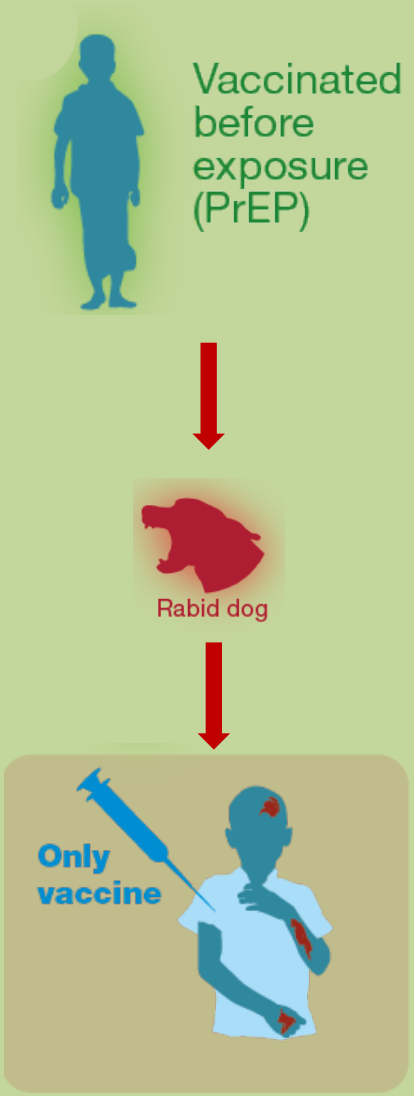
Pre-Exposure Prophylaxis (PrEP)

(reducing risk, RIG use and vaccine doses)



Questions 1, 2, 3, 4

PrEP is typically relevant to:

- Occupationally exposed
- Populations with limited access to health care in remote, highly rabies endemic areas
- Travel medicine

Key factors:

- No medical contraindication for rabies PrEP
- Life-long recall of immune response possible
- PrEP in humans will not eliminate rabies at its animal source
- Consideration of setting:
  - Feasibility to control rabies in animal reservoir (e.g. wildlife)
  - Protective measures available, type of professional or other activities influence rabies exposure risk

Summary current Recommendations:

1. PrEP is recommended for anyone who will be at **continual, frequent, or increased risk of exposure** to rabies virus, as a result of their residence or occupation
2. **Serology RVNA titre and periodic booster injections** (1 dose ID or IM) are recommended as an additional precaution for those whose occupation puts them at continual or frequent risk of exposure
3. In practice, PrEP is **hardly ever made available** to children or populations living in remote areas of high rabies risk
4. Position paper **calls for studies on** the feasibility, cost-effectiveness, and long-term impact of incorporating CCEEVs into the immunization programs of children in canine rabies endemic areas

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?

