Background paper:
PROPOSED REVISION OF THE POLICY ON RABIES VACCINES AND RABIES IMMUNOGLOBULINS

Prepared by the SAGE Working Group on Rabies vaccines and immunoglobulins and the World Health Organization (WHO) Secretariat
September 22, 2017

EXECUTIVE SUMMARY

Preamble

Rabies is a vaccine-preventable viral zoonotic disease responsible for an estimated 59, 000 human deaths every year. The majority of cases occur in Africa and Asia, and more than 40% of cases occur in children less than 15 years of age. Dogs are responsible for over 95% of all rabies transmissions to humans.

Rabies prevention involves two main, non-exclusive strategies: (i) dog vaccination to interrupt virus transmission to humans; and (ii) human vaccination i.e. post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP) using purified cell-culture and embryonated egg-based vaccines (CCEEVs).

PEP is administered promptly following exposure to rabies, and consists of timely, rigorous wound care, administration of rabies immunoglobulin (RIG) in severe exposures, and a series of intradermal (ID) or intramuscular (IM) rabies vaccines. Long, complicated PEP regimens and the high cost, low availability, uncertain quality and short shelf life of RIG are barriers to PEP implementation.

PrEP is indicated for individuals who face occupational and/or travel-related exposure to rabies virus in specific settings or over an extended period. PrEP consists of a series of rabies vaccines, followed by booster vaccinations in case of exposure.

Gaps exist between the current WHO recommendations and the present practice of PrEP and PEP administration in many rabies-endemic countries. This update addresses this mismatch using new evidence on rabies vaccine and RIG use, including: (i) shorter, more feasible PrEP and PEP protocols; (ii) cost-effectiveness of implementation; and (iii) the potential of new vaccines to improve access to care.

Key Conclusions and Proposed Recommendations

Pre-exposure prophylaxis (PrEP)

PrEP as a population-level intervention is unlikely to be cost-effective, and should only be considered in extreme circumstances, where the incidence of rabies exposures is unusually high (>6%), and RIG use low. Recommendations for PrEP boosters and serological monitoring have been updated, taking into account: (i) timely access to rabies biologics; (ii) access to rabies serological testing; (iii) immunogenicity of booster vaccination; and (iv) cost-effectiveness.
The following accelerated PrEP regimens are considered as efficacious as current PrEP regimens:

- 2-site ID regimen on days 0 and 7
- 1-site IM regimen on days 0 and 7

Individuals who receive only a single dose of PrEP should be managed with full PEP in the case of potential rabies exposure prior to the second PrEP dose. Individuals who are immunocompromised should receive a 3-visit ID or IM PrEP regimen on days 0, 7 and between days 21 and 28, and should be managed with full PEP in the case of a potential rabies exposure with particular emphasis on rigorous wound washing.

Post-exposure prophylaxis (PEP)

Intradermal vaccination is cost and dose-sparing by up to 85% compared to intramuscular vaccination. Modelling estimates show that for every 1000 vials of rabies vaccine, almost 500 additional patients could be treated using an accelerated ID PEP regimen (described below) compared e.g. to the Essen IM PEP regimen.

The following accelerated ID PEP regimen is considered as efficacious as current PEP regimens:

- 2-site ID regimen on days 0, 3 and 7 (IPC regimen)

At present, there is no clinical data to support shortening IM regimens. The working group continues to recommend the Essen IM PEP regimen: 1-site IM regimen on days 0, 3, 7 and between days 14 and 28

Changing the route of administration during a PEP course (i.e. from ID to IM or vice versa) is acceptable in unavoidable circumstances. Restarting PEP is not necessary and the schedule for the new route should be adopted if this occurs.

PEP is safe and effective for use in pregnant women. PEP should not be withheld from pregnant women.

Individuals who are immunocompromised should receive meticulous wound cleaning, the most immunogenic PEP regimen available regardless of administration route, and high-quality RIG.

Individuals experiencing bat-mediated rabies exposure should receive any WHO PEP regimen. Bites from bats may go unrecognised; cautionary principles apply to bat exposures.

Persons exposed or re-exposed to rabies who have previously received PrEP, PEP, or who have discontinued PEP after receiving at least two doses of CCEEVs should receive either:

- 1-site ID PEP on days 0 and 3; or
- 4-site ID PEP on day 0

RIG is not indicated in previously immunized individuals.

Rabies immunoglobulins (RIG)

The recommendation to calculate maximum dosage of RIG based on body weight is maintained.

Local infiltration of as much RIG as possible into and around the wound is most effective in preventing rabies. Injection of remaining RIG distant to the wound site is unlikely to confer additional protection.

Equine (eRIG) and human (hRIG) rabies immunoglobulin are considered clinically equivalent. Skin testing prior to administration of eRIG should be abandoned.

RIG is not indicated for healthy persons who have previously received PEP or PrEP.

Where RIG is not available or affordable, its use should be prioritised for persons with multiple or deep wounds; bites to the head, neck, hands, genitals or other highly innervated areas; immunocompromised patients; patients bitten by a probable or confirmed rabid animal; and patients with bites, scratches, or other mucous membrane exposure to a bat.

Scrupulous wound cleaning and deep irrigation, with application of a potent antiseptic agent, and timely administration of the first CCEEV dose, are key to increasing survival where RIG is unavailable. This is supported by evidence from field data combined with modelling which show that, even in the absence of RIG, rigorous wound washing together administration of vaccines the same day as the bite and completion of the PEP course is highly protective against rabies (>95%).

Further development and assessment of monoclonal antibodies (mAbs) should be promoted as a potentially affordable and more accessible alternative to RIG. Post-marketing surveillance is needed for both RIG and mAbs.

New vaccines and operational tools under development

New vaccines under development have the potential to induce long-lasting immunity and improve programmatic delivery. Novel vaccine delivery tools such as micro-needle patches, ID injectors devices have the potential to increase uptake of ID vaccine administration.

Further programme-directed research on immunogenicity and clinical outcomes of rabies PrEP or PEP in immunocompromised individuals would allow better understanding of factors important for seroconversion.

Further innovation, research and development in collaboration with manufacturers is required to improve community delivery of rabies biologics, and to optimize cost-effectiveness, safety and efficacy of vaccines.

Conclusion

Updated, more programmatically feasible recommendations are critical to improve public health impact from a neglected disease like rabies. The practical guidance relevant to rabies-endemic settings particularly aims to improve community delivery of rabies PEP. The recommendations will facilitate meeting the need, especially in underserved populations that should have a better opportunity to access affordable, life-saving rabies biologics more equitably, as the world strives to reach the goal of zero dog-transmitted human rabies deaths by 2030.

Table of Contents

1. ABBREVIATIONS

BHKV	Baby Hamster Kidney (cells) Vaccine
BMI	Body mass index
CCV	Purified cell-culture vaccine
CCEEV	Purified cell-culture and embryonated egg-based vaccines
CTC	Controlled temperature chain
DHIS2	District Health Information Software 2
DPT	Diphtheria, pertussis and tetanus
DRIT	Direct rapid immunohistochemistry test
EEV	Embryonated egg-based vaccine
ELISA	Enzyme linked immunosorbent assay
eRIG	Equine rabies immunoglobulin
F(ab')2	Antigen-binding immunoglobulin fragments
FAO	Food and Agriculture Organization of the United Nations
FAT	Fluorescent antibody testing
FAVN	Fluorescent antibody virus neutralisation test
GAVI	Global Alliance for Vaccines and Immunization
GARC	Global Alliance for Rabies Control
GMT	Geometric mean titre
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HDCV	Human diploid cell vaccine
HIV	Human immunodeficiency virus
hRIG	Human rabies immunoglobulin
ID	Intradermal
IM	Intramuscular
IPC	Pasteur Institute of Cambodia
IU	International units
JE	Japanese encephalitis
mAB	Monoclonal antibody
NTV	Nerve tissue vaccine
OIE	World Organisation for Animal Health
PARACON	Pan-African Rabies Control Network
PCECV	Purified chick embryo cell vaccine
PDEV	Purified duck embryo cell vaccine
PEP	Post-exposure prophylaxis
PIKA	Polyinosinic-polycytidylic acid based adjuvant
PPHKCV	Purified primary hamster kidney cell vaccine
PrEP	Pre-exposure prophylaxis
PVRV	Purified vero cell vaccine
RABV	Rabies virus
RFFIT	Rapid fluorescent focus inhibition test
RIG	Rabies immunoglobulin
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase PCR
RVNA	Rabies virus neutralizing antibodies
SAGE	Strategic Advisory Group of Experts on Immunization
SDG	Sustainable Development Goal
SIRVERA	Sistema de Información Regional para la Vigilancia Epidemiológica de la Rabia
TRC	Thai Red Cross

2. INTRODUCTION AND BACKGROUND

2.1. Key Points

- A global target of zero human rabies deaths by 2030 was set in line with the Sustainable Development Goals (SDG) 3.3 to end Neglected Tropical Diseases by 2030 and SDG 3.8 to achieve Universal Health Coverage
- Rabies is a vaccine-preventable viral disease with the highest documented case-fatality rate, close to 100%
- Rabies occurs in more than 100 countries and territories
- Infection causes an estimated 59000 human deaths every year
- Dogs are the main source of human rabies deaths worldwide, causing up to 95% of all rabies transmissions to humans.
- Rabies is an underreported, under- or misdiagnosed disease of underserved populations; data is scarce.
- There are still numerous countries where rabies vaccine and/or RIG is not part of the essential medicines list.
- Around 40% of people bitten by suspect rabid animals are children under 15 years of age.
- Prevention of rabies has two main, non-exclusive strategies: 1) dog vaccination to interrupt virus transmission; 2) human vaccination as post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP).
- Awareness on rabies and education on bite prevention are powerful tools to avoid rabies exposures
- PEP consists of immediate, rigorous wound care, administration of rabies vaccine and simultaneous administration of rabies immunoglobulin (RIG) in severe exposures. Completion of the vaccination schedule is essential.
- Rabies vaccines (CCEEVs) are safe and highly immunogenic, PEP is effective in preventing rabies
- The high cost, low availability and supply, batch to batch variation affecting efficacy, uncertain quality (no WHO prequalification) and short shelf life of RIG are barriers to implementing PEP

2.2. Introduction to Rabies:

Rabies is a zoonotic disease caused by the rabies virus (RABV). RABV belongs to the genus *Lyssavirus* in the family *Rhabdoviridae*; *Lyssaviruses* all elicit an acute progressive encephalitis in humans. The genome of RABV is single-stranded negative-sense RNA that codes for five proteins; the most important of these from an immunizations perspective is the G glycoprotein, which includes the antigenic sites targeted by rabies vaccines and passive immunization (WHO, 2013).

Rabies is of public health concern to over three billion people worldwide, and causes an estimated 59 000 human deaths annually (Hampson et al., 2015). While bats and several wildlife species can transmit rabies, dogs are the source of over 95% of human cases. Marginalized and rural populations are disproportionately affected, experiencing the greatest burden with the least access to affordable preventative treatment. The majority of cases occur in Africa and Asia (Figure 1), and more than 40% occur in children under the age of 15 (Knobel et al., 2005).

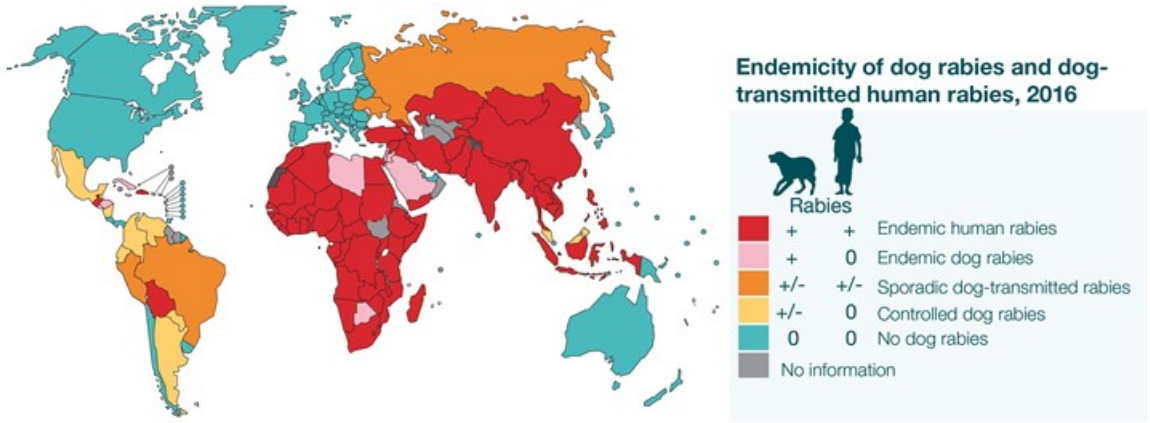


Figure 1: Endemicity of dog and dog-transmitted human rabies based on data of 2016 (WHO, 2017)

Rabies is transmitted through direct contact between the virus (e.g. in contaminated saliva), and mucous membranes or wounds. Human infection most frequently occurs following a transdermal bite or scratch from an infected animal (WHO, 2013). All age groups are susceptible, although children are at increased risk of sustaining bites to the head or neck, and may be less likely to report bites or scratches sustained in play. With the exception of organ transplants from rabid patients, human-human transmission has never been confirmed, including after close contact during health case. Very rarely, rabies has been contracted by inhalation of virus-containing aerosol. The risk of sexual transmission remains theoretical. In most cases the incubation period is two to three months. This can vary from less than one week (e.g. in the case of direct nerve inoculation) to more than one year, depending on the amount of virus inoculated, and its proximity to the central nervous system (WHO, 2013).

Inoculated virus travels via the peripheral nerves to the central nervous system. Upon reaching the brain, it replicates and disseminates rapidly to the salivary glands, throat muscles and other tissues. The rabies virus is concealed from immune surveillance and neutralization by immunoglobulin by its location inside the neurons. Therefore, antibody responses in serum and cerebrospinal fluid (CSF) are rarely detected before the second week of illness (WHO, 2013). The virus does not enter the bloodstream, and human immunoglobulin prophylaxis is considered to be effective only when the rabies virus is present in the bite wound.

Clinical diagnosis of rabies is informed by patient presentation, history of exposure to a suspect rabid animal, and whether preventative measures such as PEP have been administered. Once clinical signs appear, the disease is almost always fatal. Laboratory confirmation of human rabies can be performed ante-mortem or post-mortem on saliva, spinal fluid or tissue biopsies to detect intact virions, viral genomic RNA, antibody or antigen (WHO, 2013). With the exception of hydrophobia, clinical signs of rabies can be unreliable, and contribute to under- or misdiagnosis of rabies in humans. Additionally, rabies patients often die at home, or leave hospital when no treatment can be offered, and are therefore not included in clinical databases and mortality statistics (WHO, 2017).

The initial symptoms of rabies are fever, pain or paresthesia at the wound site. As the virus spreads through the central nervous system, a progressive fatal encephalomyelitis develops, characterized by hyperactivity and fluctuating consciousness. Other clinical symptoms include hyperactivity, hallucinations, and hydrophobia (furious rabies), or paralysis and coma (paralytic rabies), followed by death (WHO, 2013). In both furious and paralytic forms, death usually occurs by cardiorespiratory arrest within 7-10 days of the first clinical sign.

While rabies is considered nearly 100% fatal, it is also 100% preventable. It differs from many other infections in that the development of clinical disease can be prevented through timely immunization, even after exposure to the infectious agent. Rabies can be prevented both before and after exposure via pre-exposure prophylaxis or post-exposure prophylaxis. Education and awareness are key to prevent bites from and thus exposure to rabid animals.

2.3. Rationale for an update and previous recommendations from the Position Paper

2.3.1. Rationale for an update

Despite highly efficacious biologics preventing rabies when exposed, there has been a continued observation of discrepancy between the current practice of rabies PrEP and PEP in (rabies-endemic) countries and the feasibility to implement the current standard according to the WHO recommendations in many settings. This has led to major health equity gaps, particularly between urban and rural areas as well as between socioeconomic classes of populations. There was an urgent need to review accumulated new evidence for vaccine and RIG use, particularly shorter and more feasible PrEP and PEP protocols, cost-effectiveness of implementation and the potential of new vaccines with the view to improve access to care and increased public health impact, worldwide. The global conference on rabies, which was held on December 2015 in Geneva (WHO, 2016), proposed a framework that set an ambitious global goal for elimination of human dog-mediated rabies by 2030, coinciding with the Sustainable Development Goals target date. This global strategy is in line with the priorities of SDG 3.3 to end Neglected Tropical Diseases by 2030 and SDG 3.8 to achieve Universal Health Coverage.

In the effort to improve affordability and access, particularly for vulnerable populations in rabies-affected countries, rabies vaccines are a candidate for inclusion in the vaccine support programme through Gavi, the Vaccine Alliance. Every five years, Gavi reviews its vaccine investment strategy (VIS) to determine which vaccines are made available through their programme. Rabies vaccines were considered in the past two cycles, 2008 and 2013, but weak data and knowledge gaps have postponed its decision on the inclusion until the next VIS in 2018. While a solution on rabies vaccines roll out to countries in demand is in sight, channels for scaling up access to RIG as part of PEP in severely exposed patients still needs to be identified.

2.3.2. Recommendations from the 2010 position paper

The 2010 WHO position paper on rabies vaccines summarizes standards on concentrated and purified cell-culture (CCV) and embryonated egg-based (EEV) rabies vaccines (jointly referred to as CCEEVs) and re-iterates their safety, efficacy and high immunogenicity (WHO, 2010). Since the late 1980s, WHO has advocated for replacement of nerve tissue vaccines (NTVs) by CCEEVs. The production and use of NTVs is not recommended by WHO. The recommendations specify indications for and administration mode of CCEEVs, duration of immunity, including recommended PrEP and PEP regimens for healthy people of all age groups and immunocompromised people. Recommendations on PEP include further procedures for wound care, indications for and correct administration of rabies immunoglobulins for passive immunization in severe rabies exposures.

Evidence for the following conclusions was assessed and graded during the elaboration of the 2010 WHO position paper:

- Duration of immunity following pre- or post-exposure immunization with cell-culture-based rabies vaccines: Moderate scientific evidence that using cell-culture-derived rabies vaccines induces ≥10 years of immunity against rabies.
- Efficacy of cell-culture-based rabies vaccines: High scientific evidence that cell culture-derived rabies vaccines when used according to WHO's recommendations are efficacious against rabies and/or induce antibodies against rabies virus following intramuscular (IM) or intradermal (ID)administration.
- Safety of cell-culture-based rabies vaccines: Moderate level of scientific evidence that cell-culture-based rabies vaccines are safe. (However, transient local reactions may occur, in particular following ID administration)

2.4. Magnitude of the Problem of Rabies

Rabies occurs in over 100 countries and territories, where it causes an estimated 59 000 human deaths every year (Hampson et al., 2015). Underreporting and frequent misdiagnosis of rabies means this figure is likely higher. Africa and Asia bear the heaviest rabies burden (Figure 2), due to the epidemiological, cultural and

socioeconomic factors (e.g. lack of rabies awareness, lack of access to affordable healthcare) that allow many neglected tropical diseases to persist in those areas) (Knobel et al., 2005). As PEP failures are very rare, rabies deaths primarily occur in those who cannot afford or access timely and effective post-exposure treatment. In the absence of PEP, an estimated 3 million people would die from rabies worldwide each year (Hampson et al 2015).

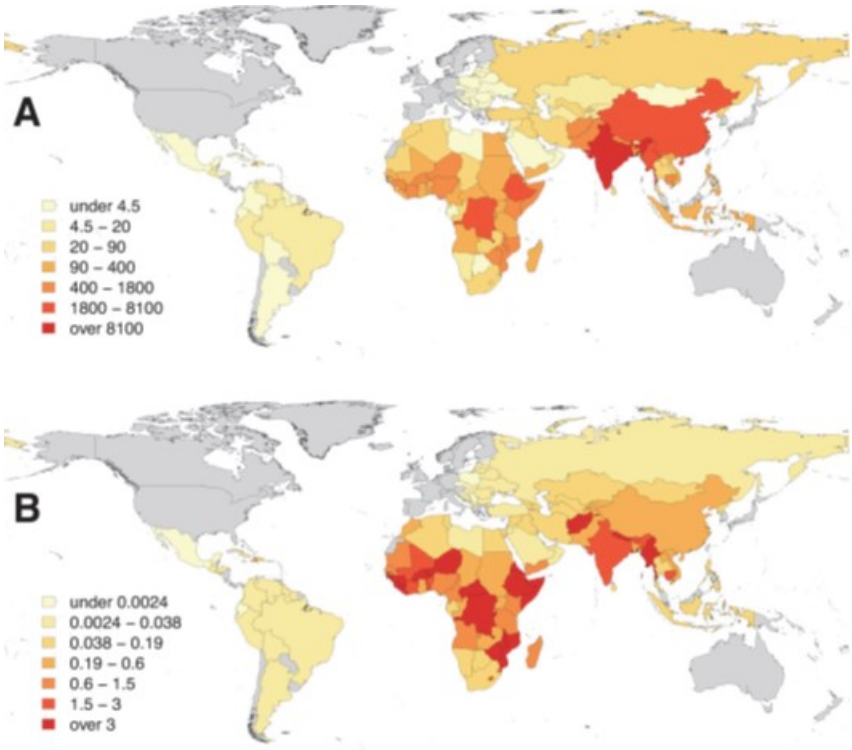


Figure 2: Hampson et al 2015, the distribution of the global burden of rabies: A) human rabies deaths, B) per capita death rates (per 100,000 persons), countries shaded in grey are free from canine rabies.

Globally, rabies carries an estimated economic burden of 8.6 billion USD per year (Hampson et al, 2015). This is comprised of economic burden due to premature death, direct cost of PEP, lost income while seeking PEP, livestock losses, dog vaccination, dog population management, and surveillance (Figure 3).

