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RABIES IMMUNOGLOBULIN: Brief history and recent experiences in Côte d'Ivoire

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A B S T R A C T

Background: Rabies is a fatal viral zoonosis mainly transmitted via dog bites.
The estimated 59′000 annual deaths caused by the disease are preventable through correct and timely administration of post-exposure prophylaxis (PEP). PEP should be initiated as soon as possible after an exposure to a rabies suspected animal and consists of a course of active vaccinations and administration of rabies immunoglobulin (RIG) in case of severe exposure. However, RIG is not accessible in most rabies endemic countries and its impact on survival in combination with modern vaccines and its cost-effectiveness is unclear. We examined the effect of equine RIG (eRIG) in a field-trial in Côte d'Ivoire, a developing country with low but chronic rabies burden and persistent lack of RIG, similar to a majority of rabies endemic countries attempting elimination of the disease.
Methods: Data from 3367 patients attending anti-rabies centers (Centres Anti-Rabiques, CARs) of the National Institute for Public Hygiene (Institut National d'Hygiène Publique, INHP) in the departments of Bouaké and San Pédro in Côte d'Ivoire was prospectively collected between April 2016 and March 2018. We identified 1594 patients at risk of rabies infection as eligible for RIG administration. Depending on local availability of eRIG and vaccination protocol applied, PEP consisted of active immunization only (non-eRIG group, $n = 1145$) or active and passive immunization (eRIG group, $n = 449$). Patients were followed-up by phone interviews at least 15 months after their exposure to assess for rabies suspected deaths.
Results: Follow-up data was available for 641 patients in the non-eRIG group (56%) and 242 in the eRIG group (54%). Three suspected or possible rabies deaths occurred in each of the two groups, corresponding to a possible rabies mortality of 1.2% (95% CI 0.3–3.6%) in the eRIG group and 0.5% (95% CI 0.1–1.4%) in the non-eRIG group. The difference in proportions was small and not statistically significant (0.7%, $p = 0.21$). Deaths in both groups were associated with treatment delay after exposure and non-compliance to PEP protocol. No death occurred after correct and timely active immunization independent of eRIG administration.
Conclusion: The provision of eRIG did not lead to a measurable reduction of rabies burden in our study population. This underlines that improved access to active vaccines will be effective in reducing rabies deaths even if access to eRIG remains difficult in developing countries. A possible benefit of eRIG administration for severely exposed patients cannot be excluded based on these results.

1. Introduction

1.1. Rabies

Rabies is a viral zoonosis transmitted by contact with saliva of infected carriers through broken skin or mucosa (Knobel et al., 2005). The global burden is estimated at about 59′000 deaths and more than 3.7 million disability-adjusted life years (DALYs) annually (Hampson et al., 2015b; Knobel et al., 2005). It causes acute encephalitis and is consistently lethal once clinical symptoms occur. However, very effective available cell culture vaccines (CCVs) could prevent the deadly burden (Quiambao et al., 2005), through elimination of the disease in the canine reservoir in the longer term (Zinsstag et al., 2009) and, until then, by immunization of humans, either before or after a potentially infectious exposure (pre- or post-exposure prophylaxis; PrEP or PEP). Elimination of the virus in the dog population would lead to a massive and sustainable reduction of human deaths (Lavan et al., 2017). However, optimal human immunization is essential to limit the burden until elimination in the dog population is achieved. In Asia and Africa, the continents with the highest rabies burden, PEP remains the main tool to protect bite victims from deadly rabies infection (Quiambao et al., 2005). Unfortunately, access to adequate PEP is limited for many victims in the most affected resource-poor countries due to low health seeking, high costs and limited availability of vaccines and weak compliance to guidelines (Hampson et al., 2008).

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1.2. Current recommendations for pep and rabies immunoglobulin (RIG)

The WHO protocol for PEP after exposure to a potentially infectious animal includes thorough wound cleansing, local disinfection and initiation of a course of vaccinations with CCV as soon as possible after the incident (World Health, 2018a). For transdermal bites and scratches, contamination of mucous membranes or broken skin with saliva from a potentially infectious animal or contact with bats (WHO grade III exposures (World Health, 2013)), passive immunization with rabies immunoglobulin (RIG) should be administered together with the first dose of vaccine in patients without previous rabies vaccination (World Health, 2018a). RIG should not be administered more than seven days after the first dose of vaccine, as it is of no use once circulating antibodies subsequent to active vaccination are present (World Health, 2018b). The maximum dose of RIG is calculated depending on patient body weight (20 IU/kg for human origin RIG (hRIG) and 40 IU/kg for equine origin RIG (eRIG)). As much of the calculated dose as is anatomically feasible, without risking compartment syndrome, should be infiltrated locally around the wound. Any dose remaining after local infiltration should be aseptically stored and used for other patients during the same day. Only in cases of high likelihood of additional small wounds, exposure to bats or exposure other than through a bite is it recommended to inject remaining RIG intramuscularly as close as possible to the presumed exposure site provided excessive pressure is avoided, as this can cause compartment syndrome. In cases of aerosol or mucosal exposure with no wound, intramuscular injection of RIG is recommended (World Health, 2018b). If the calculated RIG volume is not sufficient to infiltrate all wounds, it should be diluted with physiologically buffered saline to a sufficient volume for complete infiltration of all wounds. If RIG stock is not sufficient for all patients with grade III exposures, its allocation is prioritized according to the following criteria: multiple bites, deep wounds, bites to highly innervated areas of the body (head, neck or hands), severe immunodeficiency, confirmed or probable rabies infected aggressing animals and exposures to bats. (World Health, 2018a).

1.3. History of RIG

For better understanding of the relevance of RIG in modern PEP, we summarize the evolution of its use and commemorate the essential milestone studies.

1.3.1. Early experiments 1890–1950

In the late 19th century, rabies serum from immunized dogs was first prepared (Habel, 1945; Stuart and Krikorian, 1929). Numerous experiments evaluating its effect in animals and humans were conducted until the 1930s. The number of participants in these initial experiments was small, conditions were poorly controlled, and results on a possible protective effect against rabies infection after a bite incident remained largely inconclusive (Cabasso et al., 1971). In the 1930s and 1940s larger case series in humans and better standardized animal experiments were published, suggesting best protection after a bite incident was achieved with combined administration of active vaccine and serum together (Habel, 1945). The observation that injection of the serum around the wound site provided better protection than distant administration led to the theory of a local virus binding effect of the antibodies (Habel, 1945). A concomitant hypothesis was developed at that time that serum administration would prolong incubation period for rabies infection after a bite incident to allow the victim's immune system enough time to produce protective levels of circulating antibodies subsequent to active vaccination (Habel, 1945).

