post exposure prophylaxis [32, 33, 36, 42, 43, 45, 85, 90, 95, 98, 100] (Table 4). The exposure victims considered to be at risk of rabies either did not receive any PEP or did not receive all PEP vaccinations due to unavailability, shortage, cost barriers, insufficient knowledge about prompt PEP, category 1 exposure injury or misadvise [37, 41, 43, 45, 48, 49, 96, 99, 100]. A study has reported that the lack of PEP was the cause of 100% fatality rate in Democratic Republic of Congo [41]. There was significant difference between rural and urban exposure cases in respect to the time of arrival to the hospital and living in rural area was statistically associated with loss to follow up after the first dose [35, 48, 98, 101]. There was also high human rabies exposure rate in children and in the rural community [32, 35, 98, 101]. Insufficient knowledge

about rabies dangers and prevention, particularly prompt PEP, but also wound management, was the main cause of rabies deaths [45]. A higher proportion of human rabies exposures was caused by unprovoked dogs and of these, the majority were unvaccinated [34, 48]. Dog vaccination remains an urgent intervention gap. Among eighteen studies conducted in nine countries, none of them reported the target of 70% of dog vaccination (Table 4). The highest dog vaccination rate was reported in Algeria (67.3%) [86] and the lowest in Madagascar (10%) [47].

Table 4: Mapping research gaps and strengths in Africa

African countries	Mapping research gaps and strengths in Africa					
	Diagnostic capacity	Coordinated surveillance	Lack of PEP course completion /PEP unavailable	Inefficient control	Insufficient knowledge and practice on rabies prevention	Low dog vaccination coverage(<70 %
Algeria	N/A	N/A	N/A	√ [91]	N/A	X [91]
Cameroon	√ [37]	√ [37]	X [37]	√ [37]	N/A	X [37]
Chad	X [109]	X [109]	X [109]	X [109]	N/A	X [109]
Democratic Republic of Congo	X [35,41]	X [35]	X [35,41]	X [35,43]	N/A	X [43]
Ethiopia	X [21,34,46]	N/A	X [92]	X [34,92,102]	X [102]	X [34,92,102]
Ghana	X [49]	X [49]	X [49,85]	X [39,49,85]	N/A	X [39,85]
Ivory Coast	√ [36]	√ [36]	X [36]	X [36]	N/A	X [36]
Kenya	X [31]	X [31]	X [31]	X [31]	N/A	N/A
Madagascar	√ [32,47,87]	X [47,87]	X [32,47]	X [32,47,87]	N/A	X [32,47]
Malawi	X [93]	√ [93]	√ [93]	√ [93]	N/A	N/A

Mozambique	X [38]	X [38]	X [38]	X [38]	N/A	X [38]
Namibia	X [44]	X [44]	N/A	X [44]	N/A	N/A
Nigeria	X [94,95]	N/A	X [48,94-96]	X [48,94-96]	N/A	X [48]
Senegal	X [33]	√ [33]	X [33]	X [33]	√ [33]	X [33]
Tanzania	X [91,98]	√ [90,98]	X [42,45,90,98,100]	X [42,45,90,98,100]	X [45]	N/A
Uganda	X [88,89,103]	X [88,89,103]	X [103]	X [88,89,103]	N/A	X [88,103]
South Africa	√ [43]	√ [43]	X [43,97]	√ [43]	N/A	N/A
Zimbabwe	√ [40]	√ [40]	N/A	X [40]	N/A	X [40]

Footnote: "X: research gaps identified in different included studies; √: research strengths identified in different studies; N/A: Not applicable"

4. Discussion

This is to our knowledge, the first scoping review synthesizing publically available data on rabies in Africa and to weigh such data in support of the global goal of 'zero human rabies deaths by 2030'. The purpose of this scoping analysis was to provide a summary of evidence on rabies morbidity, mortality, integrated rabies surveillance, prevention and control in Africa. Overall, studies have shown that African countries face a range of problems from the point of view of rabies surveillance, prevention and control that have a negative effect on rabies mortality and morbidity. Reviewing rabies morbidity and mortality rates across Africa, data obtained fluctuated largely over time and space in various countries, as well as in different regions or districts across the same area. While some countries may have shown significant improvement in rabies morbidity and mortality

data, the morbidity and mortality rates in Africa generally remain high. Included studies showed no standardization in reporting human rabies outcomes, human rabies morbidity and mortality rates were reported in term of annual incidence and number of infected human rabies and deaths related to rabies. Moreover, small-scale studies may not reflect the national or regional human rabies morbidity and mortality rates. Then this was difficult to have an accurate picture per country and assess human rabies situation between African countries.

These are the consequences of lack of laboratory rabies confirmation, epidemiological surveillance, inadequate mass dog vaccination and PEP policy, and unreported clinical cases in African countries. Lack of monitoring data on rabies or low data quality is problematic, resulting in rabies being poorly addressed in most African countries. Results have also shown that, of the eleven countries in which rabies surveillance has been applied, only four studies reported that surveillance decreased rabies morbidity and mortality [36, 37, 43, 91]. Comparing old and new data (before and after the "zero rabies by 2030" target), rabies diagnostic and surveillance has not improved in most of the African countries. As a result, well-structured rabies surveillance enhanced the reporting of morbidity and mortality and also has a visible impact on rabies elimination strategy in Africa. While strategies have been subdivided into surveillance, prevention, control and management of rabies (see table of included studies), only three studies have shown the efficacy of the combination of surveillance, prevention and control of rabies [33, 38, 45]. However, passive surveillance has shown its limitations in rabies elimination because cases are reported clinically with or without laboratory-based strategies, inducing inaccurate diagnostic, scarcity of laboratory confirmation and poor reporting system [31, 44, 47, 88, 89, 103]. This is why both passive and active surveillance are preferable to strengthen rabies monitoring and reporting in African countries [110]. Strengthening rabies surveillance also is the foundation of

the provision of actionable data for efficient management of wildlife diseases [111]. Besides, the review has shown that strengthening surveillance, prevention and management of rabies has shown good evidence in three separate studies [33, 38, 45]. Coordination of surveillance, prevention and control of rabies can play an important role in the eradication of rabies in Africa. It is worth noting that specific awareness of when and where disease occurs is essential to the formulation of prevention, control and elimination strategies [111].