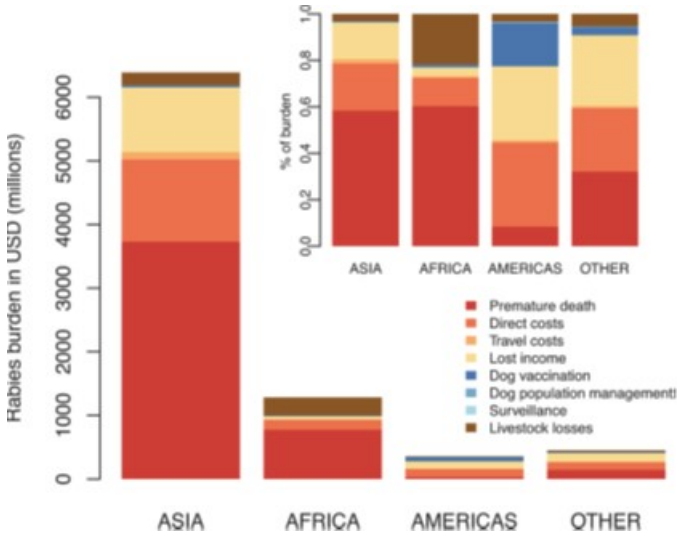


Figure 3: Division of costs associated with rabies, prevention and control across sectors by region. Inset shows proportional expenditure in different regions. (Hampson et al., 2015)

2.5. Rabies Epidemiology, Surveillance and Laboratory methods:

Rabies is present on all continents, except for Antarctica. Dogs are responsible for more than 95% of human rabies cases, however bats are thought to be the original animal reservoir. Rabies transmission to humans via wildlife other than bats is considered rare. Dog-transmitted rabies has been eliminated in Western Europe, North America, Japan, South Korea and parts of Latin America. It remains endemic in much of Asia, Africa and the Middle East, and is re-emerging in parts of China and emerging in certain previously non-affected territories (Figure 2) (WHO, 2013).

Integrated global reporting systems exist for notification of animal rabies cases to the World Organisation for Animal Health (OIE) (through the World Animal Health Information System - WAHIS) and of human cases to WHO (through the District Health Information Software or DHIS2 feeding into the global health observatory data base). Regional databases exist in Europe (Rabies Bulletin Europe), Latin America (SIRVERA) and Africa (PARACON). Widespread underreporting of human and animal rabies cases contributes to underestimation of rabies disease burden and surveillance systems require strengthening worldwide (WHO, 2017).

A clinical suspected case of rabies is defined as "*A subject presenting with an acute neurological syndrome (i.e. encephalitis) dominated by forms of hyperactivity (i.e. furious rabies) or paralytic syndromes (i.e. paralytic rabies) progressing towards coma and death, usually by cardiac or respiratory failure, typically within 7–10 days after the first sign, if no intensive care is instituted. This may include any of the following signs: aerophobia, hydrophobia, paresthesia or localized pain, dysphagia, localized weakness, nausea or vomiting.*" [1]

Laboratory confirmation in humans can be obtained ante-mortem or post-mortem using saliva, spinal fluid or tissue biopsies. Fluorescent antibody testing (FAT) is gold standard, however enzyme linked immunosorbent assays (ELISA), direct rapid immunohistochemistry tests (DRIT), lateral flow tests and reverse transcriptase polymerase chain reaction (RT-PCR) are also used. Test sensitivity depends on stage of disease, immune status, viral shedding and technical expertise. While a positive laboratory result indicates rabies, a negative result does not rule out infection (WHO, 2013). Access to rabies confirmatory testing in endemic countries is extremely limited.

The measurement of rabies virus neutralizing antibody (RVNAs) is the most convenient method of confirming an immunological response after rabies PrEP or PEP. The Rapid fluorescent focus inhibition test (RFFIT) has been the serological assay of choice for quantitatively measuring the presence of neutralizing antibodies after rabies vaccination. An ELISA to monitor antibody titres in vaccinated humans against rabies virus glycoprotein has been used as an alternative. Initially, measurement of RVNA was performed in vivo using the mouse neutralization test. Subsequently, the virus neutralizing assays, rapid fluorescent focus inhibition test (RFFIT) and the fluorescent antibody virus neutralization test (FAVN), have been recommended for post-vaccination monitoring and determination of need for booster vaccination. The level of neutralizing antibody in serum samples is determined by comparing results with a standardized reference serum. The RFFIT is considered to be a complex assay due to the fact that the sensitivity and specificity are dependent upon many factors. It is therefore important that laboratories conducting the RFFIT to adhere to strict quality control procedures and also to participate in quality assurance programs. The value of 0.5 IU/ mL (IU/mL) has been recommended by WHO as indicative that a vaccinated person has responded to rabies vaccine. It is important to understand that a serological titre of 0.5 IU/ml reported from a RFFIT on one day may be reported as 0.4 or 0.6 on another day due to the nature of the test, and that this measures antibodies as a proxy for protection, which may nevertheless be warranted by lower antibody titres (Moore & Hanlon 2010).

[1] Cases are classified as (WHO 2013):

- Suspected: compatible with the case definition.
- Probable: a suspected case with reliable history of contact with a probable or confirmed rabid animal.
- Confirmed: a suspected or probable case that is laboratory-confirmed.

2.6. Rabies pre- and post-exposure treatment

2.6.1. Principles PrEP / PEP

Risk of exposure to rabies can be reduced by bite prevention education, dog population management and responsible pet ownership, including vaccinating dogs against rabies. Rabies in humans can be prevented, both before and after exposure via PrEP or PEP, respectively. PrEP consists of a series of rabies vaccine injections to prime the immune system. This enables a fast recall of an immune response in case of re-exposure to the virus, and following administration of a post exposure vaccine booster. PEP, after a potential exposure, consists of proper wound management followed by administration of immunoglobulin, if indicated, and a series of injections of rabies vaccines (Figure 4).

Prompt post-exposure use of CCEEVs combined with proper wound management and simultaneous administration of RIG in severe exposures is close to 100% effective in preventing rabies. However, delay in seeking treatment, improper wound care, unnoticed wounds, direct nerve inoculation, and lack of patient compliance to vaccination schedules, among other factors (e.g. vaccine and cold chain quality), may contribute to treatment failure and subsequent death (Wilde, 2007). Thus, mitigation of these circumstances has been emphasized in educational programmes, particularly for those in rabies endemic areas.

The indication for PEP depends on the type of contact with the suspected rabid animal:

Category I	touching or feeding animals, licks on intact skin (that is, no exposure);
Category II	nibbling of uncovered skin, minor scratches or abrasions without bleeding;
Category III	single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva from licks, licks on broken skin, exposures due to direct contact with bats.

PEP is indicated for those with category II or III rabies exposures, and should be sought as urgently as possible following exposure (WHO, 2010). Because rabies is fatal, no contraindications exist to PEP following category II or III exposure, even months later (e.g. PEP is indicated in persons co-exposed to the bite of an animal which caused a human rabies case). PEP requires three steps: (a) wound washing and care, (b) vaccination, and (c) administration of rabies immunoglobulin. RIG should be administered in all people with category III exposure and to those with category II exposure who are immunodeficient or had a direct contact exposure to a bat. RIG, derived from the blood of humans or horses, is currently used as a component of PEP as a method of passive immunization. RIG neutralizes the rabies virus in situ, before the subject's immune system responds to the vaccination by producing rabies virus neutralizing antibodies. RIG has to be administered only once, as soon as possible and before day 7 after the first dose of vaccine. All wounds, however small, should be located and infiltrated with RIG.

The recommended first aid procedures include immediate, thorough flushing and washing of the wound with soap and water, detergent, povidone iodine or other substances with viricidal activity. Thorough wound washing is considered to reduce the risk of rabies infection. Depending on the characteristic of the wound, antibiotics, analgesics and tetanus vaccine booster might be indicated. Residents of rabies-endemic areas should be taught how to prevent dog bites, learn about simple local wound treatment, in particular to look for small or missed wounds, and to not use procedures that may further contaminate or enlarge the wound. Detailed descriptions of the currently available rabies biologics see below.

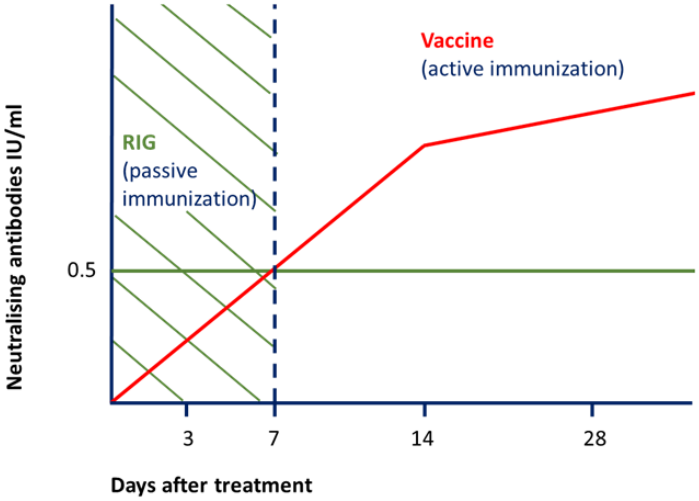


Figure 4: Principles of rabies post-exposure prophylaxis. A neutralising antibody titre of 0.5IU/ml is considered protective in all cases.

2.6.2. Types of Vaccines:

For decades, CCEEVs have been supported as safe and effective in preventing rabies. These vaccines are intended for both PrEP and PEP. Currently there are 3 human rabies vaccines that are WHO pre-qualified including: Rabavert® and Rabipur® (EVV) produced by GSK and Verorab® (CCV) produced by Sanofi Pasteur. Two additional rabies vaccines are subject to an assessment for WHO prequalification. CCEEVs are available in 0.5 ml or 1 ml vials, mostly in lyophilized form (see Table 1), the size of the vial does not impact the immunization practice. After reconstitution with sterile diluent, the vaccines should be used immediately or within 6-8 h if kept between +2°C to +8°C (WHO, 2015), as partially used vials of rabies vaccine may rapidly become contaminated.

China produces the largest number of brands of human rabies vaccines followed by India. An overview of human rabies vaccines currently in use is available in Table 1.

In a few remaining countries, populations at high risk of rabies may still depend on rabies vaccines derived from animal nerve tissues for PEP. Nerve tissue vaccines may induce very severe adverse reactions and are less immunogenic than CCEEVs; therefore, WHO has strongly recommended against their production and use (WHO, 2013).

The table below was compiled through enquiries with various networks, including the International Federation of Pharmaceutical Manufacturers, Developing Countries Vaccine Manufacturers Network and systematic online searches for manufacturers to reflect the most inclusive evidence available to date, without claiming completeness.

Table 1: Human rabies vaccines and producers worldwide, as per August 2017:

Vaccine [a]	Brand	Producer	Country	Cell line	WHO Pre-qualified	Type
PVRV	NA	Butantan Institute	Brazil	Vero cells	NO	Liquid
HDCV	Chengdu Kanghua	Changdu Kanghua	China	Human diploid cells	NO	Lyoph
PVRV	SPEEDA	Liaoning Chengda co., LTD	China	Vero cells	NO	Lyoph

PVRV	NA	Changchun Changsheng Life Sciences Ltd.	China	Vero cells	NO	Lyoph
PVRV	NA	Guangzhou Nuocheng biological products co., LTD	China	Vero cells	NO	Lyoph
PVRV	NA	Ningbo RongAn biological pharmaceutical co., LTD	China	Vero cells	NO	Lyoph
PVRV	NA	Jilin Maifeng biological pharmaceutical co., LTD	China	Vero cells	NO	Liquid
PPHKCV	NA	Zhongke biological pharmaceutical co., LTD	China	Hamster Kidney Cells	NO	Liquid
PPHKCV	NA	Henan Yuanda biological pharmaceutical co., LTD	China	Hamster Kidney Cells	NO	Liquid
PIKA rabies vaccine, inactivated, with a TLR3-based adjuvant		Yisheng Biopharma Inc	China	Vero cell	NO	?
PVRV	Verorab	Sanofi Pasteur	France	Vero cells	YES	Lyoph
HDCV	Imovax	Sanofi Pasteur	France	Human diploid cells	NO	Lyoph
PCECV	Rabavert	GSK	Germany	Chick embryo cells	YES	Lyoph
PCECV	Rabipur	GSK	India	Chick embryo cells	YES	Lyoph
HDCV	Rabivax	Serum Institute of India	India	Human diploid cells	NO	Liquid
PDEV	Lyssavac-N /Vaxirab	Zydus-Cadila	India	Duck embryo cells	Production stopped	Lyoph
PCECV	Vaxirab-N	Zydus-Cadila	India	Chick embryo cells	NO, successor of Vaxirab	Lyoph
PVRV	Indirab	Bharat Biotech	India	Vero cells	NO	Lyoph
PVRV	Abhayrab	Indian Immunologicals	India	Vero cells	NO	Lyoph
BHKV	'Вакцинация КОКАВ	Tarasevich Institute	USSR	BHK	NO	??
NTV	?	?	Bolivia	Mouse brain	NO	Liquid?
NTV	?	Pasteur Institute Algiers	Algeria	Mouse brain	NO	Liquid?
NTV	?	Ethiopian Public Health Institute	Ethiopia	Sheep brain?	NO	Liquid?
NTV	?	?	Argentina	Sheep brain?	NO	Liquid?

[a] *Purified chick embryo cell vaccine (PCECV), Purified vero cell vaccine (PVRV), Human diploid cell vaccine (HDCV), Purified duck embryo cell vaccine (PDEV), baby hamster kidney cells (BHKV), Purified Vaccine of Primary Hamster Kidney Cells (PPHKCV)*

Because rabies is a fatal disease, randomized controlled trials in rabies-exposed humans involving untreated comparison groups are unethical and not performed. Direct assessment of vaccine-induced protection is based on the efficacy of PEP following category II or III exposures from laboratory-confirmed rabid animals. Furthermore, animal models serving as human surrogates have been used to demonstrate the protective efficacy of CCEEVs after experimental infection. An indirect assessment of vaccine efficacy can be made through immunogenicity studies. All CCEEVs induce high rabies virus neutralizing antibody response to the viral G protein within ~7 days. The WHO specified minimum titre of 0.5 IU/mL of serum, measured by RFFIT or the fluorescent antibody virus neutralization test (FAVN) is a widely-used reference (WHO, 2010). In healthy individuals, this level should be achieved by day 14 of a post-exposure regimen, with or without simultaneous administration of rabies immunoglobulin and irrespective of age. When new rabies vaccines are introduced, their immunogenicity is usually evaluated by comparing the rabies-virus neutralizing antibody titres induced by the vaccine being tested with those induced by a vaccine of demonstrated efficacy.
The cost of CCEEVs limits their widespread use in many rabies-endemic areas. Intramuscular administration of rabies vaccine is safe and immunogenic. Intradermal administration of reduced dose rabies vaccine offers a preferable, cost-effective alternative. ID administration requires lower doses of rabies vaccine, and can, under optimal conditions, reduce the volume and direct cost of vaccine by up to 60-80%, compared to IM administration (Hampson et al., 2011).
Although this plays no role in preventing rabies after a given exposure, the development of immunological memory after vaccination with CCEEVs is critical for the establishment of long-lasting immunity against rabies in humans. Individuals who had received their primary series 5–21 years previously showed good anamnestic responses after booster vaccination (Kessels et al., 2017). Long-term immunity is also achieved with ID immunization and may persist even when antibody titres are below 0.5I U/ml or are no longer detectable. The ability to develop an anamnestic response to a booster vaccination is not related to the route of administration of the initial series (IM or ID), or to whether the patient received pre-exposure prophylaxis, as long as the post-exposure series was completed (Saraya et al 2010, Venkataswamy et al 2015).
In general, CCEEVs have been shown to be safe and well tolerated. However, in 35–45% of vaccinated individuals, minor and transient erythema, pain and/or swelling may occur at the site of injection, particularly following ID administration of a booster. Mild systemic adverse events following immunization, such as transient fever, headache, dizziness and gastrointestinal symptoms, have been observed in 5–15% of vaccinated individuals. Serious adverse events, mainly of allergic or neurological nature, are extremely rare (WHO, 2010).
Rabies vaccines can safely be administered alone or alongside diphtheria, pertussis and tetanus, Japanese encephalitis (JE), or polio vaccines (Kessels et al. 2017)
Previous severe reaction to any components of the vaccine is a contraindication to further use of the same vaccine. As with all other immunizations, vaccinated individuals should if possible be kept under medical supervision for at least fifteen to twenty minutes following vaccination.

2.6.3. Types of RIG:

Three classes of biological product are available for passive immunization: human rabies immunoglobulin (hRIG), equine rabies immunoglobulin (eRIG), including eRIG-derived highly purified antigen-binding immunoglobulin fragments (F(ab´)2) and monoclonal antibodies (mAbs) (Table 3). If hRIG, eRIG and F(ab')2 products are correctly administered they eliminate the virus at the wound site within a few hours. The dosage of hRIG and eRIG is weight-based, 20 IU/kg and 40 IU/kg respectively.
A single mAb product, as an alternative to RIG was licensed in 2016 for use in India.
The high cost, low availability and supply, batch to batch variation affecting efficacy, uncertain quality (no WHO prequalification), short shelf-life even with correct cold chain, and correct administration of RIG are barriers to implementing the standard previously set by WHO for PEP in individuals severely exposed to rabies.
The table below was compiled through enquiries with various networks, including the International Federation of Pharmaceutical Manufacturers, Developing Countries Vaccine Manufacturers Network and systematic

online searches for manufacturers to reflect the most inclusive evidence available to date, without claiming completeness.

Table 3: Overview on rabies immunoglobulin products and producers worldwide as per August 2017

Category	RIG product name or brand name [a]	formulation per ml / per vial	Vial size	Company name	Country
eRIG	Anti-rabies serum	N/A	N/A	Butantan Institute	Brazil
eRIG	CARIG (enzyme refine)	300 IU/ml	4 ml	Cadila Pharma	India
eRIG	Rabix-IG	200 IU/ml	5 ml	Incepta Pharmacueticals	India
eRIG	Abhay-RIG	300 IU/ml	5 ml	Indian Immunological	India
eRIG	Anti-rabies serum	300 IU/ml	5 ml	Haffkine	India
eRIG	EquiRab	300 IU/ml	5 ml	Bharat Serums and Vaccines	India
eRIG	Pars	200 IU/ml	5 ml	Newgen (Cadila Pharmaceuticals Ltd.)	India
eRIG	Anti-rabies serum	300 IU/ml	5 ml	Serum Institute of India	India
eRIG	Anti-rabies serum	300 IU/ml	5 ml	Central research Institute Kasauli HP	India
eRIG	Plasmarab	300 IU/ml	5 ml	Premium Serums	India
eRIG	TRCS eRIG	200 IU/ml	5 ml	Queen Saovabha Memorial Institute	Thailand
hRIG	Human Rabies immunoglobulin	100 IU/ml	2 ml or 5 ml	HualanBiologicalBacterin Co. Ltd.	China
hRIG	Human Rabies immunoglobulin	100 IU/ml	1 ml, 2 ml or 5 ml	Sichuan Yuanda Shuyang Pharmaceutical Co. Ltd	China
hRIG	Human Rabies immunoglobulin	100 IU, 200 IU or 500 IU/vial	N/A	China National Biotec Group (Sinopharm subsidery)	China
hRIG	Human Rabies immunoglobulin	200 IU/Vial	2 ml	China Biologic Product. Inc	China
hRIG	Imogram Rabies-HT	150 IU/ml	2 ml or10 ml	Sanofi Pasteur	France
hRIG	Pars	150 IU/ml	2 ml	Newgen (Cadila Pharmaceuticals Ltd.)	India
hRIG	Berirab-P	150 IU/ml	2ml or 5 ml	Bharat Serums and Vaccines	India
hRIG	Rabglob	150 IU/ml	2ml or 5 ml	Bharat Biotech International Ltd.	India
hRIG	Kendrab	150 IU/ml	2 ml or 10 ml	Kamada Ltd.	Israel
hRIG	Human Rabies immunoglobulin	150 IU/ml	vials with 500 IU	Bio Products Laboratory Limited	UK
hRIG	HyperRAB S/D	150 IU/ml	2 ml or 10 ml	GRIFOLS USA , LLC	USA
hRIG	Rabigam	150 IU/ml	2 ml	National Bioproducts	South Africa
RmAb	Rabishield	40 IU or 100 IU/ml	2.5 ml	Serum Institute of India	India

2.6.4. Rabies vaccine potency:

The 2010 WHO rabies vaccine position paper recommends a potency ≥ 2.5 IU per IM dose. No WHO potency recommendation exists for doses injected intradermally, which are a fraction of the IM dose. However, an additional WHO recommendation sets the volume of ID injection to 0.1 mL, thereby constraining the potency per ID dose. The need to define a minimum potency per ID dose, in addition to the recommended volume, has been a topic for discussion among experts in the past years. Such discussion was in part prompted by the

observation that the 0.5 mL Purified Vero Cell Vaccine (PVRV) vaccine vials provide maximally 5 ID doses with potency per dose ≥ 0.50 IU, whereas other vaccines supplied in 1.0 mL vials provide around 10 ID doses with potency ≥ 0.25 IU. Concerns were raised that ID vaccination may sometimes involve an insufficient amount of antigen. The national regulations of some countries (e.g. in South and South East Asia) specify rabies vaccine potency above 5 IU/ml.

To address this question, a systematic literature review was conducted by an external expert (see Annex II evidence profile on vaccine potency). The first search focused on the immunogenicity of rabies vaccines given by ID route. It identified 299 publications in the period 1997-2017, of which 38 studies were included in the analyses. A second search investigating the effectiveness of ID vaccination resulted in 227 hits for the period 2007-2017, of which 11 suitable publications were retained.