1.3.2. Establishment of RIG in rabies PEP 1954

In 1954, a long awaited opportunity to investigate the protective effect of early passive immunization by serum administration in a basic clinical trial setting occurred after a mass bite incident (Baltazard and Bahmanyar, 1955; Habel and Koprowski, 1955). In an Iranian village, a confirmed rabid wolf bit 29 people. Of the 29 victims, 18 suffered severe wounds on the head and neck, the anatomical sites for which a benefit of passive immunization was suspected at the time (Rabies and World Health, 1957). PEP was initiated less than 36 hours after the bite incident in all of the 18 severely injured victims (Rabies and World Health, 1957). Five of them were treated with active vaccinations alone. Thirteen received vaccinations and serum in combination. In the serum group only one lethal case was observed while three of the five patients in the control group died (Baltazard and Bahmanyar, 1955). Based on this clinical experience the WHO adapted its guidelines in 1957, thereafter recommending a combination of a single serum application and a course of 14 daily vaccinations as the optimal post-exposure treatment (Rabies and World Health, 1957). The benefit of RIG in combination with vaccination in PEP of patients with severe bite wounds has since then been established as scientific evidence. Because the serum in this experiment was applied intramuscularly distant from the wound site, and because levels of circulating antibodies measured in the serum of the victims correlated with their survival, the circulating antibody effect was at that time retained as the main protective mechanism of serum administration (Habel and Koprowski, 1955).

It was widely accepted that passive immunization mitigated antibody response subsequent to active vaccination (Atanasiu et al., 1956). Therefore, the experts responsible for the WHO recommendations refrained from shortening the course of vaccinations or from increasing the dose of serum applications in 1957 and the following recommendations (Rabies and World Health, 1957, 1960, 1966, 1973).

In the 1960s Dean et al. showed predominance of local virus neutralizing effect in animal experiments, questioning the theory of circulating antibody protection (Dean et al., 1963).

1.3.3. Dose definition 1971

To overcome the prevailing uncertainties about RIG dosage for sufficient early antibody protection without relevant interference with immune response, Cabasso et al., in 1971 conducted a dose-finding clinical trial with hRIG in humans (Cabasso et al., 1971). They showed that 10 IU/kg of hRIG did not provide early protective levels of circulating antibodies while 40 IU/kg heavily interfered with active immune response. A dose of 20 IU/kg provided early protection without relevant attenuation of active antibody response and was therefore determined to be the optimal dose (Cabasso et al., 1971). Due to the shorter half life of eRIG, its dosage optimum was defined at 40 IU/kg, double the dose of hRIG (Rabies and World Health, 1973). Thus, level of circulating antibodies was the determining factor for dose calculation of RIG, while the wound size and local neutralizing effect were not considered in dose definition.

1.3.4. Recent changes

For a long time, the WHO recommendations concerning RIG remained without major changes (WHO Expert committee on Rabies, 1992; Rabies and World Health, 1973, 1984). In 2005, the possibility of diluting RIG in cases of multiple wounds to assure a sufficient local infiltration of all wounds was added to the guidelines, valorizing the importance of local virus neutralization (Rabies and World Health, 2005).

In 2016 and 2017, Bharti et al. published successful reports of dose-saving RIG calculations based on wound size rather than body weight without injection distant from the wound site (Bharti et al., 2016, 2017), abandoning the theory of circulating antibody effect. The current WHO guidelines, still advise to adhere to the body-weight dependent maximum dose calculation. However, in case the full dose cannot be administered locally around the wound due to imminent compartment syndrome, it is no longer advised to inject the remaining RIG distant from the wound site if there is not a high likelihood of additional undetected, small wounds. (World Health, 2018b).

In summary, after establishment through the Iranian wolf

experiment in 1954 and dose definition in the 1970s, application of RIG did not change significantly until the recent discontinuation of systemic administration.

1.4. Current debate

Conversely, to the slow changes in RIG administration protocols, the second pillar of PEP, active vaccination, evolved massively during the same period. Highly immunogenic purified cell culture vaccines replaced the old nerve tissue vaccines, which were in use when administration of RIG in combination with active vaccination was established (Baltazard and Bahmanyar, 1955; Habel and Koprowski, 1955; Hampson et al., 2019). The new CCVs are much more potent and better tolerated than the old nerve tissue vaccines (World Health, 2007). This allowed for a relevant simplification of active vaccination protocols from courses requiring 14 to 23 intramuscular (IM) injections to modern intradermal (ID) protocols with as few as three clinic visits (World Health, 2007).

While the safety, efficacy and cost-effectiveness of active vaccination in PEP is beyond any doubt, the value of additional RIG administration can hardly be determined in clinical trials. The use of RIG was strongly advocated by clinicians from Asia through case reports of treatment failures, especially in children, when PEP was applied without RIG (Wilde, 2007; Wilde et al., 2002, 1996). For a long time, these tragic reports consolidated the status of RIG in official PEP protocols despite missing evidence for its additional clinical benefit and cost-effectiveness when applied on a larger scale. In sharp contrast to official recommendations, epidemiological studies assessing the cost-effectiveness of PEP (Hampson et al., 2011, 2008, 2019; Zinsstag et al., 2009) often did not consider RIG administration in their analyses, taking into account its inaccessibility for almost all patients in the most affected developing countries (Anderson, 2007; Hampson et al., 2019; Wilde, 2007; Wilde et al., 2002). Equally contrasting the WHO recommendations, many scientific publications assumed 100% safety of PEP administration without RIG for patients with grade III exposures in their statistical calculations and models (Hampson et al., 2011; Zinsstag et al., 2009).

In view of these discrepancies, there is a need for better data and objective evaluation of RIG benefit and cost-effectiveness in modern PEP. Recently, quantitative data about the impact of RIG administration was added to the existing case reports. In a large retrospective study about the abridgement of intradermal PEP vaccination in Cambodia, no benefit of RIG administration was observed (Tarantola et al., 2019a). A modeling study about the benefits of improved PEP provision showed unsatisfactory cost-effectiveness for RIG: While current PEP without RIG has an estimated cost-effectiveness of about 1000 US$ per death averted, additional RIG administration has been calculated to save only a marginal number of lives at costs of over 600'000 US$ each (Hampson et al., 2019). Smaller studies and case series showed the main reasons of rabies deaths among bite victims as delay of initiation or non-adherence to active vaccination protocols while the absence of RIG did not seem to have a major impact (Changalucha et al., 2018).

