Post-exposure vaccine forecasting

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Modeling to support post-exposure prophylaxis (PEP) forecasting

1. Demand planning for vaccine production
    - Depends on scale (national, subnational, local), time horizon (ideally 5+ years) & shelf-life

2. Operationalizing rollout
    - PEP in clinics affected by patient throughput, regimens used & (re)supply rates

3. Monitoring impact & prospects for elimination
    - Care seeking & access to care by those at risk (bitten by rabid dogs)
    - Risk status of bite patients (bites from rabid versus healthy animals)
    - Dog vaccination effort to control transmission in reservoir

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Many interdependencies between 1-3:
- Typically vaccine cost driven down by demand (purchasing power), with investment in volume at scale
- Current situation is a market failure, but Gavi investment in PEP is an opportunity to catalyse positive feedback

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The potential effect of improved provision of rabies post-exposure prophylaxis in Gavi-eligible countries: a modelling study

WHO Rabies Modelling Consortium ⁺ • Show footnotes

Open Access • Published: November 21, 2018 • DOI: https://doi.org/10.1016/S1473-3099(18)30512-7 •

🔄 Check for updates

The potential effe
eligible countries:

Key uncertainties now relate to responses to sensitization from Gavi-rollout & MDV, PEP provisioning practices & health systems

Key Questions for Gavi & countries

1. What PEP regimen should be used?
2. How should PEP be supplied
3. How many doses will be needed?

Key Questions for Gavi & countries

1. What PEP regimen should be used?

Regimens – frustratingly complex & national treatment guidelines vs practice vary by country
Routes of administration - IM vs ID
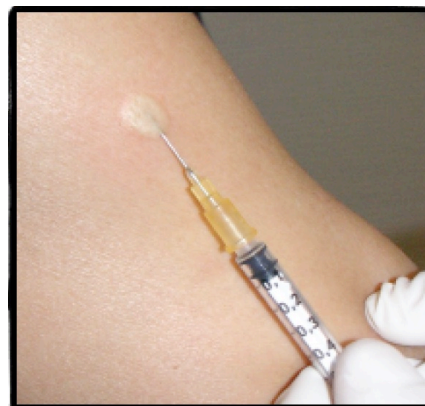Vial size – 1ml or 0.5ml affects wastage and prices
Throughput (wastage) – perceived wastage / discarded vials
Potential to treat more people during emergencies/shortages

Intermuscular (IM) - 1 vial per injection

Intradermal (ID) - 0.1 ml per injection

vials can be shared if used within 6-8 hours (same day)

Conclusions in April 2018 WHO position paper:
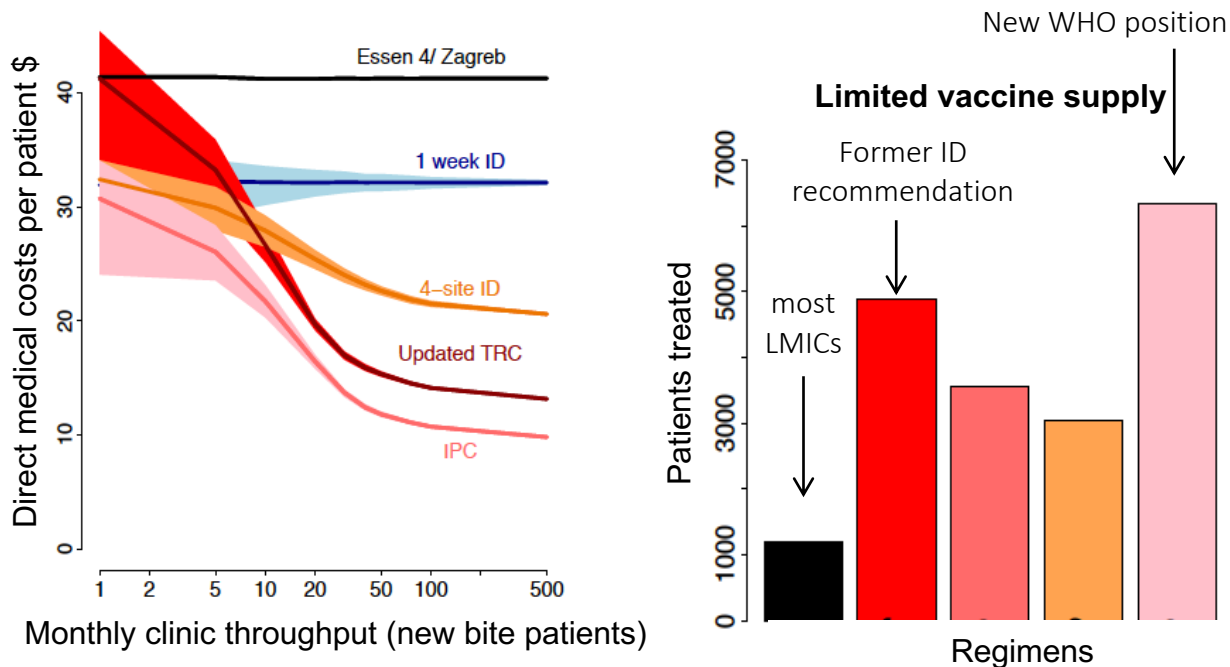
- PreEP within routine EPI → Very costly, PEP much more cost-effective
- ID most cost-effective in all settings – Abridged 1-week ID universally preferred

