Thursday, March 20th 2025		
8:30-8:40	Opening Remarks & housekeeping reminders. Gina Antaki (CEPI)	10’
Conclusion - Immune correlates/surrogates and update on regulatory status of chikungunya vaccines		
8:40-8:55	Panel NRAs to discuss feasibility of licensing vaccine with current data (cont) • HSA/Singapore, Anuradha Poonepalli (virtual)	15’
Post approval requirements		
Purpose: As developers have requested market authorization of their products based on safety and immunogenicity (correlates of protection) data, NRAs will be requesting post-marketing requirements and/or commitments referring to studies and clinical trials that sponsors conduct after approval to gather additional information about a product's safety, efficacy, or optimal use. The use of RWE and RWD will be discussed as well as its implications in the design and logistics.		
8:55-9:20	The role of real-world evidence for regulatory and public health decision-making. Steve Black	25’
9:20-10:20	Panel discussion on the Requirements for the use of RWD and RWE in vaccine post approval effectiveness/efficacy studies, • FDA, David Kaslow (virtual) • EMA, Marco Cavaleri • ANVISA, Brenda Valente • CDSCO-India, Rubina Bose	60’
10:20-10:40	Q&A from the Audience	20’
10:40-11:00	Coffee break	20’
11:00-11:45	**Data requirements for a RWE study: do countries have the appropriate infrastructure for it?** • Brazil (Jadher Percio, PNI/MOH) • Colombia (Fernando de la Hoz, UNC) • Thailand (Wichan Bhunyakitikorn, DDC/MOH) • AVAREF, Kwasi Nyarko (virtual)	45’
Outbreak protocols		
Purpose: Large outbreaks of Chikungunya may present an opportunity to generate evidence on efficacy / effectiveness of CHIKV vaccines. However, such outbreaks are unpredictable and may not provide sufficient time for trial set-up & implementation. This emphasizes the importance of advanced planning for an outbreak clinical trial. The session would focus on the development and feasibility for conducting outbreak studies and the various aspects involved in planning for such a study (e.g. pre-approved clinical trial protocols and other clinical trial documents, infrastructure and logistics)		
11:45-11:55	Concept of a library of pre-approved clinical trial protocols* for evaluation of vaccine during various outbreak scenarios. Nina Wressnigg (CEPI)	10’
11:55-12:10	Operational and other planning for conducting clinical trial of vaccines during an outbreak. Libia Hernandez (IVI)	15’
12:10-12:15	PREpare using Simulated Trial Optimisation (PRESTO) research project. Christophe Fraser (U of Oxford) (pre-recorded)	5’
12:15-12:30	Q&A from the Audience	15’

12:30-13:15	Panel discussion on planning for outbreak trials and pre-approved clinical trial protocols for vaccines • Paraguay, Pastor Perez Estigarribia (UNA) • EMA, Marco Cavaleri • Rwanda FDA, Alphonse Ndayambaje • Brazil, Maria Fernanda Thees (ANVISA) • Brazil, Jadher Precio (PNI/MOH)	45’
13:15-14:15	**Lunch**	60’
Use of chikungunya vaccines		
Purpose: A session will be held with potential users of the vaccine, representatives from National Immunization Programs, and advisors to NITAGs and RITAGs, where it is expected that they will reflect on the properties of the vaccines, risk-benefit and country and regional priorities.		
14:15-15:15	Discussions on the probability of recommending use of chikungunya vaccines with data available • Brazil, Jadher Precio (PNI/MOH) • Colombia, Fernando de la Hoz (UNC) • Kenya, George Warimwe (KWTRP and UofOx) • Thailand, Wichan Bhunyakitikorn, (DDC/MOH)	60’
Recommendations and conclusion (30 minutes)		
15:15-15:30	Recommendations and conclusion. Danielle Craig (CEPI)	15’
15:30	Close and final housekeeping reminders for in-person attendees, Gina Antaki (CEPI)	5’

CHIKUNGUNYA
Phase IV

São Paulo, Brazil March 2025

CEPI

ANVISA
Agência Nacional de Vigilância Sanitária

Conclusion - Immune correlates/surrogates and update on regulatory status of chikungunya vaccines

CHIKUNGUNYA WORKSHOP

MARCH 19-20, 2025

HSA
Health Sciences Authority

Outline

- Overview of Health Sciences Authority evaluation pathways
- Approval of vaccines based on immunogenicity endpoints

HSA
Health Sciences Authority

Our Functions & Roles

The **Health Sciences Authority (HSA)** was established as a statutory board under the Ministry of Health on 1 April 2001

Health Products Regulation Group (HPRG)

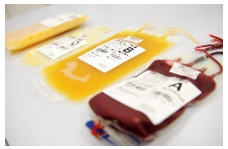
- *Clinical Trials Regulation*
- *Product Evaluation*
- *Quality Systems Audit*
- *Licensing*
- *Vigilance, Surveillance & Enforcement*


Applied Sciences Group (ASG)

- *Analytical Science*
- *Forensic Science*
- *Forensic Medicine*


Blood Services Group (BSG)

- *Blood Banking & Transfusion Services*
- *Cell Processing Lab*
- *Hemovigilance*




Evaluation Pathways (Medicines)

Different routes for medicines registration to facilitate applications

- Full Evaluation: First-in-the world evaluation
- Abridged/Verification: Risk-based approach leveraging evaluation by comparable regulatory agencies

	Prior Approval Status	Assessment	Total TAT
Full Evaluation	No prior approval by any drug regulatory agency	Full quality, non-clinical, & clinical	270 working days
Abridged Evaluation	Approved by one drug regulatory agency	Quality, clinical & abridged early phase clinical studies and non-clinical	180 working days
Verification Evaluation	Approved by two reference agencies*	Reference agency assessment report	60 working days

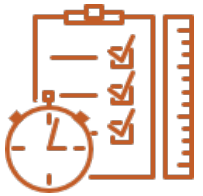
*Reference agencies: Australia TGA, EU EMA, Health Canada, UK MHRA, US FDA, Swissmedic

HSA Health Sciences Authority

Immunogenicity endpoints as efficacy surrogates-key considerations

- Acceptable if they are established as correlate of protection
- For new diseases or situations where the immune markers are not established as correlates of protection, data is required to demonstrate correlation to efficacy. This could be based on,
  - Non-clinical Data based on validated animal models with similar immune response mechanism and predictive value for clinical outcomes
    - Challenge studies demonstrating protection
    - Correlation with immune responses
    - Reproducible results across studies
  - Clinical correlation based on
    - Sero-epidemiology data
    - Clinical immunogenicity
    - Real world effectiveness data
- Threshold for acceptance also varies depending on the scenario
  - Unmet medical need/ Emergency scenario vs non-emergency

Expedited Access to Vaccines



- The legislative framework through PSAR is in place which will allow the government to respond to emergency quickly and expedite access to vaccines and therapeutics for use during a pandemic
- Whole of government coordination and concerted effort to enable expedited access facilitated by accelerated regulatory review of vaccines and therapeutics for timely access while ensuring standards for quality, safety and efficacy
- Expedite regulatory reviews through increased info sharing and interactions with stakeholders, and exercise regulatory agility by allowing rolling submissions and facilitating innovative clinical study designs, which allow efficient evaluation of multiple vaccines concurrently within a single master protocol

HSA Health Sciences Authority

Post approval requirements

Purpose: As developers have requested market authorization of their products based on safety and immunogenicity (correlates of protection) data, NRAs will be requesting post-marketing requirements and/or commitments referring to studies and clinical trials that sponsors conduct after approval to gather additional information about a product's safety, efficacy, or optimal use. The use of RWE and RWD will be discussed as well as its implications in the design and logistics.

Use of RWE for regulatory and public health decision-making for newly introduced vaccines

Steven Black MD

CEPI funded SPEAC and BRAVE Projects

Co-Director, Global Vaccine Data Network

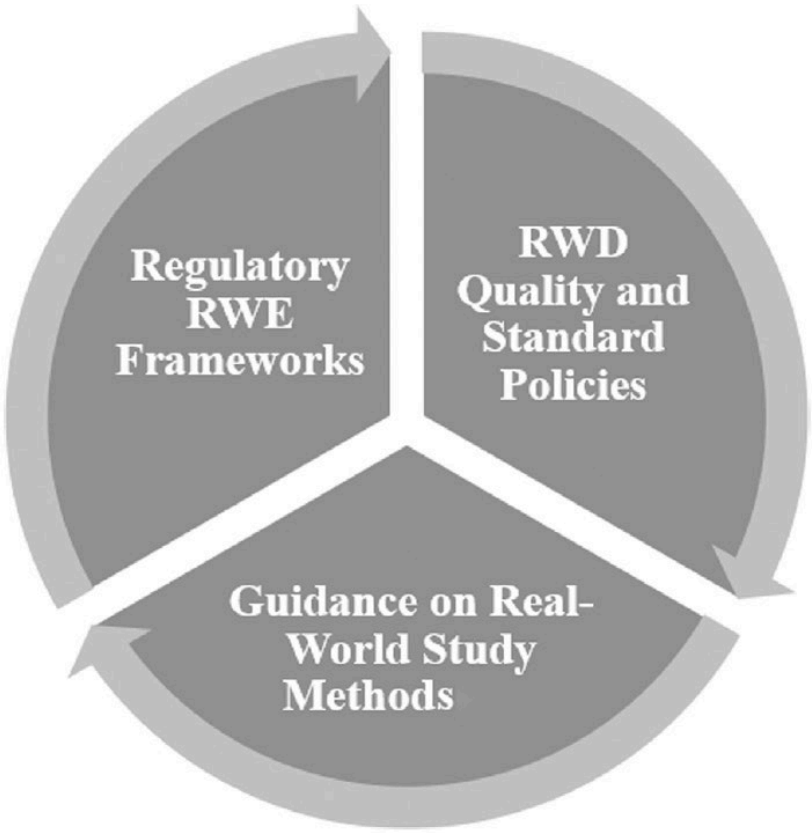
So, what is Real World Evidence??

Real World Data vs Real World Evidence
Turning Data into Evidence is Multi Step Process

Not all Real World Data is useful as Real World Evidence

Data to Evidence

- To be useful as Real World Evidence health care source data **must accurately provide insight into the question you are trying to answer.** To do so it must
  - Be assessed for completeness
  - Be assessed for data quality
    - Is data coded into a standard format (eg ICD-10)
    - Is the coding consistent? (May require EHR or chart review to assess)
    - Can cases of an event (whether vaccine preventable disease or safety outcome) be accessed through an EHR or paper record for further information such as Xray or other lab data?
  - Be accessible – Can data be exported for analysis?
    - Individual deidentified data?
    - OR must all data remain local (for rare events you would like to merge data)



Burns, Leah, et al. "Real-world evidence for regulatory decision-making: guidance from around the world." *Clinical Therapeutics* 44.3 (2022): 420-437.

FDA Perspective

GUIDANCE DOCUMENT

Draft: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Draft Guidance for Industry and Food and Drug Administration Staff

DECEMBER 2023

- FDA evaluates real-world data (RWD) to determine whether they are of sufficient quality for generating real-world evidence (RWE) that can be used in FDA regulatory decision-making
- In general, FDA considers the use of RWD to be fit-for-purpose to support generation of clinical evidence for regulatory decision-making for medical devices when we conclude that the RWD used to generate the RWE are relevant to and **reliable for informing or supporting a particular regulatory decision.**
- Types of RWD that can be sourced include registries, EHRs, claims data, patient generated data, device generated data, public health disease surveillance data.

https://www.fda.gov/media/174819/download

EMA Perspective

- EMA is working with ECDC on the Vaccine Monitoring Platform, for effectiveness and safety assessment using RWE.
- The VMP, established in 2022, enables EMA and ECDC to coordinate and oversee EU-funded, independent **post-authorisation studies** on vaccine use, safety, and effectiveness:
  - **Data gaps** for authorised vaccines
  - Diseases for which post-authorisation monitoring is a priority due to change in **vaccine composition** (e.g. flu and COVID-19)
  - Developing or re-purposing vaccines to support their use during a **public health emergency**
  - **Preparedness** for the evaluation of future vaccines (e.g. burden of a disease)
  - **Post-authorisation monitoring** of vaccines to inform their benefit / risk profile
- Much of the focus to date has been on COVID-19 vaccines, but work has begun on HPV and Mpox. Preliminary data being collected for RSV.

Global perspective

GLOBAL PERSPECTIVE

Regulatory Body	Guidance Documents
National Medical Products Administration (China)	Guideline on using RWE to support drug research & development and evaluation[33] (2020) and draft guideline for RWD used to generate RWE[51] (2020)
Taiwan Food and Drug Administration	Basic considerations for RWE supporting drug development[34] (2020)
Pharmaceuticals and Medical Devices Agency (Japan)	Guideline on pharmaco-epidemiology study for drug safety assessment based on medical information database[52] (2014), basic principles for utilization of medical information databases in post-marketing pharmacovigilance[52] (2017), and points to consider for ensuring reliability when registry data are used for approval applications[37] (2021)
FDA (United States)	Best practices for conducting and reporting pharmaco-epidemiological safety studies using EHR data[6] (2013), guidance for industry use of EHR data in clinical investigations[53] (2017), FDA RWE framework[10] (2018), and RWD guidance (planned)*
Health Canada	Elements of RWD/E quality throughout the prescription drug product life cycle[54] (2019)
EMA (Europe)	EMA Patient Registry Initiative[55,56] (2016–planned), draft guideline on registry-based studies[57] (2020), and HMA/EMA Big Data Task Force data quality and representativeness framework (planned)[58]
Medicines and Healthcare Products Regulatory Agency (United Kingdom)	Draft guideline of RCTs generating RWE[17] (2020)

In 2022, ANVISA released a statement regarding a new regulatory framework RDC 753 supporting the use of RWE for evaluation of new drugs and biologics

Burns, Leah, et al. "Real-world evidence for regulatory decision-making: guidance from around the world." *Clinical Therapeutics* 44.3 (2022): 420-437.

What questions can we answer with RWE?

Safety

Effectiveness

RWE can assist with pharmacovigilance

- PV: Monitoring the effects of vaccines or drugs after they have been licensed for use, **especially in order to identify and evaluate previously unreported adverse reactions**.

- In this context RWE will
  - Build on what is known from pre-licensure studies
  - Likely be dealing with events that were too rare to detect in pre-licensure studies or events in special populations excluded from clinical trials.

Why is this important?

- Assures that the vaccines we use are safe and have a favorable benefit risk

- Having safety data available helps maintain public confidence

Why not just rely on passive reporting of AEFI?

- Passive reporting is by its nature biased towards events that are temporally associated with vaccine.
- Passive reporting systems suffer from substantial underreporting.
- It is not possible to evaluate the level of risk or attributable risk as there is no comparison group.
- Not accepted as RWE

EXAMPLE:
A Comparison of Active versus Passive Surveillance in Burkino Faso

- Men A vaccine was introduced into the Sub-Saharan African meningitis belt in December 2010 and almost 12 million people vaccinated in one campaign in Burkino Faso
- Two safety surveillance systems established
  - Nation wide passive surveillance
  - Active Surveillance in one district

Ouandaogo, Claude-Roger, et al. "Adverse events following immunization during mass vaccination campaigns at first introduction of a meningococcal A conjugate vaccine in Burkina Faso, 2010." *Vaccine* 30 (2012): B46-B51.

Men A Introduction
Passive vs Active Surveillance in Burkino Faso

Table 1: Attack rates of minors AEFI recorded (N= 11 466 950 persons vaccinated)

AEFI	n	Attack rate*
Fever	779	6,79
Headache	310	2,70
Gastro intestinal disorders	265	2,31
Local reactions	227	1,98
Dizziness / Syncope	120	1,05
Myalgia	96	0,84
Urticaria/ Pruritis / Rash	84	0,73
Persisting crying	29	0,25
Arthralgia	24	0,21
Convulsions	17	0,15
Abscess	16	0,14
Sleeping disorders	14	0,12
Asthenia/Lethargy	15	0,13
Eczema	6	0,05

Table 3: Reported AEFI cases through active search in the district of Ziniaré

12 syndromes	Rates of health problems*			
	Active search-2010 (N=107 493 vaccinated)		Baseline data-2009 (N=97 715 surveyed)	
	N	Rate	n	Rate
Convulsions	32	29,76	26	26,60
Urticaria	18	16,74	21	21,49
Bronchospasm	14	13,02	16	16,37
Meningitis syndrome	3	2,79	3	3,07
Local abscess	1	0,93	0	0,0
Hypotonia	2	1,86	0	0,0
Toxidermia	0	0,0	1	1,02
Flaccid paralysis	0	0,0	1	1,02

Summary: Active vs Passive Surveillance

- Passive surveillance can be useful for signal detection but:
- Under-reporting can severely limit the usefullness of passive reporting.

Convulsions as assessed through passive surveillance were under-reported >100 fold in Burkino Faso.

So how do you do use RWE for pharmacovigilance?

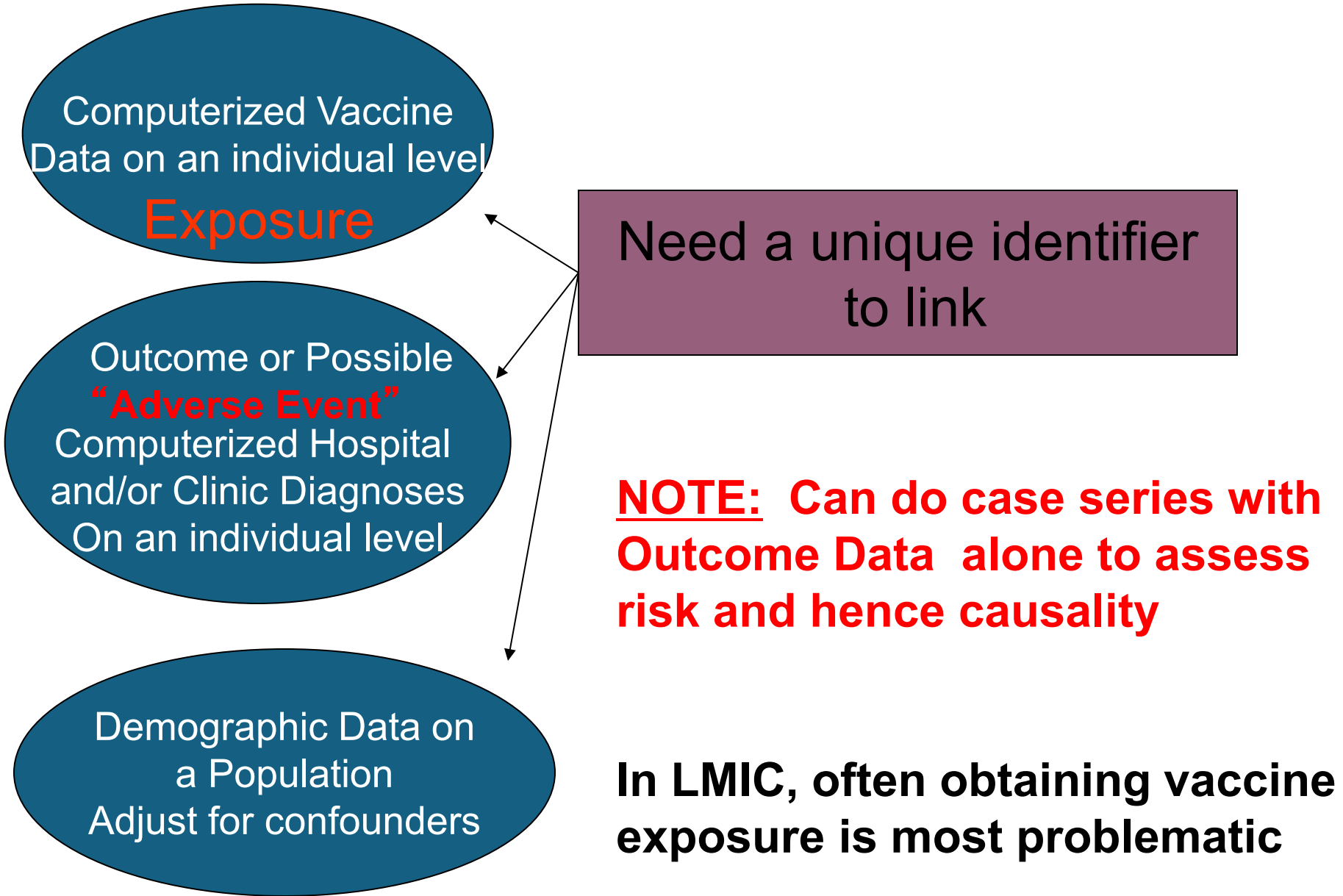
- Population based evaluations of safety: Phase Four studies, Datalink, registry and rapid cycle studies
- Background rates of events versus vaccine related events

Active Vaccine Safety Surveillance

Unlike passive reporting systems, data link studies have the potential to

- Identify cases of events in an unbiased way.
- Allow access to medical records to better characterize and understand cases.
- Calculate rates of events, relative risk and attributable risk.
- Evaluate vaccine impact and changes in disease epidemiology

What Data is needed?