The scientific community and WHO repeatedly claimed there was insufficient industrial RIG production and called for measures to overcome shortages in the most affected countries (Anderson, 2007; Wilde, 2007). Now, dog mediated human rabies is targeted by the WHO for elimination by 2030 within all endemic regions (Minghui et al., 2018) This quest requires all efforts to be joint, and the most efficient allocation of resources is key to success (World Health et al., 2018).

Taking into account the doubtful data, the epidemiological changes associated with the approaching endgame situation with lower public awareness for rabies (Klepac et al., 2013) and the obstacles related to the current absence of RIG in almost all concerned countries (Hampson et al., 2019), the call for global provision of RIG now needs to be carefully reevaluated.

In this paper, we describe our experience introducing eRIG in Côte d'Ivoire, a resource-poor country with persistent lack of RIG and low but chronic rabies burden (Tiembre et al., 2018), a setting similar to most rabies endemic countries, especially in the phase before final elimination of the disease.

2. Methods

Data for this report was collected in the framework of a One Health project funded by the Vaccine Alliance (GAVI) assessing the burden of canine rabies in West and Central Africa. To assess rabies burden, a probability tree model (Knobel et al., 2005) based on data collected at household, public health facility and veterinary level was applied. Data on animal bite frequency, the proportion of rabies suspected bites, the proportion of rabies confirmed bites and current coverage of PEP was collected in selected urban and rural areas in Chad, Mali and Côte d'Ivoire. The data contributed to an evidence base for modeling the potential effect of future investment in human rabies vaccine (Hampson et al., 2019) and a more accurate assessment of the global rabies burden (Léchenne et al., 2020).

For this report, we x analyzed the health center data collected in Côte d'Ivoire with special focus on the impact of eRIG provision on survival of patients after exposure to potentially rabies infected animals.

2.1. Study sites

Côte d'Ivoire is a developing country in Western Africa. Rabies is endemic, but incidence in humans is considered relatively low compared to other endemic countries with an estimated mortality of about 500 rabies deaths per year in a population of about 25 million inhabitants (Hampson et al., 2015a; Institut National des Statistiques, 2014)

The departments of Bouaké, in the center of the country, and San Pédro, in the southwest, were selected as study areas due to reports of continuous rabies transmission in Bouaké and as a good representation of the ethnically and culturally diverse Ivorian population. In each department capital, there is one anti-rabies center (center Anti-Rabique, CAR) of the National Institute of Public Hygiene (Institut National d'Hygiène Publique, INHP). Bite victims are regularly referred to the CARs by other local health care facilities, as they are the only health care institutes in the administrative divisions to provide rabies PEP.

2.2. Data collection

From April 2016 to March 2018, health care staff of the two departmental CARs prospectively registered data of all attending patients using Epi Info (version 3.5.4.). The data consisted of sociodemographic characteristics, rabies vaccination status of the patient and the aggressing animal, characteristics of the exposure, possible veterinary surveillance of the aggressing animal and characteristics of PEP including delay to initiation, vaccination protocol, eRIG administration and number of active vaccine doses applied.

Patients with grade I (touching or feeding an animal or licks on intact skin: no exposure; PEP not indicated (World Health, 2018b)) and grade II (nibbling of uncovered skin, minor scratches or abrasions without bleeding; PEP indicated with vaccine (World Health, 2018b)) exposures, and patients who reported previous rabies vaccination (PrEP or PEP) were excluded from further follow-up and analysis because of their non-eligibility for RIG treatment according to guidelines (World Health, 2018b). Bite victims not at risk of rabies infection were also excluded from further analysis according to the following criteria: correct vaccination status of the biting animal confirmed by the owner of the animal, survival of the biting animal after veterinary surveillance for at least 10 days following the incident or negative laboratory testing of the biting animal.

All eRIG eligible patients at risk of rabies infection were contacted

by telephone between May and July 2019, fifteen to thirty-eight months after their exposure, to screen for suspected or possible rabies deaths after elapse of probable rabies incubation period.

Survival of patients was registered during the initial phase of PEP treatment and at follow-up at least fifteen months after exposure. Cause of death was classified based on the clinical judgement of the responsible rabies health care worker at the local CAR or on a hospital physician report. Lethal cases for which the rabies health care worker recorded a cause of death other than rabies were registered as "non-rabies deaths". If no clear cause of death was recorded, "possible rabies death" was registered. If the treating rabies health care worker recorded clinically suspected rabies as cause of death, "suspected rabies death" was registered. Due to cultural constraints, there was no postmortem confirmation of clinical rabies diagnosis.

2.3. PEP administration

During the initial period of data collection, patients were treated according to the locally established intramuscular (IM) Essen[1] or Zagreb[2] PEP protocols. During this initial phase, patients did not receive eRIG, as it was not available in the country. In May 2017, about thirteen months after initiation of data registration, administration of eRIG and the intradermal (ID) Updated Thai Red Cross[3] (UTRC) protocol were introduced in the two CARs after intensive staff training. Thenceforth, patients were free to choose between the ID and the IM vaccination protocols. It was planned to administer eRIG to all eligible patients opting for the ID vaccination protocol, as this was a precondition of the sponsoring vaccine manufacturer. Patients opting for the established IM vaccination protocols did not receive eRIG due to its unavailability in the country outside of study settings and the resultant absence in regular local PEP protocols. The ID vaccinations and eRIG were provided free of charge, while the vaccines administered according to IM protocols were paid by the patient at a regular local price of about 14 US$ per dose. The eRIG dose was calculated based on body-weight of the patient according to WHO guidelines (40 IU/kg for eRIG) (World Health, 2018b). Because the study was conducted before the April 2018 change in WHO recommendations on rabies immunization, the entire calculated dose of eRIG was administered: As much of the calculated dose as was anatomically feasible was injected locally around the wound and any remaining was injected intramuscularly distant to the wound site. The eRIG used during the study was tested for sufficient titer by the Swiss Institute for Virology and Immunology (Institut für Virologie und Immunologie) prior to administration in the field. Due to logistical constraints, eRIG was not always available after introduction in May 2017. Therefore, 89 of 611 patients treated according to the UTRC protocol could not receive eRIG as planned. There was no selection of patients for eRIG administration by local health care professionals because eligible patients received eRIG any time it was available at the CAR, independent of their individual risk profile. Deviating from study protocol, twelve patients treated with IM vaccinations erroneously received eRIG. No deaths were reported among these patients. Because we could not retrospectively exclude possible selection bias by local health care professionals as a cause for the deviation from protocol, these patients were excluded from the analysis.

