Challenges in developing medical countermeasures for public health threats

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Safe & Effective Vaccines …

Public Health Emergency

Ideally, evidence established via clinical trials:

✓ Safety → *absence* of risks (can be assessed anytime)

✓ Efficacy → *presence* of a benefit (can be assessed within outbreaks only)

Before licensure:

- How urgently do we want to make a vaccine available for public health responses?
- How realistic is it to complete an exhaustive and conclusive B/R assessment based on clinical trials only (before licensure)?
- How confident are we in pre-existing / alternative / complementary evidence (vaccine platform, licensed vaccines / same viral family, animal studies etc.)?

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Outbreak Category	Clinical VE Evidence Generation	Outbreak Duration	Characteristics	Examples	VE Context	Trial Concept	RWE
Very LARGE epidemics / pandemics	**Prospective randomised clinical trial (individual randomisation)**	>> 1 year / years	**Prolonged/stable/high incidence** Significant proportion of the population infected → incidence rates can be calculated / are stable over time	- COVID-19 pandemic 2019-2023 - H1N1/09 'swine flu' pandemic 2009-2010 - Dengue	PrEP	Vaccinate → 'look for cases'	Various approaches. RWE is feasible and relevant for confirmative evidence
MEDIUM sized regional epidemics	**Prospective immediate *versus* delayed ring vaccination trial (individual or cluster randomisation)** **→ 'enrichment'**	Months to 1-2 years	**Intermediate time / cases clustered** Absolute number of cases seemingly high (thousands / tens of thousand) – but population at risk ('denominator') too large or cases too scattered to calculate stable incidence / attack rates	- Zaïre-Ebolavirus disease outbreak in West Africa 2013-16	**PEP** (PrEP)	'look for cases' → vaccinate	Test-negative case-control studies, other?
(Very) SMALL, local outbreaks	**Challenging…** **→ Single armed time-to-event (t2e) trial?** **→ Alternative approaches?**	Days / weeks / few months	**Short-lived/no incidence rate** Handful / few dozens or hundreds of cases, regionally confined. Cluster of cases → no population-based incidence rate	- Marburg virus disease - Sudan-Ebolavirus disease - Nipah virus disease **= <1,000 cases in hx …**	PEP, PrEP, Mixed? (contacts and HCWs)	Vaccinate all immediately and infer evidence from *t2e* / integrated analyses?	Not feasible?

Vaccine Efficacy: Aspects to Consider …

Small / short-lived outbreaks with high CFR

1. 'Criticality' of clinical evidence for licensure (or are there alternative pathways?)
2. Probability to conclude from one single (or a series of) outbreak(s) [= reaching statistically significant results] within a reasonable time frame
3. Risks of generating inconclusive results in scientifically unjustified / underpowered trials
4. The affected country's needs and perspective (facing a public health crisis)

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Ad 1. '*Criticality*': Alternative Pathways to Estimate Vaccine Efficacy

Method	1) Animal challenge following p*assive transfer*	2) Animal challenge post *active immunisation*	3) Clinical Immuno-bridging	4) Correlate of Protection (CoP)	5) Other supportive data
	No immune CoP established (yet)			*CoP established*	
Approach	Animal challenge post passive transfer of different concentrations of antibodies isolated from immunised humans to establish a biomarker level that is reasonably likely to predict protection. Proportions of subjects achieving this antibody level in clinical trials then used to estimate protective efficacy. Animal disease model resembles human disease.	Animal challenge post vaccination → immunological biomarker demonstrating clinical protection derived from correlation of immune response levels with protective effect in animals. Vaccine-induced immune responses in clinical trials bridged to animal responses using that biomarker. Animal immune response and disease model resembles human immune response and disease.	Comparing immunogenicity (non-inferiority) of candidate vaccine with established vaccine for which clinical efficacy has been established – using one (or more) biomarkers reasonably likely to predict benefit without protective threshold (same antigen / similar platform technology*)	Immune biomarker threshold indicating clinical protection established allowing the assessment of seroprotection rates, no comparator vaccine necessary	Controlled human infection models (CHIM) → endpoint mostly *infection*, rarely *disease* Sero-epidemiological studies Disease natural history studies
Marburg					

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*) acceptability by regulatory authorities to be explored on a case by case basis (e.g. same antigen, different platform technology)

Ad 2. *Probability*: Marburg Virus Disease History

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

Ad 3. ***Risks***: Inconclusive Evidence, Delays, …

Small / short-lived outbreaks with high CFR

- Vaccine efficacy unlikely to be 100%
  (… and it takes some time to induce a protective immune response!)
  - PreP (HCW at risk?)
  - PEP (contacts of confirmed cases as an 'enrichment' strategy – within 21 days window)
- Outbreaks are small – cases may end up in the vaccine arm (VE of '0-99%' or even 'negative')
- Interim analyses after each outbreak (spending alpha)?
- Cluster- ('rings') *versus* individual randomisation
  - 'Cluster' early in an outbreak are not independent!
- Cases in a VE efficacy trial also receive Tx (Remdesivir, mAbs) → impact on VE endpoints (disease severity)

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Ad 4. The Affected *Country's Perspective*

Small / short-lived outbreaks with high CFR

- Health emergency: Public heath response (→ stop the outbreak)
- HCWs are a critical frontline workforce – in particular in LMICs
- IMP → clinical trial (with a justified objective)
- Early phase of an outbreak *vs.* later phases (if the outbreak continues)

	Early phase (outbreak small / short-lived)	**Late(r) phases** (outbreak continues)
No. of cases	Very few	More …
Conclusive evidence	Very unlikely	Maybe (depends)
Situation in the country	First-line defence	Surveillance, NPIs, …
Vaccine availability	Limited	Extremely limited (→ IRR concept)

- The country's own B/R assessment based on existing evidence (animal studies, clinical trials, …)

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Example MVD Vaccine Development: Integrated E2E Strategy

Vaccine development:

APPROVAL

Preclinical

VE via alternative path ('paraclinical' animal studies)

Phase 1 → Phase 2a → 'Pivotal trial' → RWE

Effectiveness, safety

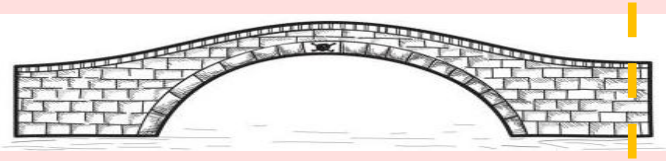
Clinical evidence with a focus on ***immunogenicity, reactogenicity***

Ph1 CTM

Ph2 CTM

Ph2/3 CTM

IRR stockpile



Vaccine stockpile

Evidence generation during outbreaks:

Clin. trial →

Clin. trial →

Clin. trial →

Clin. trial

PH interv.

Complementary clinical evidence with a focus on ***vaccine efficacy***

Conclusions

Small / short-lived outbreaks with high CFR

- B/R assessment for public health threats (with high CFR)
- The ultimate goal?
  - Clinical vaccine efficacy trial "we should at least try" (→ unclear to conclude in the next 2, 5, 10, 20 years)
  - Vaccine available for use in public health emergencies via alternative pathways (→ in the predictable near future)
- In the end, there is no 'right or wrong'
- The perspective of affected countries / countries at risk must be included
- Conventional / routine product development considerations may not be entirely applicable to public heath emergencies

Alternative pathways to accelerate vaccine licensure should be explored to make these vaccines available as quickly as possible …

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