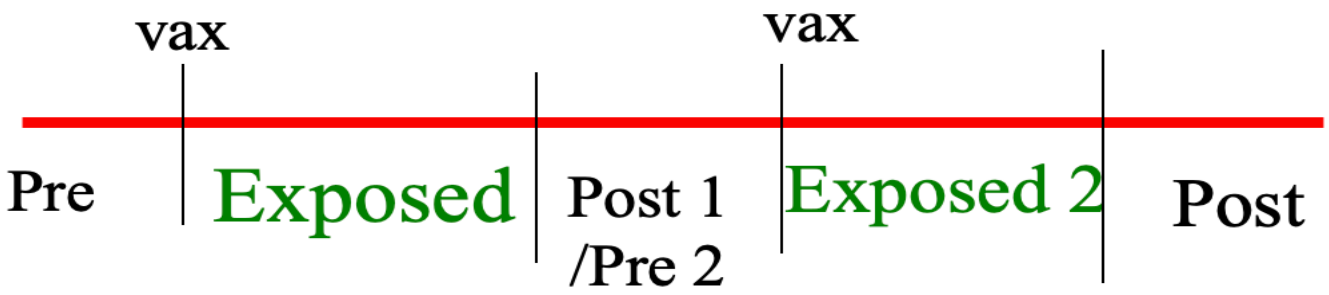


NOTE: **Can do case series with Outcome Data alone to assess risk and hence causality**

In LMIC, often obtaining vaccine exposure is most problematic

How to analyze the data:
Case Series / self control methods

- Developed by Farrington initially and since used and adapted by others.
- Allows calculation of relative risk using only cases of the outcome of interest and vaccine information.
- Probability of being vaccinated within a specified time window prior to vaccination is compared to probability of being vaccinated at other times in the cases with the outcome under study.
- If there is no association, then these two probabilities should be equal yielding an odds ratio of one.
- IMPORTANTLY: Only requires unbiased identification of cases of the event. Does not require a defined cohort or identification of a control group.



Rapid Cycle Techniques

- Requires rapid access to automated data sources to establish rates of events in baseline and following a new vaccine. Currently in use in the US CDC VSD with weekly data pulls.
- Uses sequential probability testing to test the likelihood of an observed number of cases versus expected.
- A “stopping value” is established to either rule in or rule out an association based upon the expected number of cases and risk level.
- For intussusception, a risk established after 2589 doses of vaccine given… a similar time frame as VAERS data mining.
- Also able to detect a decrease in risk of seizures, fever and other abnormal neurologic events within 12 weeks of introduction of DTaP as compared to DTwP.

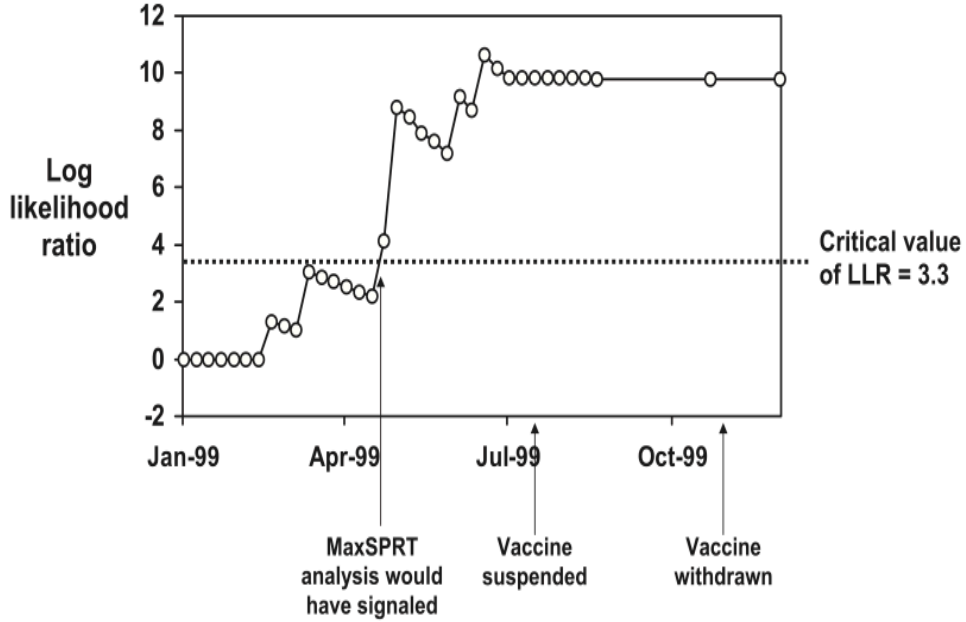


FIGURE 1. Example of signal detection using maximized sequential probability ratio testing to evaluate historical data on the risk of intussusception after Rotashield vaccination.

Lieu, Tracy A., et al. "Real-time vaccine safety surveillance for the early detection of adverse events." *Medical care* 45.10 (2007): S89-S95.

Case Study: Pre licensure and post introduction analyses of MMR-V

- Pre-licensure studies of safety are usually small
  - Focus on common local and systemic events
  - Analyses done within predefined windows
- Post licensure studies are usually much larger and have ability to look at events more flexibly

MMR-V Pre-licensure Safety

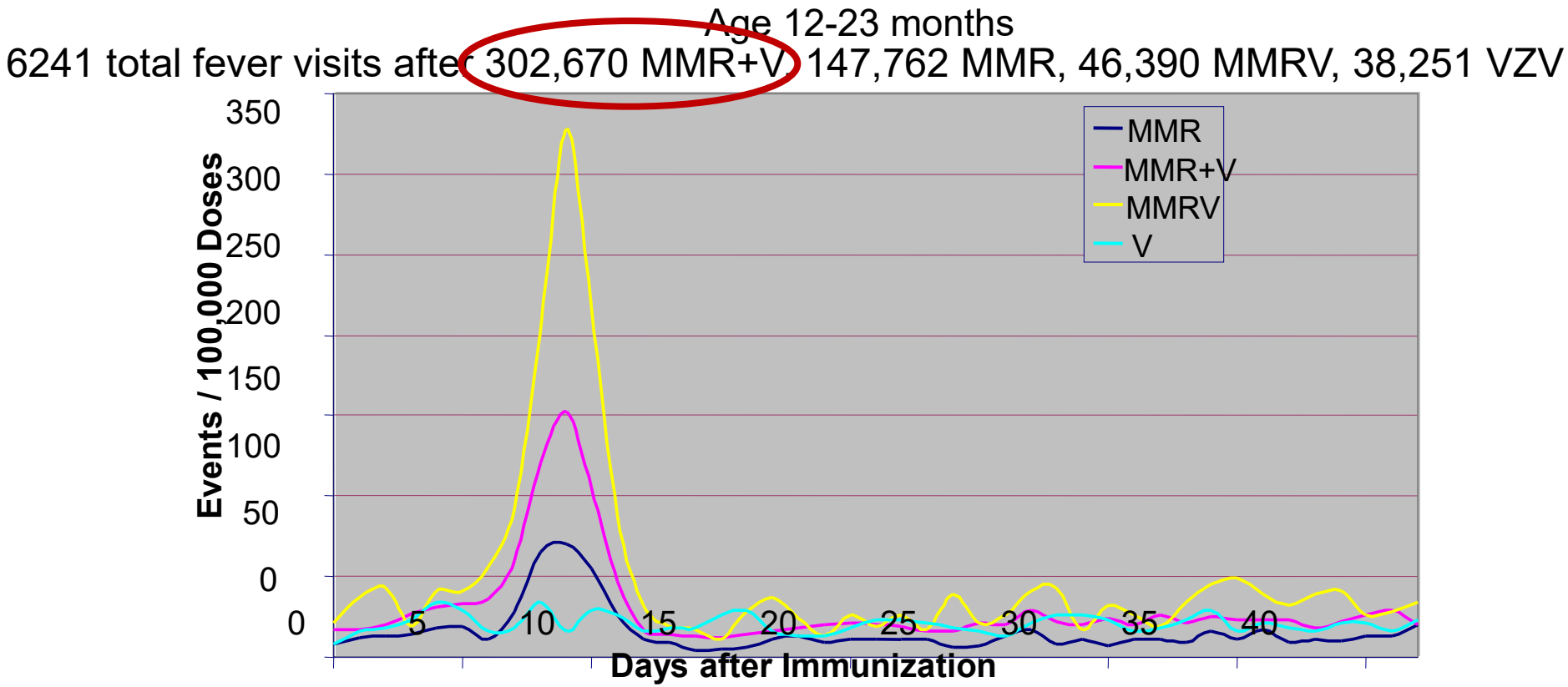
Black et al. PIDJ 24:8-12, 2005

	MMRV N=323	MMR & V N=157	P-value
Fever 0-42 days s/p vax	39.6%	34.8%	ns
Fever 5-12 days s/p vax	27.7%	18.7%	0.034
Seizures	1 on day 9	1 on day 1	ns

VSD Rapid Cycle Evaluation of MMRV

Outpatient Visits for Fever by Day after Vaccine

at Northern California Kaiser Permanente: 1995-2008



Klein, Nicola P., et al. "Safety of measles-containing vaccines in 1-year-old children." *Pediatrics* 135.2 (2015): e321-e329.

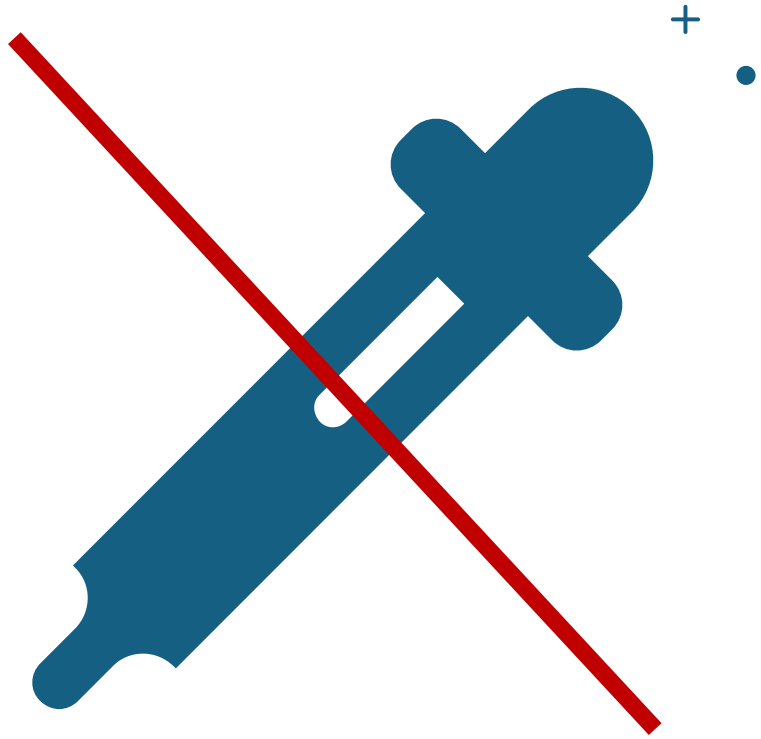
VSD Rapid Cycle Evaluation of MMRV
Risk of seizure 7-10 days post-vaccination using chart verified febrile seizures

	Odds ratio	95% Confidence Interval	P-value
MMRV versus MMR + Varicella*	**2.3**	**1.6, 3.2**	**<0.0001**
	Attributable Risk	**95% Confidence Interval**	
MMRV versus MMR + Varicella*	**5.2 / 10,000**	**2.2, 8.1**	

N= 42 for MMR-V out of 43,353 MMR-V and 124 for 314,599 doses of MMR + V for chart review confirmed seizures. Adjusted for age and influenza season. Increased risk with MMRV cannot be explained by concomitant vaccines, temporal trends in seizure, VSD site, age or influenza season.

What happens without vaccines?

The importance of knowing background rates and epidemiology



What happens without vaccines?

"AEFI" **without Vaccines**:

Autoimmune disorders in a 30day window - Outpatient Events in Teens

Outpatient care		# events Adolescents	Rate/100,000 py Teens	Rate Adults
(…)	Thyroid disorders	859	396	1412.05
556.x	Ulcerative colitis	76	35.4	117.52
555.x	Regional enteritis	68	31.6	97.18
7100	Systemic lupus erythematosus	63	52.9	120.23
7140	Rheumatoid arthritis	29	13.5	119.33
37730	Optic neuritis	10	4.7	13.56
340	Multiple sclerosis	9	4.2	64.18
71659	Polyarthritis	7	3.3	30.74

Pandemic Flu Safety

The importance of background rates of disease in assessment of vaccine safety during mass immunization with H1N1 influenza vaccines

	Number of coincident events since a vaccine dose			Baseline rate used for estimate
	Within 1 day	Within 7 days	Within 6 weeks	
Guillain-Barré syndrome (per 10 million vaccinated people)	0·51	3·58	21·50	1·87 per 100 000 person-years (all ages; UK Health Protection Agency data)
Optic neuritis (per 10 million female vaccinees)	2·05	14·40	86·30	7·5 per 100 000 person-years in US females (table 2)[16]
Spontaneous abortions (per 1 million vaccinated pregnant women)	397	2780	16684	Based on data from the UK (12% of pregnancies)[34]
Sudden death within 1 h of onset of any symptoms (per 10 million vaccinated people)	0·14	0·98	5·75	Based upon UK background rate of 0·5 per 100 000 person-years (table 2)[28]

Table 6: **Predicted numbers of coincident, temporally associated events after a single dose of a hypothetical vaccine, based upon background incidence rates**

www.thelancet.com Published online October 31, 2009

Another reason RWE evidence studies are important: Considerations of Statistical Power

Total Study Population Size Required
to Detect a Selected Increased Levels of Risk

Control Incidence (person-yrs)	Study Population to Detect 2 Fold Increased Relative Risk	Study Population to Detect 3 Fold Increased Relative Risk	Study Population to Detect 5 Fold Increased Relative Risk
1/100	4,638	1,538	570
1/1000	47,036	15,670	5,870
1/10,000	471,000	156,992	58,866
1/100,000	4,710,650	1,570,208	588,822

Assuming the test and control group have a 1:1 ratio , that the background incidence in treated = incidence in controls, two tailed alpha=0.05, 80% power.

Strom, B.L., Pharmacoepidemiology, 2nd Ed., John Wiley and Sons, 1994

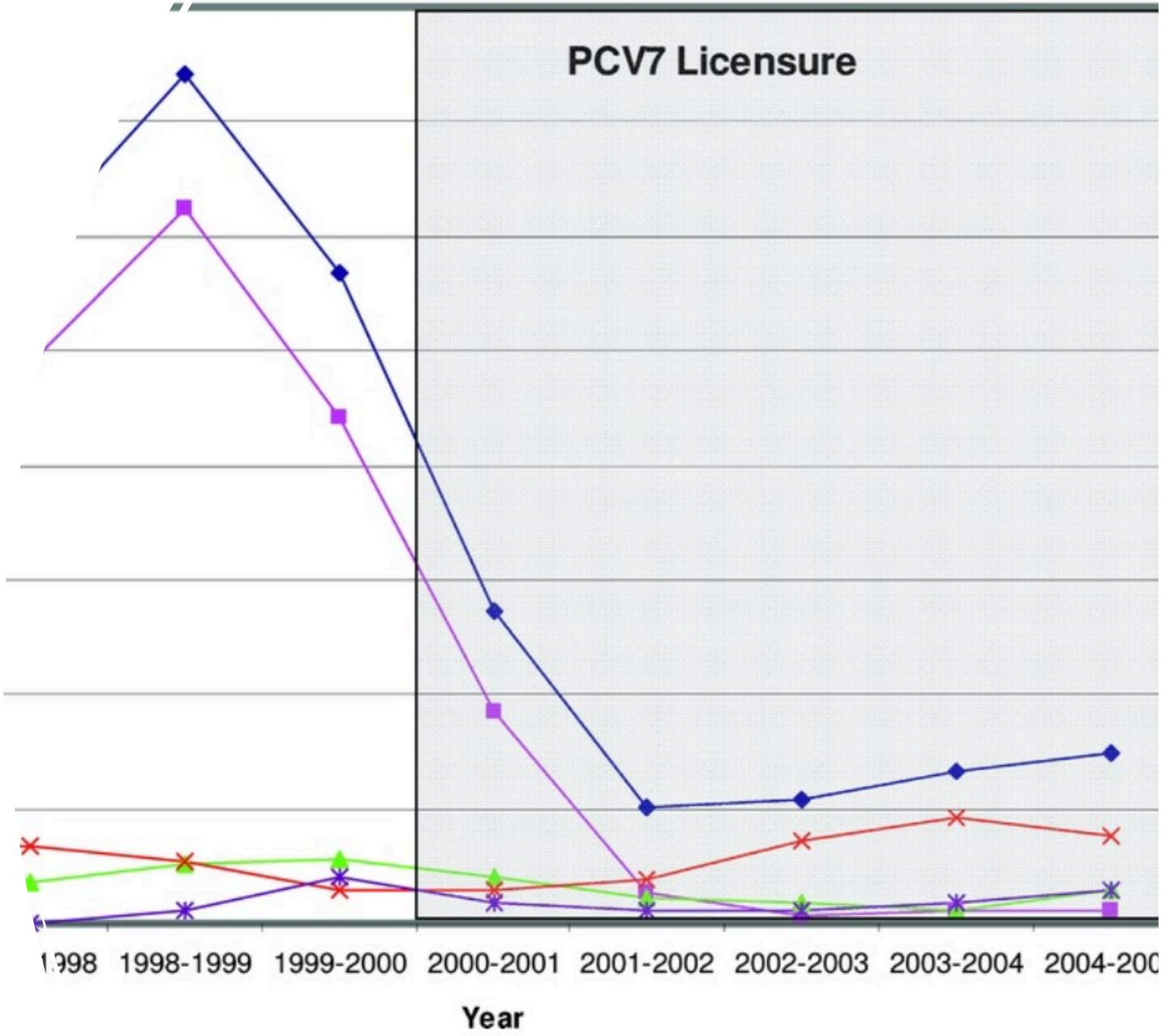
What about assessing vaccine effectiveness??

Vaccine Effectiveness versus efficacy

- Vaccine effectiveness
  - May be higher than observed in clinical trials (Pneumococcal conjugate)
  - May be lower than observed in clinical trials (Rotavirus vaccines in LMIC)
- Accurate assessment of effectiveness is critical for making appropriate public health decisions
  - Indirect effects of PCV completely changed their cost effectiveness

RWE to assess vaccine effectiveness

- Laboratory data bases can contain:
  - PCR test results for viral and bacterial pathogens
  - Bacterial culture results
- Radiology databases can contain results of X-rays, CT scans, etc.
- Electronic medical records have other necessary data.



IPD: comparison of prelicensure years to postlicensure years.

Black, Steven, et al. "Surveillance for invasive pneumococcal disease during 2000–2005 in a population of children who received 7-valent pneumococcal conjugate vaccine." *The Pediatric infectious disease journal* 26.9 (2007): 771-777.

Summary of Advantages of RWE Population Based Data Studies

- Allow calculation of incidence on AEFI and background rates of disease without vaccination
- Allow calculation of relative risk
- Allow calculation of attributable risk.
- Allow adjustment for confounders
- Allow assessment of trends including vaccine impact on disease for risk-benefit analyses

What to do if you observe a possible signal?

Evaluation of a possible consistent time association of the event with vaccination

Evaluation in a different analytic framework: self-control analysis or other reference group

Possible associations can serve as a source of hypothesis generation for further studies – ie case-control study conducted for intussusception.

What are global trends for use of RWE?

- Increasing the sample size and geographic reach
  - Regional and global consortiums
    - Offers potential to evaluate vaccines only used in developing world.
    - Maximizes statistical power
  - EXAMPLES: Global Vaccine Data Network, ALIVE network in Africa, VAC4EU in Europe
- Global Networks can address:
  - Assess rare events which requires VERY large populations to assess therefore multi-country collaborations are useful. Assessing mixed complicated schedules increases this need. Global collaborative studies provide this capacity.
  - The need to build capacity in countries not experienced in the use of RWE.

WITS Alive

VAC4EU

Global Vaccine Data Network

GVDN Partners

Six continents, 34 countries, >800 million people

Global Vaccine Data Network®

Argentina	Ethiopia	New Zealand
Australia	Finland	Scotland
Brazil	France	South Africa
China	Ghana	Taiwan
Canada	India	USA
Denmark	Indonesia	ALIVE network (Africa)
England	Japan	VAC4EU network (Europe)
	Korea	

Summary

- The use of RWE for public health and regulatory use is evolving rapidly.
- Active surveillance studies are feasible and being conducted in LMIC
- Public expectation is for a rapid response to possible concerns.
  - Without this confidence is undermined and “anti-vaccine” groups get a head start.
- Concerns will arise because events occur and occur in clusters in both vaccinees and non vaccinees due to chance alone.
- Global collaborations can increase efficiency and capacity

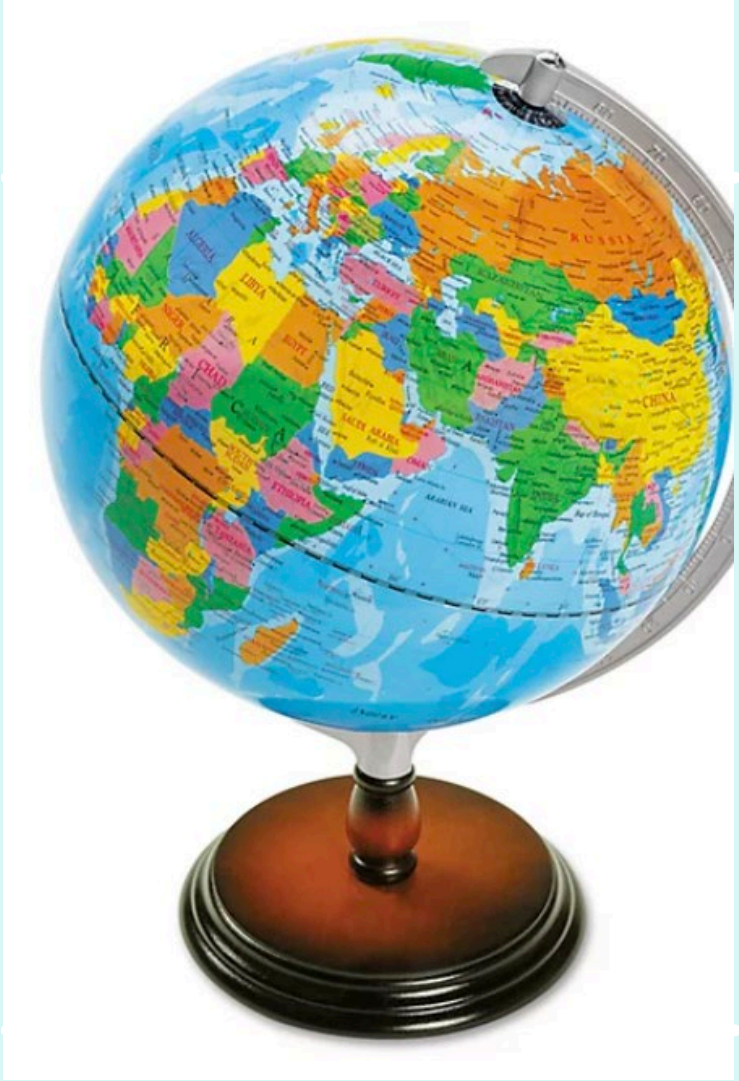
Thank you!