Hampson et al. Vaccine (2018)

Even in low throughput clinics ID is dose sparing
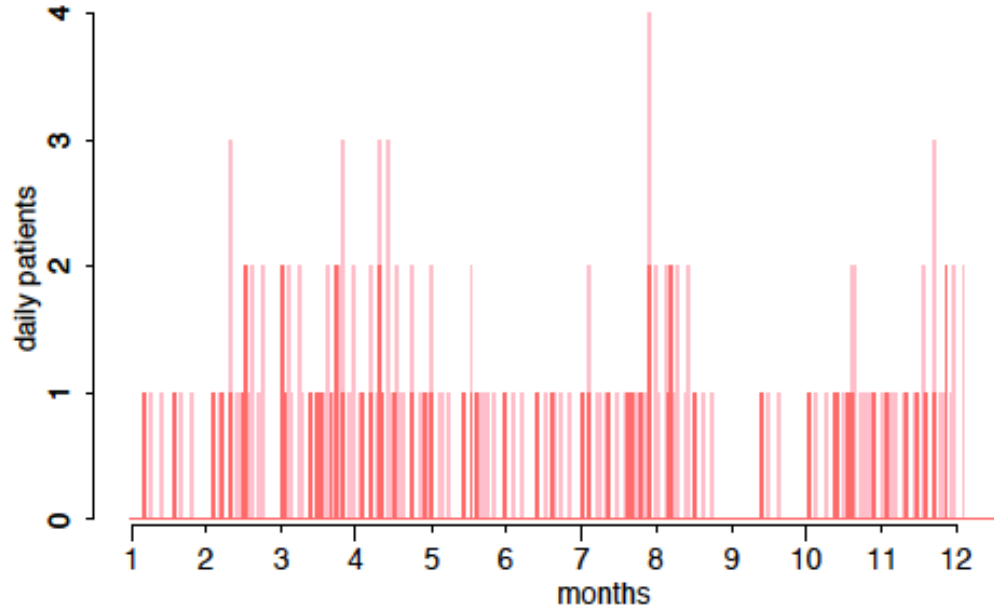
Some vials will be discarded when half-used, but overall many more vials would be used with IM

Key Questions for Gavi & countries

1. What PEP regimen should be used?

- **ID is always a better choice – treats more patients, fewer vials & fewer visits, more resilient against stockouts/ surges**
- ID difficult in practice if patients pay for PEP (current practice in most Gavi-eligible countries)
- ID requires health worker training (many practitioners not aware of route) & insulin needles
- If regimens are Off-label adoption will remain difficult

Intermuscular (IM) - 1 vial per injection

Intradermal (ID) - 0.1 ml per injection

vials can be shared if used within 6-8 hours (same day)

Key Questions for Gavi & countries

1. What PEP regimen should be used?
2. How should PEP be supplied
3. How many doses will be needed?
   - Bite patient presentations increase with:
     - Dog: human ratio, i.e. more dogs more bites
     - Free, accessible PEP i.e. health systems, policies, practices
     - Awareness/ sensitization about rabies risk & PEP need
     - Geographies e.g. urban vs rural, higher densities etc
   - PEP use depends on practitioner constraints:
     - PEP availability
     - Bite patient demand (cost to patients)
     - Epidemiological awareness/ judgement

To what extent should PEP be 'decentralized'?