The immunogenicity of current rabies vaccines was analysed in 3 different ways: proportion of subjects reaching the antibody threshold of 0.5 IU/ml after ID vaccination, relationship between potency and immunogenicity of the vaccine given intra-dermally, and comparison of antibody responses after IM or ID vaccination. Overall, vaccines administered by ID route were found to be highly immunogenic, irrespective of their IU content per IM dose. PEP by ID route appeared as least as immunogenic as that administered by IM regimens. By contrast, ID PrEP trended towards lower antibody titres than IM vaccination, but the observation was not associated with any clinical relevance.

Vaccine effectiveness was assessed by investigating survival after exposure. Data from an approximate total of 36 000 patients who received PEP indicates that vaccines administered ID are as efficacious as vaccines administered IM. The current recommendations, including both ≥ 2.5 IU/mL per IM dose and a volume of 0.1 mL per ID dose correspond to a recommendation of ≥ 0.25 IU per ID dose. Available data do not indicate that vaccines meeting this requirement lack efficacy.

2.7. Rabies Prevention and Control Strategies:

Strategies to prevent and eliminate human rabies include mass dog vaccination campaigns to halt disease transmission at its source, and the provision of accessible, affordable, timely and effective prophylaxis to people exposed to rabies. Vaccinating 70% of at-risk dog populations is considered sufficient to reliably and sustainably interrupt rabies transmission in dogs, and has ensured the elimination of canine rabies from developed countries (Coleman & Dye, 1996; Hampson et al., 2009). Global initiatives to build rabies awareness include World Rabies day (September 28) and the End Rabies Now campaign. These engage and educate communities on rabies, bite prevention, and the importance of vaccinating dogs to prevent human disease.

In 2015, stakeholders set a goal of zero human rabies deaths by 2030, worldwide (“Zero by 30”). This was followed by the launch of the Global Framework to Eliminate Dog-Mediated Human Rabies by 2030 (WHO, 2016). A Global Business Plan will be launched this year. This takes a country-centric approach, with international partners (WHO, OIE, Food and Agriculture Organization of the United Nations (FAO) and the Global Alliance for Rabies Control (GARC)) united to empower and catalyse nations to eliminate rabies (WHO, 2017). WHO is currently building the evidence base for consideration of human rabies vaccine in the 2018 GAVI Vaccine Investment Strategy. If successful, this would ensure free access to human rabies vaccine for those who need it in lower income, GAVI-eligible countries.

3. PRE-EXPOSURE PROPHYLAXIS:

3.1. Key Points

- There is no medical contraindication for rabies PrEP
- PrEP can be considered for certain exposed sub-populations in remote areas, but cost-effectiveness of this public health intervention should be assessed individually by countries within their specific context
- Modelling estimates indicate that PrEP, as a large scale public health intervention, is not cost-effective and would become only cost-neutral in situations where RIG is rarely administered and at the same time the dog-bite incidence exceeds 6%

- Options for PrEP and serological testing for sub-groups of professionals and travellers have been updated
- The WG concluded on accelerated regimes as follows:
    - a 2-site ID regimen on day 0 and 7 would be efficacious as a PrEP regimen
    - a 1-site IM regimen on day 0 and 7, would be efficacious as a PrEP regimen
    - Individuals who receive only a single dose of PrEP should complete the second dose of PrEP as soon as possible and be managed with full PEP (including RIG as indicated) in the case of potential rabies exposure prior to the second PrEP dose
    - Individuals who are immunocompromised should receive a 3-visit, 2-site ID or 1-site IM PrEP regimen (day 0, 7 and between day 21 and 28) and should be managed with full PEP in the case of potential rabies exposure

3.2. Review of Scientific Evidence

PrEP has been successfully used over decades to prevent rabies infection in people of all ages. PrEP should not distract from essential canine vaccination efforts, PEP provision, and rabies educational and advocacy programmes. A systematic review on PrEP was conducted and summarizes relevant new evidence (Kessels et al., 2017). Three studies found PrEP safe and immunogenic for children up to 5 years in combination with other childhood vaccines such as Japanese encephalitis (JE), diphtheria, pertussis, tetanus (DPT) and oral and inactivated poliomyelitis vaccines (Vien et al., 2008; Laang et al., 2009; Pengsaa et al., 2009).

3.2.1. Boosters for occupationally exposed:

PrEP is indicated for individuals who face occupational and/or travel-related exposures to rabies (virus) in specific settings or over an extended period of time.

The available evidence suggest that complete PrEP triggers a long-lasting (> 20 years) immunological memory with rapid recall of the immune response when boosted. The new evidence on occupational categories and risks of rabies exposures is limited. Therefore, the update of options for pre-exposure rabies immunization of individuals occupationally or otherwise exposed (Table 4, adapted from Müller et al. 2015) mostly relied on expert knowledge. Aspects of timely access to biologics, animal rabies epidemiology and simplification on serologic testing were taken into consideration.

Table 4: Indications for pre-exposure rabies immunization (adapted from Müller et al. 2015)

Examples of typical individuals and populations	Likelihood and nature of exposure to rabies virus	Timely access to rabies biologics	Recommendations on pre-exposure immunization [a] and serologic testing
Occupational exposure			
Individuals involved rabies research, rabies biologics production [b].	Virus may be present continuously, usually in high concentrations. Specific exposures may not be recognized. Bite, non-bite, or aerosol exposures.	Yes	PrEP recommended. Suggested timeframes for serologic testing: After primary immunization and the every ~6 months up to every 1-2 years. Routine booster vaccination [c], if antibody titre falls below 0.5 IU/ml [d].
Individuals working in rabies diagnostic laboratories [b], in hospitals with clinical rabies cases [e], animal disease control, wildlife management, bat handling or with professional activities in caves likely to lead to direct contact with bats.	Settings or areas where rabies is enzootic and where exposure may not be recognized. Presence of bats, particularly non-haematophagous bats. Bite, non-bite, or aerosol exposures.	Variable, mostly yes Variable	PrEP recommended. Serologic testing every ~2 years. Routine booster vaccination if antibody titre is below 0.5 IU/ml. PrEP recommended. No serologic testing or routine booster vaccination.
Individuals working or residing in remote areas for extended periods and involved in e.g. dog vaccination campaigns, animal disease control programmes, peace keeping, military or religious missions.	Remote settings where rabies is enzootic. Exposure typically episodic with source recognized. Bite or non-bite exposures. Partly remote settings where rabies is enzootic. Exposure typically episodic with source recognized. Bite or non-bite exposures.	Variable, mostly not Variable	PrEP recommended. Serologic testing unnecessary unless risk of exposure remains. Otherwise, test and boost if antibody titre falls below 0.5 IU/ml, or alternatively give a routine booster vaccination before departure.
Individuals involved in e.g. animal disease control with direct contact with terrestrial animals.	Settings where rabies is uncommon to rare. Exposure typically episodic with source recognized. Bite or non-bite exposures.	Variable, mostly yes	PrEP recommended. No serologic testing or routine booster vaccination.
Travellers			

Individuals with mainly leisure related exposures by potential direct contact, particularly with carnivores or bats, during activities over an extended period e.g. backpackers, bicycle or motorbike riders, people visiting friends and relatives. Consider cumulative exposure in frequent travelers.	Remote settings where rabies is enzootic. Exposure typically episodic with source recognized. Bite or non-bite exposures. Partly remote settings where rabies is enzootic. Exposure typically episodic with source recognized. Bite or non-bite exposures.	Variable, mostly not Variable	PrEP recommended. Serologic testing unnecessary unless risk of exposure remains. Otherwise, test and boost if antibody titre falls below 0.5 IU/ml, or alternatively give a routine booster vaccination before departure.
Individuals with leisure activities in caves leading to likely direct contact with bats.	Settings or areas where rabies is enzootic and where exposure may not be recognized. Presence of bats, particularly non-haematophagous bats. Bite, non-bite, or aerosol exposures.	Variable, mostly yes Variable	PrEP recommended. Serologic testing every ~2 years. Routine booster vaccination if antibody titre is below 0.5 IU/ml PrEP recommended. No serologic testing or routine booster vaccination.
Sub-populations			
Residents of remote areas where animal rabies control is impaired by difficult access, epidemiological and other factors	Settings or areas where rabies is enzootic, particularly in wildlife and where episodic exposure may not be recognized. Bite or non-bite exposures.	Variable, mostly not	PrEP recommended. No serologic testing or routine booster vaccination.
General population	Areas where rabies is enzootic or epizootic. Exposure always episodic with source recognized. Mostly bite, also non-bite exposures.	Yes	No PrEP recommended. PrEP for general populations is unlikely to be a cost-effective intervention and is usually more expensive than other measures to prevent human rabies deaths, such as post-exposure prophylaxis and dog vaccination campaigns.
In case of a WHO category II or III exposure to a rabid animal (or lyssavirus), post-exposure prophylaxis including thorough wound care is always required. People who have received PrEP should be instructed accordingly.			

[a] A primary course of pre-exposure immunization consists of either a two-site intradermal administration of 0.1 ml of vaccine on days 0 and 7 or one vaccine dose for intramuscular administration on days 0 and 7. Administration of booster doses of vaccine depends on nature and duration of the rabies exposure risk as above.

[b] Assessment of relative risk and any extra monitoring of immunization status of laboratory workers is the responsibility of the laboratory supervisor (as an example, see guidelines in the current edition of the United States Department of Health and Human Services' Biosafety in Microbiological and Biomedical Laboratories).

[c] A routine pre-exposure booster vaccination consists of one dose of modern cell culture vaccine, ID or IM (i.e., deltoid area).

[d] An acceptable antibody level is 0.5 IU/ml or 1:5 virus neutralizing antibody titre (complete inhibition in the RFFIT at a 1:5 dilution, approximately equivalent to 0.1 IU/ml). Boost if the titre falls below this level, as long as the person remains at risk of viral exposure.

[e] Human-to-human transmission of rabies has never been confirmed outside of the transplant setting. However, rabies virus can be found in saliva, tears, and nervous tissues of human rabies cases and represents a theoretical route of transmission. Therefore, pre-exposure immunization might be indicated and can alleviate the psychological burden of fear from infection of health care staff who are regularly attending to patients with clinical rabies.

3.2.2. PrEP for subpopulations

Although PrEP will not eliminate rabies at its source, it can play a valuable role in protecting high risk populations in remote areas, especially where the risk of bat rabies is not easily controlled. The systematic review includes experiences and results from national programmes implementing PrEP for high-risk populations in remote settings of the Philippines (focusing on children, mainly canine-mediated rabies), Peru and Brazil (all age groups, canine- and bat-mediated rabies) (Kessels et al., 2017). This review also addresses available evidence on cost-effectiveness of such interventions in these specific sub-populations. To overcome the scarcity of cost-effectiveness data a model was developed to quantify the potential benefits and relative costs of inclusion of rabies PrEP within a routine Expanded Programme on Immunization (EPI) schedule in settings where rabies is endemic. The results highlight that PrEP as a large scale public health intervention, e.g. PrEP delivery as part of the EPI programme, is likely to be substantially more expensive than other measures to prevent human rabies deaths, such as PEP and dog mass vaccination campaigns (see evidence profile Question 1). PrEP for entire populations is unlikely to be an efficient use of resources (Figure 5) and should only be considered in extreme circumstances, where the incidence of rabies exposures is unusually high (incidence >6%) and RIG use is low. For details refer to evidence profile on Question 8. Modelling could be used to support decision-making in specific high-exposure incidence contexts of local settings.

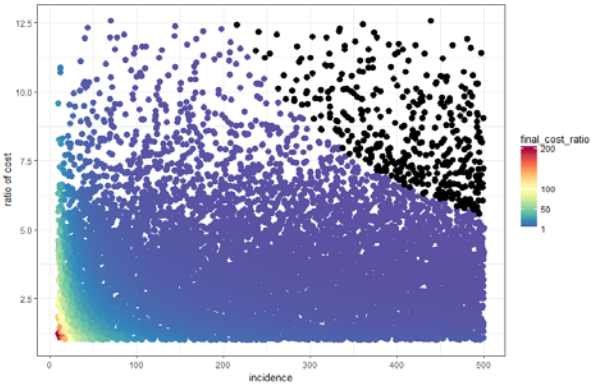


Figure 5: Ratio of the costs of PrEP +PEP versus PEP alone, by varying dog bite incidence and relative cost of PEP in naïve individuals compared to cost of PrEP + PEP in primed individuals. Note that simulations with a final cost ratio ≤1 are indicated in black.

3.2.3. Accelerated or modified PreP regimens:

Ten published studies exploring accelerated or modified PrEP regimes were considered and have shown evidence that 1-week or even single day regimens are non-inferior to the currently recommended 3-4-week regimens (see evidence profile).

a. The **2-visit regimen** with 2-site ID or 1 IM doses on days 0, 7: Evidence available is consisting of one randomized clinical trial (Soentjens et al. *A* 2017) conducted in Belgian soldiers, see Figure 6) and two observational studies (Mills et al. 2011; Wieten et al. 2013). There is substantial confidence that a day 0 and 7 ID regimen would be efficacious for rabies PrEP. From the curves of the antibody response post booster, by day 3 those who have received PrEP have already mounted an antibody response, and by day 7 all were seroconverted, indicating that the 3rd dose on day 21 is not needed. The studies (Mills et al. 2011; Wieten et al. 2013) presented data using only 2 ID injections on day 0 and 7, showing that this regimen produces similar consistent antibody responses as the current WHO-recommended PrEP regimen after priming. The randomized clinical trial conducted in the Belgian soldiers showed that 100% of the subjects (n=238) seroconverted > 0.5 IU/ml and 100% had titres > 0.5 IU/ml if boosted up to 3 years after primary vaccination. It is likely but not certain underweight children or overweight adults would respond similarly to healthy soldiers (male and female).

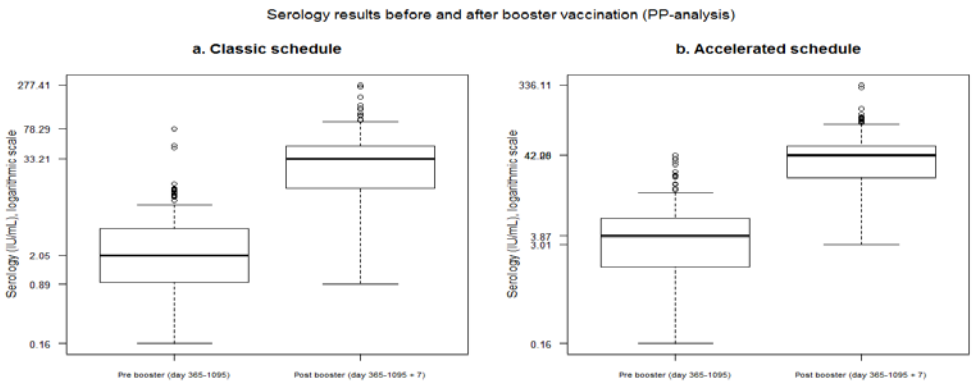


Figure 6: Median serological titres RCT, (Soentjens et al. A 2017), a) WHO recommended PreP regimen, b) investigational 2-site ID regimen days 0, 7.

b. The **single visit regimen**: Two ID or one IM injection(s) will result in an adequate antibody titre for at least one year. This has been documented using WHO pre-qualified rabies vaccines with either IM or two ID injections and subsequent booster around 1 year later (see overview trials Table 1 in the evidence profile

Questions 3&4). However, the age range of the study participants, as well as the timeframes considered for booster response, show limitations. Data from a head-to-head study in Thailand observing a single IM dose and a single day 2-site ID dose, show that ID and IM are clinically equivalent and interchangeable (Khawplod et al. 2012; Jonker & Visser 2017; Suandork et al. 2007; Kamoltham et al. 2007; Soentjens et al. *B*, 2017). The two groups demonstrated equivalent geometric mean titres (GMTs) one year after primary immunization. When boosted, both groups had an adequate recall of immune response. However, additional evidence is needed on PEP after an incomplete course of or single visit PrEP including a larger range of age groups. Per the precautionary principle, in the case of an exposure, individuals who had a single visit PrEP should either get a second dose as soon as possible or be managed as if they are immunologically naïve and given full PEP including RIG.

PrEP in immunocompromised patients

Data on accelerated or modified PrEP regimens in immunocompromised individuals are scarce and the recommendations were based on expert opinion. Immunocompromised patients may have a lower immune response to vaccine, and thus 2 sessions of vaccine administration may not be enough to confer protection. Seroconversion is likely to vary depending on the individual patient, their medical history, and the clinical management of their condition. For example, if the patient's condition is well-managed, a clinician could elect to treat the person as immunocompetent. Conversely, if the patient's condition is poorly managed or if no clinical history is available, the clinician may decide to treat the person as immunocompromised. All immunocompromised patients should receive the most immunogenic vaccine schedule (i.e. a 3-visit regimen, either 2-site ID or 1-site IM). Currently, there is no evidence to support a 2-visit PrEP regimen in immunocompromised individuals. Where serologic testing is available, clinical experience suggests that health care providers could administer a 2-visit PrEP (day 0 and 7) regimen, followed by serology, and administer a third dose of vaccine if the patient has not seroconverted.

Concurrent chloroquine drug use

There is no novel evidence on the potentially affected immune response to ID rabies vaccination of people by antimalarial drugs, particularly chloroquine, which is also used for treatment of certain auto-immune diseases. Almost all sources can be traced back to an older randomized clinical trial on PrEP and ID administration route by Pappaioanou et al. (1986). This trial did investigate the potential effect of chloroquine (and derivates thereof) on efficacy of ID PrEP with HCDRV compared to a control group. Despite statistically significant lower GMTs for the antimalarial drugs groups, titres were adequate in all study participants and above the threshold up to day 105. However, the magnitude of this difference is relatively small and is unlikely to be clinically significant. This effect was only observed if the drug was used for more than one month. Based on pharmacovigilance, there have been no reports of individuals with rabies who received appropriate PEP, with or without PrEP (according to WHO protocols), who were reported as being concurrently on chloroquine drugs. Based on the long years' clinical experience, any PrEP regimens can be recommended for people who are on chloroquine or other related drugs. Nevertheless, it should preferably be given in advance of starting antimalarial prophylaxis or treatment whenever possible. In addition, pharmacovigilance and reporting of any failures would be essential.

4. POST-EXPOSURE PROPHYLAXIS

4.1. Key Points

- There is no medical contraindication for life-saving PEP
- PEP consists of vigorous wound washing, a series rabies vaccine injections and rabies immunoglobulins, if indicated

- Timely access to affordable and effective PEP is primarily hindered by high cost to the national governments and out of pocket expenses for the patients, the long and complicated PEP regimens, low availability in remote areas and the knowledge and skills of health care staff
- Many countries face difficulties or are unable to forecast rabies biologics needs
- Based on both immunogenicity and clinical protection data, a 3-visit regimen consisting of two ID doses on day 0, 3, and 7 ('IPC regimen') is recommended. An overview table summarizes the criteria for alternate ID and IM PEP regimens.
- Although there is some evidence that there are immunogenically comparable GMTs following the 3rd session for IM, there is no clinical data to support shortening IM regimens. Therefore, out of an abundance for caution, the WG will continue to recommend a four dose Essen IM regimen, given at day 0, 3, 7 and the last dose between day 14 to 28.
- Modelling results indicate that the investigational PEP regimens were all more cost-effective than the currently approved IM or ID PEP regimens, both, in clinics with small or large patient throughput
- Modifications for PEP regimens for specific risk groups such as those who are immunocompromised and those with bat exposures have been proposed.
- Changes in the route of administration during a PEP course is acceptable in unavoidable circumstances and restarting PEP is not necessary. The schedule for the new route should be adopted.

4.2. Review of evidence:

The 2010 WHO position paper states that: "*New PEP regimens, particularly those using ID administration, even if shown to be safe and efficacious, must have clear practical or economical advantages, or both, over existing regimens if they are to be endorsed.*"

Evaluation criteria for investigational rabies regimens differ from those applied to other vaccines. In the past, criteria used to recommend a new rabies PEP regimen required at least (a) ~100 patients exposed to known rabid animals with 100% survival rates after receiving a complete regimen of PEP including RIG, (b) proven non-inferiority if used with commonly known vaccines, (c) immunogenicity data, among other potential considerations, and (d) efficacy data. Adequate antibody titres alone were not considered sufficient when trying to reduce the number of visits or doses in a regimen. The 100-person benchmark was based on experience, and not on statistical calculations. The WG concluded that new rabies regimens in order to prove non-inferiority, need to show that:

1. Immunogenicity data maintains non-inferiority in comparison to current regimens
2. Data on clinical outcomes (desirable follow up of patients = min.6 month)
3. Improved feasibility compared to current regimens
   OR
4. Cost and supply improved without compromising effectiveness

Evidence on investigational or formerly assessed PEP regimens was retrieved from 5 publications from the systematic literature review and 7 related publications (from reference lists) prior to 2007. The latter were excluded from this background paper as no longer relevant to the regimens under discussion. Additionally, recent and yet unpublished studies (epidemiological and immunological) from Institute Pasteur Cambodia were taken into consideration. An overview on the findings for the different regimens by assessment criteria is available in Table 5.

4.2.1. Assessment of investigational PEP regimens:

1-week 2-site ID 'IPC' regimen (2-2-2-0-0)

The evidence for the newly recommended 3-visit 1-week ID schedule (2-2-2-0-0) was based on a broad range of patients exposed to sick looking or confirmed rabid dogs from the rabies clinic of the 'Institut Pasteur du Cambodge' (IPC). The suggested new name for this regimen is thus "IPC regimen".