Questions ?

Supplementary slides

Other Vaccine Safety Assessment Considerations

- Registries are a recognized source of RWE especially for special populations such as pregnant women.
- Identifying subsets at risk and assessing them separately:
  - Children
  - HIV infected individuals



Vaccine Safety Assessment Inequality

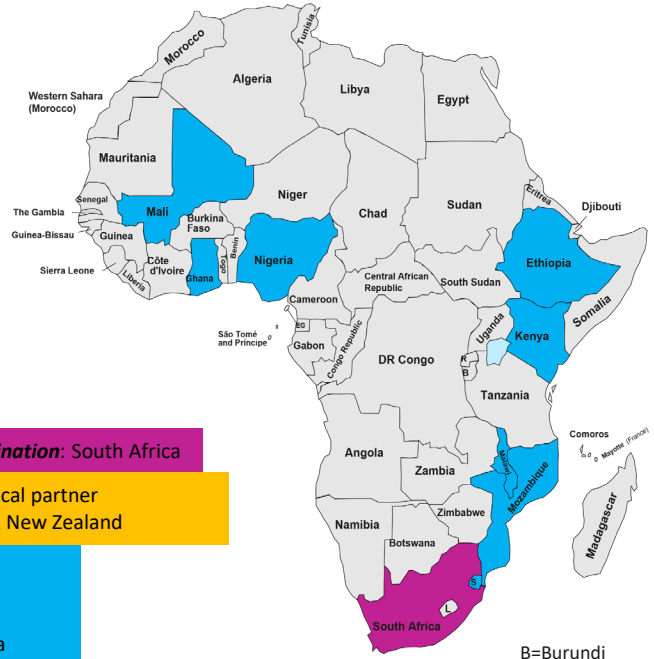
- Most of the world lives in middle or low-income countries
- Most vaccine safety infrastructure has been centralized in high income countries.
- This was considered acceptable because most new vaccines were used in high income countries for a long time prior to use in low-income countries.
- This is no longer true.

But is active surveillance feasible in LMIC ???

The GAVI funded study in the ALIVE network.

ALIVE Project Participants

Country	Site	Site lead/ contact
Mali	Bamako	Samba Sow
Ghana	Navrongo Health Research Centre	Nana Akosua Ansah
Nigeria	National	Ehimario Igumbor Stephen Obaro
Ethiopia	Gondar	Biniyam Tilahun
Kenya	Kilifi	Wangeci Kagucia
Malawi	National	Kondwani Jambo
Mozambique	Maputo city	Ilesh Jani Celso Khosa
Eswatini	National	Tholokwakhe Simelane



Coordination: South Africa

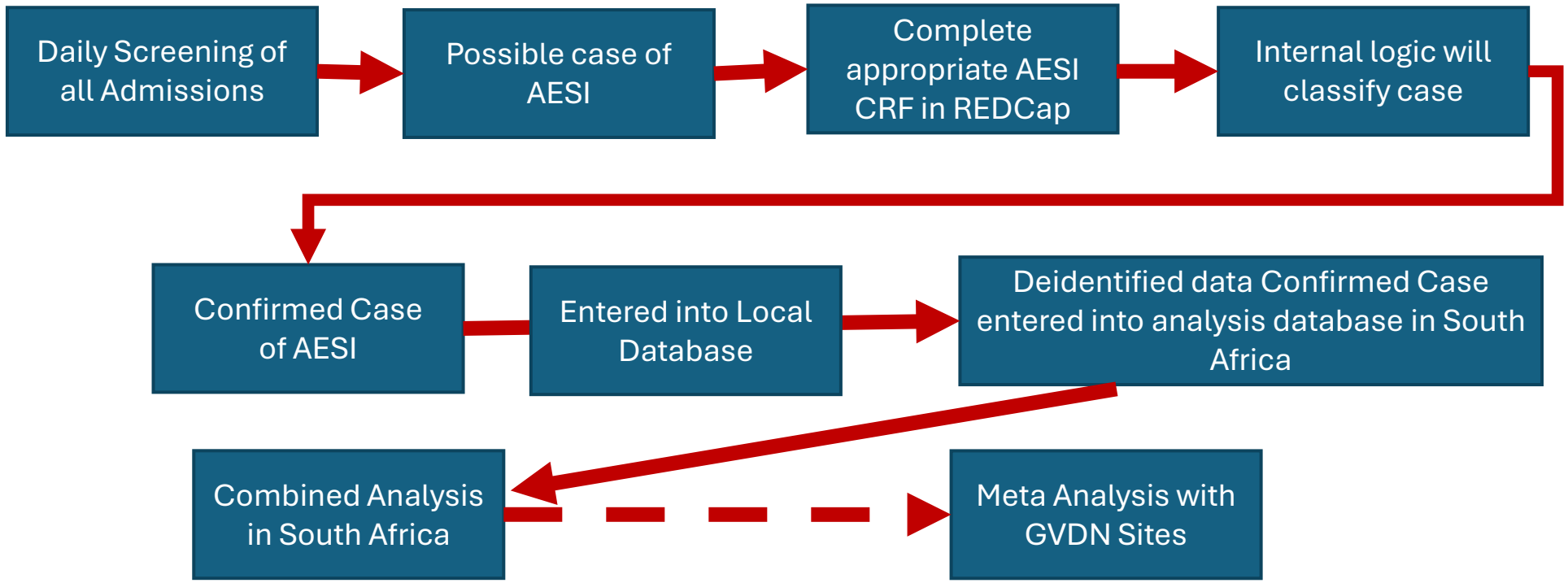
Technical partner
GVDN, New Zealand

Sites:
Mali
Ghana
Nigeria
Ethiopia
Kenya
Malawi
Mozambique
Eswatini

B=Burundi
EG=Equatorial Guinea
L=Lesotho
R=Rwanda
S=Eswatini

Coordinating Center at Witswatersrand University in South Africa
Shabir Madhi and Clare Cutland

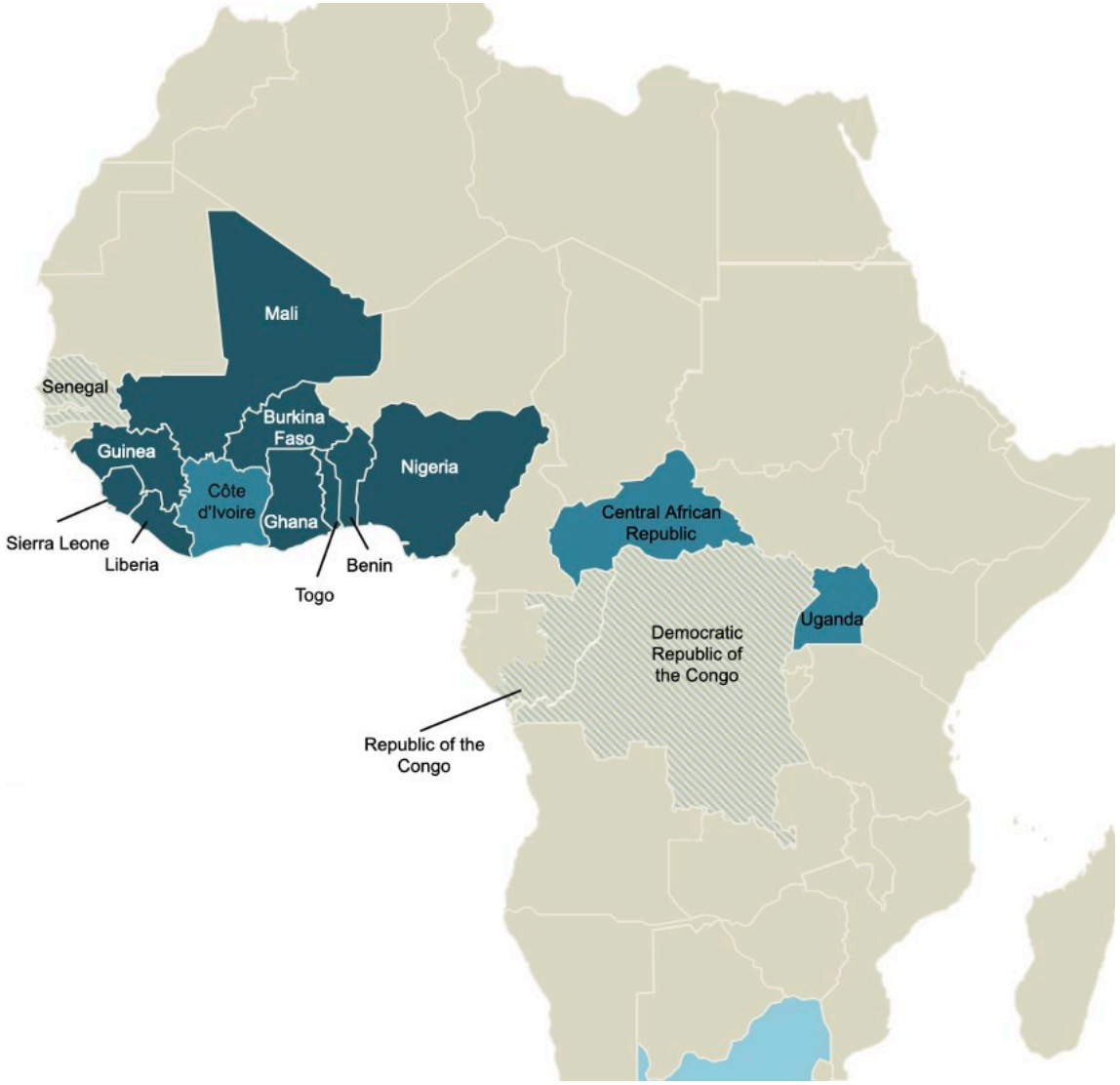
GVDN ALIVE Data Collection Model



CEPI Funded BRAVE Project

A project to develop background rates in Africa from:

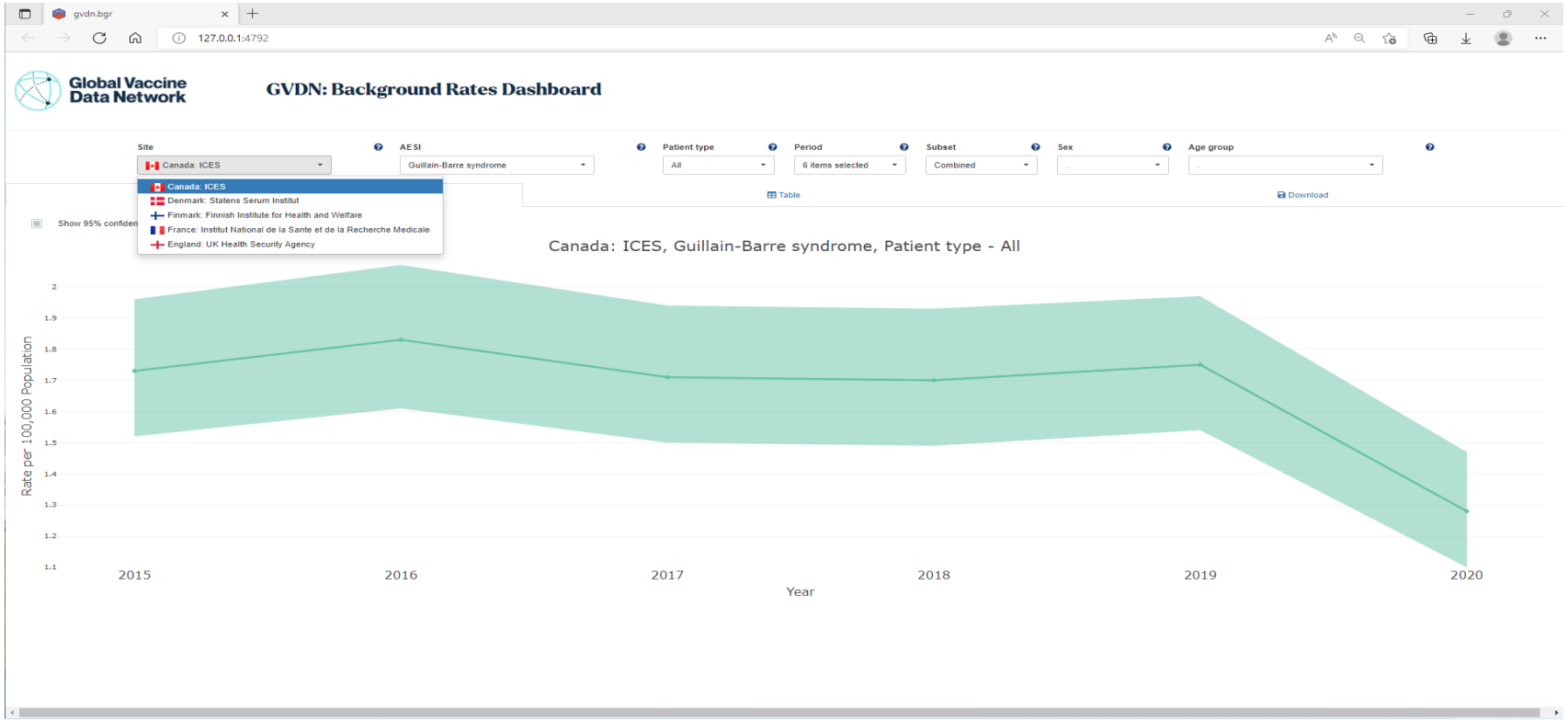
- HDSS data
- Manual hospital screening
- Electronic hospital records.



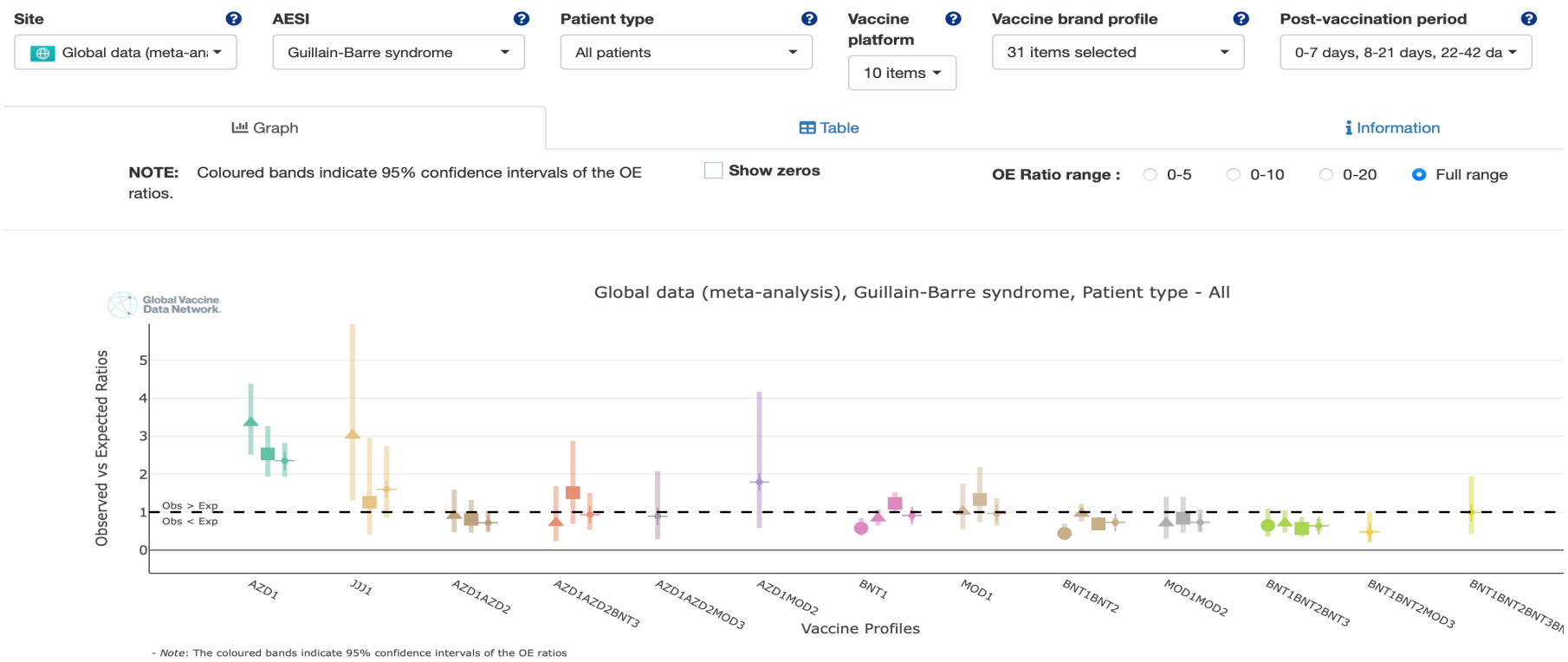
A word about genomics

- Genomics studies of drugs have revolutionized drug therapy allowing for personalized approaches to treatment.
- Identifying genetic markers of risk for vaccine adverse events would serve two purposes
  - Facilitating a better understanding of the pathophysiology of events
  - Potentially allow for personalized vaccine schedules that reduce the risk of AEFI.
- For the GVDN, Bruce Carlton of UBC in Vancouver is leading the effort to try and identify genetic markers of risk for myocarditis, VITT and Guillain-Barré Syndrome
  - 300 validated cases or more per outcome
  - Ten controls per case.

Data dashboard Example: GBS rates from ICES



GVDN Observed versus Expected Dashboard



Requirements for use of RWD/RWE in vaccine post-approval effectiveness/efficacy studies

CEPI, Gina Antaki – Moderator
FDA – USA, David Kaslow (virtual)
EMA – EU, Marco Cavaleri
ANVISA – BRAZIL, Brenda Valente
CDSCO - INDIA, Rubina Bose

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Post-approval studies for CHIKV vaccines.

Chikungunya vaccines workshop, Sao Paulo, 19-20 March 2025

- Dr. Marco Cavaleri
- Head of Health Threats and Vaccines Strategy
- Chair of EMA Emergency Task Force

IXCHIQ post-approval commitments

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Post-authorisation efficacy study (PAES): In order to confirm the efficacy of Ixchiq in individuals 18 years and older, the MAH should conduct, according to an agreed protocol, and submit the results of, a randomized, controlled trial with pragmatic elements to assess the effectiveness of Ixchiq vaccination in the prevention of symptomatic, laboratory confirmed chikungunya after a single vaccination with Ixchiq in adults in endemic areas.	Final report due date: 31 Dec 2029

IXCHIQ Risk Management Plan

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 78. Summary of safety concerns

Important Identified Risks	Chikungunya-like adverse reactions
Important Potential Risks	Vaccine-associated arthritis
	Cardiac events
	Safety in pregnant or breastfeeding women
Missing Information	Safety in patients with autoimmune or inflammatory disorders
	Safety in frail patients with acute or progressive, unstable or uncontrolled clinical conditions, e.g. cardiovascular, respiratory, neurologic, psychiatric, or rheumatologic conditions
	Long-term safety
	Co-administration with other vaccines

Vimkunya post-approval commitments

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post authorisation efficacy study (PAES): In order to confirm the efficacy of VIMKUNYA in individuals 12 years and older, the MAH should conduct and submit the results of a randomized, placebo-controlled, double-blind, event-driven study to analyse efficacy, safety, and immunogenicity of VIMKUNYA in the prevention of chikungunya disease in healthy adults and adolescents in CHIKV-endemic areas, according to an agreed protocol.	Final report due date: 31st August 2030

Vimkunya Risk Management Plan

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 102 Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use during pregnancy and breastfeeding

Post-approval evidence for CHIKV vaccines

- Paediatric studies in PIPs: safety and immunogenicity from birth
- Pregnancy registries and for specific aspects also safety studies
- Efficacy: Individually randomised trials are requested, but ability to generate robust data on efficacy unclear
- Effectiveness studies are expected to be conducted in the context of emerging outbreaks and/or endemic areas and should be part of the portfolio of options
- Test negative case control studies acceptable
- Studies should measure efficacy/effectiveness against PCR confirmed symptomatic disease, preferably as per WHO definition
- It would be relevant to collect evidence on post-acute sequalae to establish the impact of vaccination

Post-approval evidence for CHIKV vaccines

- For RCTs, good understanding of the attack rate to define adequate sample size
- Primary population should be seronegatives at baseline, even if this does not represent good estimate of real-life conditions (VE observational studies better placed)
- Outbreaks tend to be fast-spreading and short-lived: timing of vaccination critical
- Acceptance by NRAs and RECs in Countries
- Case ascertainment: active vs passive surveillance
- PCR testing: central lab vs local
- Detection of co-infection with other mosquito-borne viruses
- Pragmatic aspects related to safety reporting

Data requirements for a RWE study: do countries have the appropriate infrastructure for it?

