Vaccine Efficacy Evidence Generation in Outbreaks

Rio, 26th March 2025

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Evidence Generation

1. **<u>Vaccine Efficacy</u>** (= stat. significant evidence on **PRESENCE** of vaccine efficacy):
   - … via RCTs = conventional controlled vaccine efficacy trials
   - … via protective immune response: CoP
   - … via RWE (='Real World Effectiveness')

2. **<u>Vaccine Safety</u>** (= stat. significant evidence on **ABSENCE** of safety-related risks):
   - … via safety surveillance / RWE post licensure (Maurice Hilleman: "*3.000.000 vaccinated …*")

3. **<u>Vaccine-induced immune response</u>** (humoral, cellular, …) critical as surrogate parameter for both, efficacy and safety

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Evidence generation that should be prioritised in an outbreak …

… via clinical trials (**in particular in small, short-lived outbreaks**):

In an outbreak: → evidence generation focussed on CASES

- Vaccine efficacy (if outbreak is large / long enough)
- Review case definitions
- Evaluate diagnostic tests
- Protective immune response: Correlate of Protection (CoP), survivor studies, etc.

Outside outbreaks: → evidence on EVERTHING ELSE

- Dose / formulation selection
- Characterising vaccine-induced immune response incl. CMI, …
- Immunogenicity / immunobridging in sub- / special populations (chronic diseases, children, elderly, …)
- (Vaccine co-administration)
- Reactogenicity

Safety information unlikely from (small) clinical trials → obtained from surveillance during vaccine use (+RWE)

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Outbreak Category	Characteristics	Outbreak Duration	Examples	VE Evidence Generation Approach	VE Context	Trial concept	RWE
Very large epidemics / pandemics	Significant proportion of the population infected → incidence rates can be calculated / are stable over time	> 1 year	- COVID-19 pandemic 2019-2023 - H1N1/09 'swine flu' pandemic 2009-2010 - Dengue	**Prospective randomised clinical trial (individual randomisation)**	PrEP	Vaccinate → 'look for cases'	Various approaches. RWE is feasible and relevant for confirmative evidence
Medium sized regional epidemics	Absolute number of cases seemingly high (thousands / tens of thousand) – but population at risk ('denominator') too large or scattered to calculate stable incidence / attack rates	Months to 1-2 years	- Zaïre-Ebolavirus disease outbreak in West Africa 2013-16	**Prospective immediate versus delayed ring vaccination trial (cluster randomisation)**	PEP (PrEP)	'look for cases' → vaccinate	Test-negative case-control studies, other?
(Very) small local outbreaks	Handful / few dozens or hundreds of cases, regionally confined	Days / weeks / few months	- Marburg virus disease - Sudan-Ebolavirus disease - Nipah virus disease	**Challenging** **Single armed time-to-event trial?** **Other?**	PEP Mixed? (contacts and HCWs)	Vaccinate all immediately and infer evidence from integrated analyses?	Not feasible?

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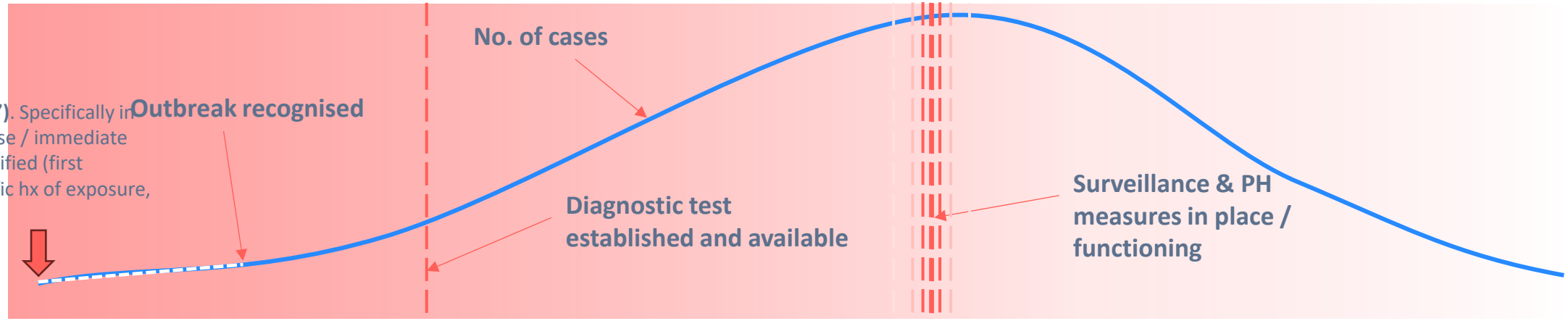
Efficacy Evidence Generation: Stages of an Outbreak …