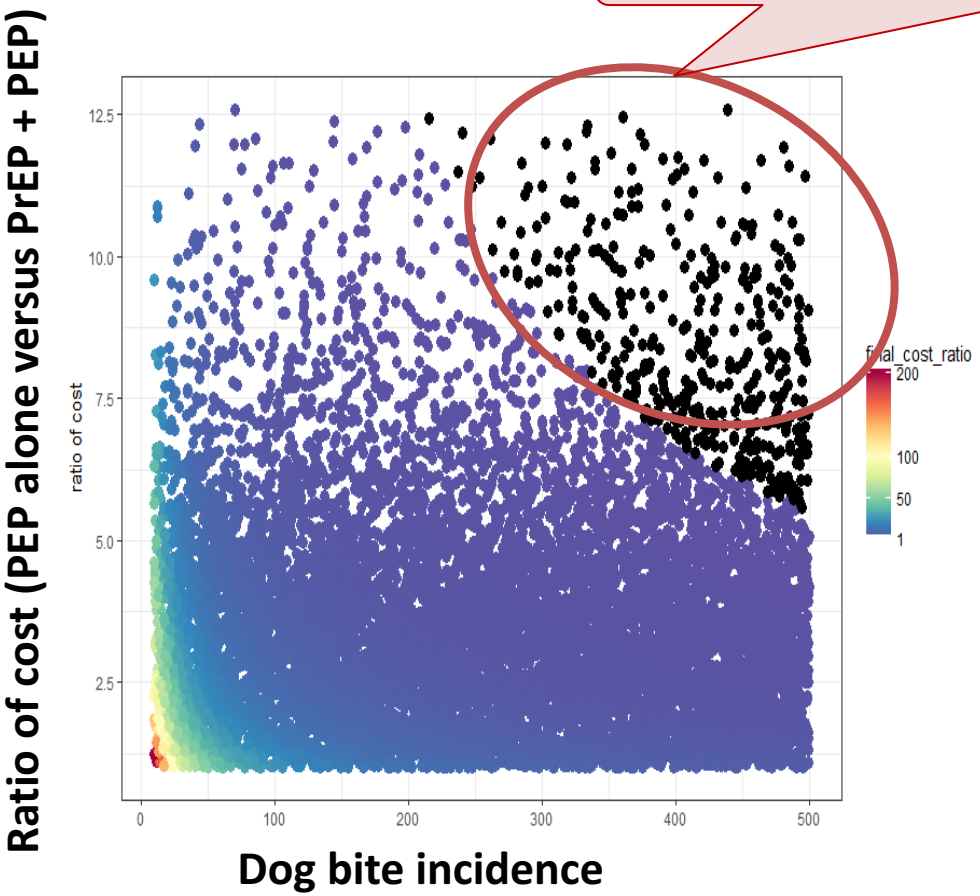
Question 1 & 2: Review of new evidence

1. One systematic literature review on PrEP, review of 2 country PrEP programmes, 3 more recent observational studies & cost-effectiveness modelling
2. Main findings:
   - Fast, effective recall of **immunological memory** when boosted possibly **life-long** (>20 y)
   - PrEP is safe and immunogenic in both infants and children, also **in combination with other (childhood) vaccines** (JE, DTP, and oral and inactivated poliomyelitis vaccines)
   - Shortened PrEP regimens would benefit all individuals eligible for PrEP
   - Modelling estimates: **PrEP**, **as a large scale public health intervention**, is **not cost-effective** except where the dog-bite incidence is extremely high ~5%
   - Combined evidence suggests an update of current indications for PrEP, PrEP boosters and RVNA serology

Modelling results: Theoretical birth cohort

(see page **18**)

PrEP + PEP more cost-effective than PEP alone



PrEP delivery as a large scale programme, is likely to be substantially **more expensive than other measures** to prevent human rabies deaths.

- Only in 4% of simulations is PrEP + PEP more cost-effective than PEP alone (± RIG)

Question 2 : Details new evidence

Table 4: Proposed Indications for PrEP immunization

(see page **43**)

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.			

Considerations for:

- Individuals and subpopulation level
- Examples of at-risk activities
- Frequency, duration and nature of viral exposure
- Timely access to biologics
- Options for serology

Summary current Recommendations :

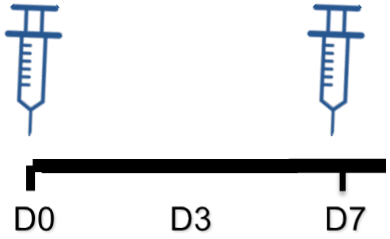
1. PrEP encompasses **3 visits** for vaccine administration with a **time frame of 21 to 28 days**
2. Dosing schedule: 0, 7, 21 or 28
   - IM doses of 1.0 mL or 0.5 mL (depending on type of vaccine)
   - ID dose of 0.1 mL

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 3 & 4: Review of new evidence

1. One systematic literature review on PrEP, further 3 published studies, and two manuscripts in preparation (RCT and observational studies)
2. Studies showed that 7 day IM or ID schedules are as immunogenic as the currently WHO recommended 3-4 week regimen:



Two-visit regimen :

- **2-site ID** (0.1ml per site); or
- **1-site IM** (1 vial per site, 0.5 or 1 ml)
- Rapid recall of immune response, antibody response by day 3 post-booster

Single visit regimen (emergency):