CEPI, Gina Antaki – Moderator
Brazil - Jadher Percio, PNI/MOH
Colombia - Fernando de la Hoz, UNC
Thailand - Wichan Bhunyakitikorn, DDC/MOH
AVAREF, Kwasi Nyarko (virtual)

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CHIKUNGUNYA vaccines: does Brazil have the appropriate infrastructure for a RWE study?

BRASIL BEM CUIDADO
MAIS SAÚDE PARA QUEM MAIS PRECISA

SUS

MINISTÉRIO DA SAÚDE

GOVERNO FEDERAL
BRASIL
UNIÃO E RECONSTRUÇÃO

Brazil – a country of continental dimensions

- 8.5 million km^2
- 27 Federation Units
- 5,570 municipalities
- 212.6 million inhabitants (2024)
- 10 border countries

Source: IBGE (https://www.ibge.gov.br/)

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SUS – Unified Health System

Established by the Federal Constitution of 1988

- Public Health Policy (distributive)
- Universality (for all)
- Integrality (health promotion, disease prevention, care and rehabilitation)
- Gratuity
- Equality and equity

Source: Law 8080/1990 (https://www.planalto.gov.br/ccivil_03/leis/l8080.htm)

BRASIL BEM CUIDADO
MAIS SAÚDE PARA QUEM MAIS PRECISA

SUS

MINISTÉRIO DA SAÚDE

GOVERNO FEDERAL
BRASIL
UNIÃO E RECONSTRUÇÃO

National Health Surveillance System

Sanitary Surveillance Environmental

Surveillance Occupational Health Surveillance

Epidemiological Surveillance

- National Immunization Program - PNI
- Arboviruses – compulsory notification
- Center for Strategic Information and Response in Health Surveillance - CIEVS

National System of Public Health Laboratories

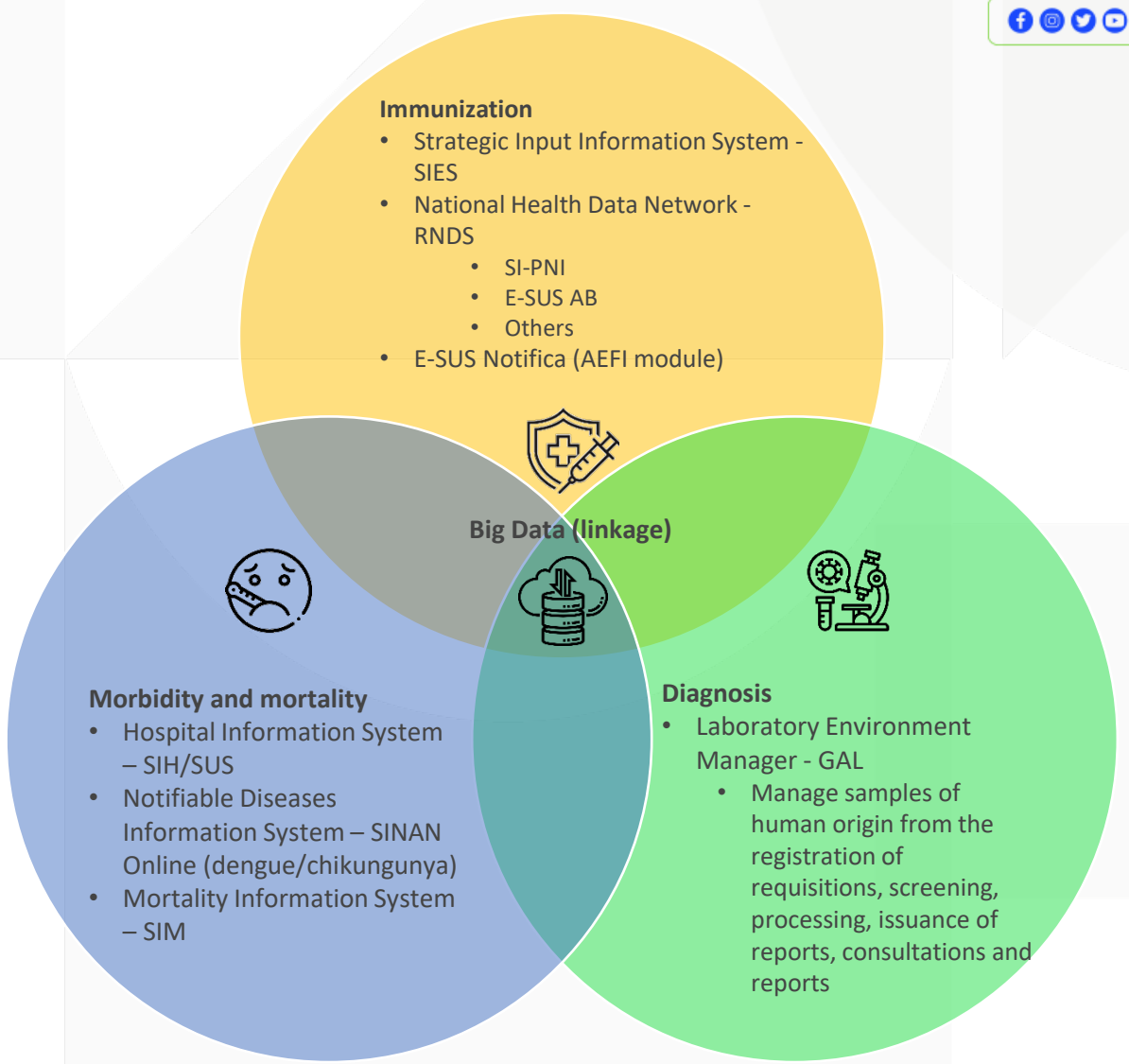
Special Indigenous Health Subsystem

Source: Consolidation Ordinance 4/2017 (https://bvsms.saude.gov.br/bvs/saudelegis/gm/2017/prc0004_03_10_2017.html#CAPITULOII)

Health Information Systems

Computerized systems that collect, process, store, and distribute health data within the scope of the SUS

- Monitor health situation
- Understand health problems
- Support decision-making
- Plan public health actions
- Manage resources and financing
- Evaluate health services and systems



Source: Ministry of Health (https://www.gov.br/saude/pt-br/assuntos/noticias/2023/julho/entenda-as-principais-caracteristicas-dos-sistemas-de-informacao-do-ministerio-da-saude)

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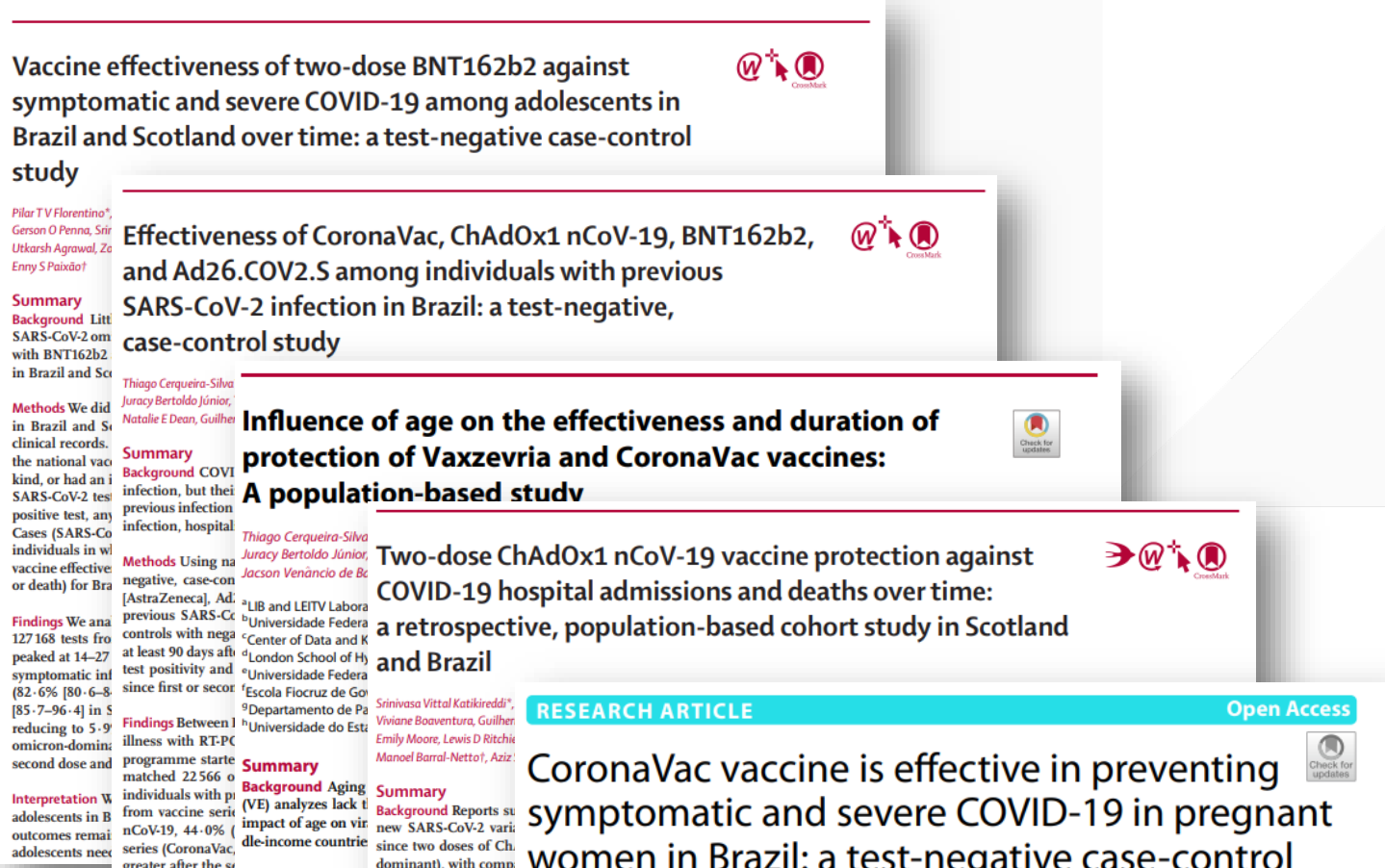
Previous experience

Several studies on the effectiveness and safety of COVID-19 vaccines and others have been carried out based on the health information systems of the Ministry of Health


Vaccine effectiveness of two-dose BNT162b2 against symptomatic and severe COVID-19 among adolescents in Brazil and Scotland over time: a test-negative case-control study

Effectiveness of CoronaVac, ChAdOx1 nCoV-19, BNT162b2, and Ad26.COV2.S among individuals with previous SARS-CoV-2 infection in Brazil: a test-negative, case-control study

Influence of age on the effectiveness and duration of protection of Vaxzevria and CoronaVac vaccines: A population-based study

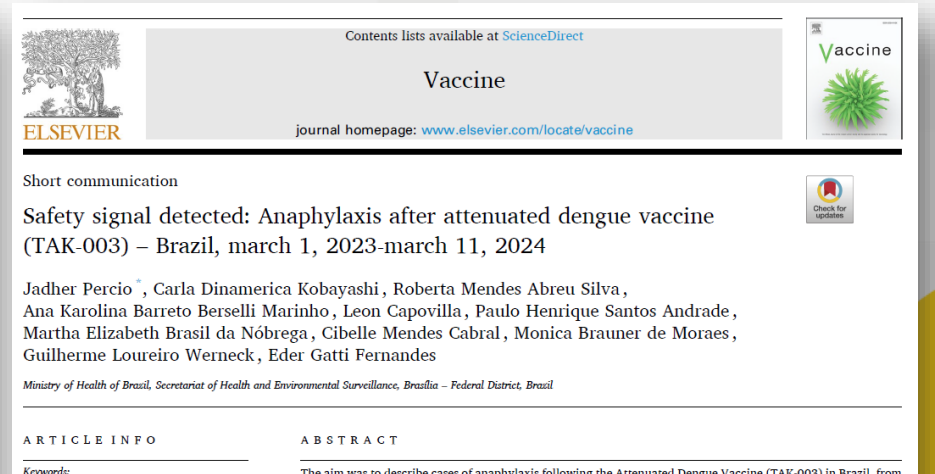
Two-dose ChAdOx1 nCoV-19 vaccine protection against COVID-19 hospital admissions and deaths over time: a retrospective, population-based cohort study in Scotland and Brazil

RESEARCH ARTICLE Open Access

CoronaVac vaccine is effective in preventing symptomatic and severe COVID-19 in pregnant women in Brazil: a test-negative case-control study

RESEARCH Open Access

Vaccine coverage and effectiveness against laboratory-confirmed symptomatic and severe Covid-19 in indigenous people in Brazil: a cohort study


Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Short communication

Safety signal detected: Anaphylaxis after attenuated dengue vaccine (TAK-003) – Brazil, march 1, 2023-march 11, 2024

Main challenges for conducting vaccine effectiveness studies in Brazil

Attributes of Health Surveillance Systems

Complexity, data quality, timeliness, representativeness, and sensitivity

Vaccine hesitancy

Trust and reliability in new vaccines and health authorities

Communication and misinformation about the efficacy and safety of vaccines

Integration between assistance and surveillance

Acceptability of health professionals to recommendations for detection, notification, investigation and clinical management of suspected cases

Final considerations

01

Real-World Evidence

Brazil has the infrastructure to carry out studies on the effectiveness and safety of vaccines

02

Health Information Systems

They are available to carry out studies and monitor the safety and effectiveness of the vaccines in use in the country

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BRASIL BEM CUIDADO

MAIS SAÚDE PARA QUEM MAIS PRECISA

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MINISTÉRIO DA SAÚDE

GOVERNO FEDERAL

BRASIL

UNIÃO E RECONSTRUÇÃO

Data requirements for a RWE study: do countries have the appropriate infrastructure for it? The Colombian case.

Fernando de la Hoz Restrepo.

Universidad Nacional de Colombia.

Departamento de Salud Publica.

Types of RWE

- Case Control studies
- Cohort studies
- Surveys
- Outbreak studies
- Ecological studies:
  - Time trends series
  - Geographical units' comparative studies
  - Case studies

Source of data

- Prospectives or retrospectives studies
  - Surveys
  - Vaccination records
  - Surveillance data
  - Clinical management data

Colombian experience

- BCG: Case control study. 1985
- Hepatitis B: Surveys. 1992, 1999, 2011, 2019
- Hib: case control study. 2002
- Hib: case study and scan analysis. 2008
- Measles. Outbreak studies. 2001.

Colombian experience

- Rotavirus: case control study, survey study, ecological analysis of epidemiological and laboratory data. 2012
- Neumococo: case control study, survey study, ecological analyss of epidemiological and laboratory data. 2010
- Varicella: ecological analysis of clinical management data and epidemiological data, survey study. 2016

Colombian experience

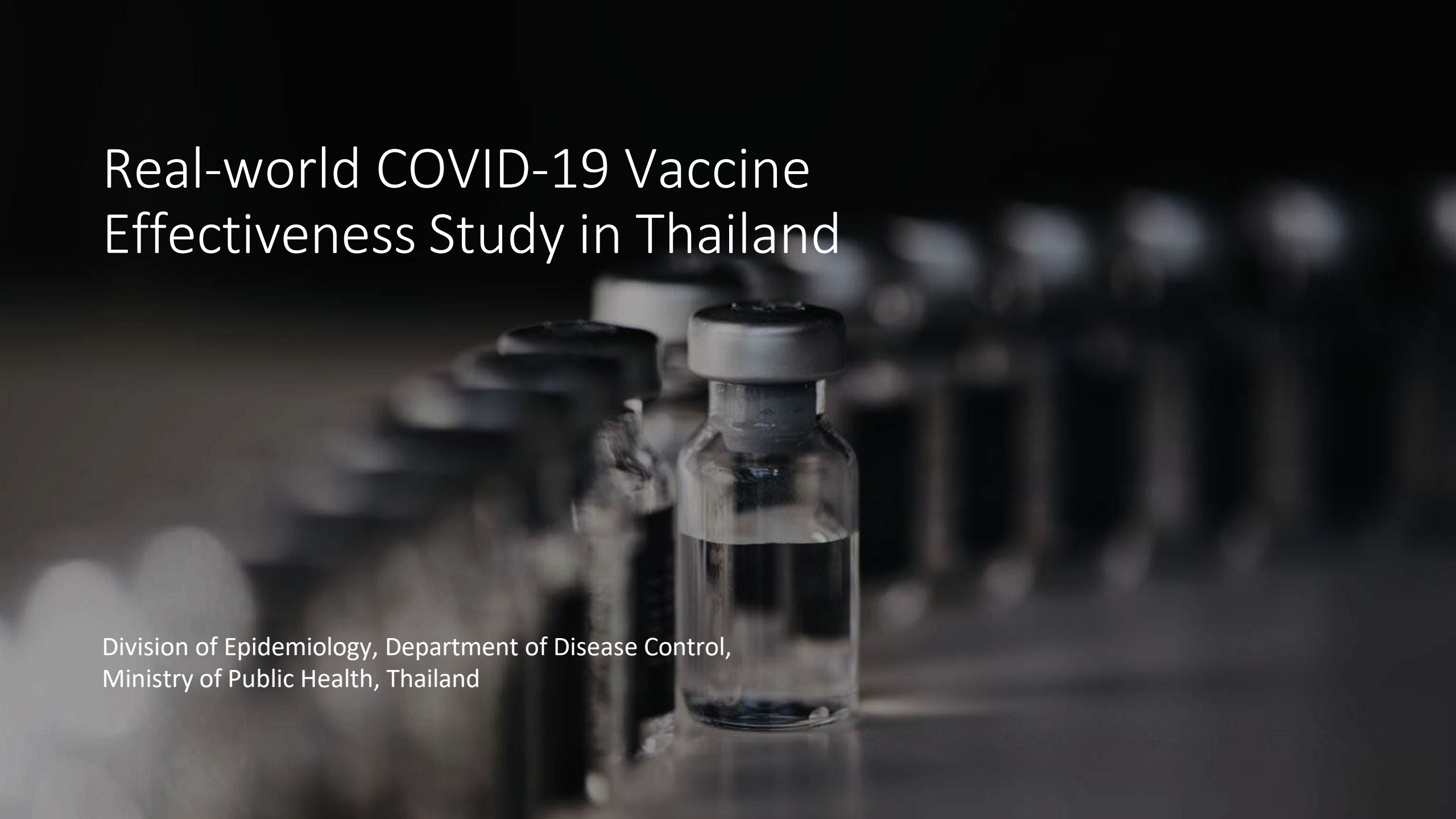
- HPV: cohort studies, analysis of clinical management data. 2022, 2024

- COVID: retrospective cohort studies, case control studies, time trends studies. 2021, 2022, 2023.