As seen above, the implementation of different rabies interventions at national level has never been reached in African countries. It is vital that African countries achieve the 2030 target of eliminating human rabies by providing readily accessible and affordable PEP in all countries in the continent where rabies infection is endemic. The exposure victims considered to be at risk of rabies either did not receive any PEP or did not receive complete PEP vaccinations due to unavailability, shortage, cost barriers, insufficient knowledge about prompt PEP or misadvise [37,41,45,49,96,99,100]. This could be emulated from Thailand, which has significantly reduced human deaths from rabies to fewer than 10 cases per year by educating the public and health workers and delivering PEP free of charge across the country before mass dog vaccination achieved the minimum 70 per cent coverage [112,113]. When provided correctly and in a timely manner, rabies PEP is almost 100% effective in the prevention of disease [73,114]. The findings of the review revealed that the dog victims found to be at risk of rabies either did not receive PEP or did not receive all the PEP vaccines due to unavailability, shortages, cost barriers, long distance travel to the hospital or misadvise [32, 33, 36, 37, 41, 42, 45, 49, 85, 90, 95, 96, 98-100]. It is important to remember that PEP combined with other treatments such as soap, water, wound dressing, antibiotics, tetanus prophylaxis and anti-rabies vaccination has been shown to be beneficial for dog bite victims. Two studies have shown that compliance with PEP regimens was

substantially higher for patients who did not receive PEP after automated reminders [43, 91]. Taken together, our results point to a sub-optimal system requiring specific improvements to achieve prompt provision of rabies PEP for persons exposed to rabies [113].

Statistical modeling studies show that the annual vaccination of 70% of the canine population would induce adequate herd immunity to effectively eradicate canine rabies and subsequent human exposure [10, 45]. The lowest and highest reviewed dog vaccination rate was 10% and 67.3% respectively [10, 47] and no reliable data on dog vaccination were reported in most of the studies. This is because many campaigns, if conducted, struggle to achieve a 70% vaccination rate [10, 14]. This is due to husbandry practices, rabies knowledge, geographical area/location, and the ages of dogs [115]. Evidence has shown the dog mass vaccination systems have demonstrated some effectiveness in reducing human rabies morbidity and mortality in countries such as KwaZulu-Natal, South Africa [50, 66], Serengeti, Tanzania [50, 67, 69], Malawi [45, 70] and Chad [71, 72]. However, the Tanzanian study has shown that, if vaccine coverage was not sustained, rabies infection would resurface extremely quickly [35]. Despite effective monitoring of rabies at the Tanzania study site from 1998 to 2001, vaccine coverage decreased from 2001 to 2003 resulting in a new rabies outbreak, with human exposures increasing by six times in 2003 relative to previous years [45]. Further, free mass dog vaccination intervention has proven to increase dog vaccination coverage. Government and stakeholders work actively to provide a free sustainable dog vaccination.

Besides, the evidence has also illustrated the effectiveness of other strategies, such as mobile phone touch tracing strategies, new rabies vaccines, integrated bite case management, wound management were correlated with PEP and/or mass dog vaccination. Africa is yet to recognize

rabies as an immediate public health problem; this may be due to a lack of awareness of the burden of disease and inadequate surveillance. Policies should be put in place to raise awareness of rabies at grassroots level and coordination between the appropriate agencies for improvements of the policies [48, 55].

The World Animal Health Information System (WAHIS) is a well-established global animal disease reporting system that reproduces the data submitted by countries to the OIE, but is also constrained by the under-reporting problems inherent in national reporting systems [116,117]. The need for regional, One Health-oriented reporting network has therefore become apparent [118,119]. The development of rabies-specific regional bulletins has been extremely effective in the Pan-American Health Organization field [118]. The Database such as the New Latin American Rabies Surveillance System (SIRVERA) should be applicable in Africa.

Indeed, the elimination of rabies is not feasible without African cooperation. No single country will retain rabies-free status unless it is brought under control in neighboring countries [114]. Regionally organized efforts are required to eradicate human rabies, taking into account country-specific needs and socio-cultural acceptability [114]. Canine-rabies-endemic regions have formed international rabies networks based on the successful the Meeting of Rabies Program Directors of the Americas (REDIPRA) model which enables them to create a unified and directed approach towards elimination within their regions [120]. REDIPRA meetings can be considered a model for coordination and governance in the world [7, 119, 120]. In Africa, the Pan-African Rabies Control Network (PARACON) was formed under the secretariat of GARC, as an Africa-focused advisory and networking initiative [120]. It was established in order to unify all sub-Saharan African countries and any related rabies networks in a One Health approach towards rabies control and

elimination [120]. The PARACON facilitates the development and implementation of national rabies elimination strategies, with a focus on sustainability through governmental support [120]. However, the probability of meeting the 2030 goal without African and international solidarity is low, as more than two-thirds of countries are in the low-level human development community [121]. Leading countries should serve as role models, sharing their knowledge and skills so that no nation is left behind. African unification with international support will enable, the common goal of zero human rabies deaths to be achieved by 2030 [121]. Therefore, regional networks support, channel and pool efforts, support monitoring platforms will help make much progress [122]. Partnerships are important to the achievement of an objective and the last mile is going to be the most demanding [122]. In addition, contact and collaboration between human health and veterinary systems is also critical for the follow-up of both human and animal cases [123]. Data collected on alleged cases of human rabies, human exposures and rabid animals must be constantly reviewed and effectively disseminated [123]. Communication between the various national levels of healthcare administration is a crucial means of disseminating outcomes [123]. Finally, stakeholders need to be engaged in the long term to ensure that surveillance is effective [123]. Knowing that the Global Strategic Plan is catalytic and not intended to replace the strategies and commitments of individual countries [122], African countries should emphasize gaps, challenges, barriers and evidence applicable in the various districts, countries and regions as indicated in this present study. One Health interventions is provided by approaches to the prevention of human rabies deaths [124]. In African countries, the Ministry of Health, Animal Resources, Natural Resources, Environment and Tourism are in charge of implementing the canine and human rabies programs in accordance with local, national and international bodies.

Human rabies is 100% preventable through two complementary measures: first, PEP, which involves administration of rabies immunoglobulin and a multi-dose course of rabies vaccination to people bitten by suspected rabid animals; second, mass vaccination of animal reservoirs (primarily domestic dogs, the reservoir in the vast majority of human cases), which reduces the risk of human exposure and can ultimately result in rabies virus elimination [124].

New rabies control tests and technologies have been developed, such as oral rabies vaccine (ORV) may be considered as an additional tool for the canine rabies control and elimination. ORV is effective for instance in skunks, red foxes and raccoons, and lessons have been learned from recent outbreaks [125]. ORV has been demonstrated to be effective for the oral immunization of foxes, some of them being competitors for long baits year consumption. Switzerland eradicated wild rabies since 1985 [123]. However, Strategies to eliminate human rabies in Africa should adapt the REDIPRA model in African context, which emphasizes that people exposed to rabies have timely access to quality immunobiologicals, that appropriate levels of vaccination coverage in dogs in highly enzootic areas are maintained, that national rabies plans are strengthened and that systematic implementation is ensured, strengthen the surveillance system for human rabies transmitted by dogs and that national rabies plans are strengthened and that systematic implementation is ensured, training, and the development of a laboratory quality control system, particularly in highly enzootic areas, strengthen education, communication and advocacy in enzootic areas, to ensure the continuous political support that is necessary, develop and adopt a guide that delineates the requirements for declaring countries or areas free of human dog-transmitted rabies [120].