2.4. Biting animals

Local joint training sessions for health care and veterinary staff were organized to facilitate intersectoral collaboration. The aim of these efforts was to increase the number of biting animals put under veterinary surveillance after a bite incident. In cases where the animal was still alive ten days after the exposure, a veterinary certificate was issued. Presentation of this certificate at the CAR allowed for discontinuation of the vaccination protocol. We also tried to increase the laboratory analysis of canine brain samples by introducing a lateral flow rapid test (ANIGEN by Bionote Inc.) and promoting delivery of samples to the Central Pathology Laboratory in Bingerville for confirmation by fluorescent antibody test. While the number of dogs put under veterinary surveillance increased significantly compared to the beginning of study activities, efforts to promote laboratory testing were not very successful with only a small number of brain samples analyzed.

2.5. Data analysis

The aim of analysis was to compare the proportion of suspected or possible rabies deaths between patients receiving PEP consisting of active vaccinations and eRIG and those receiving PEP with active vaccinations alone. Consistent with WHO guidelines, we regarded the different protocols for active vaccination as equally effective, allowing for direct comparison between the eRIG group and the non-eRIG group, independent of the vaccination protocol applied.

Data was analyzed using R version 3.5.1. (R Core Team, 2017). We first compared baseline characteristics of the two study groups including sociodemographic characteristics, nature of exposures and characteristics of the aggressing animals. We then compared administration of active vaccinations between the two groups including delay between exposure and PEP initiation and number of doses received. Categorical variables were described as frequencies and percentages, and continuous variables as median and interquartile range.

In a first analysis, we only considered clinically suspected rabies deaths. In a second analysis, clinically suspected and possible rabies deaths were considered. For both analyses, we did not correct for differences in compliance to active vaccination protocol, as we wanted to assess the benefit of eRIG under real-life conditions.

In a third analysis, we only considered patients with full compliance to the active vaccination protocol, which was defined as PEP initiation not more than one day after exposure and completion of the full course of vaccinations according to the protocol applied. We retrospectively adapted our analysis to the most recent changes in recommendations for PEP and regarded vaccination protocols as complete after administration of four doses according to an IM protocol[4] and six doses in three visits according to the ID protocol[5] (World Health, 2018a).

2.6. Ethical considerations

The study was approved by the Ethics Committee of North Western and Central Switzerland (EKNZ) and the National Ethics Committee of Côte d'Ivoire (Comité National d'Éthique de la Recherché, reference number: N / Ref: 072 / MSHP / CNER-kp). Informed consent was obtained from patients or their legal representatives before registration of data. Contact information was retained during the period of follow-up. Access to contact information was limited to agents performing follow-up and deleted after the follow-up period. All eligible patients were offered ID vaccinations and eRIG free of charge when the vaccine provided by the project and the eRIG were available at the CARs.

Through public awareness raising activities such as local intersectoral rabies committees, panel discussions, radio broadcasts and patient information, we tried to improve health-seeking behavior and increase compliance of exposed patients.

[1] Five dose Essen Regime: One IM injection on days 0, 3, 7, 14, 28 (1-1-1-1-1).

[2] Four dose Zagreb Regime: Two IM injections on day 0, one IM injection on days 7 and 21 (2-0-1-0-1).

[3] Updated Thai Red Cross Regime: Two ID injections on days 0, 3, 7 and 28 (2-2-2-0-2).

[4] Two-week IM PEP regimen (4-dose Essen regimen; 1-1-1-1-0); duration of entire PEP course: between 14 and 28 days.

[5] One-week, 2-site ID regimen (Institut Pasteur du Cambodge regimen; 2-2-2-0-0); duration of entire PEP course: 7 days.