This clinical effectiveness, active follow-up study after at least 6 months found two probable rabies deaths (99.87% rabies survival) among 1,593 persons bitten by confirmed rabid dogs who received 4 or more sessions of two intradermal doses of PVRV with or without eRIG and one death among 127 persons (99.21% survival)

who only returned to receive three sessions with or without eRIG. All three deaths were discussed with international experts and attributed to direct nerve inoculation and/or protocol deviations. Another arm of the study, in persons similarly managed after exposure to rabid-suspect, but untested dogs, found no deaths among 155 patients who received only three sessions versus 904 patients who received four sessions at least (100% survival in both groups). There were no other passively reported suspect rabies deaths among over 250,000 patients referred or self-referred to that centre during the period studied (2003-2014).
Further a prospective study was conducted in Cambodian patients received at the rabies treatment centre at IPC between 20 May 2016 to 14 June 2017. The eligible 105 study participants of all ages were all patients with a category III exposure to laboratory confirmed rabid dogs and received the updated TRC regimen (PVRV) and RIG. Serology was conducted for all patients, results are currently available for 88 patients, for the remaining 15 patients, analysis is pending. Blood samples were collected on days 0, 7, 28 and 42. The possible impact of body mass index (BMI), viral load and inoculum, escape mechanisms of RABV, impact of RIG, and concurrent other infections on immune response to rabies immunization were also investigated. The mean titre of day 7 was 1.9 IU/ml (min 0.11, max 28 IU/ml), mean titre of day 28 was 38.5 IU/ml (min. 1.1, max. 148.5), see Figure 7. All participants were protected after 3 sessions of 2 ID doses, including underweight patients (around 30%) or individuals with other diseases (e.g. parasitoses, other infections, etc). The GMT of day 28 was higher than the GMT of day 42. Twenty-two of these patients were also explored for B-cell phenotyping and no statistical difference was found between the two groups. The patients were followed up for at least 6 months, no rabies-related death was observed.
The set of studies support the PEP effectiveness on short- and medium-term protection, including clinical outcome data and in consequence support the removal of the fourth session of the updated TRC regimen on day 28. The countries implementing ID PEP administration are currently using the updated TRC regimen, so the new regimen would be easy to adopt, in that it follows the same schedule but without the fourth dose.

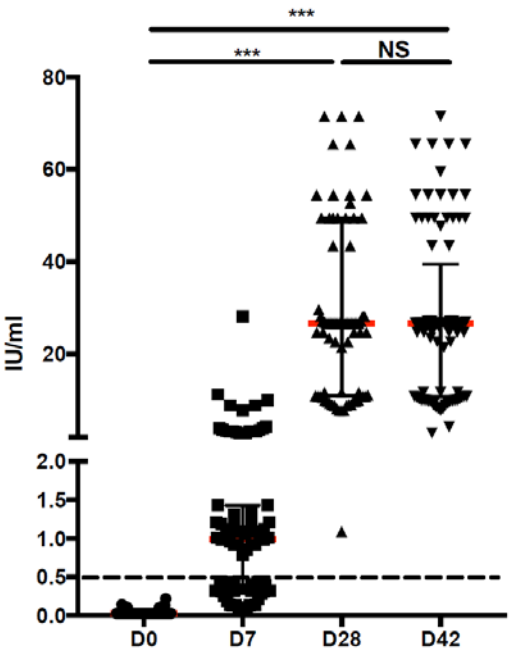


Figure 7: Dot plot of neutralizing antibody titres as measured by RFITT (considered adequate if ≥0.5 UI/ml, RESIST-2 study, Cambodia 2016-2017 (n=88)

Modified 4-site ID regimen (4-0-2-0-1)
Warrell et al. 2008 evaluated a randomized controlled trial of a simplified 4-site ID regimen (Figure 8). This regimen id an adaptation of the 8-site Oxford regimen and proposes vaccination on day 0 (4sites), day 7 (2

sites), day 28 (1 site). Although this trial proposed a 90-day schedule, the final dose is no longer used with any PEP regimen including the 8-site regimen (WHO 2010 position paper). The trial compared the 4-site ID regimen to three established regimens: 1) 2-site ID 2) 8-site ID 3) Essen 5-dose IM. Participants in all study arms had RVNA concentrations ≥ 0.5 IU/ml. Compared to the 2-site TRC ID regimen, this modified 4-site ID regimen requires fewer clinic visits, is likely to be more practical in smaller clinics and to provide a wider margin of safety in case of incomplete PEP course.

Quiambao et al. 2008 investigated on 400 healthy volunteers and people with category I or II exposures to healthy dogs or cats in the Philippines. This 4-arm study using PVRV investigated A) 96 patients for 8-site ID regimen; B) 96 patients modified 4-site ID regimen; C) 97 patients a 5-dose Essen IM; D) 99 patients a 5-dose TRC ID regimen (with eRIG or exceptionally hRIG IM). By day 14, all subjects had seroconverted. The GMT of all groups on day 14 was above 0.5 IU/ml, with the GMT of the 8-site ID group significantly higher than all other groups on day 7 (arms B-D equal). Unfortunately selected low level sera were retested and one group was given RIG, so the valid comparisons on immunogenicity of the regimens is impaired. The GMT of all groups on day 14 was above 0.5 IU/ml. There was a follow up of patients until day 90.

Ambrozaitis et al. 2006 conducted a 2-arm study in Lithuania using a modified 4-site ID regimen A) with PCECV in 91 people and B) with PVRV in 89 people. By day 7, 3% in arm A) and 6% in arm B) had titres >0.5 IU/ml while GMTs of day 7 were higher in PCVC than in PVRV. By day 14 all had adequate titres until day 105 (99-100%). This regimen was considered immunogenic with both vaccines used.

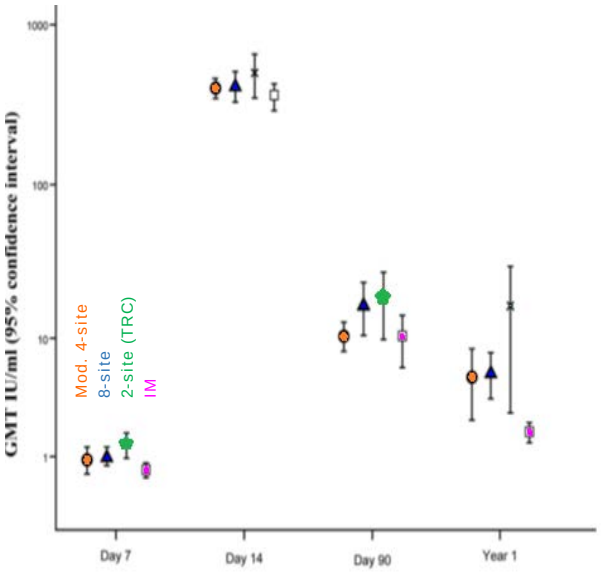


Figure 8: Rabies neutralising antibody results by RFFIT (modified from Warrell et al 2008)

1-week 4-site ID regimen (4-4-4-0-0)

Three randomized clinical trial investigated this newly proposed regimen:

Sudarshan et al. (2012) evaluated the safety and immunogenicity of a one-week ID regimen in healthy volunteers. All participants (100%) had adequate protective rabies virus neutralizing antibody concentrations until day 180. However, after one-year post immunization, only 62.5% in the PVRV group and 78.9% in the PCECV group demonstrated antibody titres above the threshold considered protective. The regimen also induced strong immunological memory, demonstrated by the quick anamnestic response observed after boosting (in participants with titres that dropped below 0.5 IU/mL after one year). The regimen was also well-tolerated and adverse event rates relatively low. They concluded that further studies are needed in individuals possibly exposed to rabies.

Shantavasinkul et al. (2010) evaluated the safety and immunogenicity of this one-week ID regimen in healthy volunteers. This study included 3 arms 1) 4-site 1-week ID schedule in healthy volunteers 2) 4-site 1-week ID schedule plus eRIG in healthy volunteers and 3) original TRC-ID regimen in patients that presented with

category III rabies exposures. The 1-week ID regimen was found to be safe and immunogenic. All participants had protective rabies virus neutralizing antibody concentrations ≥ 0.5 IU/ml on days 14 and 28. The proportion of subjects that had antibody concentrations ≥ 0.5 IU/ml on day 360 were similar across the three study arms. Narayana et al. (2015) evaluated the immunogenicity and safety of this schedule in animal bite cases (bitten by rabies suspect animals, without laboratory confirmation).
The studies support the regimen which elicited adequate and protective rabies virus neutralizing antibody concentrations ≥ 0.5 IU/ml from day 14 onwards until day 365 as per WHO criteria considered protective against rabies. The incidence of local and systemic reactions in these 3 study was comparable to that of rates reported for WHO approved regimens. While this investigational regimen proves highly immunogenic and reduces the number of visits, the number of ID doses required is above the updated TRC regimen.

4-dose Essen IM regimen and other IM regimens
The truncation of the 4-dose Essen IM regimen to 3-doses (days 0, 3 and 7) was considered. However, despite the likely valid inference that IM regimens are clinically equivalent to ID regimens (CDC 1982, Saraya et al 2010, Venkataswamy et al. 2015, Recuenco et al 2017), there are limited clinical outcome data for a 1-week, 3-dose IM regimen. The study by M. Warrell et al 2008 included comparative immunogenicity data of the 5-dose Essen IM regimen for days 0, 3, 7 and found similar GMTs for both, IM and ID administration. However, IM GMTs were slightly lower (not statistically significant). While there is no direct evidence for the immunogenicity of a 3-dose IM regimen, numerous studies assessing 4- and 5-doses (comparing investigational schedules to the standard IM Essen regimen) showed adequate antibody titres after the second dose (for example Phanuphak et al 1987, Jaiiaroensup et al 1998). No comparative study has been made of the immunosuppressive effects of RIG. Therefore, out of caution, the WG concluded that it will continue to recommend a 4-dose Essen IM regimen (day 0, 3, 7, and 14). The fourth dose can be given at any time between day 14 and 28.
The established 3-visit Zagreb IM regimen (two doses on day 0, 1 dose each on day 7 and 21) will be maintained.
The quality of another recent study (Huang et al 2014) that assessed a 1-week, 3-dose IM schedule had limitations and further investigation of this regimen would be necessary before a new policy recommendation could be made.

4.2.2. Programmatic challenges of procurement, distribution and delivery of PEP

An ongoing multi-country survey initiated by WHO evaluates the logistic and regulatory pathways how countries procure, distribute and deliver biologics for PEP. Preliminary results from over 20 countries (mainly Africa and Asia) show that the quality and format of the data or information available highly vary between countries. All countries have distribution systems for EPI vaccines, but only 2 countries use it also for rabies vaccines. However, 40% use the same cold chain as for EPI vaccines. All countries have rabies vaccine available to some extent, yet it was frequently cost-prohibitive and of limited availability in the public sector, particularly in rural areas. In countries where it is unavailable in the public sector, it is often still available in the private sector, but at a higher cost. In contrast to the relative availability of rabies vaccine, RIG was very scarce in the majority of countries and often prioritized to those with very severe or high-risk exposures. At least 6 countries reported to have no RIG available in their country. Cold chain, distribution channels and frequency, monitoring and reporting methods varied both between countries and within countries. Countries with robust rabies PEP systems have identified rabies as a national priority and/or established a national rabies control programme. There is limited information on vaccine demand and utilization due to the lack of standardized monitoring tools. Until rabies programmes get stronger and generate more data, modelling may assist in closing these knowledge gaps and levels of uncertainty (e.g. for vaccine need forecasting).

Based on first results there is a need to (a) develop standardized global guidelines for reporting and monitoring rabies PEP use, (b) inclusion of rabies PEP in joint reporting forms, (c) leveraging systems that are already

established for distribution of rabies or other vaccines and (d) employing alternative delivery strategies. Specific case studies and an overview on global findings will be highlighted in forthcoming publications.

Regarding vaccine forecasting WHO encourages countries requesting biologicals for PEP treatment of bite exposures will be requested to (i) provide future vaccine forecasts demonstrating a clear strategic plan for sustained vaccine deployment together with long term financing plan (ii) provide records on the use and impact of the biologicals supplied by the bank. This data will be used to generate quality disease data, assessing not only the impact of the stockpiles, but also other parameters necessary to track impact and disease elimination goals.

Researchers from prominent institutions worldwide are currently adapting existing models for vaccine forecasting and investment for elimination to identify and predict resource needs.

4.2.3. Cost-effectiveness and public health impact of different PEP regimens, modelling results:

There is limited information on PEP demand and utilization due to the lack of standardized monitoring tools. Until programmes get stronger and generate more data, modelling may assist in closing these knowledge gaps and levels of uncertainty. Detailed methods and results are available in the evidence profile of Question 5. Based on a simulation framework previously developed for evaluating vaccine use (Hampson et al., 2011) the potential benefits and relative costs of delivering post-exposure vaccination according to currently recommended and proposed rabies PEP regimens was quantified (Figure 9). For methodological details see evidence profile of question 6&7. Results suggest that the cost-effectiveness of IM regimens does not change with clinic throughput whereas the cost-effectiveness of ID regimens improves with patient throughput as vials (not injection material) can be shared between patients.

Clinic throughput affects the capacity for vial sharing, and therefore the cost-effectiveness of ID administration relative to IM. As throughput increases, ID regimens become increasingly cost-effective, using up to 85% less vaccine. Yet, even clinics with relatively low throughput (~10 new patients/month) would considerably reduce vial use by switching from IM to ID administration of PEP and even at lowest throughput ID administration is equivalent in cost to IM. Increased use of ID regimens could therefore prevent vaccine shortages and enable wider vaccine distribution, both increasing the number of patients that can be treated and the overall accessibility of PEP.

ID administration of PEP is generally more cost-effective than IM administration and reduces the amount of vaccine used up to 85%. This is an important programmatic consideration given the frequency with which PEP vaccine shortages occur at clinics in many rabies-endemic countries. The use of insulin syringes should provide clinicians with further confidence in vaccinating patients and reduce vaccine wastage per vial as more accurate volumes of vaccine can be injected. These savings become more apparent in clinics that receive more than 10 new bite patients presenting each month.

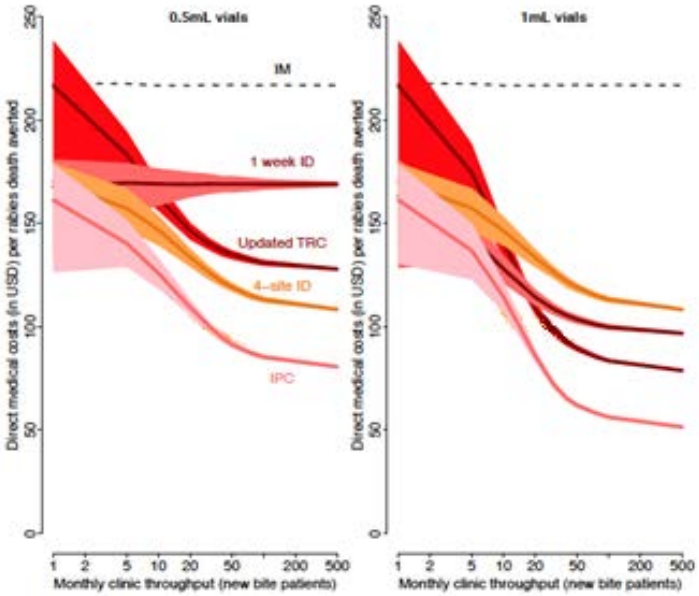


Figure 9: Direct medical costs per rabies death averted for ID regimens in relation to clinic throughput. The Essen 5-dose IM regimen is also illustrated for comparison and updated TRC regimen serves as a reference. 4-site = modified 4-site ID regimen (4-0-2-0-1)

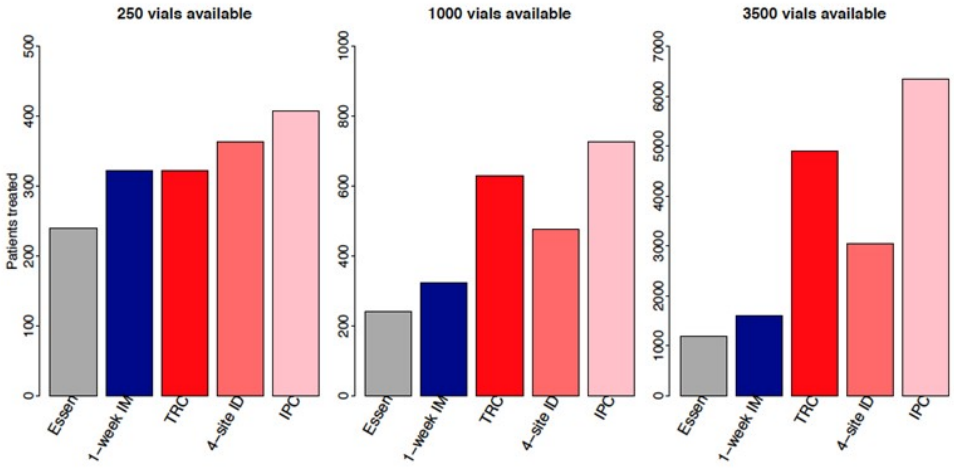


Figure 10: Patients treated under different PEP regimens given limited vaccine availability. It was assumed that clinics had only 250, 1000 or 3500 vials available over a 1-year period. Note the different y-axis limits.

In conclusion, modelling results confirm the cost-effectiveness of ID regimens, already in clinics with a limited monthly throughput. Wider adoption of ID regimens has the potential to serve more patients in settings where vaccine shortages occur.

4.2.4. Update on modified PEP protocols for specific risk groups affected by additional health conditions:

Specific risk groups affected by diverse health conditions that might affect their response to rabies vaccine were identified. These include pregnant women, immunocompromised patients and people exposed to bat-mediated rabies or other lyssaviruses.

4.2.4.1. Immunocompromised individuals

Many circumstances induce immunosuppression and different immunoregulatory pathways lead to a compromised immune response. In most settings, it is not possible to determine the source or severity of immune-suppression when patients consult for PEP.

a) Individuals with human immunodeficiency virus (HIV) infection

HIV patients under treatment and monitoring would most likely react like not severely immunocompromised patients or HIV uninfected individuals as observed in studies conducted for routine vaccines (Simani et al. 2014).

Sirikwin et al. (2009) evaluated the immunogenicity of a modified 8-site ID regimen in 27 HIV-infected patients, a risk group that is known to have reduced immune responses to vaccination. Individuals whose CD4+ cell counts both below and above 200 cells per microliter were studied. All patients had adequate antibody concentrations ≥ 0.5 IU/ml on day 14 after immunization. There was no statistically significant difference between individuals with CD4+ cell count < 200 and CD4+ cell count ≥ 200 up to day 360. Sirikwin et al. (2009) concluded that PCECV is immunogenic in HIV-infected patients with CD4+ cell counts below 200 when administered in a modified 8-site ID regimen.

Older studies (Pancharoen et al 2001, Thisyakorn et al, 2000) did not confirm that a higher antigen dose results in a more adequate immune response in seriously immunocompromised individuals.

b) Other potentially immunocompromised patients:

Sampath et al. 2005 investigated 45 malnourished children aged 8 months to 16 years who received PEP (5-dose Essen IM regimen, WHO pre-qualified vaccine) for their immune response. All children had developed RVNA levels ‡0.5 IU/ml by Day 14. There was no significant difference in antibody concentrations between the malnutrition categories.

Tanisaro et al. (2010) evaluated the use of an ID regimen in haemodialysis patients with end-stage renal failure, receiving adequate dialysis, using a 5-dose TRC-ID regimen (2-2-2-0-1-1). All subjects (n=14) had adequate antibody responses against rabies 14 days post vaccination. At day 90, 13 of the 14 patients had protective antibody levels, resulting in a 92.8% response rate. These results suggest that ID rabies vaccine administration is immunogenic in haemodialysis patients and may be suitable for use in immunocompromised individuals. However, due to the small sample size of the study, more evidence may be needed before a recommendation be made.

Rahimi et al. (2015) evaluated the immune responses of the 5-dose Essen regimen in healthy volunteers compared to patients with specific medical conditions and a category II or III rabies exposure, such as pregnancy, diabetes I or II, chronic infection with the hepatitis B virus, different types of cancer such as lymphoma, and those who were immunocompromised due to receiving corticosteroids such as rheumatoid arthritis patients and lupus erythematosus patients. On day 14 post-immunization, all subjects had neutralizing antibody concentrations ≥ 0.5 IU/ml. GMTs were 16.2 IU/ml and 8.73 IU/ml in immunocompetent and immunocompromised participants, respectively. On day 35, all subjects in both groups were also protected. The GMTs were 30.3 IU/ml (8.3-45.5 IU/ml) and 20.7 IU/ml (8-30.2 IU/ml) in immunocompetent and immunocompromised participants, respectively. Although the average antibody titres were greater for the immunocompetent participants, the GMT ranges overlap and are above the threshold in both groups, which suggests that the immune responses are comparable. Therefore, if immunocompromised patients mount comparable immune responses to the 5-dose Essen regimen, it suggests that other regimens may be suitable for specific risk groups. This is especially pertinent considering that ID regimens have been shown in other studies to elicit a stronger immune response compared to IM regimens.

In conclusion, clinical studies on PEP in immunocompromised patients are mainly available from HIV-infected individuals. Clinical experience suggests that whenever possible to allocate the best PEP options available (the most immunogenic regimen available, high-quality RIG), regardless of the route of vaccine administration. Further, meticulous and very thorough wound cleaning as first aid to bite patients is of utmost importance in

immunocompromised patients. The high variability of causes compromising the immune system in patients and the limited number of studies call for targeted studies.