5. Conclusion

This comprehensive scoping review is of crucial importance in assessing various evidence of human rabies morbidity, mortality, monitoring, prevention and management. Rabies control strategies and case effects, available studies establishment to address various gaps are also important in the management of rabies in Africa. The analysis included past, existing and future viewpoints that are important for African countries to achieve zero dog-transmitted human rabies by 2030. The findings of forty-three studies included thirty-two quantitative retrospective studies, three mixed designs (retrospective and cross-sectional studies), three prospective cohort studies, two cross-sectional studies, one case control, one clinical trial and one randomized control study. Mapping the outcomes, the review included rabies morbidity (21 studies), mortality (15 studies), rabies prevention and control (16 studies), surveillance (9 studies), surveillance and prevention (5 studies), management and control (7 studies), surveillance, prevention and control (6 studies), strong research evidence (14 studies), rabies vaccination or PEP adverse events (4 studies) and research gaps were identified (41 studies).

Evidence has shown that human rabies morbidity and mortality remain high compared to rabies globally, and human rabies morbidity and mortality fluctuate in time and space across different African countries. In order to better understand this, the review has shown that monitoring, prevention and control of rabies diseases is inadequate and insufficient in most African countries. This is attributable to a variety of gaps and challenges across African countries. In addition, this study found insufficient and ineffective surveillance of rabies, unavailability of PEP, high cost, lack of information on prevention of rabies, and poor or non-existent data on dog vaccination. However, few studies have shown a thorough design of rabies measures such as enhanced

surveillance of rabies, regulation of rabies in dogs, proper post-exposure treatment, improved community awareness and availability of PEP in all rural areas, use of cell phone intervention to enhance surveillance of rabies, prevention and control of enhanced rabies morbidity, and more. In addition, African countries can learn about different community-based obstacles that can interfere with surveillance, prevention and control of rabies diseases. This is important to point out that no single country will preserve rabies-free status unless it is brought under control in neighboring countries [120]. That is why African countries should build a forum for rabies that may be significant to exchange data and experience on rabies. Finally, African countries can also look at futuristic rabies innovations such as ORV.

6. Patients and public involvement

No patients or the public were involved in this scoping review.

7. List of abbreviations

FBKV: Fetal Bovine Kidney Virus; FAO: Food and Agriculture Organization of the United Nations; GARC: Global Alliance for Rabies Control; JBI: Joanna Briggs Institute; OIE: World Organization for Animal Health; ORV: Oral Rabies Vaccine; PARACON: Pan-African Rabies Control Network; PEP: Post-Exposure Prophylaxis; PICO: Population-Interventions-Comparisons-Outcomes; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RABV: Rabies virus; REDIPRA: Rabies Program Directors of the Americas; RIG: Rabies Immunoglobulin; SMBV: Suckling Mouse Brain Virus; SIRVERA: New Latin American Rabies Surveillance System; WAHIS: World Animal Health Information System; V-RG: Vaccinia-rabies Glycoprotein Recombinant Virus; WHO: World Health Organization;

8. Footnotes

Author Contributions: PSN initiated the study project. PSN and JLT conducted the data extraction. Both authors wrote the review in consultation with JW, RT, AM, SVN, JLT, LN, NEN, GKH, MTG, AA, SD, RB and CD. All the authors reviewed and approved the final version of the manuscript.

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Ethics Approval: Since this is a scoping review, there is no institutional requirement to obtain ethical clearance from the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences, Stellenbosch University. We used data from open source and publicly available accessed on different databases as described in the methods.

Data availability statement: All data relevant to the study are included in the article.

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Figure legend/caption

Figure 1: Human rabies distribution in thirty-two African countries (2011)

Figure 2: Flow diagram of human rabies mortality and morbidity associated with animal bites in Africa.

Figure 3: Distribution of forty-three studies in African countries.

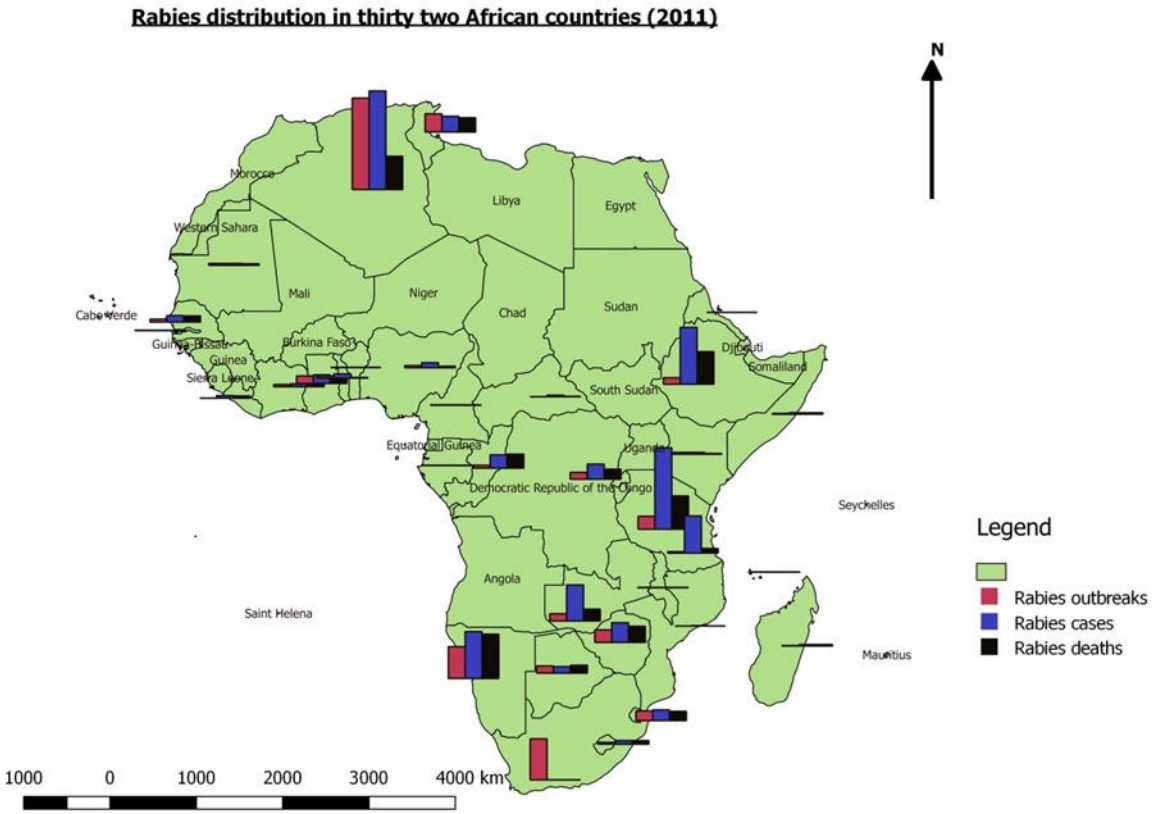

Figure 1: Human rabies distribution in thirty-two African countries (2011)