Bite patient data from Tanzania

Dog population variability:
- Urban/ rural
- Religion
- Livelihood

Human: dog ratio: ~20 range: 5 to 100+
Bite patient incidence - 5-90/ 100,0000/ yr
190 facilities supplying vaccine ~$100/ course
~350,000 population/ facility
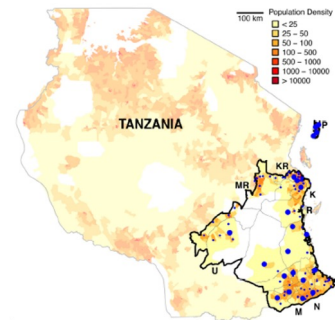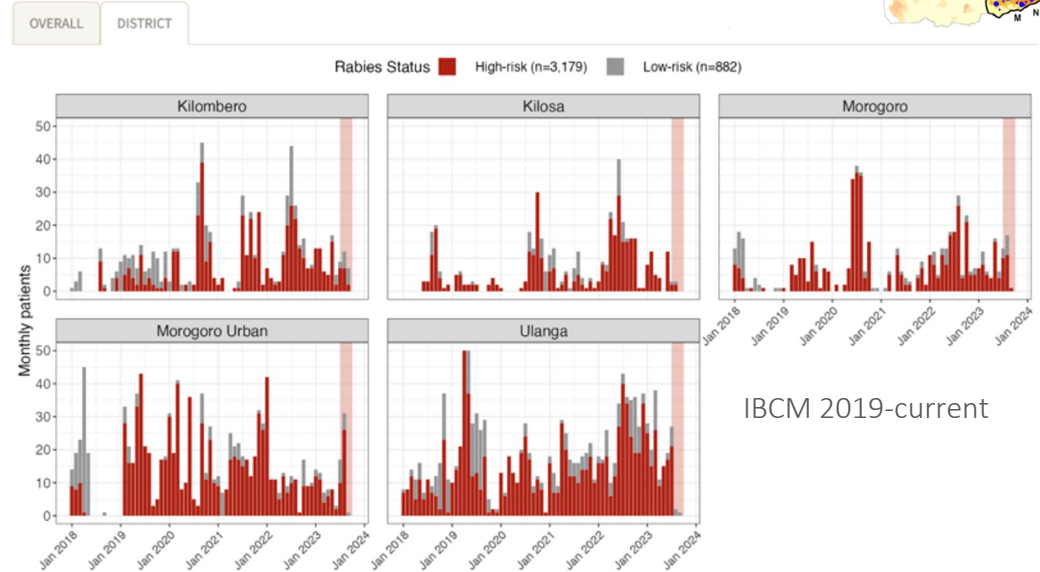
IBCM 2019-current
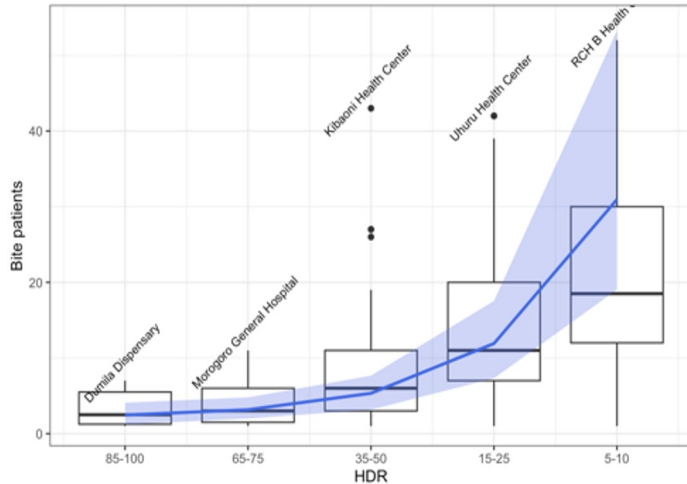
- Most patients (>70%) are high-risk due to high PEP costs & low availability, few 'worried well' (<30% patients)
- Many (>30%) travel outside district (to regional hospitals) because of stockouts
- Expect increased patients with free PEP (seen 2010-2015 during BMGF project)

Bite patient data from Madagascar

Dog population variability:
- Urban/ rural
- Religion
- Livelihood

Human: dog ratio: 17-30
Bite patient incidence - 85/ 100,0000/ year
31 Health facilities supplying free vaccine
~1 million population/ facility
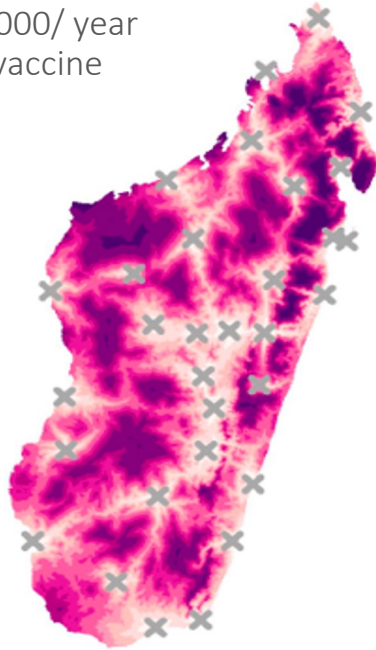
IBCM 2016-2017

- Higher bite incidence due to 'worried well' (x5)
- More patients low risk for rabies due to free PEP in stock
- Expect patients to increase with more (decentralized) facilities
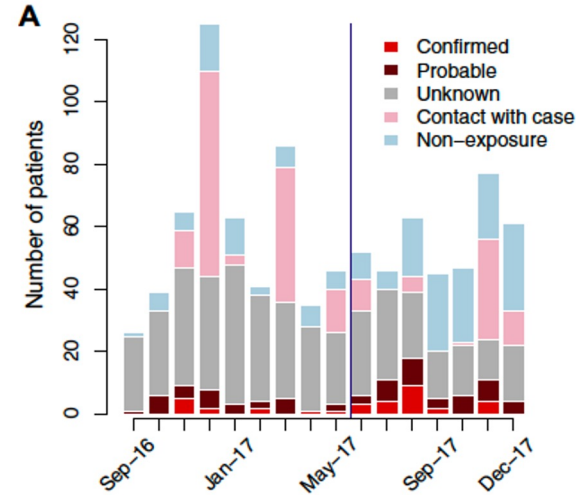
Rajeev *et al.* 2019 Vaccine; PLoS NTDs 2021

To what extent should PEP be 'decentralized'?