Conclusions

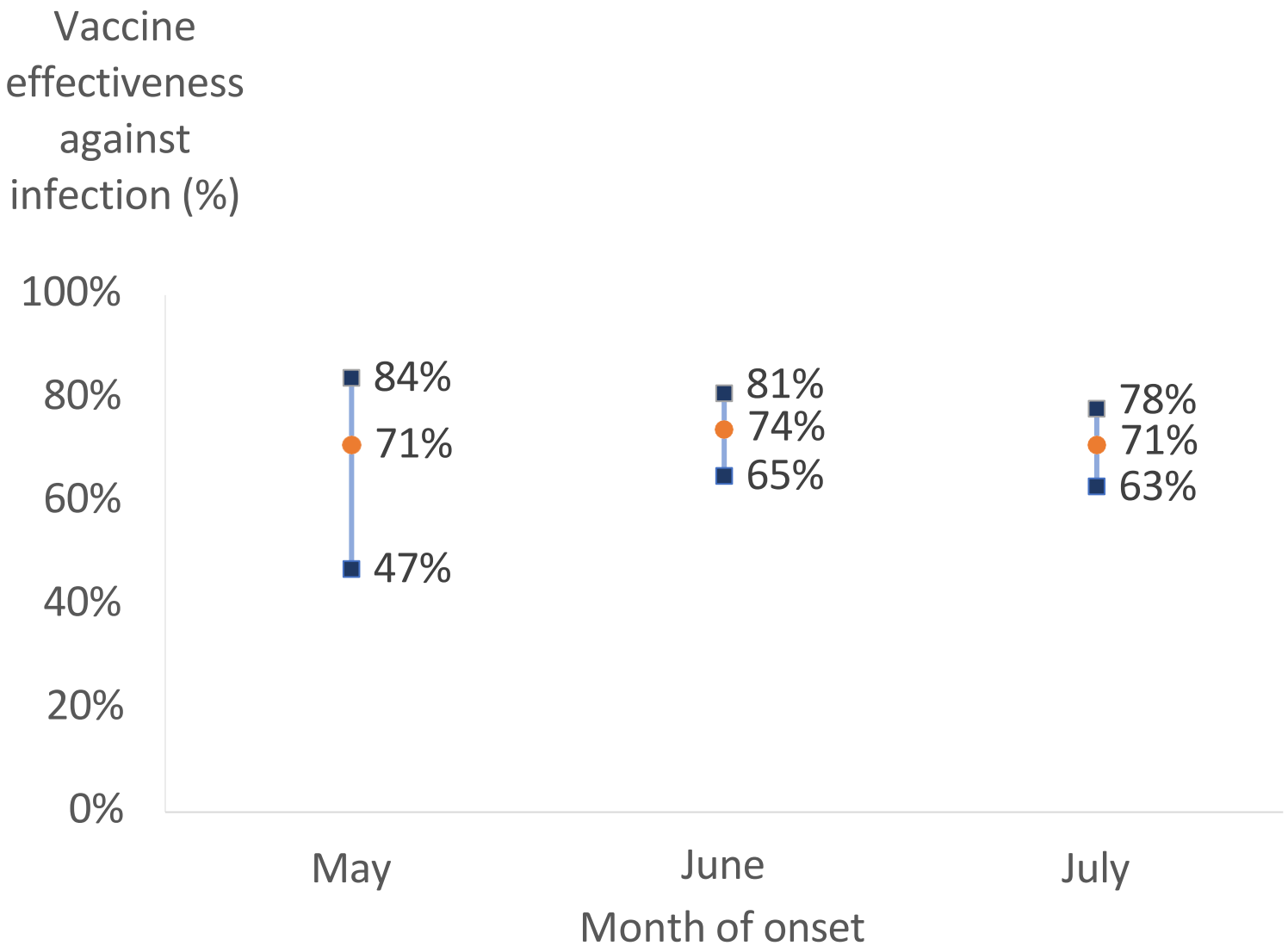
- There are several observational designs that can be used to assess vaccine effectiveness
- Colombia has many data sources that can be used to assemble a different array of studies
- Several governmental and academic research groups have extensive experience on conducting this type of studies

Real-world COVID-19 Vaccine Effectiveness Study in Thailand



Division of Epidemiology, Department of Disease Control,
Ministry of Public Health, Thailand

Results: Alpha and delta variant

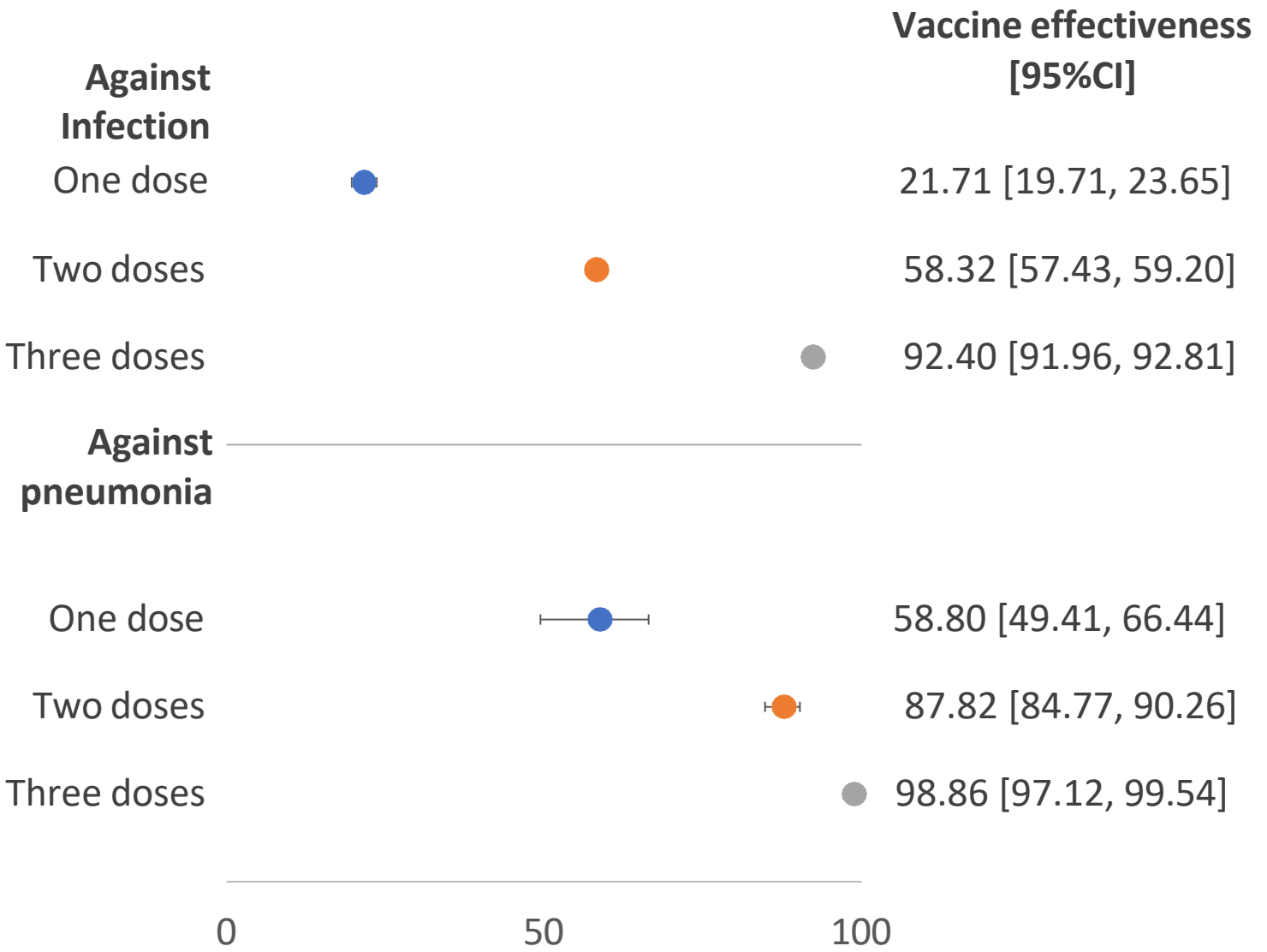


Methods: Matched case-control study among Thai healthcare workers

Time: May to July 2021 (Alpha and delta variant co-circulate)

- Two dose of CoronaVac effectiveness against COVID-19 infection
- Moderate degree of protection

Results: Delta variant

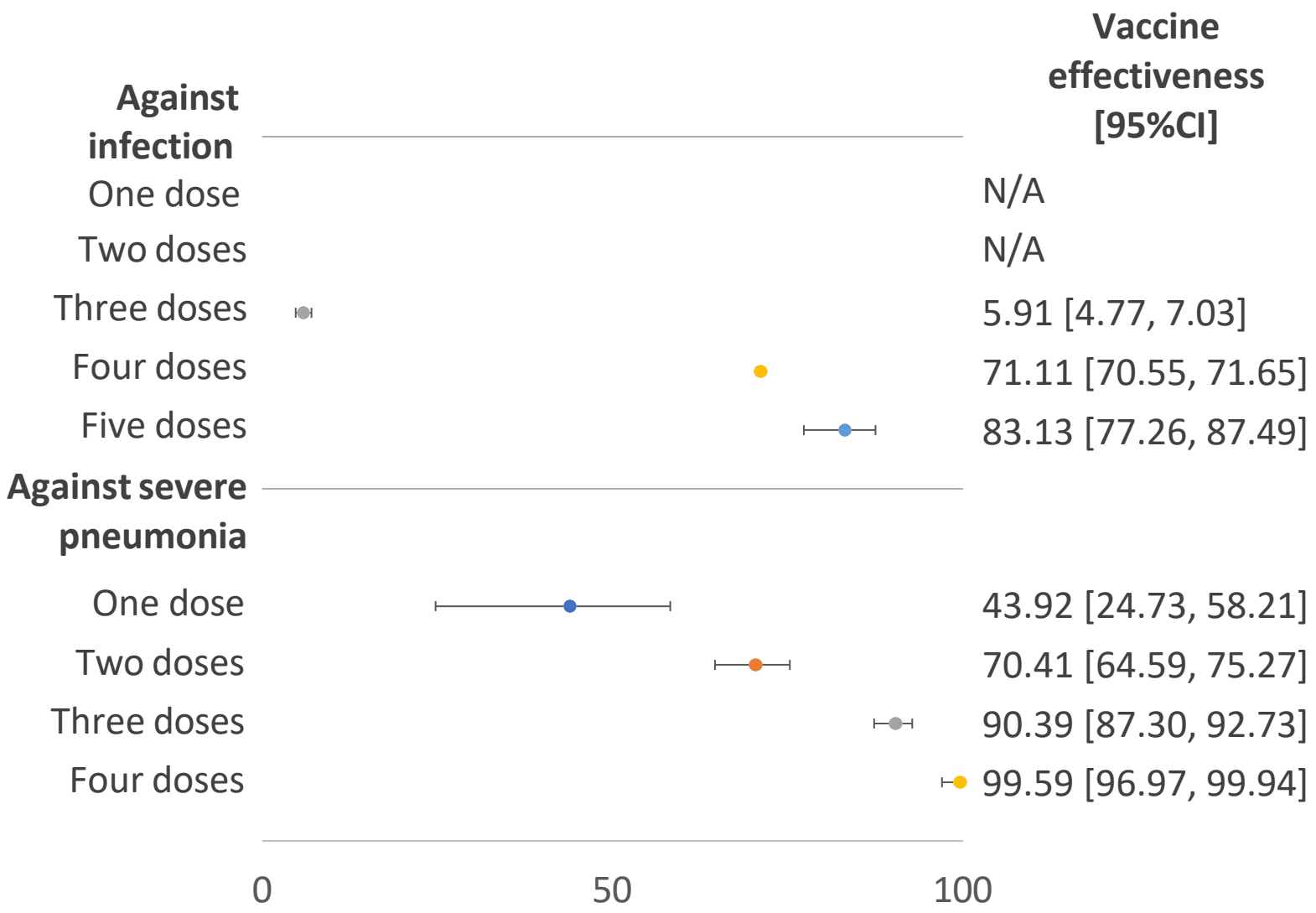


Methods: Matched test-negative case-control study among high-risk group (close contact or active case finding) with 1:2 ratio

Time: September to December 2021 (Delta variant predominant)

Note: pneumonia included pneumonia and death cases.

Results: Omicron variant



Methods: Matched test-negative case-control study among high-risk group (close contact or active case finding) with 1:4 ratio

Time: January to April 2022 (Omicron variant predominant)

Note: severe pneumonia included pneumonia with invasive ventilation support and death cases.

Key Factors for Success in Thailand

- **Infrastructure and resources**
  - Robust surveillance and data collection system
- **Expertise and workforce**
  - Skilled professionals, including epidemiologists, data analysts, and healthcare workers
  - Training programs to enhance technical skills, such as, Field Epidemiology Training Program (FETP)

Key Factors for Success in Thailand

- **Support and funding**
  - Public-private partnerships between the Ministry of Public Health and non-Ministry of Public Health organizations for research, for example,
    - GBDi providing data scientists to manage big data
    - Chiang Mai University conducting analysis using local data
  - Policy and regulatory support
    - Establishment of committees and research teams to oversee studies
    - Government endorsement to promote evidence-based decision-making

World Health Organization

African Region

AVAREF Role in Regulatory and Ethics Capacity Building for Authorization of Complex and/or Non-traditional study designs in Africa

Kwasi A. Nyarko, PhD
Implementation Portfolio, WHO AFRO

19 March 2025

UHC/UCN
Universal Health Coverage/Communicable and Noncommunicable Diseases

Outline

- AVAREF - Overview of Regulatory & Ethics Capacity in Africa
- AVAREF's Raison d'Etre - Roles, Mandate and Priorities for AVAREF
- Complex and Non-Traditional Clinical Trials designs
- Considerations for developers and ecosystem
- Key Messages and Conclusion

Overview of the African Vaccines Regulatory Forum (AVAREF)

A Vision of An African population with timely access to safe and efficacious medical products of assured quality

Established as an informal network 17 years ago by WHO

Uses a network approach to build technical/scientific expertise, competence, and skills required to support regulatory decision making

Capacity building and training in member countries for both NRAs and NECs including clinical trial optimization exercises…

Collaborating effectively with several partners and stakeholders including AU agencies such as AUDA-NEPAD, US-FDA, EMA, Paul-Ehrlich…

Africa – An Attractive Venue for Clinical Trials

- Second-largest and second-most populous continent after Asia population 1.5 billion people, about 20% of the world's population.
- Youngest population with a median age of about 19 years.
- At least 3000 distinct nations with the greatest genetic diversity
- Africa Continental Free Trade Zone – a single marketplace with a population of 1.4 billion estimated to be 2.5 billion by 2050
- African Medicines Agency, a continental regulatory agency, will tremendously influence the future of clinical trials in Africa

Survey - Level of Preparedness for 31 AFRO Member states

Survey participation

- 27 NRAs
- 19 NECs
- 29 CRO/PIs

15 countries with participation of both NRA and NEC

12 countries with participation of NRA only

4 countries with participation of NEC only

Challenges Identified by NRAs/AVAREF

- Low Clinical Trial Activity (Quantity, Quality, Diversity) levels relative to international counterparts
- Inconsistent time to final regulatory decisions
- Limitations on Technical expertise, digital infrastructure, and other resources
- Human Resources – Expert Evaluators a Critical bottleneck

WHAT IS NEW AT AVAREF ?

Targeted expertise

- In-depth Capacity Building
- Cells, Tissues, and Gene Therapies, CHIMS, Antivenom, Platform studies…

Ecosystem Approach

- Engagement with investigators and clinical trial sites
- Promoting collaboration

Emergency Preparedness

- Strengthening frameworks for vaccine manufacturing readiness
- Regulatory preparedness

Integration with AMA

- Enhancing and harmonizing tools
- Strengthening regulatory harmonization efforts

2024-2026 AVAREF Strategic Action Plan

Excellence in Capacity Building

- **Training for Regulatory, Ethics Reviewers**
  Fundamental; Specialized
- **Multi-Country Joint Review of Clinical Trial Applications (CTAs)**
- **Regulatory Harmonization**
  Tools, Guidelines, Framework development

Partnerships and Alliances

- **African Union Organizations**
- **Competent International Regulatory Agencies and Institutions**
- **Donors, Development Partners**

Trusted Expertise Technical Support

- **Emergency Registration of Medicines**
  Covid-19 Vaccines, Ebola Vaccines, Malaria Vaccines, etc.
- **Rosters of Expertise**
  to support NRAs, NECs, and realization of African Medicines Agency
- **Technical Committees for Clinical Trials**

Life Cycle Approach

- **Innovation cycle**
  Design, research, commercialization, regulation, registration, post marketing
- **Clinical Trial Sites**
- **Vaccine Manufacturing**

4 Reinforcing Pillars for Capacity Building

- **Excellence in Capacity Building**
  - Continuing Education and training of NRAs
  - Training of NECs
  - Harmonization and capacity building through Joint Scientific Advice, Joint Review of CTAs, and joint review of registration dossiers
  - Optimization of clinical trial processes
  - Assisted and facilitated Reviews
  - Webinars, Discussion Sessions
  - A focus on francophone and lusophone members

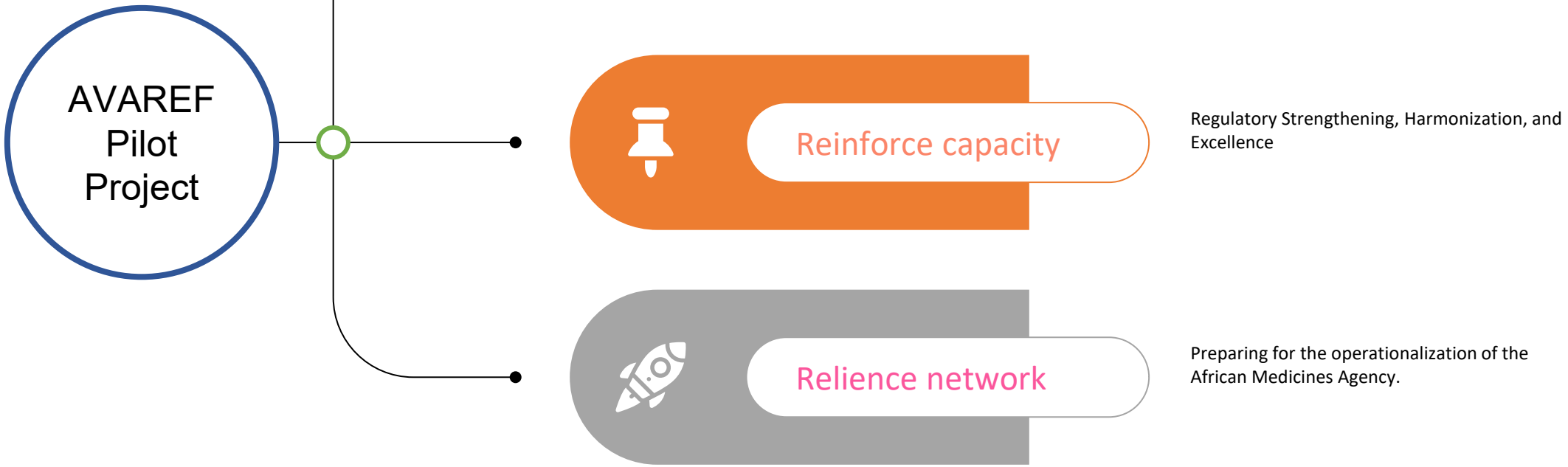
- **Partnerships and Alliances for Results**
  - Partnerships with Advanced country NRAs (USFDA,PEI), AUDA-NEPAD, EDCTP, CEPI, BMGF, Wellcome Trust, IVI, IFPMA, etc.
  - Co-development of training modules and delivery of training sessions
  - Expert Working Groups for development of Guidelines, norms, standards
  - Delivery of training with PEI, Ghana FDA, & NAFDAC

4 Pillars for Capacity Building

- **Trusted Expertise**
  - Pool of experts external to African NRAs to support all 3 pillars
  - Pool of Experts from African NRAs
  - Mentoring, Coaching, and Training
  - Assignments, Placements, and Exchange opportunities

- Life Cycle Approach
  - Basic and Applied Research
  - Clinical Research Ecosystem Strengthening
  - Clinical Trial Site Strengthening
  - Manufacturing
  - Registration of emergency medicines
  - Post-authorization safety and monitoring
  - Phase IV and pharmacopepidemiological studies

AVAREF Reliance Oversight Clinical Trials Pilot Project



Excellence in Capacity Building - Basic & Specialized Training

Development and delivery of **enhanced capacity building activities**

Training Courses in Applicable Sciences

pharmacology, toxicology, pharmacokinetics, pharmacodynamics, cell culture, project management, critical analysis of data, risk assessment, risk management, decision analysis, etc.

Training in Supportive skills

Policy Development, Quality Management Systems, Communications, Project Management, Performance Evaluation, etc.

Training in Advanced Courses

Principles of Clinical Pharmacology, **Adaptive and Master Protocol Design, Biostatistics** and Role of Randomization in Clinical Trials, Vaccine Product Development, Biosimilar Product Development

Complex and Non-traditional Designs and Capacity Building

- The efficacy studies required to support regulatory authorization of vaccines such Shigella, Invasive Non- Typhoidal Salmonella (iNTS) Vaccines, Group B Stephylocossus vaccines are prohibitive due to large patients required for phase III clinical trials, ethical issues in organizing clinical trials such as Ebola, Mpox, etc.
- Developers seeking guidance from regulatory agencies on suitable regulatory pathways to enable them accelerate product development.
- Decisions based on use of immune correlates of protection, adaptive design, etc.
- Conditional authorizations based on limited efficacy data.
- Neglected Tropical Diseases, Rare Diseases, Emergency Use Authorizations, **Chikungunya vaccines, eyc**
- Recent examples include:
  - Shigella Vaccine
  - Mpox Vaccines – Emergency use authorization and post authorization monitoring and surveillance

Comprehensive Rapid Cycle Analysis for Mpox Vaccine Safety and Disease Outcomes

Study	Arm 1	Arm 2	Arm 3
Description	Immediate Post-Vaccination Surveillance	Hospital-Based Surveillance for Delayed Mild and Serious AEFI	Clinical Characteristics and Management of Mpox Cases
Setting	Vaccination centres and primary healthcare facilities	Sentinel health facilities	Sentinel hospitals
Participants	Individuals receiving Mpox vaccination.	Vaccinated individuals presenting with potential vaccine-related conditions.	Individuals diagnosed with Mpox, regardless of vaccination status
Follow-up	30 minutes post-vaccination (on-site), then at 24 hours, 7 days, and 28 days	Duration of hospital stay, up to 28 days post-admission: for mild AEFI	Duration of hospital stay and up to 28 days post-discharge.
Primary Outcome	Immediate and mild AEFI	Delayed mild and serious AEFI characterization.	Clinical presentation, disease progression, treatment approaches, outcomes (including complete information on suspected adverse drug reactions)
Data Collection	Direct observation, participant self-reporting	Medical record review, patient interviews, laboratory results.	Medical record review, patient interviews, laboratory results.

Comprehensive Rapid Cycle Analysis for Mpox Vaccine Safety and Disease Outcomes

- **Study Design -** a multi-arm prospective observational design to comprehensively monitor Mpox vaccine safety and disease outcomes.

- The study protocol consists of three concurrent arms:
  - All three arms will run concurrently in [COUNTRY/REGION].
  - Sentinel sites have been selected based on their capacity to diagnose and manage Mpox cases, patient volume, and ability to implement the study protocol effectively.
  - Data collection across all arms will involve a combination of medical record review, patient interviews, and laboratory test results. Vaccination status will be verified using official records where possible.

- The study will run continuously, with regular interim analyses (every two weeks for Arm 1, monthly for Arms 2 and 3) to rapidly detect potential safety signals or changes in disease patterns.

- This multi-arm design allows for a comprehensive understanding of vaccine safety and disease outcomes, providing crucial data to inform public health decisions regarding Mpox vaccination and management strategies.

