Mechanisms to Enhance Availability of Vaccines Against Epidemics: a Case Study of Ebola

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PROBLEM ARTICULATION

The frequency of outbreaks due to filoviruses, known for causing hemorrhagic fever, is growing:

- Recent outbreaks: DRC (*Ebola – Zaire species / EBOV*, 2022), Uganda (*Ebola – Sudan species / SUDV*, 2022), and Equatorial Guinea & Tanzania (*Marburg / MARV*, 2023)
- Shift from **rural, hard-to-reach areas** and conflict zones to more **urban areas**
- Endemic to Sub-Saharan Africa, but can lead to significant **global health security risks**

Numerous challenges hinder timely availability of vaccines against epidemic-prone pathogens:

- **Limited commercial viability** given small and sporadic demand, leading to a higher barrier to entry and opportunity cost than typical vaccine development and commercialization efforts
- Uncertainty around **viral strain, clinical effectiveness** and **cost-effective post-licensure** use of vaccines
- **Low thermostability** puts pressure on already-strained downstream supply chains

As EBOV is the only filovirus with approved vaccines, an overview of historical outbreaks (**Figure 1**) and phases of development for vaccines (**Figure 2**) are shown below.

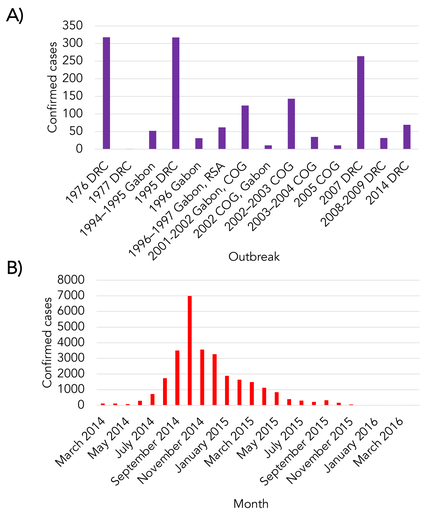

Figure 1: A) Confirmed EBOV cases reported by country and outbreak year from the first recorded outbreak in 1976 until 2014; B) monthly reported cases during the 2014-2016 West Africa Ebola Epidemic, the worst Ebola outbreak in history.

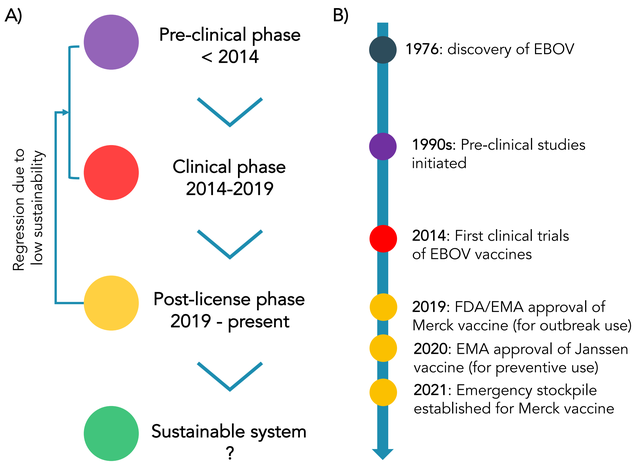

Figure 2: A) Phases in the development and commercialization of EBOV vaccines; B) Select events related to the supply of EBOV vaccines, showing a long delay to licensure by stringent authorities (FDA – U.S. Food & Drug Administration, EMA – European Medicines Agency). Two vaccines have received WHO pre-qualification: Merck – *Ervebo* (for outbreak use), Janssen – *Zabdeno/Mvabea (*for preventive use).

OBJECTIVES

Develop a dynamic hypothesis on protecting populations at-risk of EBOV infections, focusing on availability and uptake of EBOV vaccines

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Identify post-license challenges that jeopardize the sustainability of the EBOV vaccine supply chain

METHODOLOGY

Figure 3: System dynamics approach for developing causal loop diagrams (CLDs) and stock-and-flow diagrams (SFD) based on existing frameworks focused on iterative analysis (e.g., Sterman, 2000; Luna-Reyes & Andersen, 2003; Decouttere et al., 2016).

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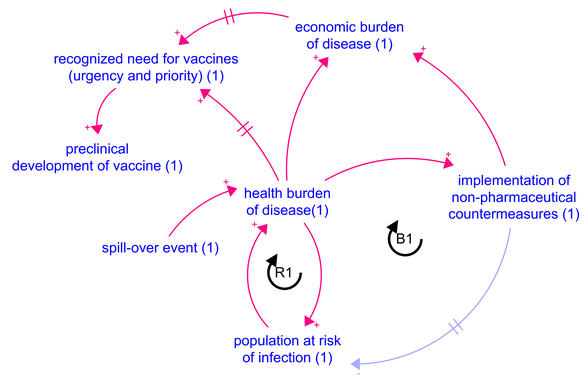
RESULTS: CAUSAL LOOP DIAGRAMS

A)



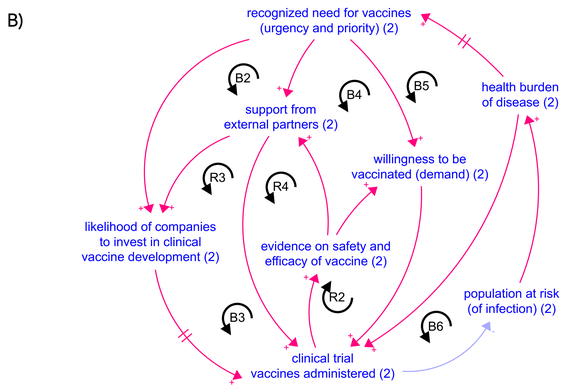
Objective: Design candidate vaccine

General dynamics: Spillover events (animal-to-human transmission) increase the disease burden, leading to rapid growth in the at-risk population (**loop R1**). Non-pharmaceutical control strategies (**loop B1**) are initially the only option to protect population, while shifting priority towards meeting vaccine needs is slow.