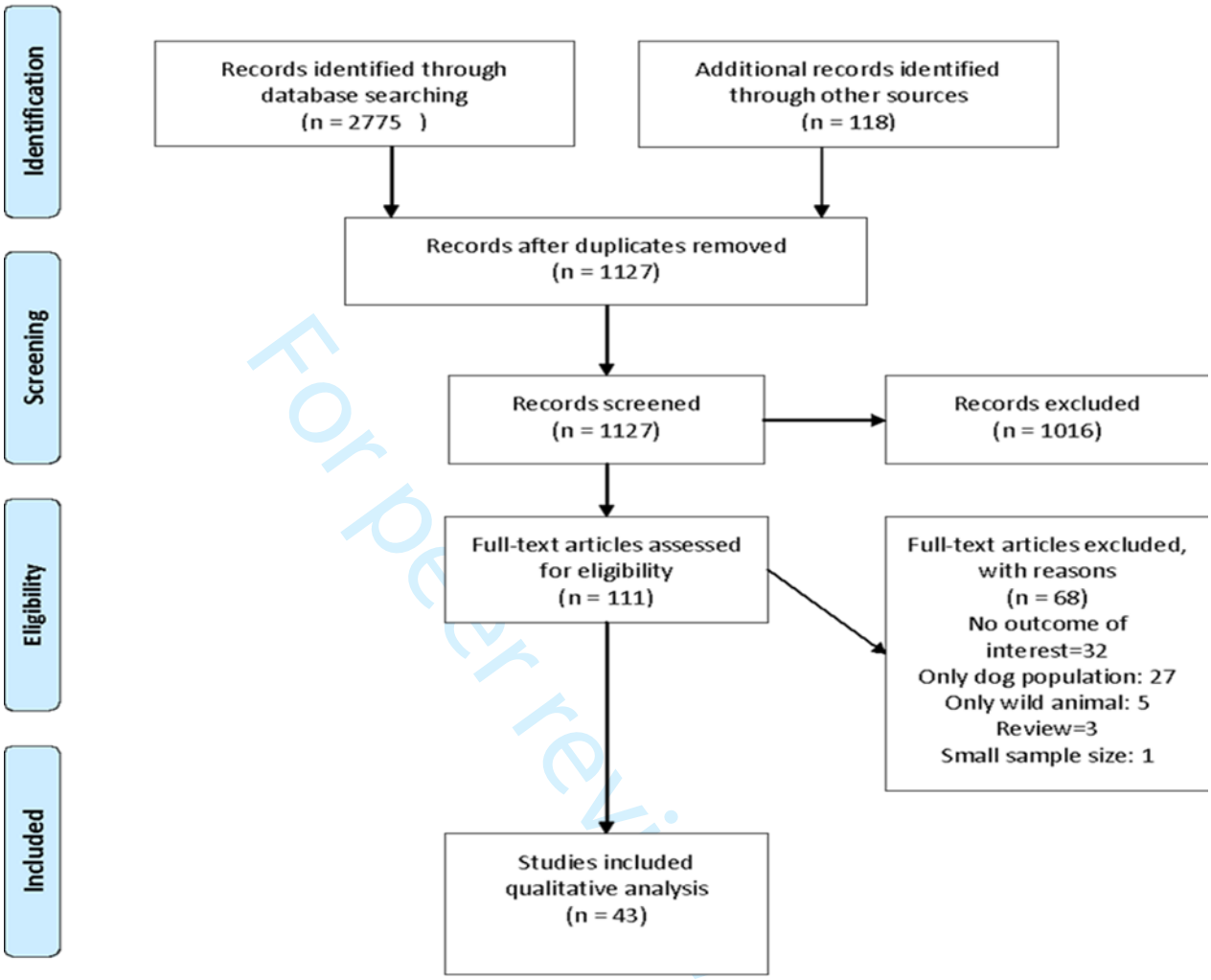

Figure 2: Flow diagram of human rabies mortality and morbidity associated with animal bites in Africa. Note From PRISMA: www.prisma-statement.org [81]

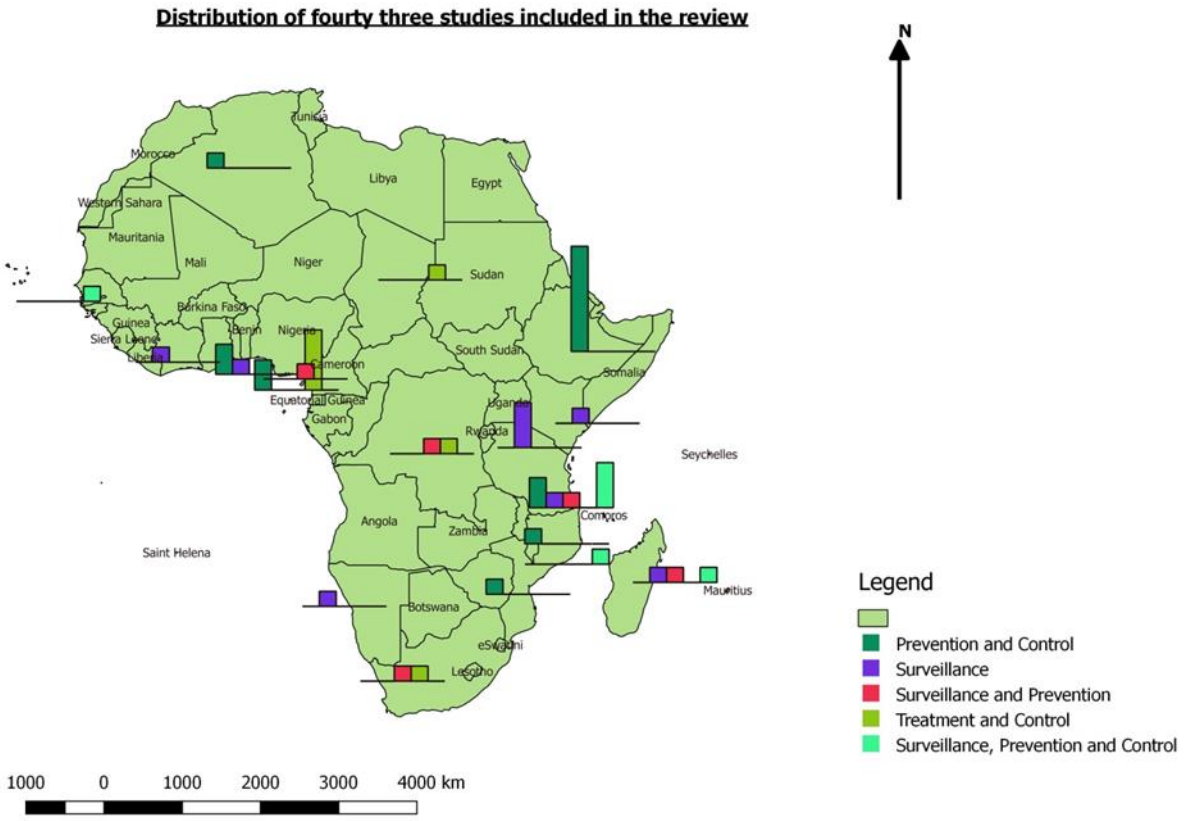

Figure 3: Distribution of forty-three studies in African countries.