4.2.4.2. Pregnant women

Recent literature reviews on vaccines and pregnancy including reference to rabies are available from de Martino et al. (2016) and Crowcroft et al. (2015) and confirm safety and efficacy of PEP in pregnant women. Huang et al. (2013) evaluated the safety of PEP using the Essen 5-dose regimen among pregnant women with potential rabies exposures. All of the infants exhibited normal development and both PVRV and PCECV were supported as safe for use in pregnant women. No rabies cases were reported for any of the subjects or babies. All three authors highlight that educational gaps exist about the safety of PEP during pregnancy. Life-saving PEP in pregnant women is safe and efficacious. PEP should never be withheld from this risk group and any of the WHO recommended PEP regimens can be used.

4.2.4.3. Bat-mediated exposures

In the Americas, rabies virus is the only lyssavirus isolated from bats. In other parts of the world, lyssaviruses other than rabies virus are present in bats. Reported exposures and bat-associated lyssavirus infections in humans are extremely rare in the 'old world'. The number of bat lyssaviruses identified has increased over the years. At present, three phylogroups of lyssavirus species are recognised in bats. Rabies virus, and also Australian, European some other bat lyssaviruses, are in phylogroup I. Experimental evidence indicates that currently available rabies vaccine strains are ineffective against lyssaviruses in phylogroup II and phylogroup III (Figure 11) (WHO, 2017). In absence of novel, pertinent evidence on improvements of PEP in individual who experienced a bat-mediated rabies or lyssavirus exposure, the recommendations on PEP regimens remain unchanged.

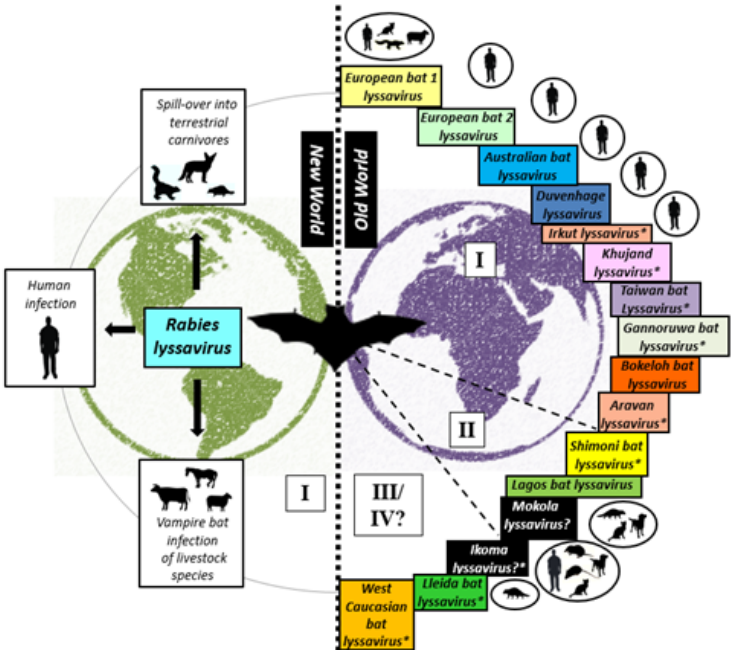


Figure 11: diversity of lyssaviruses. © Crown Copyright, 2017. Used with permission of Prof A. Fooks & Dr A. Banyard, Animal and Plant Health Agency.

4.2.4.4. PEP considerations for atypical rabies exposures:

Consuming raw milk from a rabid animal is not advised, however there is no evidence that this practice constitutes an exposure to the rabies virus, so PEP is not indicated. Pasteurized milk presents no risk.

Human cases resulting from consumption of meat from a rabid animal are extremely rare. Consuming the meat from a rabid animal is not advised, particularly when consumed raw. PEP should be considered in persons who experience a category II or III exposure during the processing of meat from a rabid animal, or persons who have consumed raw meat from a rabid animal.
Human-to-human transmission of rabies through corneal or other organ transplantation is rare but documented. Caution should be exercised before transplanting organs from people who have died with neurological symptoms or signs. It may sometimes be necessary to provide PEP to the partners of patients, as close contact and sexual intercourse in the early stages of the disease carry a hypothetical risk for transmission. Infectious rabies virus is present in the saliva, but no reports have clearly established human-to-human transmission (WHO, 2017).

4.2.5. Changes in the route of administration during a PEP course

Ravish et al. (2014) provided supporting evidence that changes in the type of CCEEV (n=43) or the route of administration (n=47) of rabies vaccines (n=24 from IM to ID and n=23 from ID to IM) are safe and immunogenic. This observational study suggests that changes in the CCEEV and/or the route of administration should be allowed in unavoidable circumstances to promote completion of the lifesaving PEP regimen. Detailed immunogenicity data are available in the evidence profile.
In a slightly different context Sudarshan et al. (2006) conducted a study on n=20 volunteers who previously received a complete course of PEP. The recall of the immune response was assessed by mimicking PEP for previously immunized people and forcing a change in route of administration. This practice has been shown safe and immunologically efficacious, even after cross-over from the ID to the IM route and vice versa.
The scarce evidence combined with expert knowledge led the group to conclude that changes in the route of administration during a PEP course is acceptable in unavoidable circumstances and restarting PEP is not necessary. The regimen of the new administration route should be adopted.

4.2.6. PEP in previously immunized individuals:

People exposed or re-exposed to rabies, who have previously received PrEP, PEP, or who have discontinued a PEP series after receiving at least two doses of CCEEVs, should receive booster vaccination with either: one site, two visit IM or ID PEP (days 0 and 3); or four site, single visit ID PEP (day 0, with four injections of 0.1ml vaccine equally distributed over the left and right deltoids, thigh or suprascapular areas). RIG is not indicated for previously rabies immunized individuals (WHO, 2017). A single study by Sudarshan et al. (2011) indicates that healthy people may not require booster vaccination, if exposed to rabies for up to three months after receiving either PrEP or PEP. Vigorous wound washing and propoer wound management is also stressed in these situations.

5. RABIES IMMUNOGLOBULINS:

5.1. Key Points

- Vigorous wound washing together with immediate administration of the first dose of vaccine and subsequent completion of the PEP regimen can save up to 99% of bite victims from fatal rabies
- The maximum dose for RIG, calculated by body weight, is maintained
- Local infiltration of RIG as much as possible into and around the wound is most effective
- Injection of the remaining dose of RIG distant to the wound site is unlikely to confer additional protection
- eRIG and hRIG are considered clinically equivalent
- The skin testing prior to administration of eRIG should be abandoned. This practice has been discouraged for several years, but remains stated on the package labels of the product
- An algorithm for prioritization of the allocation of RIG in case of shortage or other constraints has been proposed

- The newly licensed mAb product (SII RMAb) was assessed, provides an opportunity to improve availability of RIG
- Promoting mAbs as an affordable and accessible alternative or supplement to scarce RIG is of high priority
- Future improvements should be considered for a 'cocktail product' with more than 1 mAb
- The optimal pricing of this product (SII RMAb) will be crucial to assure uptake and acceptability (ideally below the market price of eRIG)
- Post-marketing surveillance is needed for both RIG and mAb

5.2. Review of Scientific Evidence

RIG, derived from the blood of humans or horses, is used as a component of PEP as a method of passive immunization. RIG neutralizes the rabies virus at the inoculation site in the time before the immune system responds to the vaccine by production of rabies virus neutralizing antibodies. Both active and passive immunization prevent the rabies virus from infiltrating the central nervous system, but become ineffective once the virus has crossed into the central nervous system. RIG is administered only once, preferably at or as soon as possible after initiation of PEP. It is not indicated beyond the seventh day after the first dose of rabies vaccine, regardless of whether the day 3 and day 7 doses were received, because an active antibody response to the CCEEV has already started, and there may be interference between active and passive immunization. RIG should ideally be administered in all people with category III exposure and to individual with category II exposure who are immunodeficient or who had an exposure with direct contact to a bat.

The high cost, low availability and supply, batch to batch variation affecting efficacy, uncertain quality (no WHO prequalification), short shelf-life, cold chain challenges and correct administration of RIG are barriers to implementing the standard previously set by WHO for PEP in category III bites. RIG is often a barrier for attaining public health impact because of a hesitation to use vaccine without RIG and therefore manufacturers and countries often do not want to make vaccines available without RIG, which means no PEP at all. In most rabies-endemic countries, RIG is in short supply and is cost-prohibitive for patients with limited financial resources. Public health authorities' budget for procurement of RIG is in most cases very limited or even absent. Conversely, in other settings there may be a tendency of overuse. It is estimated that only around 1-10% of patients who need it receive RIG as part of PEP following exposures to potentially rabid animals (Khawplod et al., 2002; Wilde et al., 2002; Warrell, 2012).

There are only a few studies with observational data on the efficacy of RIG. As rabies is a fatal disease, and RIG considered a mainstay of rabies PEP, conducting randomized controlled trials with placebos presents ethical and logistical challenges.

5.2.1. Safety and efficacy of eRIG

Currently, eRIG is an underutilized biological in part because of the misperception that scarce and costly hRIG is superior and safer. In the past, impurified eRIG conferred high rates of serum sickness, anaphylaxis and other severe adverse reactions (Madhusudana et al, 2013). But nowadays, eRIG is highly purified and enzyme-refined and contains over 85% F(ab')2 (Madhusudana et al., 2013; Shantavasinkul & Wilde, 2011; Quiambao et al., 2008, Kittipongwarakarn et al. 2011, Reveneau et al. 2017). Through purification techniques such as heat treatment, pepsin digestion and enzyme refinement, the crystallisable/constant (Fc) fragment is removed and the nonspecific protein content of the purified sera is decreased to less than 3% (Behera et al., 2011; Chawan et al., 2007). As the Fc fragment in impurified eRIG is responsible for direct complement activation and anaphylactic reactions, the high F(ab')2 content and low Fc protein content allow for increased safety and specific activity (Chawan et al., 2007; Madhusudana et al., 2013; Quiambao et al., 2008). Indeed, data show that adverse reaction rates for eRIG are similar to that of penicillin (Wilde, 2012). eRIG treatment has even been shown to be safe for pregnant women, as F(ab')2 is not shown to cross the placenta (Dixit et al., 2016). F(ab')2 fragments have a shorter half-life in vivo than intact immunoglobulins. There have been concerns that effective neutralization with F(ab')2 products therefore might wane in the critical period before active immunity and RVNAs appear. Quiambao et al. (2009) discuss that, while the clearance of F(ab')2 eRIG is faster

than that for impurified eRIG and hRIG, the F(ab')2 fragments have a higher specificity and instance of antigen-binding reactions, and therefore its efficacy is preserved. Both et al. (2012) state that purified eRIG ''is generally highly effective, [although] the reduced half-life of these experimentally induced antigen-binding fragment products might have contributed to a few anecdotal PEP failures, and related data derived from animal studies have shown that intact immune globulin products are more effective for rabies PEP than derived F(ab')2 fragments''. The differences in half-life of hRIG and eRIG was not considered clinically relevant, as RIG should be administered immediately after exposure and the half-life of RIG is days, not hours (half-life eRIG ~3 days, hRIG 21 days). Both eRIG and hRIG are highly efficacious in eliminating the virus at the wound site within a few hours.

In a similar manner to the discussion of its safety and following WHO standards for PEP in category III bites, the efficacy of eRIG is supported, considering the price and scarcity of hRIG and the 100% mortality of clinical rabies.

There are no more scientific grounds for performing a skin test prior to administering eRIG because testing does not predict possible reactions, and life-saving RIG should be given whatever the result of the test. The treating physician should be prepared to manage anaphylaxis which, although rare, could occur during any stage of administration. Unfortunately there has been a persisting gap between regulatory agencies' statements on skin tests and RIG product labels still insisting on skin testing, e.g. for liability reasons.

A revised classification of adverse effects after RIG administration is proposed (Table 6). It should be used to encourage more countries participating in post-market surveillance on RIG and reporting back to international organizations and to the RIG producers. Examples for reporting forms from other vaccines are available from the "Global Manual on Surveillance of Adverse Events Following Immunization " http://www.who.int/vaccine_safety/publications/aefi_surveillance/en/

Table 6: Types of reactions which may occur after rabies immunoglobulin administration (Adapted from Baldo, 2013; Buelow et al., 2017; Krishnamurthy & Hoang, 2017; Schryver et al., 2015)

	Signs	Frequency / Severity	Delay	Mechanism
Local	Local redness, tenderness and swelling	High / Benign	Immediate or within hours	Local trauma or inflammation due to injected volume
Serum sickness-like reaction	Fever, myalgia, epigastric pressure, rash, thrombo-cytopenia, anorexia, arthralgia	Medium / Medium	Usually within days, sometimes within hours	Type III hypersensitivity reaction, mediated by IgA/IgM
Hypersensitivity reaction (urticaria)	Rash, urticarial, wheezing, dyspnoea, hypotension, swelling, tachycardia, dizziness, chest pain, nausea	Medium / Medium	Immediate in previously sensitized patients, minutes in others	Type I hypersensitivity reaction mediated by IgE
Anaphylaxis	Skin itching, sweating, faintness, dizziness; nausea and vomiting, diarrhoea, are inconstant; Cardio-respiratory collapse then shock is possible.	Rare / Severe	Within minutes	Type I hypersensitivity reaction mediated by IgE

5.2.2. Simplification of Administration of RIG

Evidence regarding new data and improved quality of RIG suggest that the recommendations for the administration of RIG may be simplified. Clinical considerations for RIG administration use include the risk of

compartment syndrome, e.g. if large volumes of RIG are injected into a small body area with limited tissue, such as a wound located on a fingertip or the pinna. Administering RIG into subcutaneous fat reduces or delays effectiveness. Injection of RIG into the central gluteal area should be avoided due to the risk of damage to the sciatic nerve (WHO, 2013).

Dose calculated by body weight

The recommendation on body weight dosage was originally derived from studies in which impurified eRIG was administered systemically. Therefore, the body weight recommendation gave consideration for biological half-life of heterologous proteins and extent of distribution and dilution in the body (Bharti et al., 2016; Madhusudana et al., 2013). These recommendations lack empirical support and appear outdated in light of the newer, more efficacious highly purified and enzyme refined immunoglobulins containing only antigen binding components. However, to avoid any interference between RIG and vaccine induced RVNA the maximum dose calculated by body weight should be maintained.

RIG infiltration method

Following the calculation of a RIG dose by body weight, often there is too small a volume of RIG to be distributed to the wound(s), or too large a volume of RIG to be infiltrated into the wound space (Bharti et al., 2016 and 2017). When too small a volume of RIG is allotted, it is often diluted with saline so that the volume may be spread between all wounds; this action decreases the concentration of RIG (Bharti et al, 2016; Madhusudana et al., 2013). If these spaces are areas that contain many peripheral nerve endings, increases the risk of the virus entering nerves (Behera et al., 2012). When the amount of RIG allotted is too large a volume to be infiltrated into the wound this can lead to a compartment syndrome. Therefore, the remainder is currently administered intramuscularly (Bharti et al., 2016; Madhusudana et al., 2013). This practice is considered wasteful and inefficient (Madhusudana et al., 2013; Wilde, 2016). As experimental data show that neutralization by RIG occurs at the site of infection, its injection into and around the wound(s) is likely to be the most efficacious and efficient method (Bharti et al., 2016; Wilde, 2016).

Bharti et al. (2016) investigated cost-effective alternatives to the current RIG standards. The study group included 269 patients with category III suspected rabies exposure (140 from dogs, in a rabies-endemic area), to which all were administered RIG volumes just sufficient to infiltrate wounds irrespective of body weight'' (Bharti et al., 2016). The doses of RIG ranged from 0.25 mL to 8 mL, with an average volume of 1.26 mL (Bharti et al., 2016). In total, 42 vials were used to treat all patients, compared to 363 vials had the doses been calculated according to body weight, a 60% to 80% reduction in RIG dose volume compared to those of the body weight standards' group (Bharti et al., 2016). Additionally, no administered dose exceeded the dose calculated by body weight as currently recommended, therefore avoiding concerns of interference of RIG with vaccine-induced rabies-neutralizing antibodies. This aspect was supported by serological tests done on 20 of the patients around day 14 after RIG administration. The circulating RVNA of all patients were equivalent to an active immune response to the vaccine, thus no interference was observed between RIG and vaccine induced RVNA (Bharti et al., 2016). Within the 82% follow-up rate for a time period of over 9 months, there was a 100% survival rate (Bharti et al., 2016). The most recent study of Bharti et al. 2017 using the same methodology, investigated 26 WHO category III rabies exposed patients who had been bitten by laboratory confirmed rabid dogs. The patients were followed for over one year and all survived. Despite the limitations in quantity and quality of studies, the data support abandonment of IM administration of remaining RIG distant to the wound. In conclusion, the primary benefit of RIG arises from thorough and complete local injection of the product directly into the wound. In settings facing shortage of RIG or where patients face difficulties to obtain or afford RIG, the most important injection site is into the wound site. The value of RIG injected at a distance from the wound is unknown, and might be unnecessary. In settings where RIG is available in sufficient quantity, the remainder can still be administered IM. In settings where RIG is of limited availability, IM administration should be avoided to allow for the possibility to divide vials between patients in need. Open RIG vials need to be

stored aseptically and best be drawn up in separate syringes, to provide the maximum benefit for multiple patients.
Modelling results exemplify the public health impact of a change in RIG administration policy. Details on modelling methods and assumptions are available in the evidence profile of Question 10.

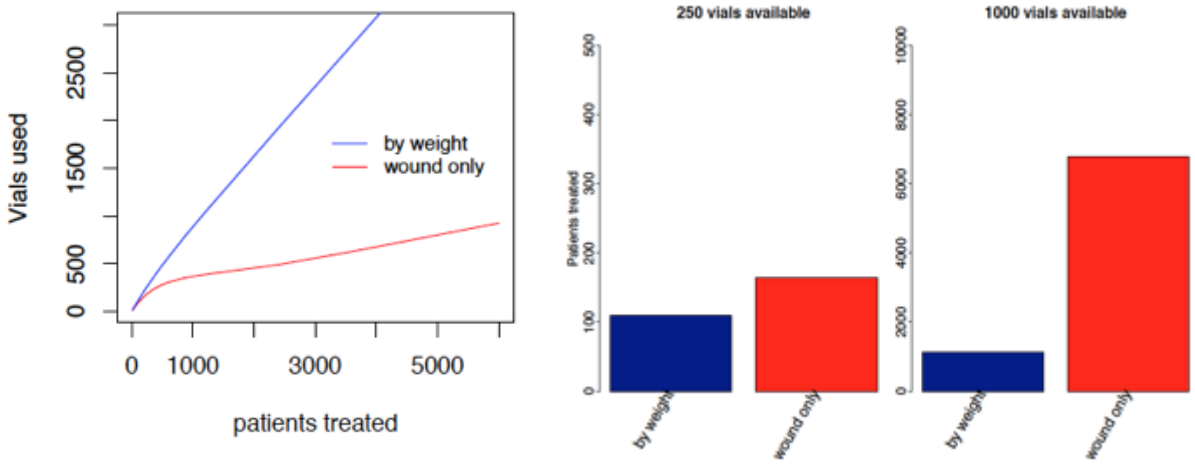


Figure 12: Patients treated with RIG when administered according to current WHO recommendations (blue) and at the site of the wound only (red). We compared vials used under different levels of patient throughput (left), and also how many patients could be treated given limited vial availability (right) with examples shown for 250 vials and 1000 vials per year.

5.2.3. Subcategories of patients to be given highest priority for RIG administration

As RIG is of low availability, clinics in canine rabies-endemic areas wait months for orders to be filled, and some remain unfilled (Wilde et al., 2002), particularly on the African continent (Dodet et al.2009). Even when RIG is available, many patients cannot afford it (Hossain et al, 2010, Mallewa et al., 2007; Hampson et al., 2008; Ly et al., 2009; Sambo et al., 2013) or it is allocated to patients who can afford it, but who do not necessarily bear the highest risk for rabies infection. In rabies-endemic, low-income countries RIG is estimated to be available for less than 1% of category III exposed patients (Warrell, 2012).
Limited published evidence identifies risk factors that increase the risk for fatal rabies infection. These include (but are not limited to) the use of a nerve tissue vaccine (instead of a recommended CCEEV), injuries to the head, neck, face, hands, or other places with a high density of peripheral nerve endings (See Table 5), immunocompromised patients and a laboratory confirmed rapid biting animal (Dimaano et al., 2011; Hossain et al., 2011; Tarantola et al., 2015; Shim et al., 2009; Wilde et al., 2013). Proper wound care with scrupulous cleaning and deep irrigation, followed by application of a potent antiseptic agent and timely administration of the first CCEEV dose are a key factor for increasing survival in cases which RIG is unavailable (Shantavasinkul and Wilde, 2011; Wilde et al., 2002).
It has long been known that anatomical sites, their degree of innervation and proximity to the brain are major determinants of incubation and transmission risks (WHO 2013). Although many authors cite nerve density as a factor positively associated with transmission, the exact role of nerve ending density and its attrition with age and sex is unclear (Gøransson et al. 2004). Post-exposure prophylaxis failures and short incubation times may be due to direct inoculation of RABV into nerve endings (Hemachudha et al 1999). Estimated probabilities of transmission after a bite are summarized by Cleaveland et al. (2002) are described in Table 5.