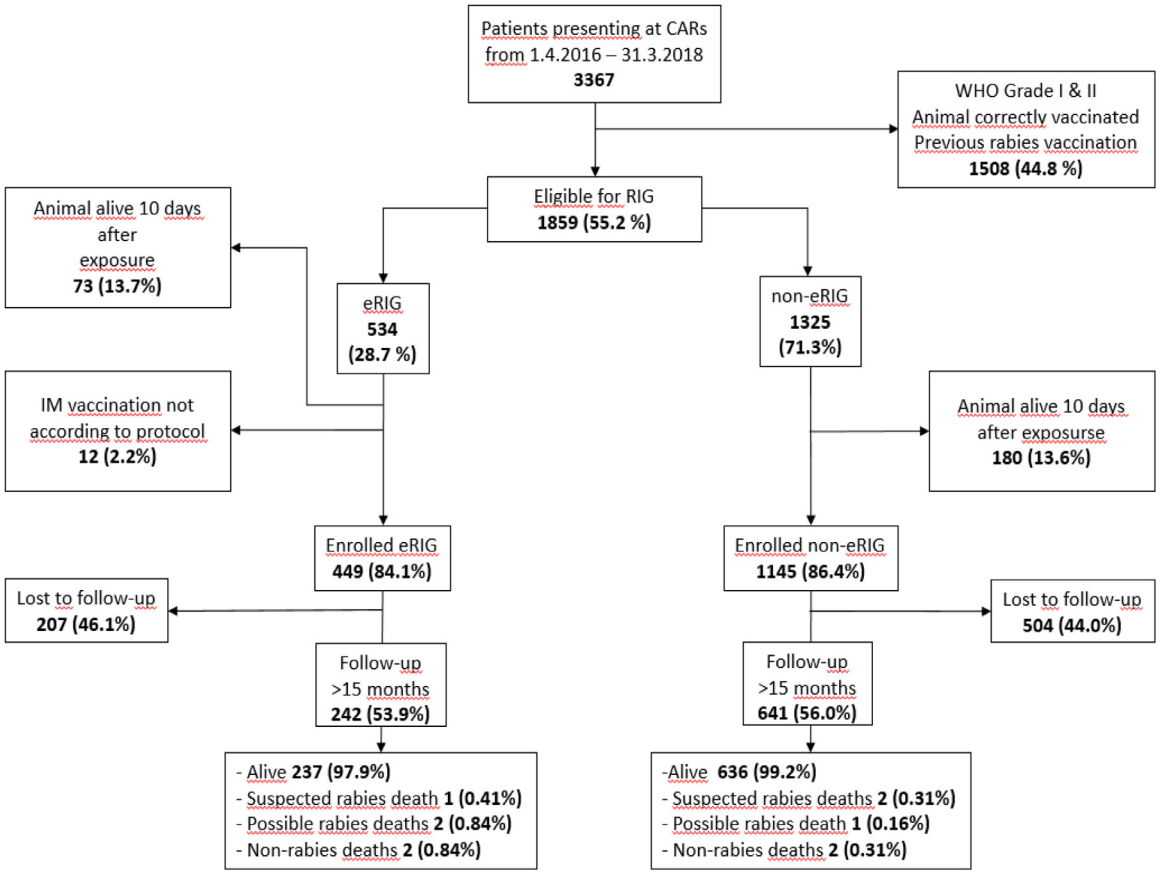

Fig. 1. Study data and flow of patients after exposure to a potentially infectious animal in Bouaké and San Pédro between April 2016 and March 2018.

3. Results

3.1. Exposure and treatment

Between April 2016 and March 2018, 3367 patients attended the two CARs in Bouaké and San Pédro after exposure to a potentially rabid animal. At the time of presentation, 1859 patients (55.2%) were eligible for RIG administration according to WHO guidelines, because they had suffered grade III exposures and reported no previous rabies vaccination. Based on the patient's choice for ID vaccinations and the availability of eRIG at time of their presentation, 534/1859 eligible patients (28.7%) received eRIG in combination with active vaccinations. Of these, 73/534 (13.7%) were retrospectively excluded from analysis because the biting animal was put under veterinary surveillance and confirmed to be healthy and alive for at least ten days after the exposure. Negative laboratory results of brain samples of the biting animal were also defined as exclusion criteria, but this was not met by any of the RIG eligible patients (Fig. 1).

12/534 victims (2.2%) receiving eRIG were treated with IM vaccinations deviating from study protocol. No deaths were reported in these patients, but to avoid potential selection bias by local health care staff these patients were retrospectively excluded from analysis. In the end, 449 RIG eligible patients exposed to a potentially infectious animal were enrolled in the eRIG group for analysis.

1325/1859 (71.3%) of the RIG eligible patients were treated with vaccinations alone because eRIG was not available at the time of presentation or because they chose PEP according to IM protocols. After retrospective exclusion of 180/1325 (13.6%) of these patients due to successful veterinary surveillance of the biting animal for at least ten days, 1145/1325 (86.4%) were enrolled for analysis in the non-eRIG group.

Compliance to PEP treatment was limited, especially concerning delay between exposure and initiation of treatment. Only 866/1594 (54.3%) patients presented within the first day after the exposure (early presenters). The share of early presenters was higher in the eRIG group with 273/449 (60.8%) versus 593/1145 (51.8%) in the non-eRIG group (OR = 1.17, p-value = 0.09). Of the 866 early presenters, only 444 (27.9% of the 1594 enrolled patients) completed a full course of active vaccinations according to current guidelines (full compliance). The share of full compliance in terms of timely presentation and completion of active vaccination protocol was significantly higher in the eRIG group with 166/449 (37.0%) versus 278/1145 (24.3%) in the non-eRIG group (OR = 1.52, p-value = 0.0002) (Figs. 2, 3 and Table 1).

3.2. Follow-Up of patients at risk

In a telephone follow-up between May and July 2019, fifteen to thirty-eight months after exposure, all patients fulfilling the criteria of RIG eligibility and true risk of rabies exposure were contacted. Follow-up rate was 54% in the eRIG group and 56% in the non-eRIG group, corresponding to 242/449 and 641/1145 patients, respectively. The difference in follow-up rate between the groups was not statistically significant ($p = 0.45$).

3.3. Deaths

In total, eleven deaths were registered among the 3367 patients attending the two CARs during the period of study.

3.3.1. Non-rabies deaths

Four victims had other diagnoses than rabies registered as cause of death (epilepsy, diabetes, drepanocythemia, gastrointestinal problems). All four cases were detected during the telephone follow-up. In other words, the health care professional registering the data did not examine

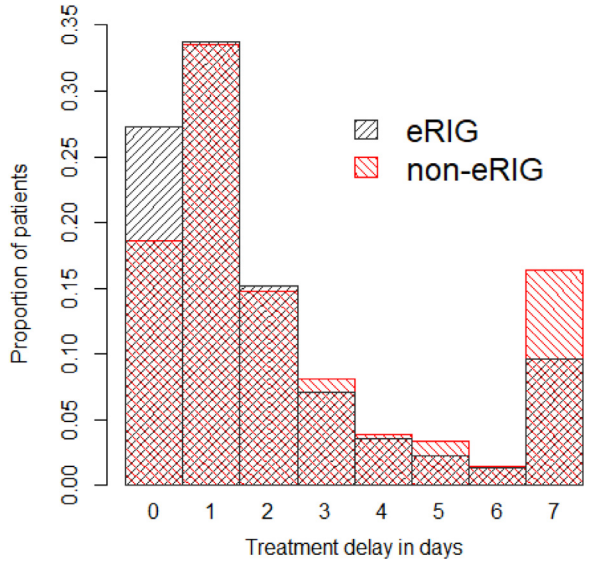

Fig. 2. Distribution of treatment delay in days. "7" represents a delay of seven or more days. Distribution of treatment delay within the two groups was similar except for a higher proportion of PEP initiation on the day of the incident in the eRIG group and a higher proportion of treatment delay of seven or more days in the non-eRIG group.