- Consider change in current practice in Tanzania (67 million population) to decentralize PEP
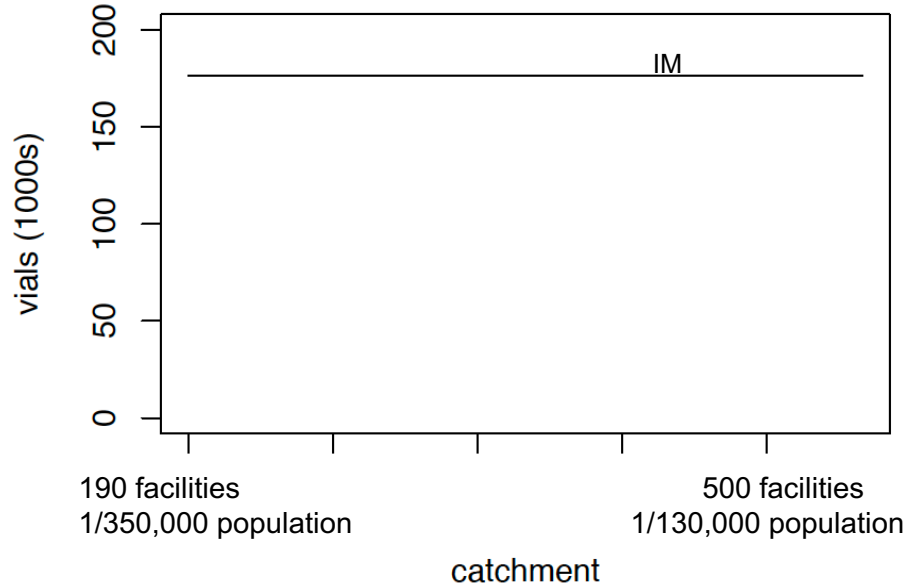
Consider impacts in Madagascar (29 million population) with 31 facilities (~1 million population catchment)
Relatively little impact on vial use → much improved patient access
Main challenge is supply chain (but EPI reaches much further than examples here)
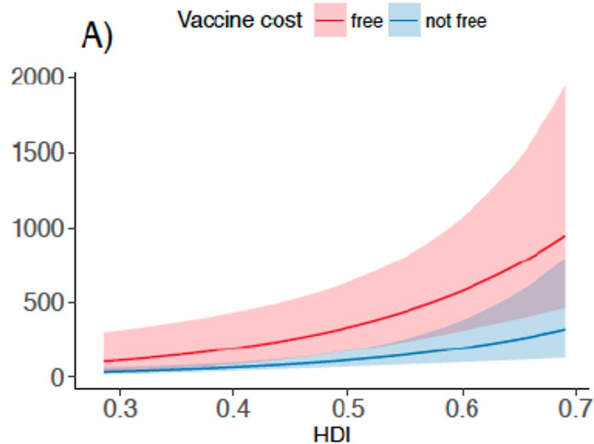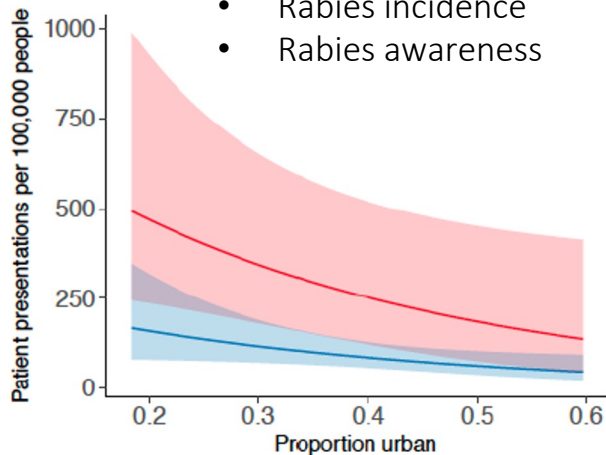
Key Questions for Gavi & countries

1. What PEP regimen should be used?
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3. How many doses will be needed?