Table 5: Estimated probability of rabies transmission following the bite of a rabid dog, by anatomical site (Cleaveland et al. 2002)

Area of bite	Transmission risk
Head/Neck	30-60%
Arm	15-40%
Hand	15-40%
Finger	15-40%
Genitalia	15-40%
Trunk	0-10%
Leg	0-10%
Foot	0-10%

Observational data on patients with incomplete PEP courses with or without RIG and clinical outcome:

1) Cambodia (2003 – 2014): After being bitten by a confirmed rabid dogs, seven patients did not complete the TRC regimen (only 3 sessions of ID vaccines TRC), while the second group of 45 patients received 4 or 5 sessions of the TRC regimen. RIG was unavailable for both groups(shortage). All survived, as did 69 patients who received 3 sessions and 120 who received 4 or 5 sessions and also no RIG after a bite from a suspect rabid, but untested dog.
2) Tanzania: From 2,196 persons bitten by animals which were subsequently traced and classified as clinically suspect rabid animals 88 human rabies deaths were identified. The vast majority of these patients did not receive any PEP and none of these bite victims received RIG. Amongst the bite victims that started PEP promptly, only one death occurred and that was the result of the patient, who was bitten on the head, receiving only the first dose of vaccine. Among the patients that had delayed PEP, 4 deaths occurred out of 261 patients who presented 1 day late, 5 deaths occurred out of 319 patients that presented 3 or more days late, and 1 death occurred out of 130 patients that started PEP >7 days late. These data also highlight that most patients do not seek or obtain PEP promptly – 19% of rabid bite victims fail to obtain PEP, 36% of bite victims obtain PEP at least one day late and 9% obtain PEP 1 week late.
3) Observational contact tracing data supported by modelling: Data from persons bitten by suspected rabid dogs were grouped into four categories according to the part of the body where bitten: head and neck, trunk, arm and hand, and leg and foot. For individuals with multiple bites only the highest risk bite was used for this categorization, established via the hierarchy of risk reported by Shim et al. (2009) that proposed (from highest to lowest risk) head, arms, legs, trunk. Based on the health outcomes of bite victims that did not receive PEP the probability of developing rabies following a bite to a specified part of the body was calculated. The risk hierarchy was checked, the data re-categorized with the new hierarchy: head, trunk, arms, legs and the probability of death according to bite site recalculated. The overall probability of rabies transmission from a suspect rabid animal bite (p=0.1656, based on simulation from a mixture model) was then estimated based on the proportion of bite victims bitten on different parts of the body and the risk of developing rabies given the bite site. The protective effect of imperfect PEP for individuals bitten by suspect rabid animals ($P_{effective}$) was based on a subset of these data with individuals that received RIG (n=1) or whose deaths were caused by tetanus or injury (n=1 and n=5 respectively) removed. Nine suspect rabies deaths were identified from 891 patients bitten by suspect rabid animals but given imperfect PEP, i.e. the probability of death under imperfect PEP is 0.010 therefore $P_{effective}$ is 0.990. Eight of these deaths were attributable to delays in PEP administration and the other was associated with timely PEP delivery of the first 2 PEP doses only (similar observations from Haiti).

In practice, prioritization is happening due to shortage of RIG (and vaccines), cost, age, severity of exposure, etc. Based on published data, clinical experience and expert knowledge an algorithm for more prudent and equitable use of RIG is proposed to support clinical management of bite patients potentially exposed to rabies.

This decision support for clinicians for most appropriate use of biologicals and patient care, would also ease ethical and logistical challenges.

5.2.4. Monoclonal Antibodies:

A prospective alternative to RIG is an anti-rabies monoclonal antibody cocktail. While mAbs were initially used for diagnostic and experimental purposes, they are now often employed as treatment and therapeutic agents in a variety of clinical settings. Efficacious and safe anti-rabies mAbs would increase access and affordability of PEP and subsequently decrease rabies deaths.

The first mAb against rabies (a single monoclonal antibody) was recently licensed by the Serum Institute of India (SII) (Gogtay et al., 2017) and is expected to be launched in Indian clinics for use in PEP in late 2017 (personal communication from SII, 19 August 2016). SII shared pre-clinical and clinical data with WHO and this evidence was reviewed by independent experts. The data shows that this mAb neutralizes a broad panel of globally prevalent rabies virus isolates, has shown equivalent response to HRIG in a hamster challenge model and the PEP regimen consisting of this mAb mounts rabies neutralizing activity to a level that is similar or higher than that with PEP containing hRIG in patients with Category III exposure. Additional evidence from the scientific literature was considered (see evidence profile Question 13).

As the first product has only been licensed recently, in consequence there is limited clinical and published evidence available. However, due to circumstances of low affordability and access to RIG, finding alternatives or supplements for RIG would have a big public health impact. Therefore and for the first time, WHO will propose a recommendation to include the use of mAbs for passive immunization against rabies.

mAbs can be produced in standardized quality and large quantities, eliminate the use of animals in the production process, reduce the risk of adverse events and reduce cost. Though it is hypothesized that mAbs should include two or more mAbs with non-overlapping epitopes, till date, only SII mAb has demonstrated safety and efficacy in clinical trials when used in PEP, and offer a potential solution to the lack of availability of RIG.

Considering the above factors this mAb should be used as part of PEP. The currently available single mAb and its use in selected geographic and epidemiological settings will serve as an important learning process for future mAb products. Post-marketing surveillance and close monitoring of adverse events, including in depth investigations on suspected PEP failures associated should be conducted. The uptake of mAb will also depend on pricing

Passive prophylaxis in the PEP in the form of RIGs is a critical component of rabies prevention. Though RIG have been available for last several decades, their use has been rather limited because of various reasons like limited availability, cost, concerns of allergic reactions, practice of unnecessary skin sensitivity tests, potential transmission of blood borne pathogens, etc. For the first time, a monoclonal antibody as a potential replacement to RIGs (SII RMAb) has been developed and licensed for use in rabies PEP as a passive antibody component. The data so far shows equivalence of its performance to hRIG. The availability of this mAb has the potential to address critical public health gaps. Since this mAb is made by recombinant technology, it will be less prone to problems such as availability, safety and purity. This mAb should be recommended for use in the public health programmes, based on epidemiological and geographic settings, along with monitoring of its safety and efficacy (clinical outcomes) during the post marketing use.

6. OVERVIEW OF NEW RABIES VACCINES AND OPERATIONAL TOOLS UNDER DEVELOPMENT

6.1. Key points

- New vaccines in the pipeline have the potential to lead to long-lasting immunogenicity and improve programmatic delivery
- Further innovation, research and development in close collaboration with manufacturers is needed to optimize cost-effectiveness, easier storage, longer shelf-life and still retain vaccine safety and efficacy

- Novel vaccine delivery tools have the potential to facilitate ID vaccine administration in a wider range of settings

6.2. Review of Evidence of the potential of new vaccines

Novel vaccines have the potential to simplify delivery and increase affordability of PEP and PrEP (Table 7). New vaccines are in different phases of development, and some are being reviewed by national and international regulatory bodies.

Table 7: Overview on novel vaccine candidates and a preliminary assessment of their potential

Vaccine type/group	Suitable for PEP	Suitable for PrEP	Administration mode (ID, IM, SC, other)	Safety	Efficacy, imunogenicity	Cost-effectiveness	Potential for improvements in delivery
Attenuated rabies vaccines	yes	yes	IM/ID/oral	depends	High	yes	Variable, 1 dose
Deactivated, genetically modified rabies virus	yes	yes	IM/ID	high	High	maybe	Lyophilized 2 doses
Protein vaccines	yes	yes	IM/ID	high	to be determined	No	Yes 3 doses
Peptide vaccines	no	no			Low		
DNA/RNA vaccines	no	yes	IM/ID	high	Low	maybe	Yes 3-5 doses
Adenoviral vectors	no	yes	IM/potentially oral	high	High	yes	Yes 1 dose
Other viral vectors	no	yes	IM/potentially oral	variable	Variable	maybe	Variable 1 dose
Bacterial vectors	no	yes	IM/potentially oral	depends	Low	no	No, 1 dose

Stages of adjuvant development for rabies

In clinical trials

PIKA vaccine: Rabipur and Polyinosinic-Polycytidylic Acid Based Adjuvant - allows for reduction in vaccine dose (2 IU instead of ~6) and accelerated vaccination (2 doses on day 0, 2 on day 3, 1 on day 7).

Vaccine in clinical testing

In clinical trials:

RNA-active rabies vaccine: Based on 3 doses of an mRNA encoding the rabies virus glycoprotein.

Phase II, Rabies G protein nanoparticle vaccine: Based on 3 doses of a baculovirus-derived glycoprotein that spontaneously form micelles (nanoparticles).

Scheduled for clinical testing:

E1-deleted adenovirus vector of chimpanzee-origin expressing rabies virus glycoprotein (Oxford/Wistar): Planned trial will test a one dose regimen followed by a late boost with 2 doses of a conventional vaccine to assess recall responses. Clinical results are expected to become available by late 2020. The trial includes an arm that tests a new method to enhance thermostability at ambient temperatures. Discussions are underway with partners for larger scale clinical trials. It is expected depending on the efficacious dose that the vaccine

may eventually be made available for <$1. Thermostabilization, a long-term goal, may increase the overall cost.

In conclusion, there are a number of novel, promising vaccines that may prove useful in the future to overcome challenges of delivery of the vaccine to the patient. Programme-directed research, innovation and development in close collaboration with manufacturers is needed to optimize cost-effectiveness, delivery at community level, easier storage, thermostability, longer shelf-life and still retain vaccine safety and efficacy. Research and development have to take into consideration the requirements for vaccines that are mainly needed in resource-limited settings where considerable logistic and operational challenges might be associated. Mutual exchanges between manufacturers, academia and WHO would allow to better adapt objectives and progress of development of new vaccines or adjuvants to programmatic needs in countries.

6.3. Operational tools under development to improve programmatic delivery

Novel intradermal immunization devices are currently being developed to simplify and improve delivery of ID vaccination. These include needle-based devices such as intradermal adaptors, mini-needles and microneedles; disposable-syringe jet injectors; and microneedle patches. The prices of such devices are still a barrier and appropriate training of health care providers will be needed. WHO prequalification protocols are already established for jet injectors, and under development for needle and syringe based ID devices.
Innovation in controlled temperature chain (CTC) would allow for the storage and transport of compatible vaccines outside of conventional 2° to 8° Celsius cold chain, increasing cost-effectiveness, efficiency, and reach of immunisation programmes. A number of CTC compatible vaccines have been developed and prequalified, or are undergoing prequalification, and at present six counties have implemented CTC strategies. Studies suggest CTC could reduce vaccine delivery costs by up to 50% (Kahn et al., 2017).
The majority of individuals affected by rabies live in low resource and marginalized communities, therefore innovative delivery of medical drugs and vaccine are under consideration, such as delivery through drones. Enhanced efforts to train health care staff in ID administration of rabies vaccines, research on (easier) subcutaneous administration of rabies vaccines, coordinated use of existing cold chains and decentralisation of animal bite treatment clinics will would further support the goal of improved health equity.

7. QUALITY OF EVIDENCE ASSESSMENT

7.1. Introduction and objectives:

The SAGE working group (WG) on rabies was established in mid-2016 (Appendix 1). In accordance with the guidance document for the development of evidence-based vaccine related recommendations [2], the WG held a series of conference calls and face-to-face meetings to identify priority questions, for which recommendations need to be developed, for consideration by SAGE. The WG prioritized a list of issues for good practice recommendations, landscape analysis and for formal Grading of Recommendations, Assessment, Development and Evaluation (GRADE) review. A total of 14 key questions, and two additional questions relating to rabies vaccine potency and rabies vaccines under development, were identified. The key questions and outcomes **in bold** were agreed upon for a formal GRADE review. Evidence for the remaining questions was either entirely or partly based on modelling estimates (Questions 1, 5, 6, 7) or we conducted a landscape analysis on best practice or expert opinion available (Questions 2, 10, 14 and information on new vaccines). Evidence to Recommendation Tables are available for questions 3, 4, 6, 7, 10, 11, 12, 13, 14.

[2] http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf

Question 1: Does novel evidence support the use of PREP in particular sub-populations, apart from persons bearing an occupational rabies exposure risk?

Question 2: Does novel evidence support the need for rabies booster doses in persons at continual or frequent risk of occupational rabies exposure?

Question 3: Can the duration of the entire course of current PREP regimens be reduced while maintaining immunogenicity and clinical protection?

Question 4: Can the number of doses administered in current PREP regimens be reduced while maintaining immunogenicity and clinical protection?

Question 5: Which (operational) parameters affect cost-effectiveness of intradermal (ID) compared to intramuscular (IM) administration route of PEP? a. in urban settings; b. in rural settings.

Question 6: Can the duration of the entire course of current PEP regimens be reduced while maintaining immunogenicity and clinical protection?

Question 7: Can the number of doses administered in current PEP regimens be reduced while maintaining immunogenicity and clinical protection?

Question 8: Does novel evidence support recommendations on modified PEP protocols vs current PEP protocols for specific risk groups of rabies exposed patients, such as: Immuno-compromised patients (e.g. HIV-infected); patients concurrently using antimalarial drugs; pregnant women; bat exposures (i.e. for bat lyssavirus)?

Question 9: Does a change in route of administration (IM or ID) during a single course of a PEP regimen affect immunogenicity of PEP?

Question 10: Are there novel approaches to RIG (-sparing) injection vs current practice as part of PEP for category III exposed patients?

Question 11: Is there clinical equivalence in the safe use of eRIG compared to hRIG in category III exposed patients?

Question 12: Is there clinical equivalence in the efficacious use of eRIG compared to hRIG in category III exposed patients?

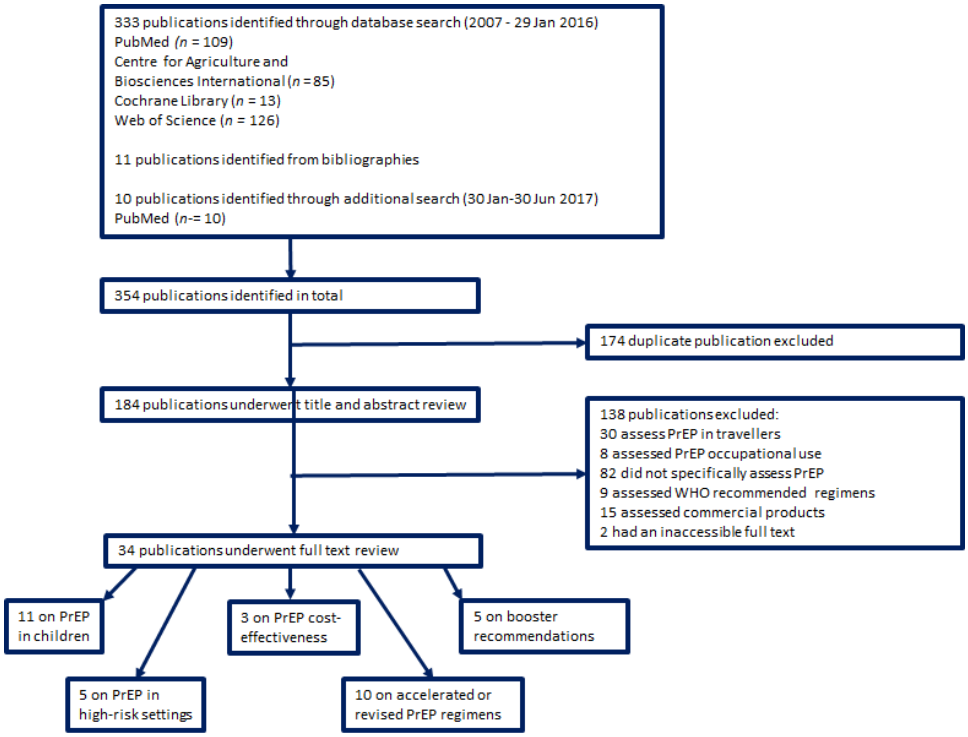
Question 13: Can monoclonal antibodies be safely and efficaciously administered in category III exposed patients compared to standard RIG?

Question 14: In cases of RIG shortage and constraints, can subcategories of patients be identified who should be given highest priority for RIG administration?

7.2. Methodology:

Systematic literature reviews were performed for questions addressing PEP and RIG. For questions related to PrEP a systematic literature review was already available (Kessels et al.). Searches were primarily conducted in the English language, using the literature databases PubMed, Cochrane reviews, Science Direct and the WHO GIFT database. Given the relatively small number of randomized clinical trials (RCTs) available in the field of rabies, the WG included observational and unpublished data, and did not restrict the GRADE review to randomized controlled trials only. The WG focussed on data available since 2007, as the 2010 position paper considered most of the relevant literature before 2007. However, the WG considered key publications before 2008 for any question, and particularly where limited new evidence was available. References prior to 2007 were included from citations of relevant publications where applicable. Articles were not considered to be mutually exclusive, and could provide evidence for more than one question of interest.

The publication on **PrEP** by Kessels et al systematically reviews relevant published literature from 01 January 2007 to 29 January 2016, and case studies of rabies elimination programmes where PrEP has been used from Peru and the Philippines. The systematic literature review was updated to June 2017 to account for three published studies, and two manuscripts in preparation, on accelerated PrEP schedules (Questions 3 & 4), two additional publications for questions on PrEP boosters (Question 2) and one publication on PrEP as a public health intervention in sub-populations (Question 1). The results of the systematic literature review are available in Figure 13. Question 1 was further supported by modelling results (see evidence profile).



PrEP: pre-exposure prophylaxis; WHO: World Health Organization

Figure 13: Results systematic literature review on PrEP

The **systematic literature review on PEP** (Figure 14): The search was conducted without language restrictions for articles published between January 2007 and June 2017. Search terms used in PubMed: ("Rabies Vaccines"[nm] AND "Humans"[MeSH terms]) AND ("post-exposure"[title/abstract] OR "postexposure"[title/abstract]). The 17 included articles comprised 5 randomized controlled trials, 7 observations studies and 5 review articles. These were considered relevant to address the WG Questions 6, 7, 8 and 9. The evidence base was extended by data from an ongoing clinical study in Cambodia, expert opinion and unpublished data from clinical practice in countries. Evidence for Question 5 was mainly retrieved from modelling results and programmatic experiences of countries (see evidence profile). For Question 9 evidence for decision was mainly derived from expert opinion, as the thorough literature search revealed only 2 relevant publications.

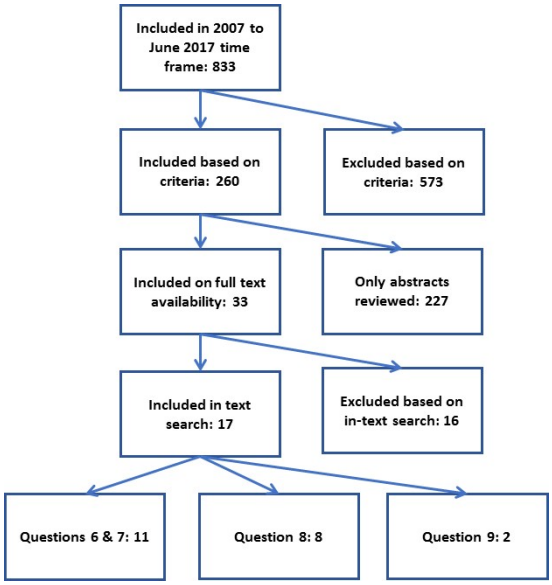


Figure 14: Search results for PEP

The **systematic literature review on RIG** encompasses all relevant literature from January 2007 to June 2017. General search terms for RIG were applied first, followed by distinguishing searches for each of the questions (Figure 15). A total of 9 relevant publications were considered for each of Questions 10, and the combined questions 11 & 12 (Figure 16). 21 publications were added to the evidence base for Question 14, which consists mainly of unpublished observational data and expert opinion.

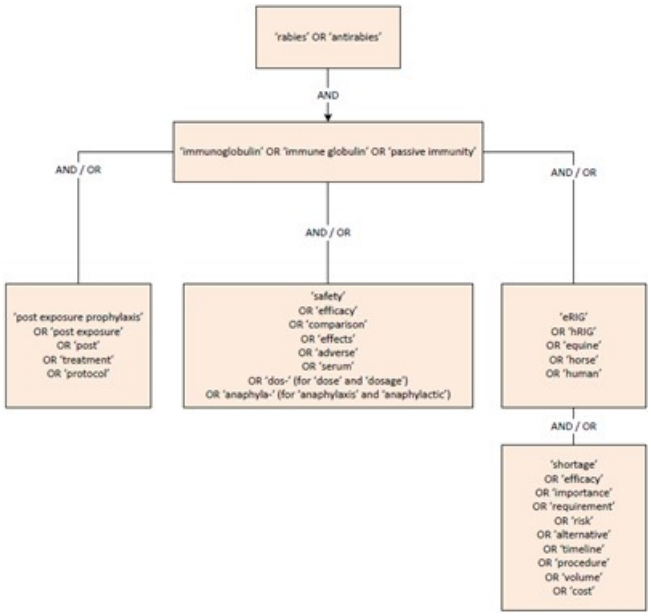


Figure 15: Search strategy for RIG

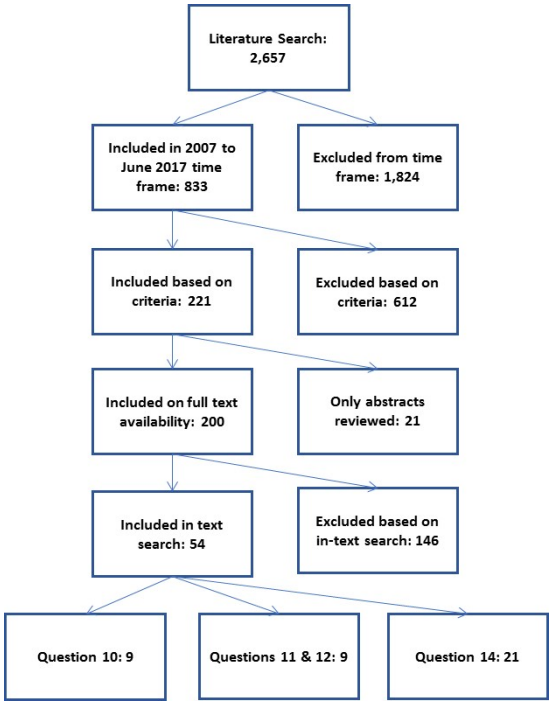


Figure 16: Results systematic literature review on RIG

A total of 59 recently published studies were included in the GRADE review: 18 for PrEP, 13 for PEP and 28 for RIG. Outcomes of interest for safety included any adverse event, any serious adverse event, and death. However, no published articles that were reviewed captured new information on rabies risk categories and boosters for occupational hazard or PrEP in immunocompromised individuals. Question-specific evidence profiles (Appendix II), including summaries of publications and unpublished evidence, were prepared using a standard template. All relevant publications for PICO format questions were assessed and GRADEd in terms of their risk of bias, level of indirectness, degree of imprecision, strength of association, and degree of residual confounding.