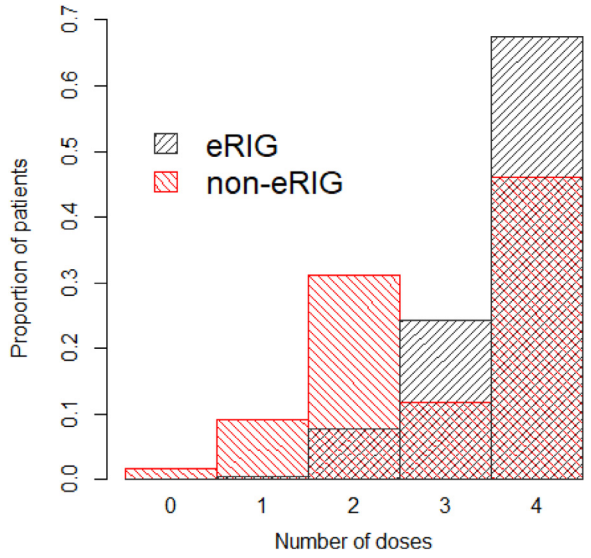

Fig. 3. Distribution of numbers of active vaccine doses received. Number of doses for ID protocol was divided by two to allow direct comparison with IM protocols. Patients receiving five doses according to the IM Essen regime are included in "4". The share of patients completing a full course of vaccines was significantly higher in the eRIG group.

these patients before their death, but only verbally received information on the patient diagnosis from relatives. For the two victims diagnosed with epilepsy and drepanocythemia, two pathologies that could present with a similar clinical picture as rabies, the relatives confirmed that a physician made the final diagnosis and that the victim was known to chronically suffer from the respective disease. Based on this information, a missed rabies diagnosis appeared unlikely, so these cases were retained as non-rabies deaths.

One other lethal case was not considered for further analysis, because the victim suffered only a grade II exposure and was therefore not eligible for RIG.

Table 1
Distribution of sociodemographic data and exposure characteristics of patients with severe exposure to a potentially rabid animal in Bouaké and San Pédro between April 2016 and March 2018.

		eRIG group (n = 449)	non-eRIG group (n = 1145)
Study Site (%)	Bouaké	346 (77.1)	897 (78.3)
	San Pédro	103 (22.9)	248 (21.7)
Setting (%)	Rural	69 (15.4)	274 (23.9)
	Urban	380 (84.6)	870 (76.0)
	Unknown	0 (0.0)	1 (0.1)
Median date of exposition [Quartiles]		24.11.2017 [19.09.2017, 22.01.2018]	09.01.2017 [12.08.2016, 11.06.2017]
Median age in years [Quartiles]		16 [8, 34]	14 [7, 33]
Sex (%)	Female	205 (45.7)	468 (40.9)
	Male	244 (54.3)	675 (59.0)
	Unknown	0 (0.0)	2 (0.2)
Profession (%)	Student	213 (47.4)	511 (44.6)
	Public servant	15 (3.3)	33 (2.9)
	Farmer	22 (4.9)	60 (5.2)
	Self-employed	85 (18.9)	181 (15.8)
	Privately employed	19 (4.2)	34 (3.0)
	Unemployed	94 (20.9)	292 (25.5)
	Unknown	1 (0.2)	34 (3.0)
Level of education (%)	Analphabet	117 (26.1)	378 (33.0)
	Preschool	8 (1.8)	35 (3.1)
	Primary	189 (42.1)	380 (33.2)
	Secondary	102 (22.7)	211 (18.4)
	Superior	32 (7.1)	87 (7.6)
	Unknown	1 (0.2)	54 (4.7)
Number of wounds (%)	One	137 (30.5)	332 (29.0)
	Two	122 (27.2)	285 (24.9)
	Three	55 (12.2)	137 (12.0)
	Multiples	119 (26.5)	287 (25.1)
	Unknown	16 (3.6)	106 (9.3)
Type of aggression (%)	Bite	435 (96.9)	1057 (92.3)
	Scratch	14 (3.1)	58 (5.1)
	Lick on broken skin	0 (0.0)	3 (0.3)
	Unknown	0 (0.0)	25 (2.2)
Wound site (%)	Head & neck	14 (3.1)	47 (4.1)
	Arm & shoulder	44 (9.8)	146 (12.8)
	Hand	79 (17.6)	162 (14.1)
	Leg & buttocks	161 (35.9)	231 (20.2)
	Foot	124 (27.6)	433 (37.8)
	Trunk	25 (5.6)	80 (7.0)
	Genitals	0 (0.0)	1 (0.1)
	Unknown	2 (0.4)	45 (3.9)
Aggressing animal (%)	Dog	405 (90.2)	1016 (88.7)
	Cat	32 (7.1)	82 (7.2)
	Monkey	4 (0.9)	9 (0.8)
	Bat	0 (0.0)	1 (0.1)
	Unknown	8 (1.8)	38 (3.2)

3.3.2. *Possible rabies deaths*

For three RIG eligible patients, the cause of death was not clinically defined or was not registered, so these were listed as possible rabies deaths. All possible rabies deaths occurred within three months after exposure. One patient died on the day of presentation, which was two months after the exposure incident. He did not receive eRIG so was allocated to the non-eRIG group. The two others received PEP according to the UTRC regimen with a delay of two and three days after the exposure. Both received eRIG together with the active vaccinations so were allocated to the eRIG group.

3.3.3. *Clinically suspected rabies deaths*

Three patients died due to clinically suspected rabies. Two of these

were treated with active vaccinations alone (non-eRIG group), while one of them received eRIG together with active vaccinations. Two clinically suspected rabies victims suffered from wounds in two different locations, the third one from multiple wounds. In two patients, the major wounds were located on the foot while the third victim was bitten on the head. They all presented with a major delay of 28, 55 and 65 days after exposure, and none of them received a full course of active vaccinations due to death before completion of vaccination protocol.

3.3.4. Time of death

During the period of PEP at the CARs, six of the eleven deaths were registered, including all three suspected rabies deaths, two RIG eligible possible rabies deaths and the possible rabies death of the patient with grade II exposure that was not included for further analysis. In the follow-up, five deaths were registered, including the four non-rabies deaths and the possible rabies death of a six-year-old boy who was lost to follow-up after two sessions according to the UTRC protocol (equal to 4 doses) and subsequently died at home with no medical diagnosis.

Unfortunately, the exact date of death was not registered for all victims, but it was established that all clinically suspected rabies deaths and all possible rabies deaths occurred within three months after exposure (Table 2).

3.4. ERIG benefit

3.4.1. Survival benefit

In a first analysis, only suspected rabies deaths were considered. The rate of suspected rabies deaths was 1/242 (0.4%) in the eRIG group and 2/641 (0.3%) in the non-eRIG group.

In a second analysis, we considered all suspected and all possible rabies deaths. The rate of suspected and possible rabies deaths was 3/242 or 1.2% (95% CI 0.3–3.6%) in the eRIG group and 3/641 or 0.5% (95% CI 0.1–1.4%) in the non-eRIG group. The difference in proportions was small and not statistically significant (0.7%, $p = 0.21$).