Supplementary material 1

Search Strategy:

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to May 25, 2020>

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1 exp rabies/ or exp Rabies virus/ or rabies.mp.

2 africa*.mp. or exp Africa/

3 (Algeria or Angola or Benin or Botswana or Burkina Faso or Burundi or Cameroon or Cape Verde or "Central African republic" or Chad or Comoros or Congo or "Democratic Republic of Congo" or DRC or Djibouti or Equatorial guinea or Egypt or Eritrea or Ethiopia or Gabon or Gambia or Ghana or Guinea or Bissau or Ivory coast or "“Cote d ivoire" or Jamahiriya or Kenya or Lesotho or Liberia or Libya or Madagascar or Malawi or Mali or Mauritania or Mauritius or Mayotte or Morocco or Mozambique or Namibia or Niger or Nigeria or Principe or Reunion or Rhodesia or Rwanda or "Sao Tome" or Senegal or Seychelles or "Sierra Leone" or Somalia or "South Africa" or "St Helena" or Sudan or Swaziland or Tanzania or Togo or Tunisia or Uganda or Zaire or Zambia or Zimbabwe or "Central Africa" or "West Africa" or "East Africa" or "Southern Africa" or South Africa).mp.

4 2 or 3

5 1 and 4

6 mortality/ or mortality.mp.

7 fatality.mp.

8 morbidity.mp. or Morbidity/

9 surveillance.mp. or Population Surveillance/

10 (vaccine or vaccines).mp. or Vaccination/

11 6 or 7 or 8 or 9 or 10

12 Rabies Vaccines/

13 5 and 11

14 4 and 12

15 13 or 14

16 limit 15 to english language

Supplementary Table 1: Extracting and charting data table

Author(year) and country	Study designs	Participants/Comparators	Interventions and Control conditions/Exposures	Outcomes	Key findings/Gaps/Challenges
Rabies prevention and control					
Harry 1984 Nigeria	Randomized control trial	136 patients aged three to 74 years.	Controlled treatment of dog-bite victims with suckling mouse brain (SMBV) versus fetal bovine kidney (FBKV) rabies vaccines.	By day 7, 26.7% of SMBV recipients and 28.6% of FBKV recipients showed antibody response These percentages increased to 95.1 and 81.1, respectively, by day 14, and by day 20 (for SMBV recipients) or day 30 (FBKV recipients) the	We have concluded that both vaccines are equally efficacious and well tolerated.

				response was 100%. Titres dropped by day 90, but in no case to below 1 EU ml^{-1}	
Tefera 2002 Ethiopia	5-year retrospective study	15,940 people dog bite victims	post exposure anti-rabies prophylaxis treatment	320 people were reported to have died of rabies.	The result supports the hypothesis that there is a lack of appropriate reporting system on prevalence of rabies and its impact on humans.
Deressa 2010 Ethiopia	8-year retrospective study	17,204 people received post exposure treatment	Post Exposure Prophylaxis 5% suspension of phenolized sheep brain tissue.	The fatal human cases were 386 humans with annual range of 35 to 58. The age and sex specific distribution showed that the most fatal cases were 42% from the age-group 0-14 category.	PEP against rabies varies from 35.96% to 64.4% across the study. The recorded data showed the underestimate of rabies diagnosis, post exposure prophylaxis and fatal human cases, which could be attributed due to the

				According to this record 66.66% of deaths were males and 33.33% were females.	absence of national rabies surveillance system.
Olugasa 2010 Nigeria	Clinical trial	Of these 70 healthy individuals, 29 (41.4%) consisting of 15 zoological garden workers (75.0%), 13 veterinarians (65.0%) and 1 veterinary student (3.3%)	A purified chicken-embryo cell rabies vaccine One dose (1 ml of ≥2.5 IU/ml vaccine potency) was administered intramuscularly every two years immune to rabies virus (antibody titre >0.5 equivalent units per ml), while 41 (58.6%) were not immune.	Overall, antibody levels increased from 1-5 years to 10-30 years on the job.	Almost all those who had spent at least 10 years on the job had higher levels of rabies vaccination compliance and were immune.
Mazigo 2010 Tanzania	A 5-year retrospecti ve study	A total of 767 bite injuries inflicted by rabies-suspected animals were reported.	Adherence to post-exposure prophylaxis (PEP) regimen	mean annual incidence of ~58 cases per 100,000 (52.5% males, 47.5% females)	Only 28% of the victims completed the vaccination regime.

Jemberu 2013 Ethiopia	Cross-sectional and year prospective cohort study	120 selected dog owners 5 traditional healers in North Gondar zone, Ethiopia.	clinical observation A questionnaire on rabies people's knowledge and practices	Annual estimated rabies incidence of 2.33 cases per 100,000 in humans. During the follow up period, a total of 32 in humans were recorded from which 3 humans ended with fatality.	Vaccination of dogs, proper post exposure management, and increasing the awareness of the community are suggested to reduce the disease burden.
Edward 2014 Ghana	3-year retrospective study	546 dog-bite victims were reported; 295 (54%) were children < 15 years, 169 (31%) were between 15-59 years and 82 (13%) were above 60 years.	Post-exposure prophylaxis	54 dog-bite victims bitten by rabies-positive dogs were reported.	24% of dog-bite victims did not complete the post exposure anti human rabies vaccine course and were not likely to be postexposure prophylaxis.
Ramos 2015 Ethiopia	A retrospective, registry-based study	A total of 683 persons (51.1% females, 73% children) with animal-related bites.	All the patients received an anti-rabies nervous-tissue vaccine.	No important complications were reported.	99% of whom completed the vaccination course.

Kardjadj 2019 Algeria	A 13- year retrospecti ve study	Annual average of PEP cases: 96,203 people	post-exposure prophylaxis and dog vaccination	Annual average of 20.6 human rabies deaths	Overall dog rabies vaccination coverage rate of 68.78%.
Pfukenyi 2009 Zimbabwe	A retrospecti ve study	A total of 57 rabies-suspect human samples were examined and the 15–19-year age group had the highest number of cases.	Dog vaccination coverage	Among rabies-suspect, 42 (73.7%) were positive.	During the study period, there was an inverse relationship between dog vaccination coverage and dog rabies cases. Dog vaccination coverage decreased across the study from 100% to 50%.
Punguyire 2017 Ghana	6-year retrospecti ve records review	680 dog victims, the median age of rabies victims was 30 (range 3-80 years).	Post-exposure prophylaxis of rabies Dog rabies vaccination	13 cases of human rabies were recorded.	Less than 35% of the suspected rabies dogs that bit people over the period were vaccinated. About 20% of the offending dogs had unknown vaccination status.
Teklu 2017 Ethiopia	Four-year Retrospect ive Study	In total, 2180 human rabies exposure cases were registered and followed for their PEP. the greatest exposed age	Prior to PEP administration for humans. Dog vaccination	The incidence of human rabies exposure cases calculated per 100,000 populations was 35.8, 63.0, 89.8	The total annually allocated PEP to the region, nearly 60% was utilized.