CONSIDERATIONS FOR DEVELOPERS AND ECOSYSTEM

- Regulatory and Ethics Capacity Building
  - Continuing Education – Training, workshops, seminars, webinars, etc
  - Simulated reviews
  - Multi-country joint reviews and scientific advice via AVAREF platform
  - Specialized trainings such as Biostatistics, Adaptive Designs, etc
  - Provision of actual regulatory dossiers for training
- Conduct more Clinical Trials In Africa
  - Early phase to late phase including phase IV studies
  - Increase African Principal Investigator led clinical trials
  - Increase clinical research, including North-South partnerships with Africa
  - Support regulatory systems strengthening initiatives with other partners such as Conference of Partners

Key Messages and Conclusions

1. AVAREF platform enables NRAs and NECs to build regulatory and ethics capacity while establishing a reliance network to support complex and non-traditional clinical trials.
2. The network approach promotes regulatory harmonization, excellence, and increased quality of reviews resulting from dedicated pool of reviewers within the 16-member reliance network.
    1. 1 submission package for multiple countries with streamlined administrative processes
3. Use of ecosystem and life cycle approach ensures a focus on all parties from researchers to manufacturers, procurers, and patients
4. Integration of rapid cycle analysis for effectively monitoring of safety to support these non-traditional study designs.
5. Increase Clinical Trials in Africa and Support Regulatory and Ethics Capacity Building on the continent

Contact AVAREF:

Dr Kwasi Nyarko: nyarkok@who.int

AVAREF Coordinator
WHO Regional Office for Africa
Brazzaville, Republic of Congo

Outbreak protocols

Purpose: Large outbreaks of Chikungunya may present an opportunity to generate evidence on efficacy / effectiveness of CHIKV vaccines. However, such outbreaks are unpredictable and may not provide sufficient time for trial set-up & implementation. This emphasizes the importance of advanced planning for an outbreak clinical trial. The session would focus on the development and feasibility for conducting outbreak studies and the various aspects involved in planning for such a study (e.g. pre-approved clinical trial protocols and other clinical trial documents, infrastructure
and logistics)

CEPI

Pre-approved clinical trial protocols for vaccine evaluation during outbreaks

Nina Wressnigg

Sao Paulo, 19-20 March 2025

CEPI's plan to prepare for future epidemics & pandemics

CEPI **2.0**

Vision statement

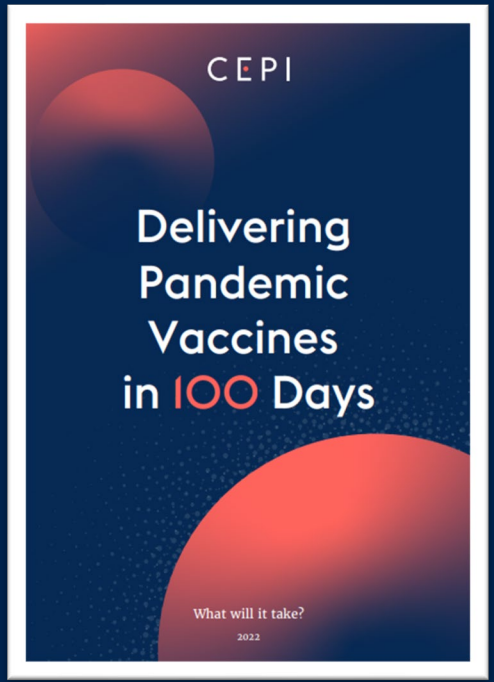
A world in which epidemics and pandemics are no longer a threat to humanity

Mission statement

Accelerate the development of vaccines and other biologic countermeasures against epidemic and pandemic threats so they can be **accessible** to all people in need

100

Days Mission

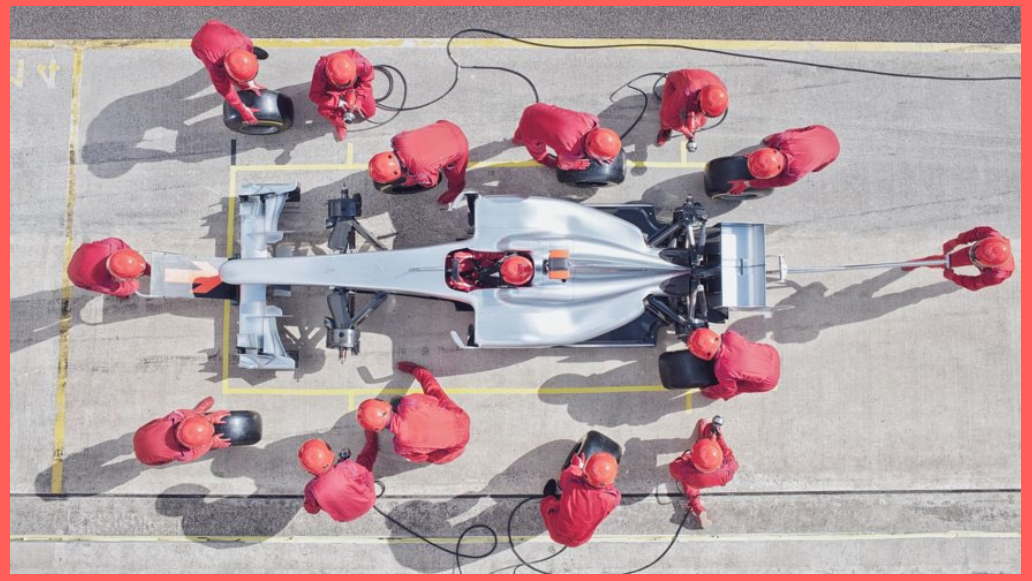


'Vaccines should be ready for **initial authorisation and manufacturing at scale** within 100 days of **recognition of a pandemic pathogen**, when appropriate.'

97% reduction

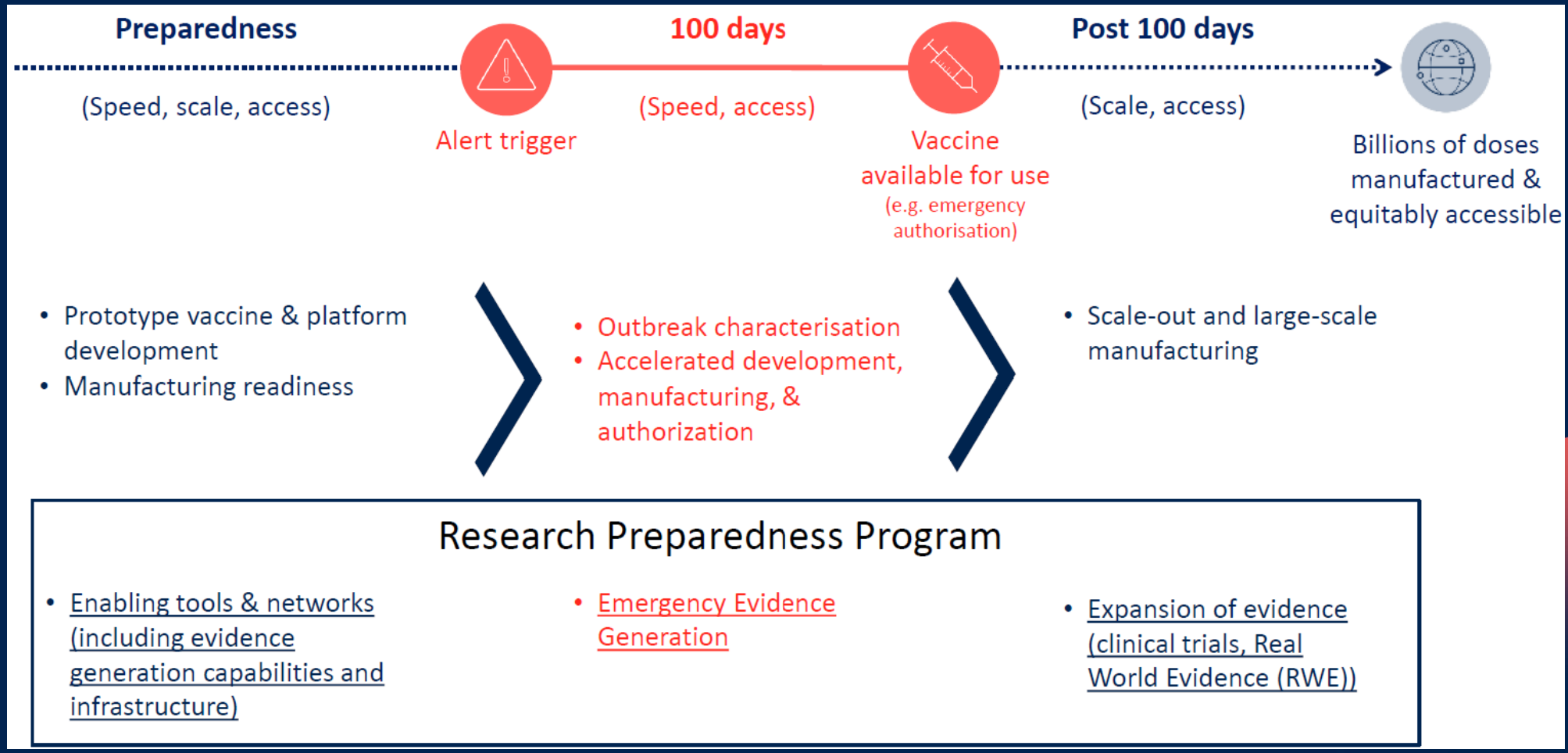
in elapsed time

1 minute



2 seconds

Evidence Generation is Critical for CEPI's 100 Days Mission



Research Preparedness Program

Leveraging capacity for routine clinical vaccine development to prepare for future outbreaks

Track A

Routine
clinical vaccine development

- ✓ Targeting CEPI's priority diseases
- ✓ Supporting all candidates on a portfolio level
- ✓ Working closely with *front runners* of each disease portfolio to optimize timelines
- ✓ Targeting key geographies
- ✓ Leverage and sustain infrastructure for emergency response (Track B)

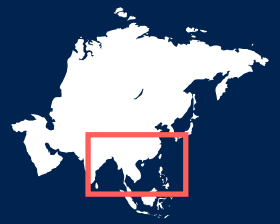
Track B

Emergency response
during future outbreaks / 100 days mission

- ✓ Embedding all infrastructure strengthening in national and supra-regional preparedness plans
- ✓ Conducting extensive stakeholder engagement with governments in close collaboration with Africa CDC and other supra-national public health agencies
- ✓ Working towards self-sustained infrastructure

West Africa
(e.g. Lassa fever, Marburg)
*** Pilot region ***

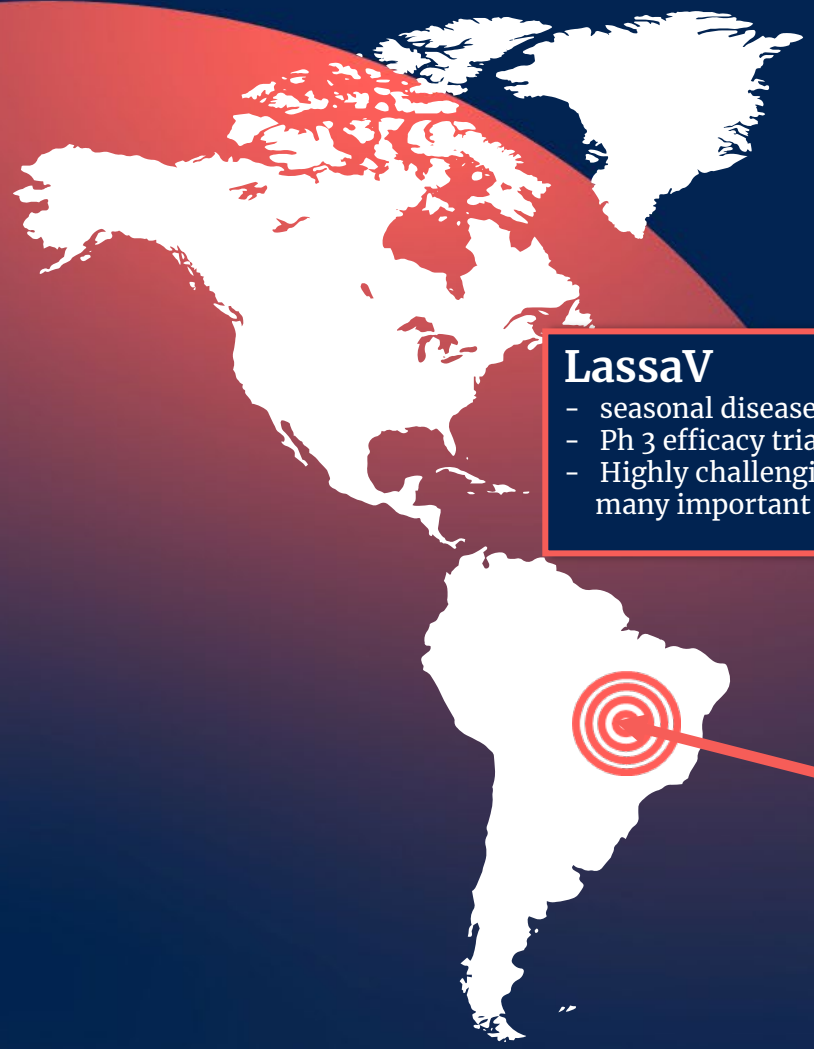
East / Central Africa
(e.g. SUDV, RVF)



South Asia (e.g. Nipah)

LATAM (+others) (e.g. Chikungunya)

Multi-level Approaches - One single strategy does not fit all



SARS-CoV-3
The next pandemic ???

SUDV
- the next outbreak will come (soon?), in the past only 2 countries (?), yet difficult to predict
- trial governance, sponsorship must be on stand-by
- Many stakeholders involved

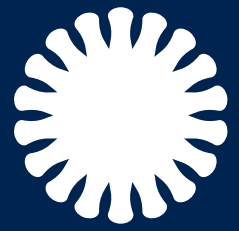
NipahV
- outbreaks in Bangladesh, Malaysia, India, Singapur
- currently Ph 3 trials no option

LassaV
- seasonal disease, changing spatial epidemiology
- Ph 3 efficacy trial complex, but possible
- Highly challenging ecosystem in West Africa w/ many important stakeholders to consider

CHIKV
- Can occour almost everywhere where the mocquito occurs....

Multi-level Approaches: One single strategy does not fit all

Different outbreak & pathogen characteristics



Platform-specific

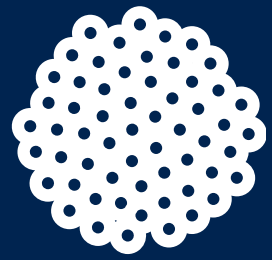
Early vs. late-stage development
Available (platform) data
Benefit-risk ratio
Regulatory status

Outbreak-specific

Local
Regional or multi-national
Epidemic or pandemic
Self-limited
Short-lived or multi-year

Pathogen-specific

Transmission
Virulence
CFR
R_0
Strain change etc.



Region-specific

Availability / effect of other public health containment measures

Library of Scenario-Specific Designs & Strategies

Pathogens
Chikungunya
Nipah
Filoviruses
Rift Valley Fever
MERS
SARS-CoV 1, 2
Disease X

Building a Library of pre-aligned Scenario Specific Designs & Strategies

- Scenario planning and evidence generation framework
- PRESTO project for trial simulation and feasibility
- Sophisticated sample size calculation embedded in simulation framework
- Develop scenario-specific, vaccine agnostic, clinical efficacy/effectiveness outbreak protocols
- Plug & play innovative clinical trial elements (eg. BoD, case-driven VE, Bayesian designs accommodating historical data borrowing, population enrichment, CoP)

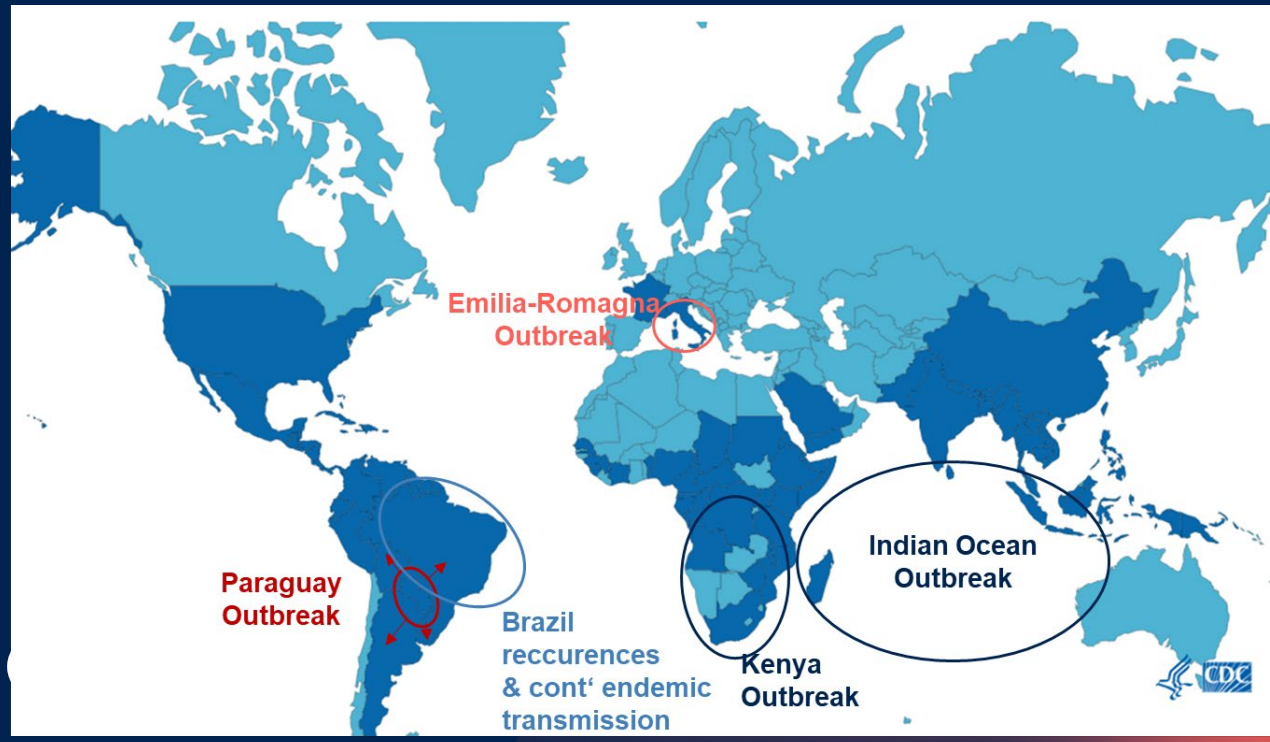
Library of clinical trial scenarios

Outbreak

Tailored scenario-specific **pre-approved protocol** (& other CTDs) **ready to use**

Chikungunya – Scenario-specific strategies to generate VE data

- Conducting vaccine efficacy trial for CHIKV vaccines is challenging mainly due to unpredictable epidemiology even in endemic regions
- While large outbreaks may present an opportunity to generate efficacy evidence, it may still not provide sufficient time for trial set-up & implementation
- This emphasizes the importance of advanced planning – logistically as well as financially
- **Ready-to-go, pre-approved protocols** may allow rapid initiation of time-sensitive clinical trials, adaptable to different vaccine candidates during an outbreak.



Source: modified from CDC

Thank You

CEPI

Operational and Other Planning for Conducting Clinical Trials of Vaccines During an Outbreak

Libia Milena Hernandez Medina.
International Vaccine Institute (IVI)

CHIKV Regulatory Workshop – CEPI,
Mar 19-20 , Brazil 2025

International Vaccine Institute

Introduction

These pathogens result in outbreaks with unpredictable spatiotemporal incidence, though transmission of some of these pathogens at ongoing low levels may not be classified as a PHE of international concern (PHEIC).

- **Chikungunya**
- COVID-19
- Lassa fever
- Crimean-Congo Haemorrhagic Fever (CCHF)
- Ebola virus disease and Marburg virus disease
- Middle East respiratory syndrome coronavirus (MERS-CoV)
- Nipah and henipaviral diseases
- Rift Valley Fever (RVF)
- Mpox

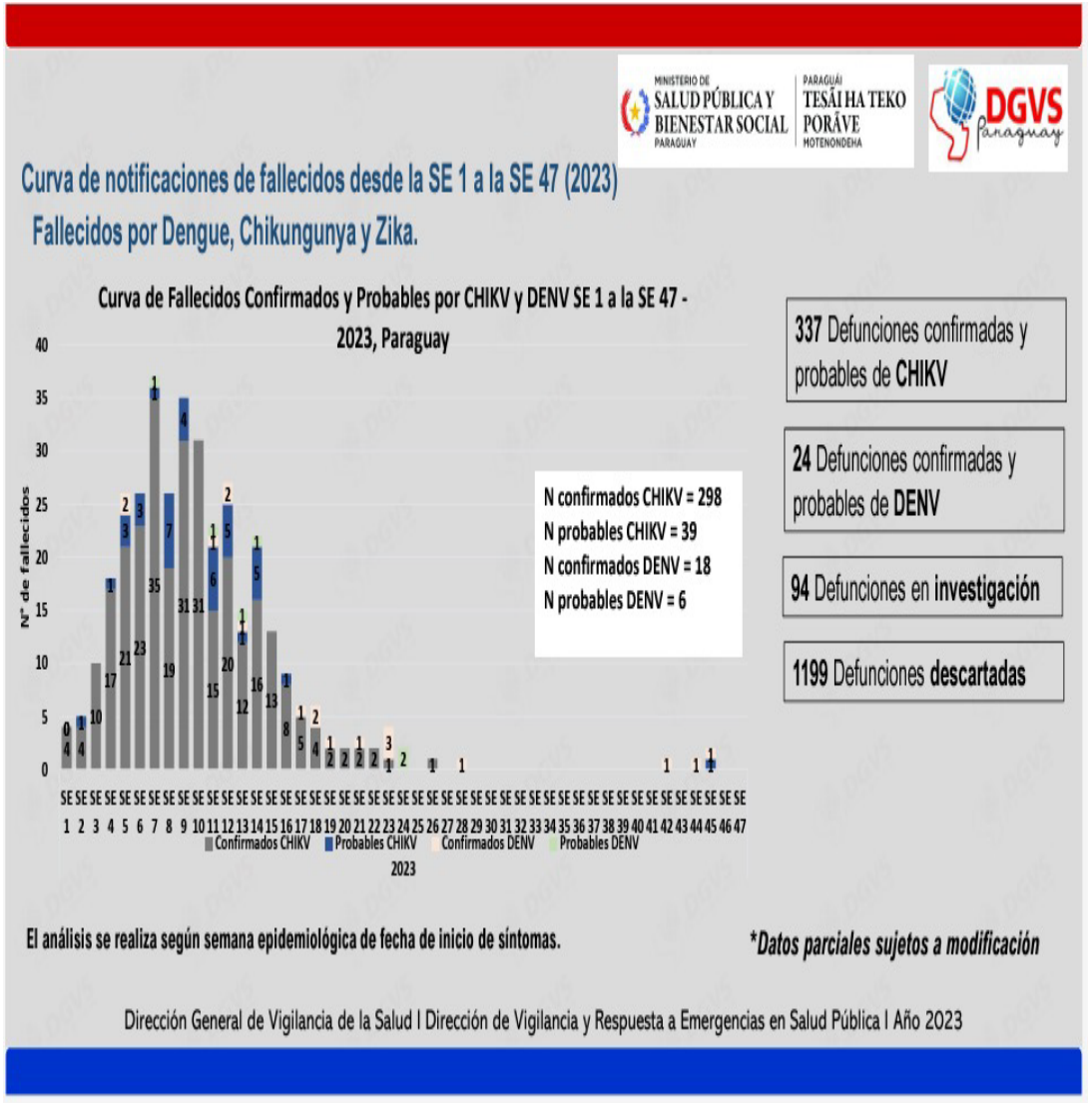
Conducting a randomized controlled vaccine efficacy trial is challenging due to the unpredictable nature disease outbreaks, which are explosive and relatively short in duration.