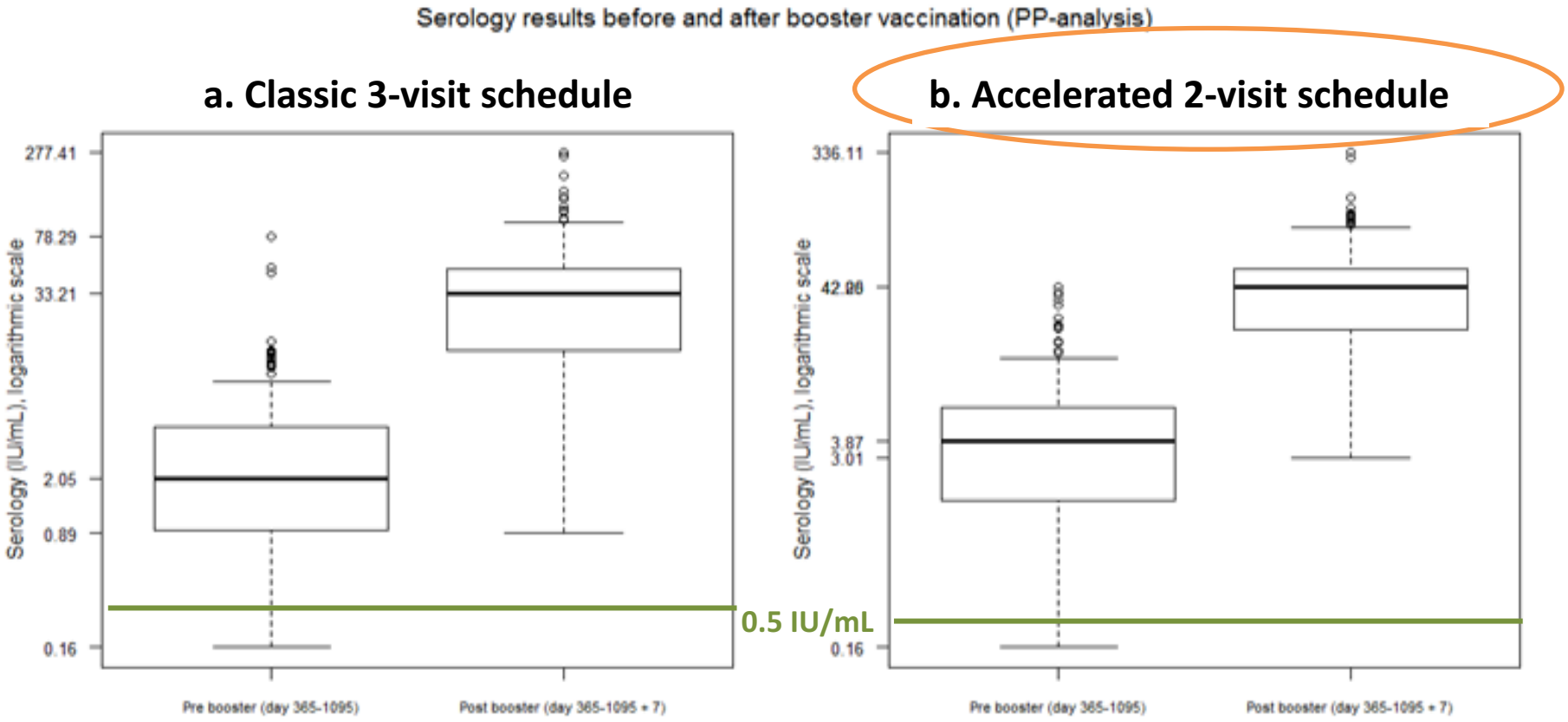
- **2-site ID** or **1-site IM** injection(s)
- Adequate antibody titres for at least one year
- **Limitations**: Age range of study participants, timeframe assessed for boostability
- -> administer a second dose as soon as possible (or full PEP if exposed)

Question 3 & 4: Details on evidence

RCT Soentjens et al 2017

2-visit (day 0, 7), **2-site** (0.1ml per site) **ID PrEP**

Immunogenicity results show equivalence



Conclusions PrEP questions

- There is **no** medical **contraindication** for rabies PrEP
- More flexible indications for PrEP and serological testing for sub-groups of professionals and travellers
- PrEP, as a large scale public health intervention, is not generally cost-effective, local epidemiology and setting need to be considered
- Proposal accelerated efficacious regimes:
  - a 2-site (0.1 ml per site) ID regimen on day 0 and 7
  - a 1-site IM regimen on day 0 and 7
  - Individuals who completed only a single visit PrEP session should get the second session of PrEP as soon as possible and be managed with full PEP (including RIG as indicated) in the case of a potential rabies exposure