		group was >=15 years in all the study years		and 73.1 in 2012, 2013, 2014 and 2015, respectively.	Data on the coverage of preventive dog vaccination and demography were not evident in the study area.
De Nardo 2018 Tanzania	6-year retrospecti ve study	14,624 patients attended the clinics because of animal's bites. Eighty-three per cent (12,098) individuals came from Dodoma Region.	The adherence to post-exposure prophylaxis (PEP)	Mean incidence of 74 bites considered at risk of rabies transmission per 100,000 persons per year.	Overall, 46.0% of the total number of individuals exposed to potentially rabid animals completed the PEP course, while 6.5% (698) did not receive any dose. Living in rural area was statistically associated with loss to follow up after the first dose ($p<0.001$) or after the second dose ($p<0.001$) Females were more likely to be lost after the first dose ($p = 0.006$).
Yizengaw 2018 Ethiopia	2-year retrospecti ve cross-sectional study	A total of 924 human rabies exposure cases received the anti-rabies post-exposure prophylaxis. Of these, males accounted 55.2%	Anti-rabies post exposure prophylaxis	High incidence rate of rabies exposure was reported during spring (339%) and	There was significant difference between rural and urban exposure cases ($p = 0.001$) in respect to the time of arrival to the hospital. There was high

		and the median age was 18 years (ranges: 1–80 years).	A structured data collection questionnaire	summer (26.4%) seasons.	human rabies exposure rate in children and in the rural community. The health status of most dogs (67.3%) involved in biting was unknown (they were stray dogs) and 28.8% were sick: develop the signs of rabid animal within ten days follow up.
Gebru 2019 Ethiopia	One-year retrospecti ve study	368 human rabies exposure cases. Age group of 5 to 14 years old.	Recommendation to start PEP immediately after exposure, depending on the type of exposure. Dog vaccination 14.1%	Incidence of human rabies exposure was 40 per 100,000 populations.	A higher proportion of human rabies exposures was caused by unprovoked dogs (96.5%; 95% CI, 94.0–98.0), and of these, the majority were unvaccinated (85.9%; 95% CI, 81.9–89.1).
Zimmer 2019 Malawi	6-year Retrospect ive study	Children victims of dog bite. The average age was seven years (range 3–11).	Pre and post a comprehensive canine vaccine campaign	14 paediatric rabies cases were found during the study period. More males than females were affected (males: 10	The study shows the importance of eliminating human rabies through canine rabies vaccination.

				(71%); females: 4 (29%)).	
Rabies surveillance					
Fevre 2005 Uganda	Cross-sectional study	A total of 517 patients were interviewed in 10 randomly selected districts in Uganda in the 3 months of the study.	Passive surveillance Survey of dog bite injuries and rabies post-exposure treatment activities in treatment centres supplied with rabies vaccine.	Death in absence of post-exposure prophylaxis (PET), 592 (95% CI 345–920) deaths One dose of PET is sufficient for protection following a rabid animal bite, 20 (95% CI 5–50) deaths annually. Complete course of PET is required for protection following a rabid animal bite, up to 210 (95% CI 115–359) deaths would occur, as 41% of patients did not	Most patients are bitten by dogs, and that a considerable proportion of these are young children, who are at greater risk of developing rabies in the absence of treatment due to the location of the bites they receive. Active animal bite surveillance studies are required to improve our mortality estimates and determine the true burden of rabies in the Ugandan population

				complete their course of PET.	
Reynes 2011 Madagascar	6-year retrospective study	11 human samples were tested for rabies.	Laboratory Surveillance of domestic or tame wild terrestrial mammal and dog brains tested.	Nine of the 11 suspected human cases tested were laboratory confirmed for rabies.	Rabies remains endemic in Madagascar. this study has found the lack of epidemiological data in Madagascar
Nyakarahuka 2012 Uganda	9-year retrospective study	Cumulative total of 117,085 rabies cases were reported in 9 years.	Surveillance reports from all the districts.	A total of 371 deaths of rabies were recorded.	Findings emphasize the need for active surveillance; follow up of people bitten by animals and mass dog vaccinations to alleviate this zoonotic threat.
Sambo 2013 Tanzania	Cross-sectional study	Human population (district) Ulanga: 193280 Kilombero: 321611 Serengeti: 176057 The ages of suspect bite victims ranged from 1 to	Extensive investigative interviews were used to estimate the incidence of human deaths and bite exposures.	Average annual incidence/ 100,000 Bites: 37.1;11.3 and 33.5 respectively Death: 2.4; 0.8 and 1.4 respectively	Ninety-four percent (391/415) of these suspects bite victims reported to health facilities for PEP.

		90 years. The majority of suspect bite victims (51%) were children less than 15 years of age.			
Adomako 2018 Ghana	3-year retrospecti ve study	Overall, 4821 dog victims' bites. Most of the cases were in children aged below 10 years.	The health and veterinary services on issues related to surveillance and data quality.	Annual incidence of rabies cases of 172 per a population of 100,000.	In the 82% of cases where data was available, no postexposure prophylaxis (PEP) was administered. The fatality rate was 100%. The study found gross disparities in the number of reported events and overall impression of underreporting.
Masiira 2018 Uganda	A 14-year retrospecti ve review	A total of 208,720 patients with animal bite injuries were treated at health facilities across the country. Up to 81% were patients >=5 years of age and 19% (n = 9,102) were below 5 years of age.	Epidemiological surveillance data .	A total of 486 suspected human rabies deaths were reported.	Strengthening rabies surveillance, controlling rabies in dogs and ensuring availability of post exposure prophylaxis at lower health facilities are the best approach of eliminating rabies.

Tiembre 2018 Ivory Coast	A 2-year descriptive prospective observational study	2968 weekly reports, all were received by the NIPH Anti-rabies Center. Almost one-half of the human rabies cases were in children <=15 years old.	Human rabies surveillance system in those 28 NIPH local units, with specific goals of improving the infrastructure, training, communication, and government involvement.	50 cases of human rabies (15±18 cases/year; annual incidence = 0.06−0.08per 100,000) and more than 30,000 animal exposures (annual incidence = 41.8−48.0 per 100,000).	The study is the result of enhancing human rabies surveillance in Ivory Coast None of cases had received PEP. Post-exposure prophylaxis with rabies vaccine was administered to all animal exposure victims presenting at the NIPH local units; only about 57% completed the full immunization schedule.
Ngugi 2018 Kenya	5-year retrospective study	Among 7307 records analyzed, 7201 (98.6%) had age recorded. The median age was 22 years	Surveillance of PEP was given, and number of PEP doses administered.	Human animal-bite injuries incidence was 289 per 100,000 persons with the highest incidence reported at 302 per 100,000 and lowest at 121 per 100,000 persons.	The study concluded preventing dog bites would most effectively reduce bite injuries by improving public health education among children below 15 years, encouraging early PEP initiation and completion, development and implementation of responsible dog ownership and animal behaviour, educational programmes as well as improving human