Background

- Conducting a randomized controlled vaccine efficacy trial is **challenging** due to the **unpredictable** nature of CHIK disease outbreaks, which are explosive and relatively short in duration.
- Chikungunya causes a febrile episode with **severe joint pain**, malaise and in some cases, it progresses to *Chronic arthritis*. People with pre-existing conditions, neonates, infants, and the elderly may experience **severe complications** and **death**.
- Large outbreaks can overwhelm healthcare systems in resource-limited settings.
- CHIK:~**337 deaths** in Paraguay (2023); with most occurred within **23 weeks.**

- The IXCHIQ (VLA1553) Vaccine received approval based on **immune response data** from a clinical study conducted in the US adults. *Roques P JCI Insight. 2022 Jul 22;7(14):e160173*
- However, this may change in case of a sufficiently large outbreaks i.e. CHIK , and present an opportunity for generating efficacy data.
- **Advanced planning** and **preparation** would be key such as '**ready-to-go**' clinical trial documents including protocols.

Outbreak in Paraguay 2023



Epidemiology and Economic Burden of Chikungunya: A Systematic Literature Review. Trop. Med. Infect. Dis. 2023, 8, 301. https://doi.org/ 10.3390/tropicalmed8060301

Challenges in the Preparation and Conduct of Clinical Trials

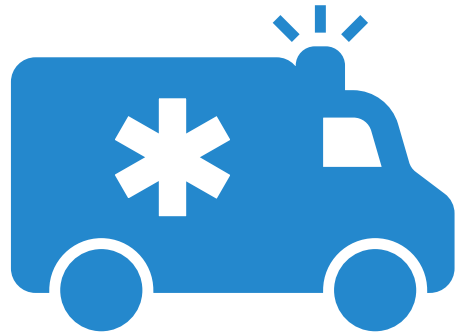
Clinical trials face challenges across various contexts:

- Normal epidemiological conditions

- **Outbreak situations**, and

- **Outbreaks situations** in **remote areas**/specific locations

(Poor infrastructure, lack of trained personnel, and inadequate storage & Lab capacity)



Challenges of Conducting Vaccine Trials During an Outbreak

- **Time Constraints: Rapid onset and spread** limit the window for trial initiation. **Starting as soon as possible** is crucial, as outbreaks are short

- **Regulatory Challenges : Lengthy approval processes**

-The regulatory capacity of the national **regulatory authority** & **ethics committee** impacts the revision and approval timelines

- **Political situation and Cultural aspects:** Influence trial feasibility and acceptance,

- **Logistical Challenges:** Infrastructure, site readiness, supply chain constraints and availability of Experienced personnel in clinical trials.

- **Community Engagement:** Building trust and ensuring participation during a health crisis

- **Financial :** Expedited funding to initiate trials

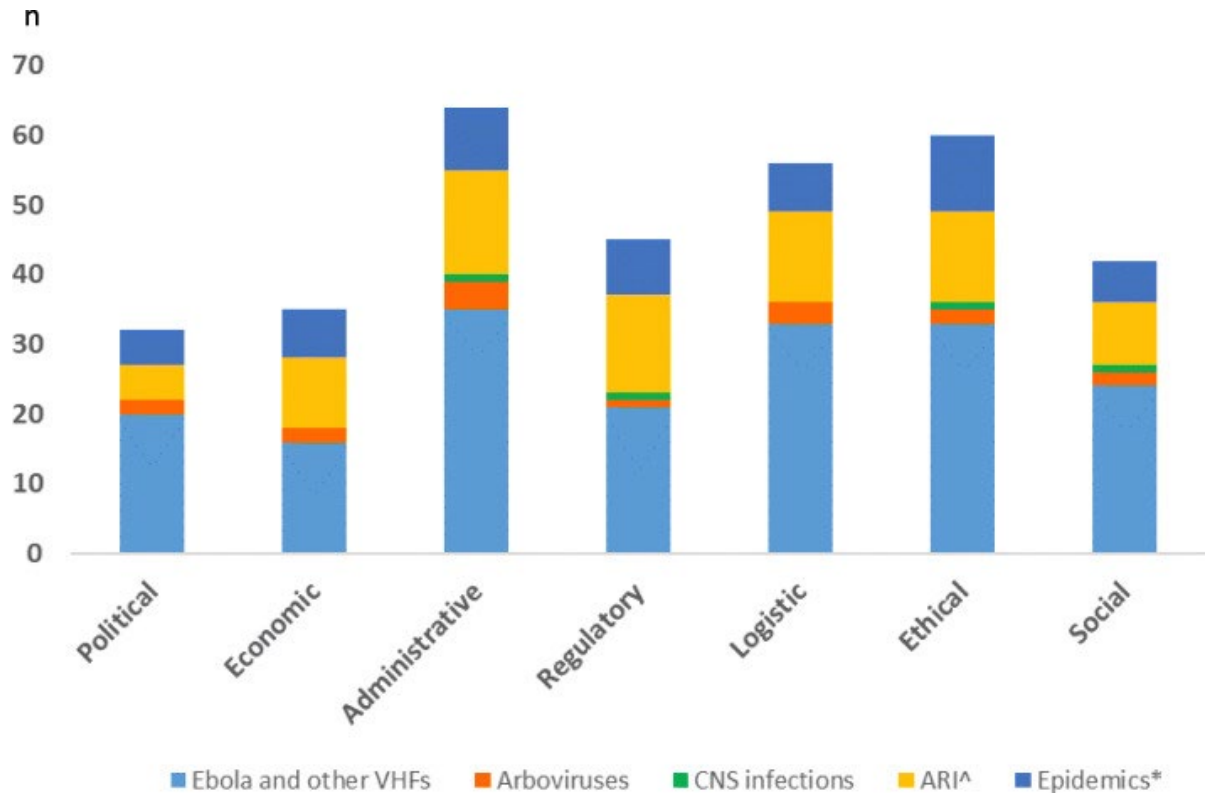


Fig. 2 Type of outbreak and PEARLES domains addressed. ^Articles focused on influenza, severe acute respiratory infections and pandemics;*Non-specified emergency epidemics. VHF, viral haemorrhagic fevers; Arboviruses, arthropod-borne viruses; CNS, central nervous system; ARI, acute respiratory infections

Matuvanga et al. (2022). *Setting up an Ebola vaccine trial in a remote area of the DRC: Challenges, mitigations, and lessons learned.* Vaccine, 40(23), 3191-3198. *https://doi.org/10.1016/j.vaccine.2022.04.094*

Sigfrid et al. (2020). *Addressing challenges for clinical research responses to emerging epidemics and pandemics: A scoping review.* BMC Medicine, 18:190. https://doi.org/10.1186/s12916-020-01624-8

Critical considerations when designing vaccine trials during outbreaks

The **urgency** of the situation requires **agility**, **intense activity** and **adaptability** to context

Identify Reference Sites – to accelerate trial readiness & to support other sites at other locations.

Regulatory **flexibility** , approvals must **move faster**

Securing funds quickly

Earn Trust – Community engagement is key

The need of **rapid data collection**

*Identifying key considerations in planning trials during outbreaks is essential to **anticipate challenges** and devise strategies that prioritize participants welfare*

Importance of Pre-Approved Protocols and Regulatory Readiness

- "Pre-approved, pre-positioned study protocols was a key solution recommended to reduce set-up delays in previous outbreaks."

Sigfrid et al. (2020). *Addressing challenges for clinical research responses to emerging epidemics and pandemics: A scoping review.* BMC Medicine, 18:190. https://doi.org/10.1186/s12916-020-01624-8

Developing **pre-approved** clinical trial protocols to minimize delays

Establishing **adaptive trial designs** for flexibility in different outbreak scenarios

Engaging with NRAs and ECs

before an outbreak occurs for expedited review processes and rapid trial activation

Stakeholder Engagement for Trial Readiness to address operational and logistical barriers to trial implementation & to mitigate possible community resistance

A mechanism for **achieving consensus regarding elements of the protocol** is required (e.g., Managing data (CRF), sharing samples, mediating disagreements)

Importance of Pre-Approved Protocols and Regulatory Readiness

Stakeholder Engagement & **Regulatory Pathway** : to ensure trial feasibility and pre-approval

Outbreak Scenario modelling

Phase 1
Early Expert Consultations

- ✓ **Experts & clinical trial methodologists** from the affected countries/regions, WHO, CEPI
- ✓ **Refine study designs**
- ✓ **Establish Best practices:** Reviewing vaccine development strategies and trial precedents

Phase 2
NRA Regulatory and ECs Engagement

- ✓ **Align regulatory requirements** and facilitate pre-approval of trial protocols.
- ✓ **Approval process mapping**: Assess country-specific regulatory landscapes for faster document approvals & trial activation during outbreaks
- ✓ **Address key ethical concerns**, including risk-benefit considerations & informed consent challenges in outbreak settings.

Phase 3
Stakeholder and community Engagement for Trial Readiness

- ✓ Vaccine developers, ministries of health, outbreak response teams & Community
- ✓ Address **operational** and **logistical barriers**
- ✓ **Build trust** and address concerns in outbreak settings
- ✓ **Mitigate** community **resistance**
- ✓ **Training**

Implementation reediness

- Protocol Preapproval
- Regular protocol updates

Possible outbreak scenarios for trial readiness → **Development of scenario specific trial protocols** → **Identifying and pre-qualifying clinical trial sites in high-risk regions:** → **Finalize all clinical trial documents** → **Site Readiness**

Logistical Challenges : Infrastructure and Site Readiness

Use predictive models early in different countries

Identifying and **pre-qualifying clinical trial sites** in high-risk regions

-**Identify the requirements** for the clinical trial sites

-**Site feasibility**

-**Develop Standard Operating Procedures (SOPs**

-**Quality Control Plan**

-**Cold chain** preservation activities(e.g. temperature monitoring)
- **Back up** refrigerator/freezers for vaccine and sample storage
- **Back-up power** to the trial site.

Laboratory capacity for sample processing and diagnostics

-Investigational Product **accountability**

Training staff and healthcare workers ahead of outbreaks.

- **Availability of sufficient local trial staff**

-Prepare **study documents** & their respective translation .

ICFs should be less complex , subject Diary

-**Insurance policy**

-**Approved** recruitment materia

-Strengthening **supply chains** for investigational vaccines*, lab materials, and PPE

-**Finance**

SITE INITIATION VISIT & SITE READINESS ASSESSMENT/ ACTIVATION by Sponsor / (CRO)

***Vaccine shipment, transfer to Depot , transfer to sites**

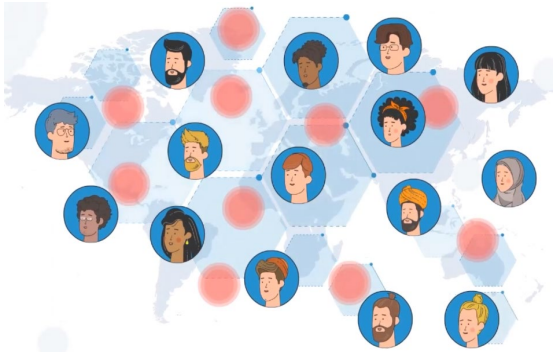
Data Management and Real-Time Monitoring

- **Implementing digital tools for real-time data collection and remote monitoring**
- **Ensuring robust data security and integrity for regulatory compliance**
- **Planning for interim analyses to support rapid decision-making**
- **CRFs**
- **DSMB charter /meetings**

Incorporating real time data monitoring allows resear chers to make informed decision rapidly , ensuring safety and efficacy of the vaccine under study

Collaboration with International Stakeholders : Key strategies and Expected outcomes

- **Effective partnerships** : countries & international organizations, WHO, CEPI, GAVI, PAHO, (NGOs, pharmaceutical companies, NRAs, and with local governments (socio-political network).
- Engaging **manufacturers early** for rapid vaccine deployment.
- Aligning with global networks for **data-sharing** and cross-border regulatory harmonization.



- ✓ Ensure Global **political awareness**.
- ✓ **Strengthen collaboration** among international organizations, national leaders & local stakeholders.
- ✓ **Establish** a **WHO-led governance framework** to guide research efforts during disease outbreaks.

- ✓ **Integrate research** in international outbreak response.
- ✓ **Ensure interventions are supported by all stakeholders**
- ✓ **Foster** close collaboration among local and international researchers from the beginning, **emphasizing capacity building** & **genuine cooperation.**

- ✓ Promote **National Leadership** in research
- ✓ **Invest in national public health research institutes**

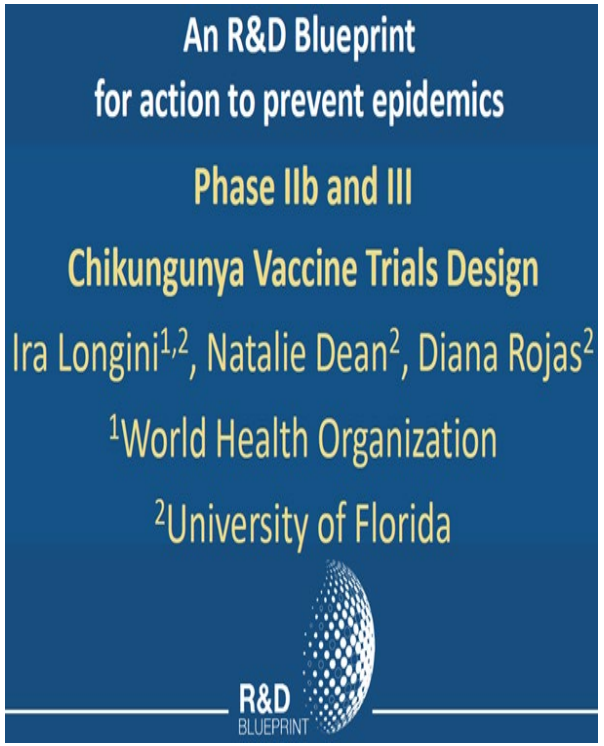
*"While several barriers to conduct clinical trials in LMICs have been identified, former experiences suggest that these can be overcome through **international collaboration**"*
Matuvanga et al. (2022). *Setting up an Ebola vaccine trial in a remote area of the DRC: Challenges, mitigations, and lessons learned.* Vaccine, 40(23), 3191-3198.

Canario Guzmán JA et al. Ethical challenges in international research during the Zika outbreak in the Dominican Republic. *Health Res Policy Syst.* 2017;15(82).

Recruitment Strategies

- ✓ It is essential to consider **rapid** recruitment strategies
- ✓ Recruitment strategies must **be tailored** to the **context of the outbreak**, addressing barriers to participation and ensuring diverse representation in the trial.
- ✓ Ensure **adequate compensation** for participants' costs during trial activities.

Take into account Acute Case definition : *based on WHO definition*



- **Emergency setting (reactive/outbreak use):** protection of **at-risk persons in the area of an ongoing outbreak of chikungunya.**
- **Non-emergency setting (preventive use)**: Populations living in areas where chikungunya is endemic.

When transmission is detected, start community-based (e.g. door-to-door) enrollment of participants

UNDERSTANDING THE SPREAD OF CONTAGION

- **(i) "focal"** transmission involving individuals residing in spatiotemporal proximity to the residence of an infector,
- **(ii) "local"** transmission of infections occurring among residents from the same area that were not considered focal, and
- **(iii) "exported cases"** defined as not residing in but with a known epidemiological link to Anzio.

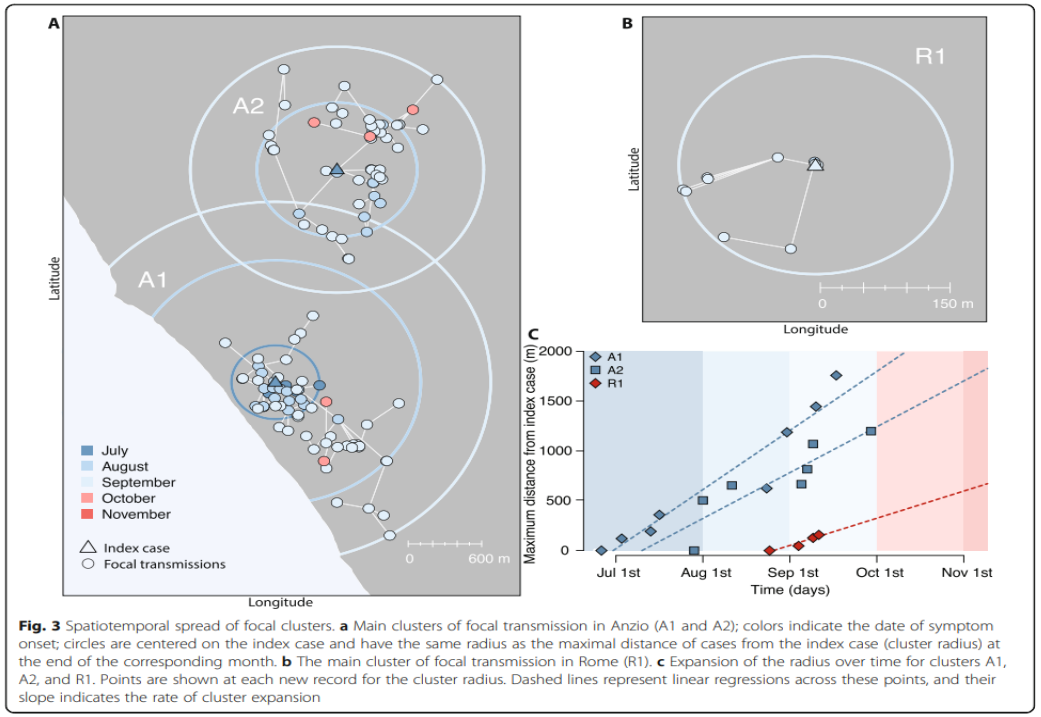


Fig. 3 Spatiotemporal spread of focal clusters. **a** Main clusters of focal transmission in Anzio (A1 and A2); colors indicate the date of symptom onset; circles are centered on the index case and have the same radius as the maximal distance of cases from the index case (cluster radius) at the end of the corresponding month. **b** The main cluster of focal transmission in Rome (R1). **c** Expansion of the radius over time for clusters A1, A2, and R1. Points are shown at each new record for the cluster radius. Dashed lines represent linear regressions across these points, and their slope indicates the rate of cluster expansion

Guzzetta, G., Vairo, F., Mammone, A. et al. Spatial modes for transmission of chikungunya virus during a large chikungunya outbreak in Italy: a modeling analysis. BMC Med 18, 226 (2020). https://doi.org/10.1186/s12916-020-01674-y

FUNDING

- ✓ Establish **dedicated** funding sources in **inter-epidemic** times.
- ✓ Establish **international agreements** on financial mechanisms for **rapid release** of funding and for addressing clinical trial liability coverage.
- ✓ National governments **to strengthen investments in preparedness** and **response.**
- ✓ Coordinate funding to ensure it **is rapid and sufficient** by using **international coalitions** and economies of scale.
- ✓ Ensure sufficient, specific **and flexible funding for research staff** to avoid healthcare opportunity costs.
- ✓ Explore **industry funding** to **complement** public funding.
- ✓ Provide **appropriate compensation** for **participation** in research.