Key determinants:
- Human: dog ratio
- Accessibility of PEP
- Rabies incidence
- Rabies awareness

Highly variable dog populations:

Setting	Human: dog ratio
Rural christian	4-10
Rural muslim	25-50
Urban christian	10-30
Urban muslim	>70

Variation by urbanization & religion:

| Country	% urban	% christ/other
Burkina Faso	30	35
Cameroon	54	75
Ethiopia	19	63
Ghana	54	71
Cote d'Ivoire	54	50
Kenya	26	86
Lao PDR	39	95
Madagascar	35	85
Malawi	16	80
Mali	40	5
Nigeria	48	50
Pakistan	39	4
Senegal	44	3
Tanzania	32	63
Zambia	41	95

Vaccine cost: free / not free

Tanzania – projected bite patients
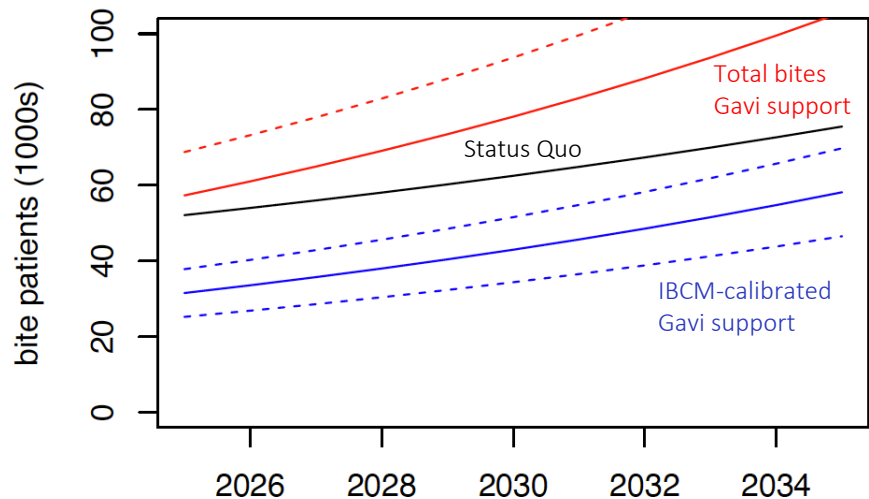
UNCERTAINTIES

- Data:
  - Total bites (IDSR) ~20-80% higher than calibrated IBCM records.
    - Includes many facilities without PEP.
    - Double counts patients at local clinics (no PEP) that travel to hospitals (for PEP)
    - Yearly variation +/- 20%

- Model:
  - Uncertain how PEP seeking & compliance will change with free in-stock PEP
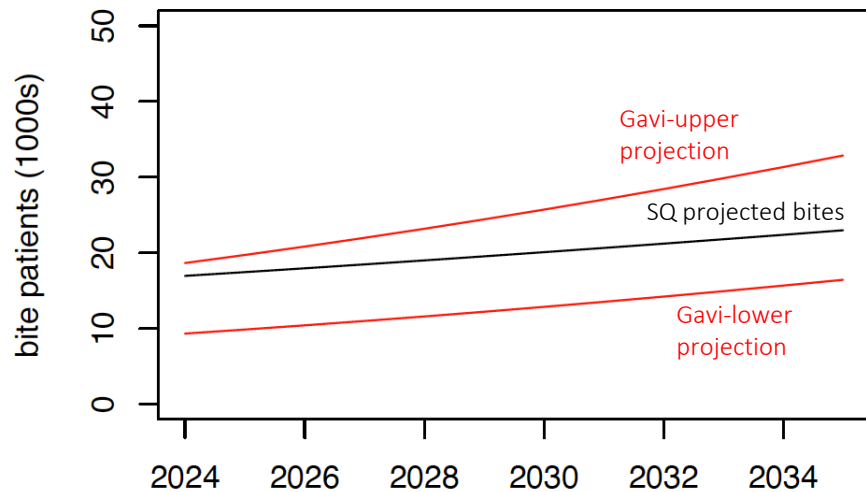 - Population growth expected

Tanzania – projected vaccine vials
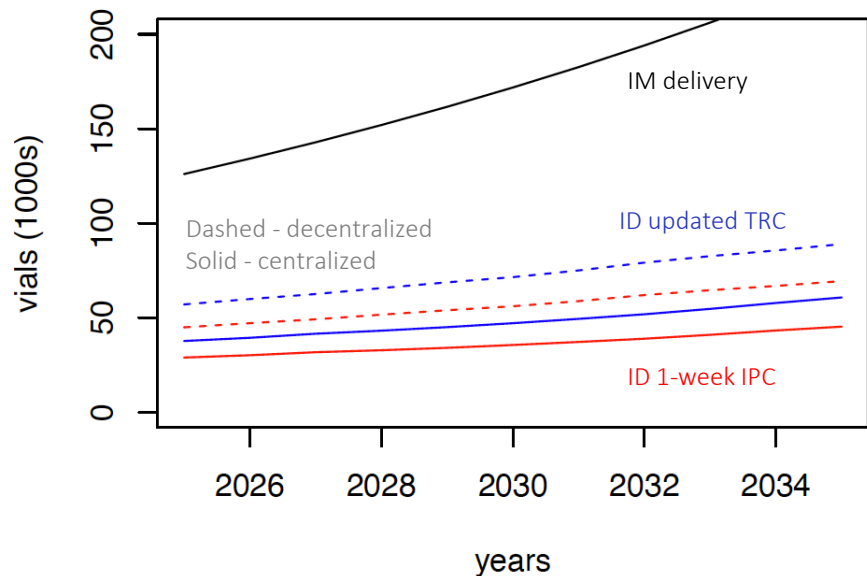
Scenarios