					and veterinary health linkages.
Hikufe 2019 Namibia	6-year retrospecti ve study	Of the total number of 113 cases, the majority (67%) were children and teenagers below 16 years of age, peaking at 5–9 years.	Human rabies surveillance data were retrieved from the epidemiological database of the Ministry of Health. Surveillance in animals is based on the reporting of all suspected cases.	Rabies cases have been above 16 cases per year from 2011 until 2015 with a maximum of 23 cases observed in 2015. Incidence: 1.0 and 2.4 per 100,000 inhabitants and per year on average.	Kavango, the region with the highest human rabies incidence was also the region with the lowest animal rabies surveillance intensity.
Rabies surveillance and prevention					
Andriamandi mby 2013 La Reunion, Mayotte, and Madagascar	6-year Retrospect ive study	24 946 patients visited the ARMC at the IPM, of which 97.2% (n = 24 299) received PEP. Males represented 54.3% (n = 13 556) of the cases and ranged in age from one to 97 years (median	Laboratory surveillance of rabies Post-exposure prophylaxis of rabies	31 positive cases of human rabies	None of these patients received PEP except for one who started PEP late, 10 days after the suspected bite.

		= 18 years). Children under 15 years old represented 40.5% (n = 10 107) of the consultants.			Dog vaccination coverage in Madagascar was 10%
Kubheka 2013 South Africa	3-year retrospecti ve study	2 601 patients who were offered rabies PEP. The median age of the people bitten by dogs during the two years was 20 years (with a range from 1- 92 years). The majority (61.3%) were aged 5-29 years old.	human rabies surveillance database the uptake of the rabies PEP and patients telephone contact.	An average annualized rabies attack rate of 136 rabies cases per 100 000 dog-bite injuries (7/5 139). 6/7 died	83.7% [95% confidence interval (CI): 82.4-85.2] completed the PEP treatment.
Sofeu 2018 Cameroon	A one year retrospecti ve study	A total of 1,402 animal exposures were reported in the West region of Cameroon.	The surveillance network consisted of local, regional, and national health and veterinary authorities. PEP and immunizations received prior to the current exposure; and the wound treatment were recorded.	Overall incidence rate of 6.1 exposures per 100,000 people. One was confirmed positive for rabies	Overall, at least 421 (60%) of the exposure victims considered to be at risk of rabies either did not receive any PEP or did not receive all PEP vaccinations. Only 12.6% (117/925) of dogs were reported to have been vaccinated and only 14.4% of the animal exposure cases were

					followed-up with a visit by a veterinarian No adverse events to PEP were reported.
Mtema 2016 Tanzania	A 5-year retrospecti ve study	Reports recorded bite patients seeking PEP (14,565 records, 49%), detailing visits of approximately 5,800 patients.	Automated SMS (short message service, commonly known as a "text" message) reminders to patients due for further PEP doses. Mass dog vaccinations Mobile Phones as Surveillance Tools	Human rabies cases (42 reported) reflected issues with PEP supply. Incidence of bite patients seeking PEP declined substantially (>50%)	Compliance with PEP regimens was significantly higher for patients following the implementation of automated reminders in comparison to patients attending clinics prior 7% of patients failed to obtain PEP.
Twabela 2016 DRC	A 5-year retrospecti ve study	A total of 5,053 attacks were recorded in the veterinary clinics.	Laboratory surveillance PEP and immunizations	29 were found positive to rabies.	Rabies cases were three times higher in peri-urban zone than in urban zone. It was observed that among the 5,053 attacks registered, 83 (1.6%) animals were killed and 15 (0.3%) disappeared just after attack

					without a follow-up or a veterinary observation.
Post exposure management					
Osaghae 2011 Nigeria	A twelve-year retrospective study	105 episodes of human and animal bites Recorded. Comparators: N/A	Wound Management Twenty (%) domestic dogs were vaccinated while 11(%) and six (%) were not vaccinated and without known vaccination status respectively.	A 10-year-old girl had rabies and died on the second day of admission.	The anti-rabies vaccine was not administered to the children bitten by the vaccinated animals.
Alabi 2014 Nigeria	3-year retrospective study and cross-sectional study	Only 195 (50.9%) of the 383 bite victims linked to a positive dog specimen could be traced. About three quarters (141 (73%)) of the victims were aged <16 years.	A review of detailed profiles of dog bite victims managed in the clinics.	54% of the victims took complete PEP. For those who did not complete PEP, 93% of the biting dogs were not vaccinated.	It has shown lack of enforcement of regulations for licensing of dogs and rabies vaccination.

Muyila 2014 DRC	A 8-month retrospecti ve study	21 cases were observed, rather three cases per month. There were 12 boys (57.1%) and 9 girls (42.9%). Biting animal was found to be dog in all cases (100%).	(9.5%) had their wounds treated and received an anti-rabies vaccine (ARV) after the bite incident. Two (9.5%) patients received rabies immunoglobulin (RIG).	100% of patients showed furious rabies manifestations The case-fatality rate was 100%.	The study revealed the dogs were not immunized for rabies.
Frey 2013 Chad	Cross-sectional study	Of 86 people exposed to a suspected rabid animal. The median age was 18 years, with a range between. 2 months and 79 years.	Post-exposure vaccination and wound cleaned.	Estimated annual incidence of bites from suspected rabid animals of 12.9/100 000 and an incidence of 0.7 human rabies deaths/ 100 000, resulting in 7 estimated deaths (95% confidence interval 4–10 deaths) per year.	50% received post-exposure vaccination and a further 8% had their wound cleaned.
Ogundare 2017 Nigeria	A retrospecti ve study	In all, 84 cases of dog bite injuries were managed constituting 0.89% of the total consultations. Most of	Treatments received in the hospital ranged from washing the bite site with soap and water, to suturing of	Six (7.1%) of cases had rabies and died.	Although seventy-eight (92.9%) of the victims had post-exposure prophylaxis (PEP) with anti-rabies vaccine, only 45 (53.6%) of

		the victims were aged 6-12 years (60.7%) and majority (71.4%) was boys.	lacerations and wound dressing, analgesics, tetanus prophylaxis, anti-rabies vaccination (ARV), intravenous fluids and diazepam administration as well as antibiotics administration.		them were managed successfully and subsequently discharged after ensuring adequate wound healing and completion of the vaccination regimen. Thirty-three (39.3%) were lost to follow up.
Abubakar 2012 Nigeria	A 10-year retrospecti ve study	81victims of dog bite injuries. The majority, 45 (55.6%), were children less than 18 years while 36 (44.4%) were adults.	Wound care PEP and the Immunization schedule	Two cases of clinical rabies were seen during the study period.	Prevalence of dog bite was highest, 41 (50.6%), during the hot season (April–June) and low, 14 (17.3%), during the wet season (July–October). None of the victims was previously immunized against rabies.
Kent 2012 South Africa	A 4-year retrospecti ve study	A total of 821 patients complaining of dog bite. Male children aged 6 - 10 years are most likely to present with dog bites.	Advice only Wound management Give vaccine Give anti-rabies immunoglobulin	Of the 821 bites, 642 (78%) were grade 3; 84 (10%) were grade 2; and 43 (5%) were grade 1. In 52 cases (7%), grade of bite was not recorded. Treatment with	Males present more frequently than females, and young males (ages 6 - 10) are most likely to present. This trend reverses after the age of 40 years, when females are more likely to present than males. We also showed that 99%