Index case ('patient zero'). Specifically in MVD outbreaks, index case / immediate cluster will likely be identified (first severely ill patient, specific hx of exposure, HCW, …)

Stage 1
('early')
UNKNOWN/UNCONTROLLED

Causative pathogen unknown. Outbreak recognised (e.g. cluster of cases with severe haemorrhagic fever). No diagnostic in place locally.

Outbreak uncontrolled. There is a delay in reporting, awareness / surveillance not yet functioning. HCWs workforce critical AND at high risk…

Stage 2
('incremental')
KNOWN/UNCONTROLLED

Causative pathogen known. RT-PCR diagnostic in place. Surveillance not yet fully functioning.

Outbreak uncontrolled: Containment interventions not yet in place / effective. Secondary cases are confirmed in hospital retrospectively, additional cases occur among identified and isolated contacts – while new incident cases in the community are confirmed prospectively.

Stage 3
('winding down / ending')
KNOWN/CONTROLLED

Causative pathogen know. RT-PCR diagnostic in place. Surveillance fully functioning.

Outbreak controlled. Containment interventions in place and effective. Cases and contacts identified / isolated. No further new incident cases occur in the community. All additional cases exclusively occur among previously identified and isolated contacts / HCWs.

Outbreak (Epidemic) type	Scenario	Outbreak size (total n)	Characteristics	Feasibility of conventional VE trials (individually RCT)	Feasibility of IvD ring vaccination trial concepts	Feasibility of unconventional trials (e.g. single arm trial in HCWs)	RWE
# 1	**Stage 1 only**	Handful (e.g. 1-5 cases total)	Outbreak over by the time it is recognised [e.g.: MVD, Nipah]	Not feasible	Not feasible	Not feasible	Not feasible
# 2	**Stage 1 → Stage 3**	Dozens (not much more than 100)	Pathogen identification leads to: - immediate implementation of surveillance and control measures - Further cases occurring exclusively among previously identified contacts [e.g. MVD, Nipah]	Not feasible	Not feasible	Feasible	Not feasible
# 3a	**Stage 1, 2, 3 (Stage 2 small)**	Hundreds	Delay between pathogen identification and outbreak fully controlled (= full coverage of effective surveillance and outbreak containment measures in place) – yet: stage 2 rather short [e.g. some Sudan-Ebola outbreaks]	Not feasible	Questionable (depends how quick trial procedures and vaccine are in place)	Feasible	Not feasible
# 3b	**Stage 1, 2, 3 (Stage 2 very large)**	Thousands, ten thousands (less than 100,000)	See #3b – however, increased outbreak dynamics and control measures less effective: prolonged staged 2 [Zaire-Ebola outbreak in West Africa 2014-2015]	Questionable (depends how quick trial procedures and vaccine are in place)	Feasible	Feasible	Feasible?
Pandemics / very large & prolonged epidemics			Continuous transmission for >1 year, incidence rates in the general population can be calculated ['swine flu', COVID-19, continental Dengue, Chikungunya epidemics]	Feasible	(Feasible)	Feasible	Feasible