7.3. Results:

Detailed results of the evidence and GRADE review are included in the respective evidence profiles under Appendix II. The quality assessment of the evidence for questions 3 and 4 were combined as the publications considered usually address both aspects. The same procedure was applied for Questions 6 and 7, 11 and 12. The key results of the GRADE tables by question are summarized below.

The GRADE values for supporting evidence for recommendations on rabies immunization practices are characterized by the limited availability of high quality randomized clinical trials in this field. The key evidence frequently relies on observational studies and field data. Studies on rabies PEP regimens and RIG administration practices on this 100% fatal disease can't be carried out as placebo-controlled trials as ethically unacceptable. Because rabies is a fatal disease that affects marginalized and low-resource populations, any interventions that improve chances of survival, increase accessibility, and affordability of rabies biologics will outweigh undesirable outcomes or levels of uncertainty.

Question 1: Does novel evidence support the use of PREP in particular sub-populations, apart from persons bearing an occupational rabies exposure risk?

Conclusion: Evidence supports a moderate level of confidence that PrEP is safe and immunogenic in children and other sub-populations living in at risk areas, including when administered with childhood vaccinations or Japanese encephalitis vaccines in children and adults.

Question 3: Can the duration of the entire course of current PREP regimens be reduced while maintaining immunogenicity and clinical protection?

Question 4: Can the number of doses administered in current PREP regimens be reduced while maintaining immunogenicity and clinical protection?

Conclusion: Evidence supports a moderate of confidence that accelerated PrEP regimens (2 visits, 1-week) are non-inferior to current WHO recommended PrEP regimens and result in an adequate level of neutralizing antibody titres of > 0.5 I.U. and an accelerated immune response upon boosters or PEP.

Question 6: Can the duration of the entire course of current PEP regimens be reduced while maintaining immunogenicity and clinical protection?

Question 7: Can the number of doses administered in current PEP regimens be reduced while maintaining immunogenicity and clinical protection?

Conclusion: Evidence supports a low to moderate level of confidence that accelerated or reduced PEP regimens are non-inferior to current WHO recommended PEP regimens and result in an adequate level of neutralizing antibody titres of > 0.5 I.U., clinical protection and improved cost-effectiveness.

Question 8: Does novel evidence support recommendations on modified PEP protocols vs current PEP protocols for specific risk groups of rabies exposed patients, such as: Immuno-compromised patients (e.g. HIV-infected); patients concurrently using antimalarial drugs; pregnant women; bat exposures (i.e. for bat lyssavirus)?

Conclusion: Evidence supports a very low level of confidence that modified PEP protocols for specific risk groups are non-inferior to current recommendations

Question 10: Are there novel approaches to RIG (-sparing) injection vs current practice as part of PEP for category III exposed patients?

Conclusion: Evidence supports a very low to low level of confidence that wound injection of RIG compared to wound injection and injection of remaining RIG IM distant from the wound is efficacious

Question 11: Is there clinical equivalence in the safe use of eRIG compared to hRIG in category III exposed patients?

Question 12: Is there clinical equivalence in the efficacious use of eRIG compared to hRIG in category III exposed patients?

Conclusion: Evidence supports a very low level of confidence that there is clinical equivalence of eRIG compared to hRIG in terms of safety and efficacy.

Question 14: In cases of RIG shortage and constraints, can subcategories of patients be identified who should be given highest priority for RIG administration?

Conclusion: Evidence supports a very low level of confidence that subcategories of patients can be prioritized for RIG allocation

Potency: Currently required potency of cell culture and embryonated egg-based rabies vaccines is above 2.5 IU per dose, does this need review based on the current practice of vaccination?

Conclusion: Evidence supports a moderate level of confidence that the immunogenicity of current rabies vaccines administered by ID route for PEP appears as least as good as that of IM vaccination regimens. While ID PrEP seems associated with lower antibody titres than IM PrEP, the observation has not been associated with any clinical relevance.

8. PROPOSED RECOMMENDATIONS FOR SAGE CONSIDERATION

8.1. PREP

Q 1 (PrEP as a preventive intervention in particular sub-populations)

1. Due to the low cost-effectiveness in most settings, PrEP as a large-scale intervention is not recommended. PrEP can be considered in areas where control in the animal reservoir is impossible (e.g. areas endemic for bat and wildlife rabies), and where there is limited access to timely and adequate PEP. This should be based on strong epidemiological evidence and local context. *(See Table 4)*

Q2 (need for boosters, occupational risk)

1. Individuals at a very high risk of rabies exposure from occupation, travel or limited access to timely and adequate PEP, should be considered for PrEP and/or vaccine boosters in accordance with recommended vaccine schedules (see Table 4).
2. Routine boosters are only recommended for those who face occupational exposure. If available, pre-booster serology can inform the need for a booster (see Table 4).

Table 4: **Indications for pre-exposure rabies immunization (PrEP),** adapted from Müller et al. 2015

Examples of typical individuals and populations	Likelihood and nature of exposure to rabies virus	Timely access to rabies biologics	Recommendations on pre-exposure immunization [a] and serologic testing
Occupational exposure			
Individuals involved rabies research, rabies biologics production [b].	Virus may be present continuously, usually in high concentrations. Specific exposures may not be recognized. Bite, non-bite, or aerosol exposures.	Yes	PrEP recommended. Suggested timeframes for serologic testing: After primary immunization and the every ~6 months up to every 1-2 years. Routine booster vaccination [c], if antibody titre falls below 0.5 IU/ml [d].
Individuals working in rabies diagnostic laboratories [b], in hospitals with clinical rabies cases [e], animal disease control, wildlife management, bat handling or with professional activities in caves likely to lead to direct contact with bats.	Settings or areas where rabies is enzootic and where exposure may not be recognized. Presence of bats, particularly non-haematophagous bats. Bite, non-bite, or aerosol exposures.	Variable, mostly yes Variable	PrEP recommended. Serologic testing every ~2 years. Routine booster vaccination if antibody titre is below 0.5 IU/ml. PrEP recommended. No serologic testing or routine booster vaccination.
Individuals working or residing in remote areas for extended periods and involved in e.g. dog vaccination campaigns, animal disease control programmes, peace keeping, military or religious missions.	Remote settings where rabies is enzootic. Exposure typically episodic with source recognized. Bite or non-bite exposures. Partly remote settings where rabies is enzootic. Exposure typically episodic with source recognized. Bite or non-bite exposures.	Variable, mostly not Variable	PrEP recommended. Serologic testing unnecessary unless risk of exposure remains. Otherwise, test and boost if antibody titre falls below 0.5 IU/ml, or alternatively give a routine booster vaccination before departure.
Individuals involved in e.g. animal disease control with direct contact with terrestrial animals.	Settings where rabies is uncommon to rare. Exposure typically episodic with source recognized. Bite or non-bite exposures.	Variable, mostly yes	PrEP recommended. No serologic testing or routine booster vaccination.
Travellers			
Individuals with mainly leisure related exposures by potential direct contact, particularly with carnivores or bats, during activities over an extended period e.g. backpackers, bicycle or motorbike riders, people visiting friends and relatives. Consider cumulative exposure in frequent travelers.	Remote settings where rabies is enzootic. Exposure typically episodic with source recognized. Bite or non-bite exposures. Partly remote settings where rabies is enzootic. Exposure typically episodic with source recognized. Bite or non-bite exposures.	Variable, mostly not Variable	PrEP recommended. Serologic testing unnecessary unless risk of exposure remains. Otherwise, test and boost if antibody titre falls below 0.5 IU/ml, or alternatively give a routine booster vaccination before departure.
Individuals with leisure activities in caves leading to likely direct contact with bats.	Settings or areas where rabies is enzootic and where exposure may not be recognized. Presence of bats, particularly non-haematophagous bats. Bite, non-bite, or aerosol exposures.	Variable, mostly yes Variable	PrEP recommended. Serologic testing every ~2 years. Routine booster vaccination if antibody titre is below 0.5 IU/ml PrEP recommended. No serologic testing or routine booster vaccination.
Sub-populations			
Residents of remote areas where animal rabies control is impaired by difficult access, epidemiological and other factors	Settings or areas where rabies is enzootic, particularly in wildlife and where episodic exposure may not be recognized. Bite or non-bite exposures.	Variable, mostly not	PrEP recommended. No serologic testing or routine booster vaccination.
General population	Areas where rabies is enzootic or epizootic. Exposure always episodic with source recognized. Mostly bite, also non-bite exposures.	Yes	No PrEP recommended. PrEP for general populations is unlikely to be a cost-effective intervention and is usually more expensive than other measures to prevent human rabies deaths, such as post-exposure prophylaxis and dog vaccination campaigns.
In case of a WHO category II or III exposure to a rabid animal (or lyssavirus), post-exposure prophylaxis including thorough wound care is always required. People who have received PrEP should be instructed accordingly.			

[a] A primary course of pre-exposure immunization consists of either a two-site intradermal administration of 0.1 ml of vaccine on days 0 and 7 or one vaccine dose for intramuscular administration on days 0 and 7. Administration of booster doses of vaccine depends on nature and duration of the rabies exposure risk as above.

[b] Assessment of relative risk and any extra monitoring of immunization status of laboratory workers is the responsibility of the laboratory supervisor (as an example, see guidelines in the current edition of the United States Department of Health and Human Services' Biosafety in Microbiological and Biomedical Laboratories).

[c] A routine pre-exposure booster vaccination consists of one dose of modern cell culture vaccine, ID or IM (i.e., deltoid area).

[d] An acceptable antibody level is 0.5 IU/ml or 1:5 virus neutralizing antibody titre (complete inhibition in the RFFIT at a 1:5 dilution, approximately equivalent to 0.1 IU/ml). Boost if the titre falls below this level, as long as the person remains at risk of viral exposure.

[e] Human-to-human transmission of rabies has never been confirmed outside of the transplant setting. However, rabies virus can be found in saliva, tears, and nervous tissues of human rabies cases and represents a theoretical route of transmission. Therefore, pre-exposure immunization might be indicated and can alleviate the psychological burden of fear from infection of health care staff who are regularly attending to patients with clinical rabies.

Q 3&4 (decrease in duration/number of doses)

1. The following PrEP schedules for healthy individuals of all ages are recommended:
    - Two ID doses on days 0 and 7
    - One IM dose on days 0 and 7
2. Although a 1-day course of PrEP likely confers some protection, it is not recommended at this stage. However, if it is impossible to complete the entire course of PrEP, those who have received PrEP only on day 0 should receive a second dose as soon as possible. In the event of a potential rabies exposure prior to the second dose, full PEP should be given.
3. Individuals who are immunocompromised should receive a 3-visit course of PrEP (days 0, 7 and 21 to 28) either ID (2-site) or IM, as these individuals may have a decreased immune response to vaccine. Moreover, a 2-visit course of PrEP (days 0, 7) in immunocompromised individuals has not been studied. Where possible, serology can be used to assess seroconversion after two doses, and additional doses can be administered if needed.
4. There is limited evidence on the effect of chloroquine or other related drugs on immune response to rabies vaccine if administered ID. Individuals under treatment with chloroquine or related drugs should receive PrEP or PEP as indicated for the general population. For well-planned travel, PrEP should be given before antimalarial treatment is started.

8.2. PEP

Q5 (cost-effectiveness ID vs IM)

1. More efforts are needed to reach the rural and marginalized populations most often affected by rabies. We recommend innovation to improve access, affordability of PEP, awareness and programmatic delivery.
2. ID administration, even in low-throughput clinics, is always more cost-effective

Q6 & 7 (decrease in duration/number of doses)

1. WHO-approved and shortened PEP regimens which are described in Table 5. Countries considering new or alternate regimens should take into account (a) feasibility (i.e. cost and number of doses), (b) immunogenicity and (c) clinical protection of the schedule.

Table 5: **Overview existing approved and investigational PEP regimens and criteria for evaluation of non-inferiority to WHO recommended regimens**

Assumptions patient throughput per month: Small clinic < 10 patients; large clinic ≥ 10 patients
Legend: ✓ Criteria fulfilled; ○ partly fulfilled;
REF: Cost-effectiveness baseline reference = updated Thai Red Cross regimen (TRC)

PEP regimens	**Characteristics**	**Key evaluation criteria**					
	Number of injection sites per visit on days 0, 3, 7, 14, 21 to 28	Immuno-genicity data	Clinical outcome data	Cost-effectiveness		Feasibility	Acceptability
				small clinic	*large clinic*		
WHO recommended intradermal regimen							
IPC regimen, 1 week	2-2-2-0-0	✓	✓	>	>	✓	✓

WHO recommended intramuscular regimens							
Essen regimen, 14 to 28 days	1-1-1-1-0	✓	✓	≤	<	✓	✓
Zagreb regimen, 21 days	2-0-1-0-1	✓	✓	≤	<	✓	✓
Alternate immunogenic intradermal regimens							
Updated Thai Red Cross regimen, 1 month	2-2-2-0-2	✓	✓	REF	REF	✓	✓
Simplified 4-site regimen, 1 month	4-0-2-0-1	✓	O	>	>	O	✓
4-site regimen, 1-week	4-4-4-0-0	✓	O	=	<	O	O

Q8 (PEP for specific risk groups)

1. Rabies vaccines and RIG are safe and efficacious to use in pregnant women and should be administered using any of the recommended regimens.
2. In individuals who are immunocompromised (e.g. unmanaged HIV/AIDS), a full course of PEP with RIG is recommended in both category II and III exposures. Immunocompromised individuals who have received a complete course of PrEP should still be treated with a full course of PEP including RIG if exposed. Where available, serology and/or consultation with a specialist are advised.
3. Exposures to bats (e.g. single or multiple transdermal bites or scratches, licks on broken skin, contamination of mucous membrane with saliva from licks, nibbling of uncovered skin, and minor scratches or abrasions without bleeding) should be treated as category III exposures that require full PEP including RIG. For exposures in which there is no wound, RIG should be injected as close to the site of exposure as anatomically feasible.

Q9 (change in route of administration)

1. Changes in the CCEEV and/or the route of administration during the same PEP course is acceptable in unavoidable circumstances to promote completion of the lifesaving PEP regimen. There is no evidence that restarting PEP is necessary after switching product or administration route. Additionally, the schedule for the new route should be adopted after switching route.

8.3. RIG

Q10 (RIG administration)

1. The maximum RIG dose is calculated by weight, for hRIG at 20 IU/kg and for purified eRIG F(ab')2 products at 40 IU/kg body weight.
2. After calculating the RIG dose, as much RIG as anatomically possible (e.g. to avoid compartment syndrome) should be administered carefully and thoroughly into and around the wound. The maximum benefits of RIG are gained when administered directly into the wound. When the calculated volume is too small to fully infiltrate the wound (e.g. in large or multiple wounds), the RIG may be diluted with sterile normal saline to a volume sufficient for complete infiltration of all wounds.
3. It is current practice that, after completed infiltration of the wounds, the remaining RIG (if any) be administered IM at a site distant from the wound. However, updated evidence suggests that this may be of limited benefit. In settings where RIG is of low availability, the relative benefits of IM RIG injection distant to the wound should be considered against the possibility of providing the remaining RIG for local injection to other patients, to confer maximum public health benefit. This requires aseptic retention of the RIG (e.g. in smaller, individual syringes).

Q 11&12 (safety and efficacy eRIG)

1. Equine immunoglobulins (eRIG) are clinically equivalent to human rabies immunoglobulins (hRIG) and are considered safe and efficacious life- and cost-saving biologics. Both eRIG and hRIG neutralize the virus at the wound site within a few hours. For all RIG products meeting quality standards, the safety and efficacy profiles result in no product preference between eRIG and hRIG.

2. Considering the increase in product purity and safety, skin testing before eRIG administration is unnecessary. Thus, skin testing is not recommended and should be abandoned.

Severe adverse events or perceived lower efficacy of RIG (e.g. batches of insufficient potency or lower purification degree) should be monitored, recorded and reported, so that biological producers receive immediate feedback and can respond accordingly. A classification of adverse events is available in Table 6. Post-marketing surveillance is recommended.

Q13 (monoclonal antibodies)

1. Monoclonal antibodies (mAbs) have demonstrated safety and efficacy in clinical trials when used as a component of PEP, and offer a potential solution to the limited availability of RIG.
2. Cocktails using two or more mAbs working synergistically show higher efficacy and increased breadth of neutralization. Ideally, the production of mAbs for supplementation of RIG should aim to be affordable and include two or more mAbs with nonoverlapping epitopes. We recommend that a registry be maintained to monitor clinical use and outcomes of mAb products.

Q 14 (prioritization of RIG)

1. Even if RIG is not available or affordable, prompt local treatment of all bite wounds or scratches, and for category II and III exposures a complete course of rabies vaccine is indicated.
2. For patients who can reliably document previous post exposure prophylaxis that is equivalent to a PrEP regimen, RIG is not indicated.
3. In cases of shortage or unaffordability, the following groups should be prioritized for RIG allocation:
   - Multiple bites
   - Deep wounds
   - Highly innervated parts of the body, as head, neck, hands, genitals
   - Immunocompromised patients
   - History of biting animal indicative of confirmed or probable* rabies
   - A bite or scratch or exposure of a mucous membrane by a bat can be ascertained

* *An animal rabies case is defined as an animal that presents with any of the following signs:*

- *Hypersalivation*
- *Paralysis*
- *Lethargy*
- *Unprovoked abnormal aggression (biting 2 or more people or animals, and/or inanimate objects)*
- *Abnormal vocalization*
- *Diurnal activity of nocturnal species*

Cases of animal rabies are classified as follows:

- ***suspected**: a case that is compatible with a clinical case definition of animal rabies*
- ***probable**: a suspected case plus a reliable history of contact with a suspected, probable, or confirmed rabid animal, and/or a suspect animal that is killed, died, or disappears within 4-5 days of observing illness*
- ***confirmed**: a suspected or probable case that is laboratory-confirmed**

9. RESEARCH PRIORITIES

1) Efficacy and clinical outcomes associated with 2-visit ID PEP schedule (Day 0 and 7)
2) Efficacy and clinical outcomes associated with 1-week IM PEP schedule (day 0, 3 and 7)
3) Efficacy of PEP schedule after incomplete PrEP (e.g. emergency 1-day PrEP)
4) Efficacy of subcutaneous rabies vaccine administration
5) Immunogenicity and clinical outcomes in immunocompromised individuals to better understand factors for seroconversion
6) IV administration of RIG

7) Pharmacovigilance and reporting of any breakthrough events if a person has received PrEP with concurrent chloroquine treatment
8) Potential to store individually labelled vials for single-patient use to minimise wastage, in line with WHO's policy on the use of opened multi-dose vaccine vials[3].
9) Effect of analgesics on PEP and RIG if used as a component of wound care
10) Pharmacovigilance for mAbs including development of a register to monitor mAb use and outcomes
11) Development of a policy paper or a protocol describing data and sample size needed (supported by statistical calculations) to recommend a new PEP regimen.
12) New vaccines: Programme-directed research, innovation and development in close collaboration with manufacturers is needed to optimize cost-effectiveness, delivery at community level, easier storage, thermostability, longer shelf-life and still retain vaccine safety and efficacy, e.g.
    a. Can the vaccine induce protective antibody titres after one dose?
    b. How rapidly do antibody titres develop?
    c. Does the vaccine induce memory B cell responses that can rapidly be recalled after exposure?
    d. Will the vaccine be cost-effective?
    e. Will the vaccine be stable at ambient temperature?
    f. Can the vaccine be given orally?

10. ACKNOWLEDGEMENTS

The Working Group would like to acknowledge the WHO Collaborating Centres on rabies and experts for their contributions to this work. The openness and responsiveness of the manufacturers in providing supplementary data as requested and identified by the Working Group has been a great support to finetune global recommendations. The work would not have been possible without the numerous countries who generously provided selected data to bridge information gaps. The Working Group would also like to acknowledge the contributions of the WHO rabies modelling consortium, colleagues from other WHO Departments, as well as external consultants for their collaboration and valuable contributions. WHO's partner organizations FAO, OIE and GARC are acknowledged for their continued exchanges and discussions.

[3] http://www.who.int/immunization/documents/general/WHO_IVB_14.07/en/

11. REFERENCES

Ambrozaitis, A., Laiškonis, A., Balčiuniene, L., Banzhoff, A. and Malerczyk, C., 2006. Rabies post-exposure prophylaxis vaccination with purified chick embryo cell vaccine (PCECV) and purified Vero cell rabies vaccine (PVRV) in a four-site intradermal schedule (4-0-2-0-1-1): an immunogenic, cost-effective and practical regimen. *Vaccine*, 24(19), pp.4116-4121.

Baldo, B., 2013. Adverse events to monoclonal antibodies used for cancer therapy: focus on hypersensitivity responses. *Oncoimmunology*, *2*(10), p.e26333.

Behera, T.R., Satapathy, D.M., Pratap, A.K. and Tripathy, R.M., 2011. Post-exposure Prophylaxis for Rabies with ERIG and IDRV in Children.

Behera, T.R., Satapathy, D.M. and Pratap, A.K., 2012. Safety of equine rabies immunoglobulin injection into fingers and toes. *Asian Biomedicine*, *6*(3), pp.429-432.