Ebola case: During outbreaks, emphasis is on containment strategies (e.g., isolation) and promoting behavioral practices (e.g., safe and dignified burials). Since outbreaks were mostly in rural areas and short-lived, there was limited investment in pre-clinical vaccine development other than for biosecurity reasons.

Criteria for transition: A sufficiently long period of EBOV transmission to further prioritize vaccines and start clinical trials.

B)



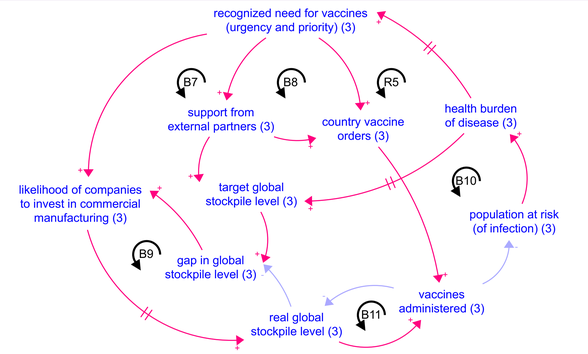
Objective: Conduct clinical trials to demonstrate safety and efficacy

General dynamics: A substantial disease burden galvanizes attention and funds for vaccines, increasing investment in clinical trials that have the potential to protect the at-risk population (**loops B2-B6**). Evidence from clinical trials further increases willingness to be vaccinated (**loop R2**) and support from external partners (**loop R3 & R4**) for bringing the vaccine to market.

Ebola case: Although vaccines were in development for 10+ years, clinical trials only started at the end of 2014 during the West Africa Ebola Epidemic (declared a Public Health Emergency of International Concern by the WHO). As cases waned, further Phase 3 studies could only be done during the 2018-2020 Kivu Ebola Epidemic.

Criteria for transition: Sufficient evidence to submit dossier to regulatory agencies, typically starting with a stringent (mature) authority and WHO pre-qualification.

C)

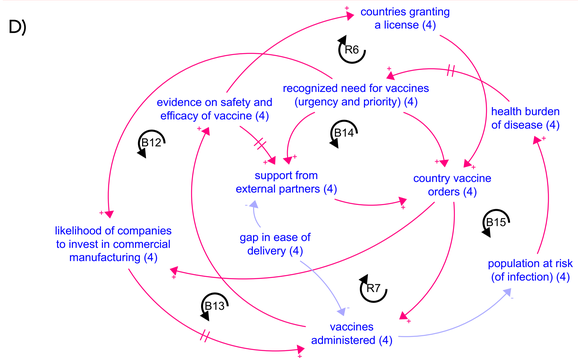


Objective: Meeting country needs during outbreaks

General dynamics: Funding for an emergency stockpile, based on historical burden, provides demand stability for a manufacturer, ensuring continuous replenishment so doses can be rapidly retrieved and administered in case of outbreaks (**loops B7-B11**). If orders exceed the stockpile quantity, a delay in replenishment can lead to a more severe outbreak (**loop R5**).

Ebola case: An emergency stockpile of 500,000 Merck doses was established in 2021, following US$ 178 million in GAVI funding between 2020-2025. Countries requests are made following lab-confirmed EBOV cases, with delivery expected within 7 days.

D)



Objective: Meeting country needs prior to outbreaks

General dynamics: Evidence on the cost-effective use of preventive vaccines in non-outbreak settings drives orders (**loop R6 & R7**). Support from various external partners (e.g., technical WHO SAGE Working Group, GAVI) reinforces orders, increasing doses manufactured and administered, thus protecting the at-risk population before outbreaks occur (**loops B12-B15**).

Ebola case: Guidance on the post-license use of the Janssen vaccine has not been finalized, creating a bottleneck for funding a preventive vaccine program by GAVI and limited incentives for countries to make orders. Studies are ongoing to generate additional evidence.

Criteria for transition: Determine a viable and stable market size to ensure a sustainable vaccine supply chain, otherwise manufacturer(s) may drop out, thus increasing the at-risk population. Consider interaction effects between products, especially their use and demand over time, as they both protect the at-risk population.

Figure 4: Description of dynamics following phases (colors) described in Figure 2: A) pre-clinical phase, B) clinical phase, C) post-license phase, specifically, emergency vaccine stockpile for use during outbreaks (Merck), and D) post-license phase, specifically, preventive vaccine use prior to outbreaks (Janssen)

CONCLUSIONS

- Challenges emerge from diverging priorities (e.g., commercial, humanitarian, public health) and their incentives
- Support from partners (e.g., product development, GAVI funding) has significant impact on aligning supply/demand
- For each CLD, unique sources of delay and loop dominance influence dynamics, pointing to levers for transitioning towards a more sustainable system and lower disease burden

FUTURE WORK

Translate insights into SFDs and policy design to enhance sustainability

- Data collection, parameter estimation, and sensitivity analysis
- Replicate reference modes and validate complex supply-demand dynamics with a broad group of stakeholders
- Quantitative simulation and scenario comparison for key problems in the post-license phase (e.g., vaccination strategies)

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