Marburg Disease Outbreaks

- First described in 1967
- Total no. of cases: 574

[https://www.cdc.gov/marburg/outbreaks/index.html]

No.	Country	Year	No. of cases (deaths)	CFR	Outbreak type	Likelihood of contributing evidence within any (individual or cluster) RCT#	Comments
1	Tanzania	Dec 2024 - Jan 2025	10 (10)	100%	2	0%	8/10 suspected cases. Two districts Biharamulo and Muleba – primary source of infection unclear
2	Rwanda (7/30 districts)	Sep - Nov 2024	66 (15)	24%	2	0%	Primary case / source: Mineworker exposed to bats. Cases accruing mainly in contacts incl. HCWs in Kigali area.
3	Tanzania	Mar – May 2023	8 (5)	63%	2	0%	Kagera region in the Northwest
4	Equatorial Guinea	Feb – May 2023	17 (12)	75%	2	0%	4 survivors and 1 unknown outcome among the 17 confirmed cases. An additional 23 suspected cases died. Five districts affected.
5	Ghana (Ashanti region)	Jul - Sep 2022	3 (2)	67%	1	0%	Within family
6	Guinea (Gueckedou)	2021	1 (1)	100%	1	0%	
7	Uganda (Kween)	2017	4 (3)	75%	1	0%	Within family
8	Uganda (Kampala)	2014	1 (1)	100%	1	0%	8/197 contacts developed symptoms but were tested negative
9	Uganda (Kabale)	2012	15 (4)	27%	1	0%	
10	Netherlands (ex Uganda)	2008	1 (1)	100%	1	0%	40 yo women, visited cave in Maramagambo forest (Ntl. Park). Died 10 days post symptom onset
11	USA (ex Uganda)	2008	1 (0)	0%	1	0%	Visited Maramagambo forest, fully recovered. MARV diagnosed in retrospect
12	Uganda (Kamwenge)	2007	4 (1)	25%	1	0%	
13	Angola (Uige)	2004 - 2005	252 (227)	90%	3a	unlikely??	Origin believed to be in Uige province, starting in October 2004
14	DRC (Durba)	1998-2000	154 (128)	83%	3a	unlikely??	Primarily young male workers in a gold mine
15	Russia (laboratory infection)	1990	1 (1)	100%	1	0%	Laboratory contamination
16	Kenya	1987	1 (1)	100%	1	0%	15 yo Danish boy after visiting Kitum cave in Mount Elgon Ntl. Park
17	Kenya	1980	2 (1)	50%	1	0%	Kitum cave in Mount Elgon Ntl. Park
18	RSA (ex Zimbabwe)	1975	3 (1)	33%	1	0%	A man travelled back home to RSA. Travel companion and HCW infected.
19	Germany (Marburg)	1967	31 (7)	23%	n/a	n/a	Simultaneous outbreaks occurred in laboratory workers handling African green monkeys imported from Uganda