Additionally, we ran a sensitivity analysis considering any cause of death. The overall mortality was 5/242 or 2.1% (95% CI 0.07–4.8%) in the eRIG group and 5/641 or 0.8% (95% CI 0.3–1.8%) in the non-eRIG group. The difference in proportions was small and not statistically significant (1.3%, $p = 0.11$).

In all, 89 patients in the eRIG group (19.8%) and 171 patients in the non-eRIG group (14.9%) were fully compliant to PEP protocol, in terms of prompt initiation and completion of active vaccination protocol. No confirmed or possible rabies death occurred in the group of patients with full compliance to PEP protocol.

3.4.2. Costs

In total, 609 patients received eRIG. For 534 (87.7%), the indication for eRIG was correct at the time of administration (grade III exposure and no previous rabies vaccination). 73/534 (13.6%) were retrospectively declared not at risk of rabies infection, because the aggressing animal remained alive and healthy at least ten days after the exposure. Average quantity of eRIG administered per patient was 1571 IU (SD +/- 631 IU), corresponding to a wholesale price of about 15 US$ per patient. When dividing total costs of eRIG (15 US$ x 609 patients = 9′135 US$) by the number of patients with correct indication and retrospective risk of infection ($n = 461$), costs per patient at risk rise to about 20 US$ per patient.

Efforts to introduce eRIG into a market where it had not been available for a long time were considerable. Legal and administrative issues, logistics and staff training were time-consuming and costly. For staff training at the two CARs, we spent approximately 2′630 US$. Extrapolated to national level (27 CARs) this would result in total costs of about 35,500 US$. We did not quantify costs for administrative and logistical issues separately, but they were substantial and must be considered in budget planning for eRIG introduction into a new region.

Table 2
List of suspected and possible rabies death cases after severe exposure in Bouaké and San Pédro between April 2016 and March 2018.

Nr	Date of exposition	Study eite	Setting	Age	Sex	Type of wound	Wound location	Number of wounds	Species	Grade of exposure	Delay to PEP in days	PEP protocol	RIG	Number of doses received	Cause of death	Date of death
1	01.05.17	Bouaké	Rural	25	M	Bite	Head or Neck	Two	Dog	III	28	Unknown	Yes	Unknown	Suspected rabies death	31.05.17
2	25.11.17	Bouaké	Rural	13	F	Bite	Foot	Two	Dog	III	65	Unknown	No	Unknown	Suspected rabies death	29.01.18
3	01.12.17	San-Pédro	Urban	10	F	Bite	Foot	Multiple	Dog	III	55	UTRC	No	1	Suspected rabies death	26.01.18
4	02.06.17	Bouaké	Urban	5	M	Bite	Arm or Shoulder	Two	Dog	III	61	Unknown	No	Unknown	Possible rabies death	02.08.17
5	19.08.17	San-Pédro	Rural	6	M	Scratch	Head or Neck	Multiple	Dog	III	2	UTRC	Yes	3	Possible rabies death	Exact date unknown, in 09.2017
6	27.11.17	Bouaké	Urban	33	F	Bite	Hand	One	Dog	III	3	UTRC	Yes	2	Possible rabies death	Exact date unknown, during PEP

3.4.3. Biting animals

During the study period, brain samples of nine killed dogs and one cat were analyzed for rabies virus in Bouaké. All of them tested rabies positive by lateral flow rapid test and subsequent confirmation with fluorescence antibody test at the Central Pathology Laboratory in Bingerville. According to veterinary statistics, fourteen patients were exposed to the ten rabies positive animals. Unfortunately, only seven of the patients could be identified unequivocally in the database of the CAR. Four of the seven victims of positively tested animals were excluded from analysis because they only suffered grade II exposures and were therefore not eligible for RIG. The three victims suffering grade III exposures by rabies confirmed animals all belonged to the non-eRIG group. One was bitten on the hand and two on the trunk. They all received a full course of vaccinations with a delay between the aggression and treatment initiation of zero, two and five days, respectively. Two were treated with the IM Zagreb regime and one with the ID UTRC protocol. At the time of the last vaccination 21, 26 and 30 days after exposure, all three grade III victims of rabies confirmed animals were healthy and alive. Two of them were reported as in good health on telephone follow-up 20 and 32 months after the incidents. The third victim, who was bitten on the hand and had PEP initiated on the day of exposure, was lost to follow-up.

In San Pédro, no laboratory analysis for any biting animal was registered during the study period.

4. Discussion

This study aimed to assess the real-world benefit of eRIG on patient survival after potential rabies exposure in Côte d'Ivoire, a resource-poor country with longstanding absence of RIG. This is similar to the setting encountered in most rabies endemic countries. Côte d'Ivoire is also a good representative for the endgame situation before elimination of rabies, with rather low but chronic transmission and associated lack of awareness (Klepac et al., 2013; Tiembre et al., 2018).

In this study, we could not observe survival benefit for patients after grade III exposure to a potentially infectious animal in Côte d'Ivoire when rabies PEP consisted of active vaccination and eRIG compared to PEP with active vaccination alone. In line with other reports (Changalucha et al., 2018; Fooks et al., 2017; Wilde, 2007), all three clinically suspected rabies deaths in our study population occurred after major treatment delay and noncompliance to the active vaccination protocol. No patient who received a timely and complete course of active vaccination died from rabies, independent of eRIG administration. Due to the nature of observational studies, we cannot exclude the possibility of bias and confounding. A potential benefit of eRIG administration for severely exposed patients cannot be excluded based on the presented results. However, combined with the findings of recent modeling and observational studies (Hampson et al., 2019; Tarantola et al., 2019a), we suspect only marginal benefit and insufficient cost-effectiveness for unselective eRIG administration on a larger scale.

Several limitations need to be considered when interpreting the results of this study. Primarily, the median date of presentation was more than ten months later in the eRIG group than in the non-eRIG group (24.11.2017 versus 09.01.2017) because of the delay between initiation of data registration and introduction of eRIG in the two CARs. We believe that this should not lead to a major bias since there is no indication for relevant fluctuation of rabies incidence over time in Côte d'Ivoire.

Secondly, patients in the eRIG group were vaccinated according to the ID UTRC protocol, while the patients in the non-eRIG group were treated with IM vaccinations. As approved by WHO and shown by various studies (Briggs et al., 2000; Quiambao et al., 2005), the different vaccination protocols applied should not lead to bias because of similar immunogenic potential of all protocols. The only possible difference between the protocols concerns the postulated earlier protective antibody response after ID vaccinations, which might have potentially favored survival in the eRIG group.