- IM regimen (updated Essen 4 visits)
- ID updated TRC (4 visits), 1 mL vials
- ID IPC (3 visits), 1 mL vials

- Centralized to district hospitals
- Decentralized at 4 facilities/ district

- qualitatively similar results for 0.5 ml vials
- partial compliance uses ~25% less vials
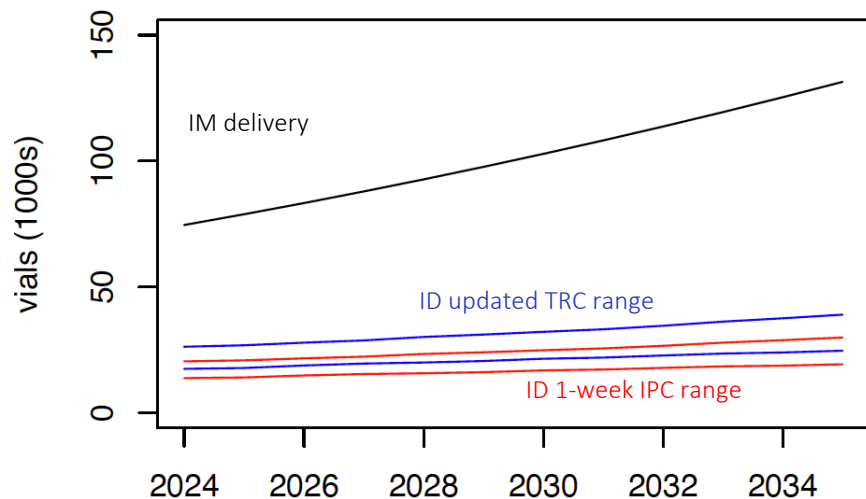- projections calibrated from IBCM

Zambia – projected bite patients

UNCERTAINTIES

- Data:
  - Investigate how DHIS2 bites relate to patients that obtain PEP

- Model:
  - Unclear how PEP seeking & compliance will change with free and in-stock PEP

Zambia – projected vaccine vials

Scenarios

- IM regimen (updated Essen 4 visits)
- ID updated TRC (4 visits), 1 mL vials
- ID IPC (3 visits), 1 mL vials

Assume PEP remains centralized (changes expected if most PEP currently from private providers)

Assume full PEP compliance

Requires calibration (with IBCM if possible)

Key conclusions for PEP provisioning

- ID regimens ALWAYS use less vials even in low throughput clinics
  - ID difficult to administer if PEP not free to patients (major reason for lack of use)
  - Requires training & insulin needles
  - Off-label regimens are a barrier to uptake
  - ID use can act as buffer to fluctuations in patient numbers
  - Low compliance is a negligible risk compared to not starting PEP
- Benefits of decentralizing vaccines (at least to district-level) outweigh costs
  - Vaccine use could increase up to 80% (difference likely smaller)
  - Should improve compliance while still using much less vaccine that IM
  - Monthly restocking (EPI supply chain) to threshold levels should allow for surge capacity to outbreaks

Key conclusions for PEP forecasting

- PEP needs expected to vary considerably between (and within) countries according to:
    - Current provisioning
        - Free vs charged
        - Access (decentralized, private v government providers etc)
        - Stockout frequency & duration
    - Human: dog ratio (dog population variability)
    - Rabies awareness & sensitization through Gavi support
    - Rabies incidence

- Bite patient data important for calibrating forecasts
    - Check facility-level subnational data / IBCM to investigate risk
    - Review national data for completeness and variation