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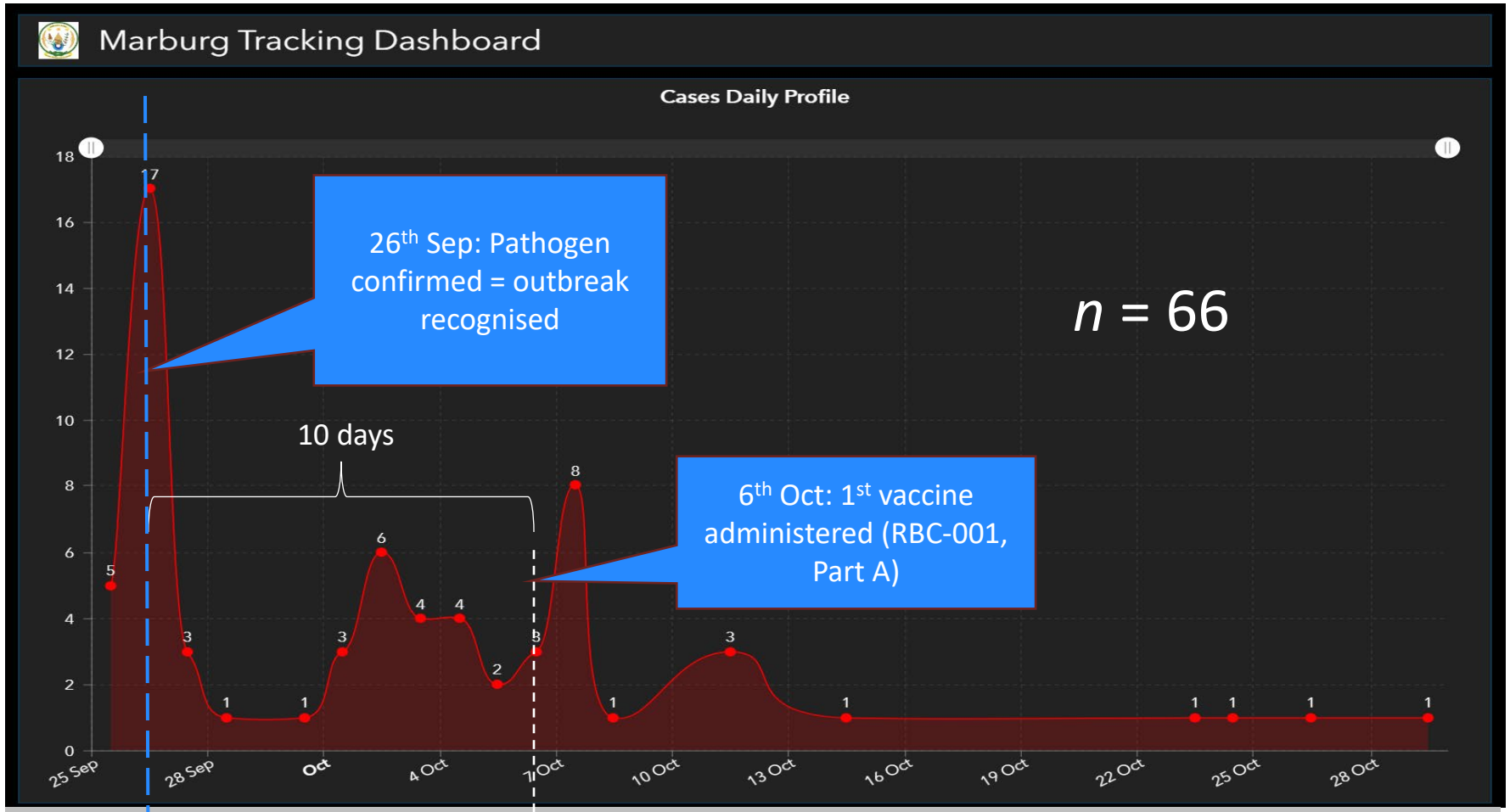
Marburg Disease Outbreak: Rwanda Sep – Dec 2024



Outbreak stage:	**Stage 1**		**Stage 3**
MVD cases:	**22**	**24**	**20**
		Immunization time	

[htpps://rbc.gov.rw/marburg/]

Summary / Conclusions

- Extensive evidence generation in inter-epidemic phases
- In an outbreak: Focus on evidence related to cases – if possible
- Vaccine efficacy:
  - Evidence generation approach tailored for outbreak-type
  - Prepare before an outbreak (science, logistics, align with countries at risk, NRAs, …)
- For pathogens exclusively occurring in small outbreaks (to date): Establish alternative pathways towards licensure
  - Animal rule (US-FDA)
  - Animal challenge / passive transfer
  - CoP / immunobridging
  - … plus post-licensure commitments / RWE generation over time (if possible) …

Outbreaks remain public health emergencies → the affected country's perspective and needs have to be accounted for!

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