Thirdly, treatment delay and adherence to PEP protocol differed significantly between the two groups. The earlier presentation after exposure in the eRIG group might be explained by local awareness raising activities conducted by the study team and their partners during the initial phase of the study. This might slightly reduce the transferability of our results, but improving care of bite victims was an important aim of our project. The better adherence to vaccination protocol in the eRIG group might be linked to the fact that the vaccine for ID application was offered free of charge while patients had to pay the regular price for IM vaccinations. Tetchi et al. showed that free provision of vaccine improves compliance significantly in this setting (Tetchi et al., 2020). The improved awareness and the free provision of vaccine for ID protocols should both have favored survival in the eRIG group and, therefore, do not limit the significance our finding of no additional benefit of eRIG with PEP compared to PEP with vaccination alone.

Fourthly, only a very small proportion of biting animals were tested for rabies infection. Therefore, the vast majority of bite victims were only potentially exposed to rabies infection. This restricts the transferability of our results, because we are not able to quantify the proportion of true exposures in our study population.

Another limitation is the follow-up by telephone. Obviously, patients who died during the follow-up interval could not be contacted personally. However, for a considerable proportion of patients, the phone number of a friend or relative was registered, and they could respond in cases of death. Five lethal cases were detected that way during the follow-up. Rabies infection risk decreases significantly three months after the exposure (Fooks et al., 2014, 2017; Rupprecht et al., 2002). Also in our study, all deaths reported more than three months after the bite incident were caused by other pathology than rabies. Therefore, it is not probable that the number of lethal rabies cases occurring after elapse of treatment duration at the CAR was very large. However, we are not able to quantify the proportion of patients lost to follow-up due to death without report.

The main problem of eRIG benefit assessment in rabies PEP is its minor significance compared to the effect of active vaccinations. To reveal the true effect of eRIG, only patients with a timely and correct administration of active vaccinations should be included into analysis. In our study population, no death occurred after timely and correct active vaccinations, independent of eRIG administration. Due to the low number of patients with full PEP compliance, our findings do not have the power to quantify the benefit of eRIG under optimal conditions.

The listed limitations severely restrict the significance of our results from a pharmacological point of view. However, with rabies vaccine or RIG, randomized, controlled human trials and cohort studies involving untreated comparison groups are not possible because of the lethal character of the disease (Tarantola et al., 2019b; World Health, 2007). Therefore, observational field studies are essential to generate new knowledge and improve treatment strategies. In this study, we had the rare opportunity to prospectively monitor the effect of eRIG introduction in a real world setting into a country with previous longstanding absence of RIG. This provides valuable information independent of the described limitations.

Optimal allocation of resources is a decisive factor in the reduction of human rabies burden to zero (World Health et al., 2018). After over a century of applying passive immunization in rabies PEP without clear evidence for its cost-effectiveness, it is imperative to reevaluate its benefit and associated future investments cautiously. Nowadays, most rabies-related deaths occur due to limited access to adequate PEP in the poorest countries in Africa and Asia. Financial obstacles are often a major factor restricting access to PEP. Therefore, any strategy that directs global resources from the most cost-effective measures to less cost-effective ones will aggravate social injustice related to financial obstacles that impede PEP access and lead to unnecessary deaths among

the poorest. Clearly, assessment of existing guidelines and development and implementation of new and more cost-effective strategies is a highly important topic from a social justice perspective (Wentworth et al., 2019).

Our results are in agreement with the findings of a recent modeling study (Hampson et al., 2019) and other observational studies (Changalucha et al., 2018; Tarantola et al., 2019a) suggesting that eRIG provision according to the current guidelines is not a cost-effective measure to reduce rabies burden in countries with low transmission and poor resources. Due to the above-mentioned constraints, the presented results do not exclude a potential benefit for eRIG administration for a subgroup of severely exposed patients among grade III exposures.

On a secondary prevention level, improved access to adequate PEP with active vaccinations and correct wound care by well-trained staff are likely to save many more lives than provision of eRIG (Hampson et al., 2019; Wilde et al., 2002). This could be achieved by provision of free vaccine, better supply chains to prevent stock outs and awareness raising in the population to prevent treatment delays after potentially infectious incidents (Fooks et al., 2017).

On a primary prevention level, mass dog vaccination is the most cost-effective strategy for human rabies burden reduction. It is the most sustainable measure with the potential of eliminating dog-mediated human rabies by direct action on the reservoir (Lavan et al., 2017; Zinsstag et al., 2009). Other primary prevention strategies to reduce number of infectious dog bites based on capacity building, awareness raising and promotion of responsible dog ownership are also known to be highly beneficial (Fooks et al., 2017). Our findings suggest that such alternative approaches should be prioritized over eRIG provision when aiming to reduce rabies burden at maximal cost-effectiveness in the above-described settings.

Population wide PrEP has rarely been considered a feasible strategy for rabies prevention in countries with low resources. In view of the current global shortage of rabies vaccine, it is unlikely to become an option in the next years. However, the current two-visit ID PrEP protocol is simple and requires only small quantities of vaccine (World Health, 2018b). In case of improved supply and decreasing costs for vaccine in the future, this strategy might become more attractive for rabies endemic countries if resources for rabies control are increasing (Fooks et al., 2017). Further studies would be needed to compare its cost-effectiveness to RIG provision if resources became available for such costly and logistically challenging measures. The Global Vaccine Alliance (GAVI) developed a vaccine investment strategy (VIS) supporting eligible countries with active rabies vaccine for PEP from 2021 onwards. Our findings show that the main factor leading to human rabies death after exposure to a potentially infectious animal is poor access to timely and correct active vaccinations. This implies that the GAVI investment on improved access to active vaccinations will be a major contribution to reach the goal of zero human rabies by 2030 even without the additional provision of eRIG.

5. Conclusion

We conclude that the absence of eRIG is not the major factor leading to rabies deaths among bite victims in Côte d'Ivoire but rather treatment delay due to lack of awareness and poor access to active vaccinations. This underlines that improved access to active vaccinations will be effective in reducing rabies deaths even if access to eRIG remains difficult in developing countries. A potential benefit of eRIG administration for severely exposed patients cannot be excluded based on the results of this study.

Author Statement

We hereby declare that all co-authors of the above manuscript contributed to one or more of the following activities in the preparation of this manuscript: The organization and planning, data collection, data analysis, article writing and revision, quality control and English language revision.

Declaration of Competing Interest

The authors declare no conflict of interest.

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