Bharti, O.K., Madhusudana, S.N., Gaunta, P.L. and Belludi, A.Y., 2016. Local infiltration of rabies immunoglobulins without systemic intramuscular administration: An alternative cost effective approach for passive immunization against rabies. *Human vaccines & immunotherapeutics*, *12*(3), pp.837-842.

Bharti, O.K., Madhusudana, S.N. and Wilde, H., 2017. Injecting rabies immunoglobulin (RIG) into wounds only: A significant saving of lives and costly RIG. *Human Vaccines & Immunotherapeutics*, *13*(4), pp.762-765.

Both, L., Banyard, A.C., van Dolleweerd, C., Horton, D.L., Ma, J.K. and Fooks, A.R., 2012. Passive immunity in the prevention of rabies. *The Lancet infectious diseases*, *12*(5), pp.397-407.

Buelow B, Routes JM. Immediate Hypersensitivity Reactions: Background, Pathophysiology, Epidemiology. 2015; published online Feb 9. http://misc.medscape.com/pi/iphone/medscapeapp/html/A136217-business.html (accessed April 4, 2017).

Centers for Disease Control (CDC). Recommendation of the Immunization Practices Advisory Committee (ACIP). Supplementary statement on pre-exposure rabies prophylaxis by the intradermal route. MMWR Morb Mortal Wkly Rep 1982; 31: 279–80, 285.

Chawan, V.S., Tripathi, R.K., Sankhe, L., Fernandes, A.C. and Daftary, G.V., 2007. Safety of equine rabies immunoglobulin in grade III bites. *Indian Journal of Community Medicine*, *32*(1), p.73.

Cleaveland, S., Fevre, E.M., Kaare, M. and Coleman, P.G., 2002. Estimating human rabies mortality in the United Republic of Tanzania from dog bite injuries. *Bulletin of the World Health Organization*, *80*(4), pp.304-310.

Coleman, P.G. and Dye, C., 1996. Immunization coverage required to prevent outbreaks of dog rabies. *Vaccine*, *14*(3), pp.185-186.

Crowcroft, N.S. and Thampi, N., 2015. The prevention and management of rabies. *bmj*, 350, p.g7827.

de Martino, M., 2016. Dismantling the taboo against vaccines in pregnancy. *International journal of molecular sciences*, 17(6), p.894.

Dimaano, E.M., Scholand, S.J., Alera, M.T.P. and Belandres, D.B., 2011. Clinical and epidemiological features of human rabies cases in the Philippines: a review from 1987 to 2006. *International Journal of Infectious Diseases*, *15*(7), pp.e495-e499.

Dixit, R., Herz, J., Dalton, R. and Booy, R., 2016. Benefits of using heterologous polyclonal antibodies and potential applications to new and undertreated infectious pathogens. *Vaccine*, *34*(9), pp.1152-1161.

Dodet, B., 2009. The fight against rabies in Africa: From recognition to action. *Vaccine*, *27*(37), pp.5027-5032.

Gogtay, N.J., Munshi, R., Ashwathnarayan, D.H., Mahendra, B.J., Kshirsagar, V., Gunale, B., Moore, S., Cheslock, P., Thaker, S., Deshpande, S. and Karande, S., 2017. Comparison of a novel human rabies monoclonal antibody to human rabies immunoglobulin for post-exposure prophylaxis: A phase 2/3 randomized, single blind, non-inferiority, controlled study. *Clinical Infectious Diseases*, p.cix791.

Gøransson, L.G., Mellgren, S.I., Lindal, S. and Omdal, R., 2004. The effect of age and gender on epidermal nerve fiber density. *Neurology*, *62*(5), pp.774-777.

Hampson, K., Dobson, A., Kaare, M., Dushoff, J., Magoto, M., Sindoya, E. and Cleaveland, S., 2008. Rabies exposures, post-exposure prophylaxis and deaths in a region of endemic canine rabies. *PLoS Neglected Tropical Diseases*, *2*(11), p.e339.

Hampson, K., Dushoff, J., Cleaveland, S., Haydon, D.T., Kaare, M., Packer, C. and Dobson, A., 2009. Transmission dynamics and prospects for the elimination of canine rabies. *PLoS biology*, *7*(3), p.e1000053.

Hampson, K., Cleaveland, S. and Briggs, D., 2011. Evaluation of cost-effective strategies for rabies post-exposure vaccination in low-income countries. *PLoS neglected tropical diseases*, *5*(3), p.e982.

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

Hemachudha, T., Mitrabhakdi, E., Wilde, H., Vejabhuti, A., Siripataravanit, S. and Darika, K., 1999. Additional reports of failure to respond to treatment after rabies exposure in Thailand. *Clinical infectious diseases*, *28*(1), pp.143-144.

Hossain, M., Bulbul, T., Ahmed, K., Ahmed, Z., Salimuzzaman, M., Haque, M.S., Ali, A., Hossain, S., Yamada, K., Moji, K. and Nishizono, A., 2011. Five-year (January 2004–December 2008) surveillance on animal bite and rabies vaccine utilization in the Infectious Disease Hospital, Dhaka, Bangladesh. *Vaccine*, *29*(5), pp.1036-1040.

Huang, G., Liu, H., Cao, Q., Liu, B., Pan, H. and Fu, C., 2013. Safety of post-exposure rabies prophylaxis during pregnancy: a follow-up study from Guangzhou, China. *Human vaccines & immunotherapeutics*, 9(1), pp.177-183.

Jaiiaroensup, W., Lang, J., Thipkong, P., Wimalaratne, O., Samranwataya, P., Saikasem, A., Chareonwai, S., Yenmuang, W., Prakongsri, S., Sitprija, V. and Wilde, H., 1998. Safety and efficacy of purified Vero cell rabies vaccine given intramuscularly and intradermally.(Results of a prospective randomized trial). *Vaccine,* 16(16), pp.1559-1562.

Jonker, E.F. and Visser, L.G., 2017. Single visit rabies pre-exposure priming induces a robust anamnestic antibody response after simulated post-exposure vaccination: results of a dose-finding study. *Journal of Travel Medicine*, 24(5).

Kahn, A.L., Kristensen, D. and Rao, R., 2017. Extending supply chains and improving immunization coverage and equity through controlled temperature chain use of vaccines. *Vaccine*, *35*(17), pp.2214-2216.

Kamoltham, T., Thinyounyong, W., Phongchamnaphai, P., Phraisuwan, P., Khawplod, P., Banzhoff, A. and Malerczyk, C., 2007. Pre-exposure rabies vaccination using purified chick embryo cell rabies vaccine intradermally is immunogenic and safe. *The Journal of pediatrics,* 151(2), pp.173-177.

Khawplod, P., Wilde, H., Tepsumethanon, S., Limusanno, S., Tantawichien, T., Chomchey, P., Na Ayuthaya, A.B. and Wangroonsarb, Y., 2002. Prospective immunogenicity study of multiple intradermal injections of rabies vaccine in an effort to obtain an early immune response without the use of immunoglobulin. *Clinical infectious diseases*, *35*(12), pp.1562-1565.

Khawplod, P., Wilde, H., Benjavongkulchai, M., Sriaroon, C. and Chomchey, P., 2007. Immunogenicity study of abbreviated rabies preexposure vaccination schedules. *Journal of travel medicine*, 14(3), pp.173-176.

Khawplod, P., Jaijaroensup, W., Sawangvaree, A., Prakongsri, S. and Wilde, H., 2012. One clinic visit for pre-exposure rabies vaccination (a preliminary one year study). *Vaccine*, 30(19), pp.2918-2920.

Kittipongwarakarn, S., Hawe, A., Tantipolphan, R., Limsuwun, K., Khomvilai, S., Puttipipatkhachorn, S. and Jiskoot, W., 2011. New method to produce equine antirabies immunoglobulin F (ab') 2 fragments from crude plasma in high quality and yield. *European Journal of Pharmaceutics and Biopharmaceutics*, *78*(2), pp.189-195.

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

Krishnamurthy K, Hoang, V. Serum Sickness. Decision support medicine. 2017. http://www.mdedge.com/ccjm/dsm/548/dermatology/serum-sickness (accessed April 4, 2017).

Lang, J., Feroldi, E. and Vien, N.C., 2007. Pre-exposure purified vero cell rabies vaccine and concomitant routine childhood vaccinations: 5-year post-vaccination follow-up study of an infant cohort in Vietnam. *Journal of tropical pediatrics*, 55(1), pp.26-31.

Ly, S., Buchy, P., Heng, N.Y., Ong, S., Chhor, N., Bourhy, H. and Vong, S., 2009. Rabies situation in Cambodia. *PLoS Neglected Tropical Diseases*, *3*(9), p.e511.

Madhusudana, S.N., Ashwin, B.Y. and Sudarshan, S., 2013. Feasibility of reducing rabies immunoglobulin dosage for passive immunization against rabies: Results of In vitro and In vivo studies. *Human vaccines & immunotherapeutics*, *9*(9), pp.1914-1917.

Mallewa, M., Fooks, A.R., Banda, D., Chikungwa, P., Mankhambo, L., Molyneux, E., Molyneux, M.E. and Solomon, T., 2007. Rabies encephalitis in malaria-endemic area, Malawi, Africa. *Emerging infectious diseases*, *13*(1), p.136.

Mills, D.J., Lau, C.L., Fearnley, E.J. and Weinstein, P., 2011. The Immunogenicity of a Modified Intradermal Pre-exposure Rabies Vaccination Schedule—A Case Series of 420 Travelers. *Journal of travel medicine,* 18(5), pp.327-332.

Moore, S.M. and Hanlon, C.A., 2010. Rabies-specific antibodies: measuring surrogates of protection against a fatal disease. *PLoS neglected tropical diseases*, 4(3), p.e595.

Müller, T., Freuling, C.M., Rupprecht, C.E., Both, L., Fooks, A.R., Lembo, T., Knopf, L., Briggs, D.J. and Taylor, L.H., 2015. Elimination of Rabies—A Missed Opportunity. In *Zoonoses-Infections Affecting Humans and Animals*(pp. 527-571). Springer Netherlands.

Narayana, A., Manoharan, A., Narayan, M.S., Kalappa, S.M., Biligumba, G., Haradanahalli, R. and Anand, A.M., 2015. Comparison of safety and immunogenicity of 2 WHO prequalified rabies vaccines administered by one week, 4 site intra dermal regimen (4-4-4-0-0) in animal bite cases. *Human vaccines & immunotherapeutics*, 11(7), pp.1748-1753.

Pappaioanou, M., Fishbein, D.B., Dreesen, D.W., Schwartz, I.K., Campbell, G.H., Sumner, J.W., Patchen, L.C. and Brown, W.J., 1986. Antibody response to preexposure human diploid-cell rabies vaccine given concurrently with chloroquine. *New England Journal of Medicine*, 314(5), pp.280-284.

Pengsaa, K., Limkittikul, K., Sabchareon, A., Ariyasriwatana, C., Chanthavanich, P., Attanath, P. and Malerczyk, C., 2009. A three-year clinical study on immunogenicity, safety, and booster response of purified chick embryo cell rabies vaccine administered intramuscularly or intradermally to 12-to 18-month-old Thai children, concomitantly with Japanese encephalitis vaccine. *The Pediatric infectious* disease journal, 28(4), pp.335-337.

Pancharoen, C., 2001. Failure of pre-and postexposure rabies vaccinations in a child infected with HIV. *Scandinavian journal of infectious diseases,* 33(5), pp.390-391.

Phanuphak, P., Khawplod, P., Sirivichayakul, S., Siriprasomsub, W., Ubol, S. and Thaweepathomwat, M., 1987. Humoral and cell-mediated immune responses to various economical regimens of purified Vero cell rabies vaccine. *Asian Pac J Allergy Immunol*, 5(1), pp.33-7.

Quiambao, B.P., DyTioco, H.Z., Dizon, R.M., Crisostomo, M.E., Laot, T.M. and Teuwen, D.E., 2008. Rabies post-exposure prophylaxis in the Philippines: health status of patients having received purified equine F (ab') 2 fragment rabies immunoglobulin (Favirab). *PLoS neglected tropical diseases*, 2(5), p.e243.

Quiambao, B.P., Dy-Tioco, H.Z., Dizon, R.M., Crisostomo, M.E. and Teuwen, D.E., 2009. Rabies post-exposure prophylaxis with purified equine rabies immunoglobulin: one-year follow-up of patients with laboratory-confirmed category III rabies exposure in the Philippines. *Vaccine*, *27*(51), pp.7162-7166.

Rahimi, P., Vahabpour, R., Aghasadeghi, M.R., Sadat, S.M., Howaizi, N., Mostafavi, E., Eslamifar, A. and Fallahian, V., 2015. Neutralizing antibody response after intramuscular purified Vero cell rabies vaccination (PVRV) in Iranian patients with specific medical conditions. *PloS one*, 10(10), p.e0139171.

Ravish, H.S., Vijayashankar, V., Madhusudana, S.N., Sudarshan, M.K., Narayana, D.H., Andanaiah, G., Ashwin, B.Y., Rachana, A.R. and Shamanna, M., 2014. Safety and Immunogenicity of purified chick embryo cell rabies vaccine (VaxiRab N) administered intradermally as post exposure prophylaxis. *Human vaccines & immunotherapeutics*, 10(8), pp.2433-2437.

Recuenco, S., Warnock, E., Osinubi, M.O. and Rupprecht, C.E., 2017. A single center, open label study of intradermal administration of an inactivated purified chick embryo cell culture rabies virus vaccine in adults. *Vaccine*, *35*(34), pp.4315-4320.

Reveneau, E., Cottin, P. and Rasuli, A., 2017. Two decades of pharmacovigilance and clinical experience with highly purified rabies immunoglobulin F (ab') 2 fragments. *Expert review of vaccines*, *16*(3), pp.273-287.

Sambo, M., Cleaveland, S., Ferguson, H., Lembo, T., Simon, C., Urassa, H. and Hampson, K., 2013. The burden of rabies in Tanzania and its impact on local communities. *PLoS neglected tropical diseases*, *7*(11), p.e2510.

Sampath, G., Parikh, S., Sangram, P. and Briggs, D.J., 2005. Rabies post-exposure prophylaxis in malnourished children exposed to suspect rabid animals. *Vaccine*, 23(9), pp.1102-1105.

Saraya, A., Wacharapluesadee, S., Khawplod, P., Tepsumethanon, S., Briggs, D., Asawavichienjinda, T. and Hemachudha, T., 2010. A preliminary study of chemo-and cytokine responses in rabies vaccine recipients of intradermal and intramuscular regimens. *Vaccine*, 28(29), pp.4553-4557.

Schryver, S.D., Netchiporouk, E. and Ben-Shoshan, M., 2015. Severe Serum Sickness-Like Reaction: Challenges in Diagnosis and Management. *J Clin Exp Dermatol Res*, *6*(279), p.2.

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

Shantavasinkul, P. and Wilde, H., 2011. Postexposure prophylaxis for rabies in resource-limited/poor countries. *Adv Virus Res*, *79*, pp.291-307.

Shim, E., Hampson, K., Cleaveland, S. and Galvani, A.P., 2009. Evaluating the cost-effectiveness of rabies post-exposure prophylaxis: a case study in Tanzania. *Vaccine*, *27*(51), pp.7167-7172.

Simani, O.E., Izu, A., Violari, A., Cotton, M.F., van Niekerk, N., Adrian, P.V. and Madhi, S.A., 2014. Effect of HIV-1 exposure and antiretroviral treatment strategies in HIV-infected children on immunogenicity of vaccines during infancy. *AIDS*, 28(4), pp.531-541.

Sirikwin, S., Likanonsakul, S., Pattamadilok, S., Kumperasart, S., Chaovavanich, A., Manatsathit, S., Malerczyk, C. and Wasi, C., 2009. Antibody response to an eight-site intradermal rabies vaccination in patients infected with Human Immunodeficiency Virus. *Vaccine*, 27(32), pp.4350-4354.

Soentjens P et al. A, Statistical report RCT1: Simplifying the Rabies Pre-exposure Vaccination: Two visit priming (double intradermal injections of 0,1 ml microdoses) . Registered randomised clinical trial EudraCT 2011-001612-62

Soentjens P et al. B, Statistical report RCT2: Boostability for rabies in last-minute travellers: One Day Rabies Pre-exposure Intradermal Vaccination followed by one day Postexposure intradermal Vaccination . Registered randomised clinical trial EudraCT 2014-00183612

Sudarshan, M.K., Madhusudana, S.N., Mahendra, B.J., Narayana, D.H., Giri, M.S., Muhamuda, K., Ravish, H.S. and Venkatesh, G.M., 2005. Boosting effect of purified chick embryo cell rabies vaccine using the intradermal route in persons previously immunized by the intramuscular route or vice versa. *The National medical journal of India*, *19*(4), pp.192-194.

Sudarshan, M.K., Madhusudana, S.N., Mahendra, B.J., Narayana, D.H., Giri, M.S., Muhamuda, K., Ravish, H.S. and Venkatesh, G.M., 2005. Boosting effect of purified chick embryo cell rabies vaccine using the intradermal route in persons previously immunized by the intramuscular route or vice versa. *The National medical journal of India*, *19*(4), pp.192-194.

Sudarshan, M.K., Ravish, H.S. and Narayana, D.H.A., 2011. Time interval for booster vaccination following reexposure to rabies in previously vaccinated subjects. *Asian Biomedicine*, *5*(5), pp.589-593.

Sudarshan, M.K., Narayana, D.H.A., Madhusudana, S.N., Holla, R., Ashwin, B.Y., Gangaboraiah, B. and Ravish, H.S., 2012. Evaluation of a one week intradermal regimen for rabies post-exposure prophylaxis: results of a randomized, open label, active-controlled trial in healthy adult volunteers in India. *Human vaccines & immunotherapeutics*, 8(8), pp.1077-1081.

Tanisaro, T., Tantawichien, T., Tiranathanagul, K., Susantitaphong, P., Chirananthavat, T., Praditpornsilpa, K., Sitprija, V. and Eiam-Ong, S., 2010. Neutralizing antibody response after intradermal rabies vaccination in hemodialysis patients. *Vaccine*, 28(12), pp.2385-2387.

Tarantola, A., Ly, S., In, S., Ong, S., Peng, Y., Heng, N. and Buchy, P., 2015. Rabies vaccine and rabies immunoglobulin in Cambodia: use and obstacles to use. *Journal of travel medicine*, *22*(5), pp.348-352.

Thisyakorn, U., Pancharoen, C., Ruxrungtham, K., Ubolyam, S., Khawplod, P., Tantawichien, T., Phanuphak, P. and Wilde, H., 2000. Safety and immunogenicity of preexposure rabies vaccination in children infected with human immunodeficiency virus type 1. *Clinical infectious diseases*, 30(1), pp.218-218.

Venkataswamy, M.M., Madhusudana, S.N., Sanyal, S.S., Taj, S., Belludi, A.Y., Mani, R.S. and Hazra, N., 2015. Cellular immune response following pre-exposure and postexposure rabies vaccination by intradermal and intramuscular routes. *Clinical and experimental vaccine research*, 4(1), pp.68-74.

Vien, N.C., Feroldi, E. and Lang, J., 2008. Long-term anti-rabies antibody persistence following intramuscular or low-dose intradermal vaccination of young Vietnamese children. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *102*(3), pp.294-296.

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

Warrell, M.J., 2012. Current rabies vaccines and prophylaxis schedules: preventing rabies before and after exposure. *Travel medicine and infectious disease*, *10*(1), pp.1-15.

Wieten, R.W., Leenstra, T., van Thiel, P.P., van Vugt, M., Stijnis, C., Goorhuis, A. and Grobusch, M.P., 2012. Rabies vaccinations: are abbreviated intradermal schedules the future?. *Clinical infectious diseases*, 56(3), pp.414-419.

Wilde, H., Chomchey, P., Prakongsri, S., Puyaratabandhu, P. and Chutivongse, S., 1989. Adverse effects of equine rabies immune globulin. *Vaccine*, *7*(1), pp.10-11.

Wilde, H., Khawplod, P., Hemachudha, T. and Sitprija, V., 2002. Postexposure treatment of rabies infection: can it be done without immunoglobulin?. *Clinical infectious diseases*, pp.477-480.

Wilde, H., 2007. Failures of post-exposure rabies prophylaxis. Vaccine, 25(44), pp.7605-7609.

Wilde, H., Wacharapluesadee, S., Saraya, A., Lumlertdacha, B. and Hemachudha, T., 2013. Human rabies prevention (comment from a canine-rabies-endemic region).

Wilde, H., Lumlertdacha, B., Meslin, F.X., Ghai, S. and Hemachudha, T., 2016. Worldwide rabies deaths prevention—A focus on the current inadequacies in postexposure prophylaxis of animal bite victims. *Vaccine*, *34*(2), pp.187-189.

World Health Organization, 2010. Rabies vaccines: WHO position paper= Vaccins antirabiques: note d'information de l'OMS. Wkly epidemiol rec, 85(32), pp.309-320.

World Health Organization, 2013. *WHO expert consultation on rabies: second report* (No. 982). World Health Organization.

World Health Organization, 2015. *WHO guidance note: vaccine diluents, revision 2015.* World Health Organization.

World Health Organization, 2016. Global elimination of dog-mediated human rabies: report of the rabies global conference, 10-11 December 2015, Geneva, Switzerland.

World Health Organization, 2017. *WHO expert consultation on rabies: second report* (advanced draft). World Health Organization.

12. LIST OF APPENDICES

Appendix I: SAGE WG on rabies (terms of reference, members, declaration of interest)

Appendix II: Evidence profiles Questions 1-14 including GRADE tables and evidence review on potency of rabies vaccine, if fractionated

Appendix III: Evidence to recommendation tables Questions 3, 4, 6, 7, 10, 11, 12, 13, 14