				rabies vaccine was started in 90% of cases of grade 1 bites, 97% of grade 2 bites and 99% of grade 3 bites. Immunoglobulin was administered for 53% of grade 1 bites, 84% of grade 2 bites and 82% of grade 3 bites.	of grade 3 bite patients are treated with rabies vaccine, but the rate of treatment with immunoglobulin is lower (82%).
Rabies Diseases Surveillance, Prevention and Control					
Lushasi 2020 Tanzania	Multi-center retrospecti ve study	1,291 victims' bite. The study was undertaken across 20 districts in 4 regions in Southern, Central, and Northern Tanzania.	Integrated Bite Case Management (IBCM). We trained government staff to implement IBCM, comprising risk assessments of bite patients by health	Only 63 of these bite patients were referred to other facilities for PEP with 43 assessed as being suspect rabies exposures. Sixteen human deaths due to	Throughout the study regions, PEP was unavailable for 74 bite patients (5.7%) upon presentation to a health facility, during the period of IBCM implementation.

			workers, investigations by livestock field officers to diagnose rabid animals, and use of a mobile phone application to support integration.	rabies were reported within the IBCM study districts. Overall bite patient presentations corresponded to an incidence of 17.4 bites per 100,000 persons per annum.	
Changalucha 2019 Tanzania	5-year retrospective and cross-sectional study	About 36% of patient presentations at health facilities were due to bites from probable rabid dogs (1,878/5,162 patients that sought care) as assessed through contact tracing, with the remainder from healthy animals or animals with unknown status.	Mobile phone-based surveillance records PEP was supplied free-of-charge to hospitals and selected outlying facilities in each district and training was provided to over 300 health workers in use of the updated Thai Red	We detected an average of 75.6 and 19.3 probable rabies exposures per 100,000 persons per year. Of 1005 individuals identified during contact tracing who received late and/or incomplete postexposure vaccination, 14 died showing	Upon seeking care, a further 15% of probable rabies exposed persons did not obtain PEP due to shortages, cost barriers or mis advice. Of those that initiated PEP, 46% did not complete the course. Decentralized and free PEP increased the probability that patients received PEP and reduced delays in initiating PEP.

			Cross ID regimen (5-dose Essen IM regimen). Qualitative interviews with stakeholders at different levels within the health system to characterize the logistics associated with PEP provision.	clinical signs of rabies.	
Rajeev 2019 Madagascar	One-year retrospective study	1019 patients reported to the anti-rabies medical centers (ARMC).	A combined strategy of mass dog vaccination, enhanced surveillance, and expanded access to PEP.	Annual incidence of 42–110 rabies exposures and 1–3 deaths per 100,000 persons annually. Extrapolating an annual burden of 282–745 human rabies deaths with current PEP provisioning averting 1499–3958 deaths each year.	A high proportion of rabies-exposed persons from Moramanga sought (84%) and completed PEP (90% of those that initiated PEP).

Diallo 2019 Senegal	A prospective cohort study was carried out from April 1,2013 to March 31, 2014,	1036 patients sought a consultation at the Pasteur Institute of Dakar for suspicion of rabies exposure.	Post-exposure prophylaxis implementation (consists of injection of four intramuscular doses of a purified vero cell rabies vaccine). Dog rabies vaccination treatment (local treatment of injuries, antibiotics administration, and previous rabies vaccination), knowledge of rabies and attitudes in respect to animal bite.	No death was reported during the study period. Adverse events were reported after the first two doses by 6% of the patients (42/678) (including 5 patients who also received equine RIG at D0), and after the third dose, by 3% (16/493). Most of them were minor: headache (46.5%), fever (31%) and pain at the injection site (22%), and mostly (74%) occurred on the same day of the vaccine injection (up to 7 days).	Out of the patients receiving PEP, 162 (18%) patients received two doses only at D0, 185 (20.5%) three doses at D0 and D7 and 493 (54.5%) completed the full 4-dose schedule.

Hampson 2008 Tanzania	5-year retrospecti ve study	1080 people were traced and interviewed who had been bitten by animals.	Contact tracing was used to gather data on rabies exposures, post-exposure prophylaxis (PEP) delivered and deaths case reports from livestock offices and community-based surveillance activities.	Twenty-eight deaths from suspected rabies were recorded during the five-year period in the two districts, an average of 1.5/100,000 per year in Serengeti and 2.3 in Ngorongoro	Insufficient knowledge about rabies dangers and prevention, particularly prompt PEP, but also wound management, was the main cause of rabies deaths. Received PEP: 685 (71%) Attended hospital: 971 (85%) PEP dramatically reduced the risk of developing rabies (OR 17.33, 95% CI 6.39–60.83).
Salomão 2017 Mozambique	A case control study	819 cases of animal bites were registered, of which 64.6% (529/819) were from Maputo City. Same neighborhood close to the human rabies victim's house were used as controls (case: control ratio of 1:4).	Affixing posters in health units regarding treatment of animal bites and post-exposure prophylaxis. Delivery of additional quantities of anti-rabies vaccine to the Prophylaxis.	A total of 14 cases of fatal rabies, among them 12 died.	No rabies victim received full post-exposure vaccination Factors significantly associated with human rabies were age <15 years (p = 0.05), bite by stray dog (p = 0.002), deep wound (p = 0.02), bite in the head (p = 0.001), bite by

			Decentralization of post-exposure prophylaxis. Vaccination of dogs in the neighborhoods where human rabies cases had occurred. Mass vaccination campaign of dogs. Participation of private veterinary clinics in animal vaccination. Collection of stray dogs in selected neighborhoods. Community education regarding prevention and control measures.		unimmunized dog (p = 0.01), no use of soap and water (p = 0.001), and no post-exposure prophylaxis (p = 0.01).

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	Page 1; Lines 1-2
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	Page 3-4; Lines 32-57
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	Page 6-11; Lines 77-207
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	Page 11; Lines 199-207
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	Not applicable
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	Page 12; Lines 214-220
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	Page 12; Lines 222-224
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Page 12; Lines 225-226
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Pages 12-13; Lines 226-230
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	Page 13; Lines 232-250
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	Page 14; Lines 251-260
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	Page 14; Lines 261-263
Synthesis of results	13	Describe the methods of handling and summarizing the	Page 14;

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
		data that were charted.	Lines 264-270
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Page 15; Lines 273-278
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Page 16; Lines 280-314
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Not applicable
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	page 60-73
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Page 17-34; Lines 316-533
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	Page 35-41; Lines 534-679
Limitations	20	Discuss the limitations of the scoping review process.	Page 5; Lines 66-75
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	Page 41-42; Lines 680-710
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	Page 41; Line 728

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.