- Recalibrate forecasts with data from rollout

- PEP is an essential lifesaving intervention, but demand can become uncoupled to risk
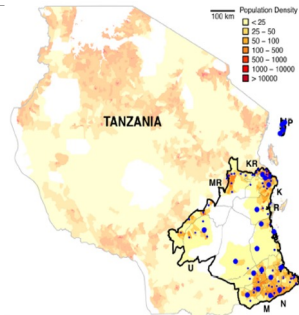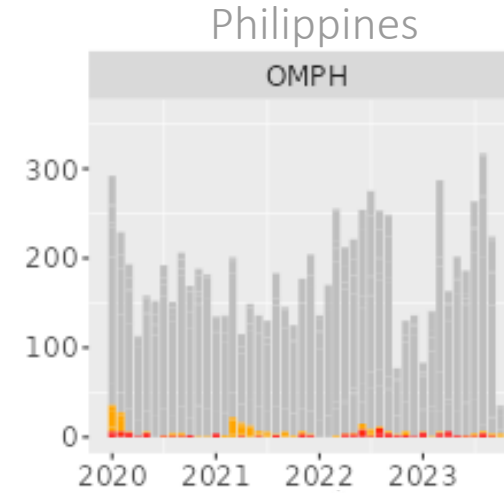   - Dog vaccination is only intervention that reduces risk of exposure

PEP demand may uncouple from rabies incidence

Tanzania — Ulanga

Philippines — OMPH
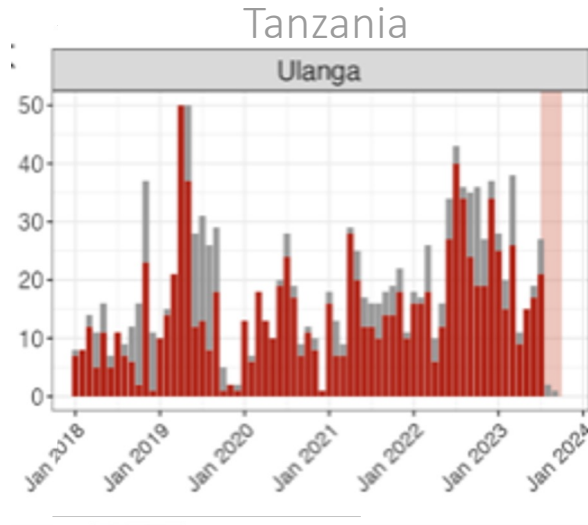
Similar rabies incidence

Ratio of bite patients
low risk (healthy) v high risk (likely rabid)

1:3 v 100:3

- Only dog vaccination can reduce exposure incidence
- IBCM may reduce unnecessary PEP use & improve PEP access for those at risk
But IBCM implementation challenging & needs tailoring to local contexts

Acknowledgements

Many collaborators!

Ellie Rees

Regimens are frustratingly complex!

| Regimen	Clinic visits	Schedule (day)	Injections per visit	Vials	Volume (mL)**	Route	Approval
Essen 5-dose	5	0,3,7,14,28	1,1,1,1,1	5	5(2.5*)	IM	WHO 1992-
Essen 4-dose	4	0,3 7,14	1,1,1,1	4	4(2*)	IM	ACIP 2009-
Zagreb	3	0,7,21	2,1,1	4	4(2*)	IM	WHO 1992-
8-site	4	0,7,28,90	8,4,1,1	4(5*)	1.4-1.7	ID	WHO 2005-
TRC ID	5	0,3,7,28,90	2,2,2,1,1	5	0.8	ID	WHO 2005-
Updated TRC ID	4	0,3,7,28	2,2,2,2	4	0.8	ID	WHO 2005-
1 week ID	3	0,3,7	4,4,4	3	1.2-1.5	ID	To investigate
1 week ID updated	3	0,3,7	2,2,2	3	0.6	ID	To investigate
1 week IM	3	0,3,7	1,1,1	3	3	IM	To investigate
2 visit IM	2	0,7	2,1	3	3	IM	To investigate

Regimens no longer considered

Default regimens:
IM: Zagreb – fewest patient visits & most doses received if compliance poor
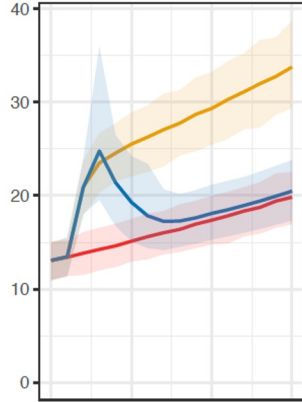ID: Updated TRC

New regimens to consider

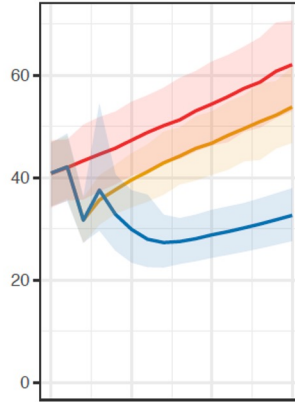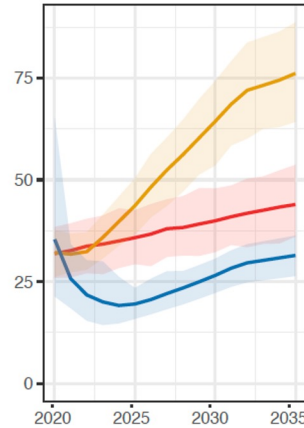# Examples of country-specific model projections
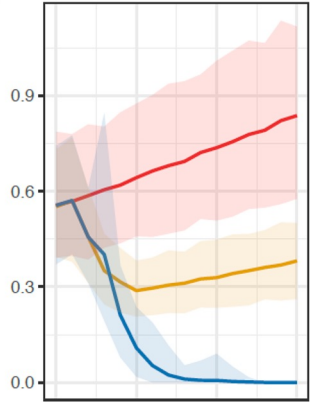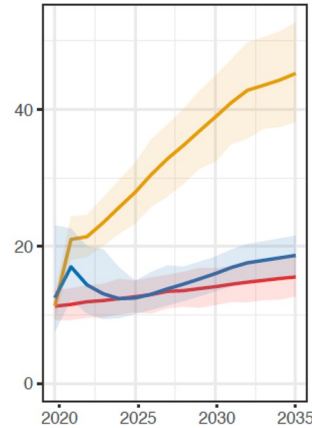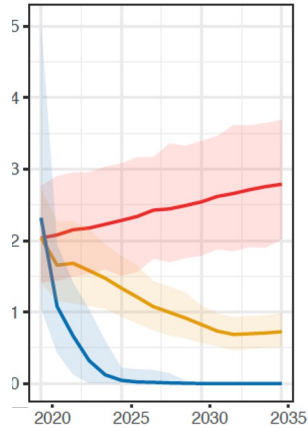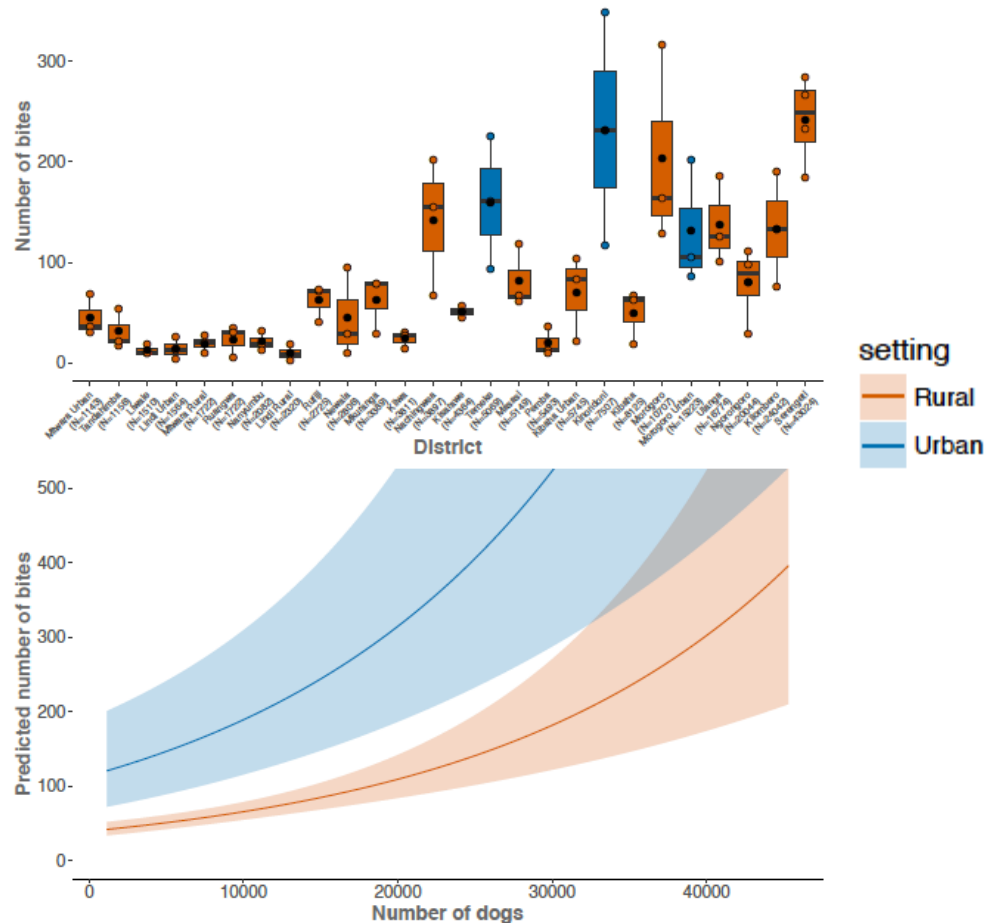

- Uncertainties with introduction of sensitization from Gavi-rollout & MDV
- Uncertainties PEP provisioning from devolution, private providers, required health system strengthening

Within country dog bite incidence depends on dog population

Across countries, bite incidence (patients at clinics) depends on HDI and vaccine provision (free/ charge to patient)