Sigfrid et al. (2020). *Addressing challenges for clinical research responses to emerging epidemics and pandemics: A scoping review.* BMC Medicine, 18:190. https://doi.org/10.1186/s12916-020-01624-8

Challenges in Conducting Clinical Trials Across Different Contexts

Category	General Clinical Trials	During an Outbreak	Country-Specific including remote location
🛑 **Ethical Approval**	• Ethical and regulatory frameworks designed for non-acute epidemics • Standard IRB/EC approval required	• IRB/EC Expedited review possible, but possible delays due to high volume of urgent applications.	• **Delays** in obtaining EC clearance are particularly common in countries with **lower clinical research experience.** • **Limited ethics committees,** potential delays, and lack of experience in outbreak research.
📜 **Regulatory Approval**	• IND/CTA submission • Standard	• Emergency pathways (e.g., EUA) • Accelerated approval pathways, but regulatory overload may slow the process.	• In LMICs, the national regulatory authorities have **limited regulatory capacity** and **lacks the resources** to ensure effective oversight and regulation • It has occurred **that there is no official communication channel** whereby the **regulatory requirements are documented**, such as **website** that outlines the **submission and processing timelines** • Clinical trial regulations are becoming **more complex** and **costly**, delaying trial completion in LMICs and slowing vaccine and drug approvals.
🏥 **Site Requirements**	• GCP-compliant sites • Certified research sites • Well-equipped sites with trained staff and infrastructure.	• Special licensure for non-certified sites • Flexible site selection due to urgency • Some sites may be overwhelmed with outbreak response, limiting resources for trials. • Remote training	• Research sites should comply with the minimum requirements. • **Poor infrastructure**, lack of trained personnel, and inadequate storage and laboratory capacity.
⚠️ **Safety Monitoring**	• Standard reporting • Robust safety monitoring with established procedures and oversight	• Real-time/adaptive monitoring	• **Limited safety monitoring** due to lack of trained personnel, resources, and technology
🗣️ **Community Engagement**	• Standard recruitment	• Rapid engagement needed; fear and misinformation may create resistance. • Intensive risk communication	• **Difficulties in communication, cultural barriers, and mistrust in medical researc**

Lessons Learned from Previous Outbreak Studies

1. Rapid Vaccine Development Using Novel Platforms

- **mRNA and DNA Vaccines Enable Fast Response *(Lesson from COVID-19, Ebola)***
  - These platforms allow for quick design and manufacturing compared to traditional vaccines.
  - Example: COVID-19 mRNA vaccines reached clinical trials within months of sequencing the virus.

2. Adaptive Trials and Surrogate Markers Reduce Reliance on Large-Scale Efficacy Trials

  - Example: **VLA1553 (Chikungunya vaccine** leveraged immune markers to support approval without a large field trial.

3. Regulatory Strategies to Expedite Vaccine Availability

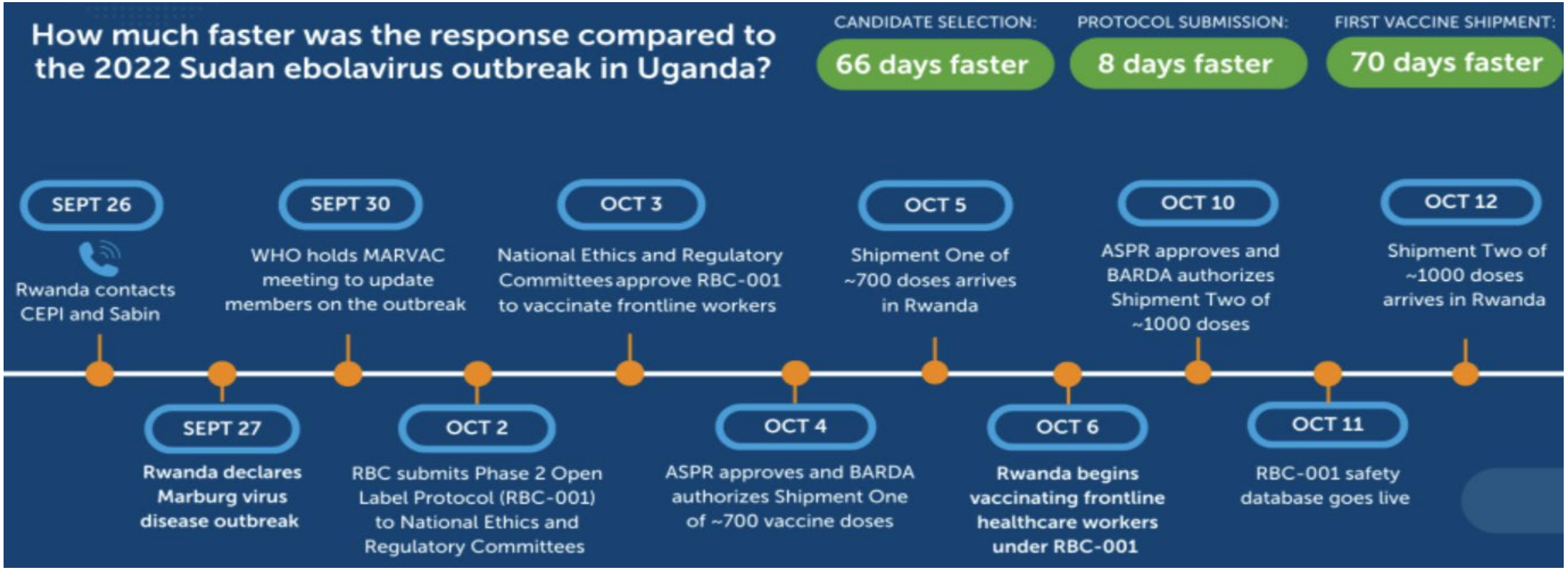
- **Regulatory Flexibility and Emergency Use Authorization (EUA) Pathway *(Lesson from COVID-19, Ebola, Mpox)***
  - EUA frameworks allow vaccine deployment before full approval during public health emergencies.
  - Example: COVID-19 vaccines were distributed under EUA, saving lives before full licensure.
  - Licensure in other centers
  - Improvement in infrastructure readiness

4. Proactive Preparedness to Avoid Delays in Vaccine Distribution

- **Global Collaboration and Preventive Stockpiling *(Lesson from Influenza, Ebola, COVID-19)***
  - Ensuring vaccine availability before outbreaks reduces response time.
  - **COVAX-like financing mechanisms** could ensure equitable access to vaccines in high-risk regions before outbreaks.
  - Example: **Strategic stockpiling** of Ebola vaccines enabled rapid deployment in the 2022 Uganda outbreak.

10 Days From Marburg Outbreak Declaration to Vaccination: A High-Level Timeline
Rapid Response to Marburg Outbreak in Rwanda

- Vaccine Deployment: Sabin, Rwanda MoH, BARDA, and partners delivered **investigational vaccines** within 9 days
- Frontline Health Worker Vaccination: Started the next day under an open-label trial
- 2,700+ doses shipped to Kigali
- Outbreak Ended: December 20, 2024 (66 cases, 15 deaths). Low Fatality Rate: 23% vs. 50% average



Sabin Vaccine Institute. *10 days from Marburg outbreak declaration to vaccination: A high-level timeline.*
https://www.sabin.org/resources/10-days-from-marburg-outbreak-declaration-to-vaccination-a-high-level-timeline/

Conclusion and Key Takeaways

- Advanced planning is essential to mitigate delays and maximize trial impact
- Pre-approved protocols and regulatory readiness can significantly shorten study start-up times
- Strong partnerships and community engagement are critical for success
- Several barriers to conduct clinical trials in LMICs can be overcome through international collaboration.
- Leveraging digital and adaptive trial methodologies enhances efficiency
- Maintaining the site's infrastructure is desirable.
- Final thought: Investing in preparedness today will accelerate vaccine deployment during future outbreaks.

Thank you

International Vaccine Institute

PRESTO

PREpare using **S**imulated **T**rial **O**ptimisation


Christophe Fraser


James Hay

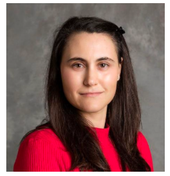

Caitlin Pley


Lucie Abeler-Dörner


Rob Hinch


Ian Roberts


Luca Ferretti


Jasmina Panovska-Griffiths

UNIVERSITY OF OXFORD

PANDEMIC SCIENCES INSTITUTE

CEPI

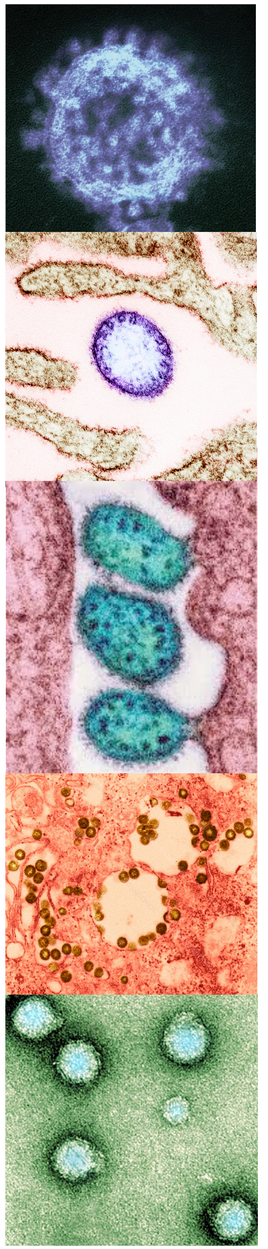
PRESTO

PREpare using Simulated Trial Optimisation

- **New project** funded by CEPI to use modelling to help optimise trial design

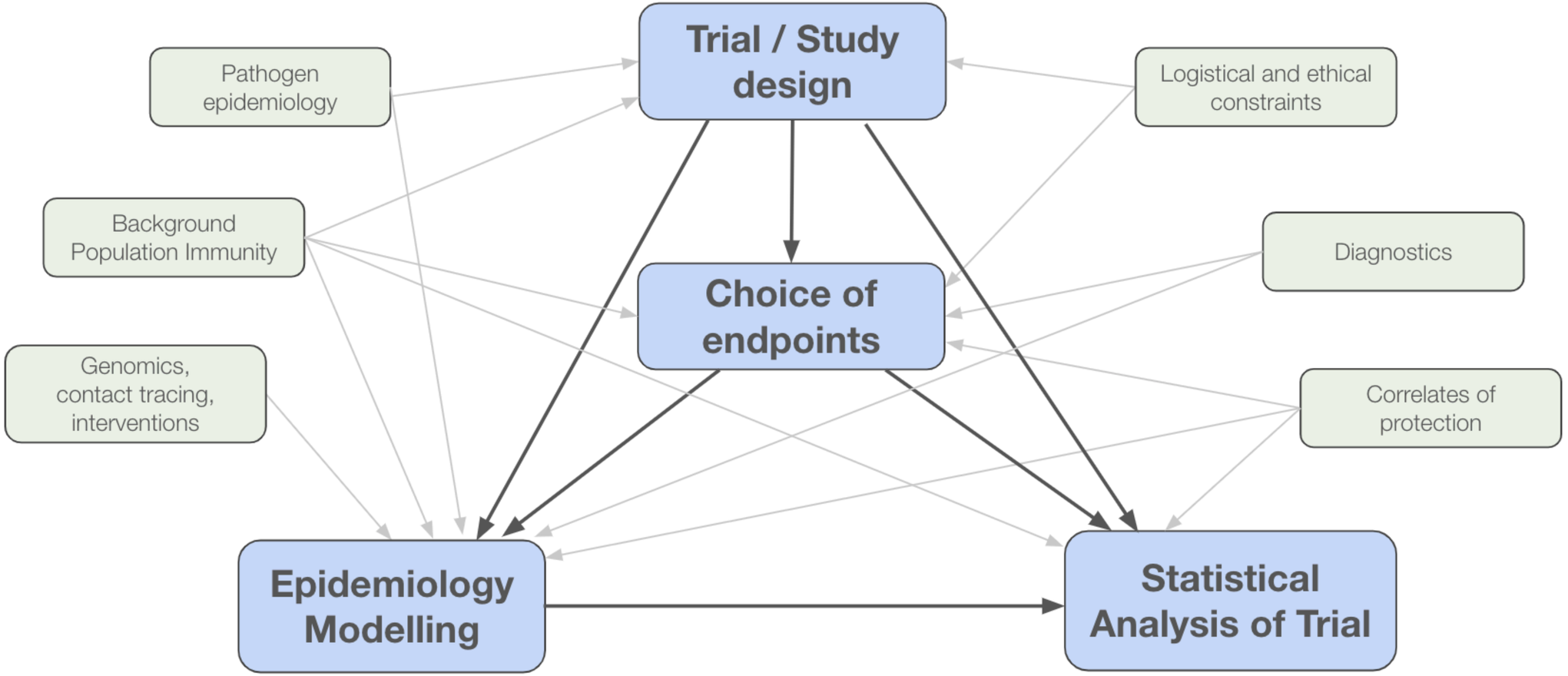
- **Purpose** - to accelerate the estimation of vaccine efficacy and real-world effectiveness by simulating vaccine trial and study designs taking into account logistical constraints

- **Scope -** the seven pathogens identified by CEPI as priority pathogens and potential variants with epidemic/pandemic potential: Nipah, MERS-COV, Lassa, Ebola, Rift Valley Fever, Chikungunya, Disease X — and now mpox



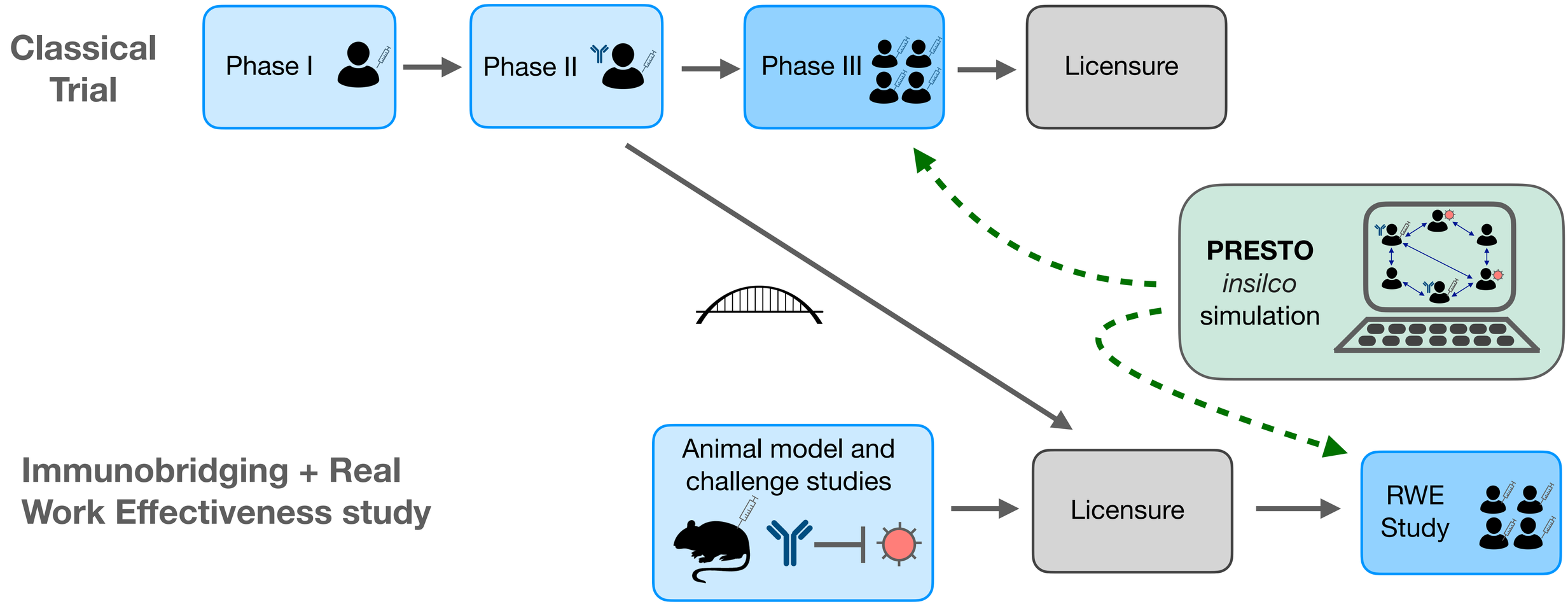
PRESTO

PREpare using Simulated Trial Optimisation

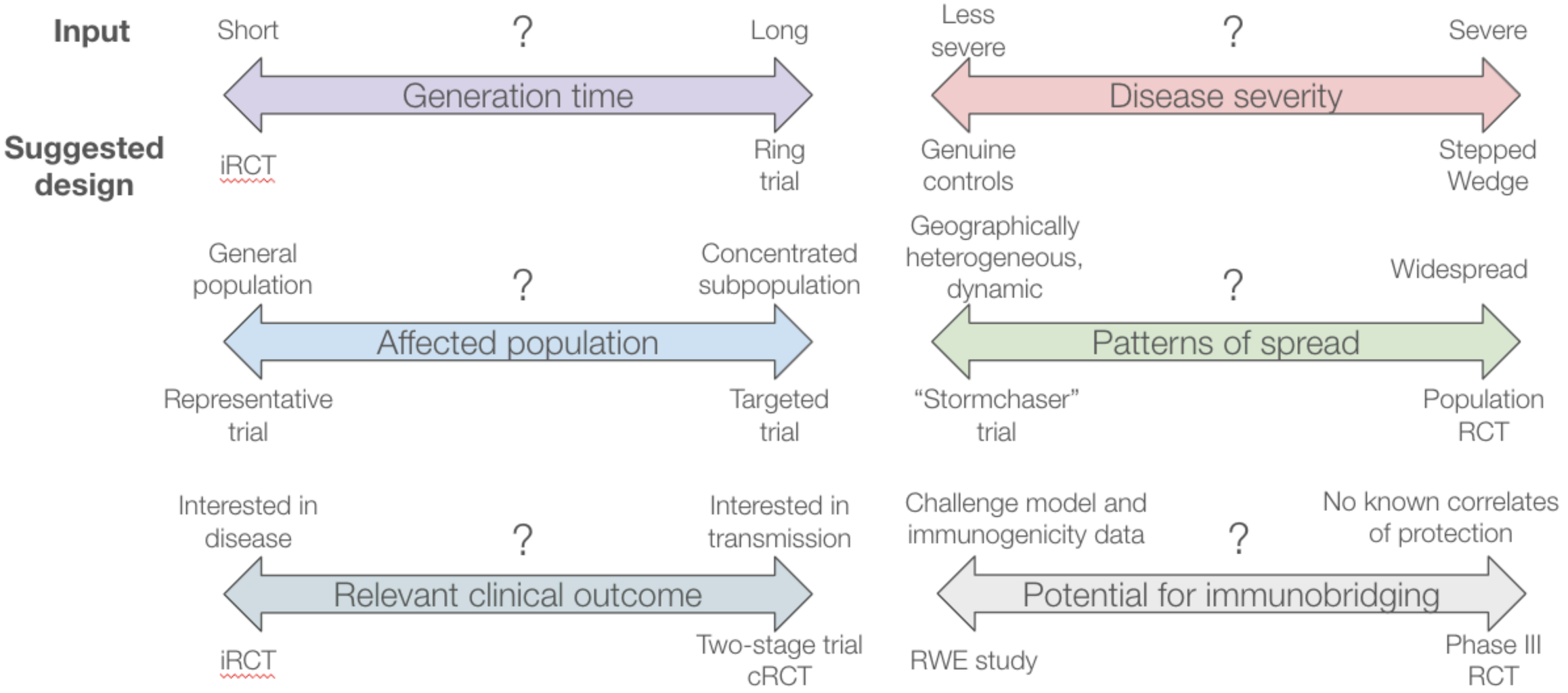


PRESTO

Vaccine Trial Types

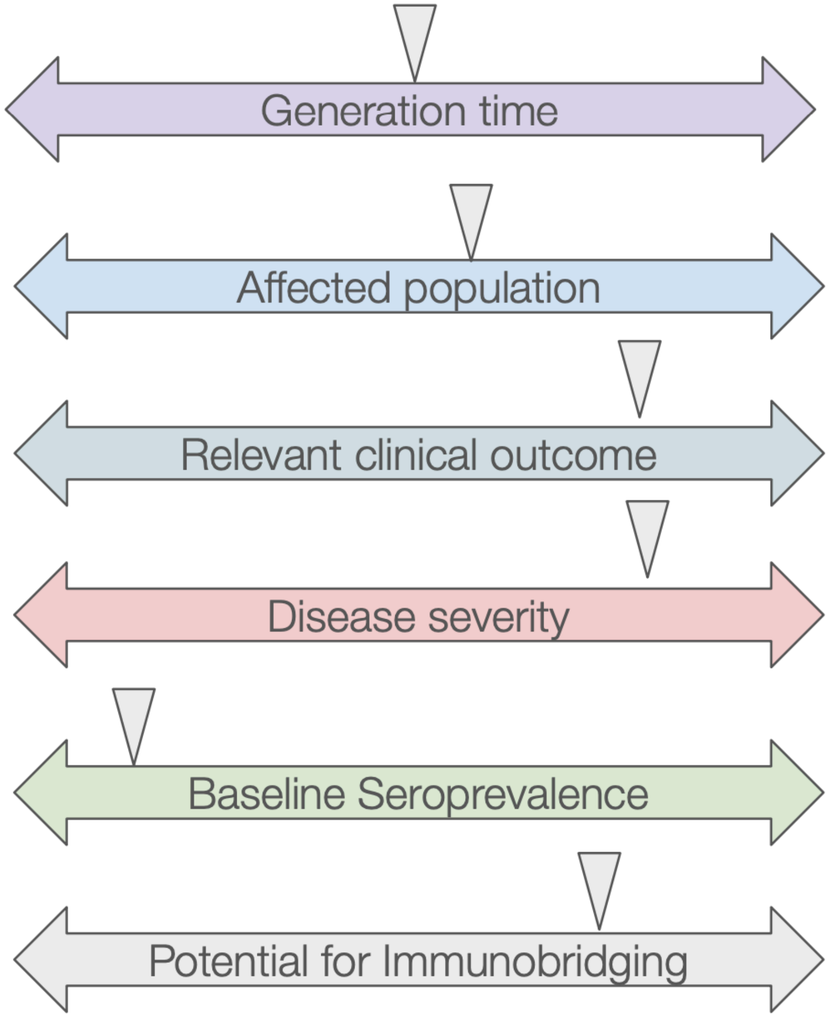


Choosing the right trial design is a multi-dimensional problem with interdependent factors



PRESTO

Example Analysis Sheet



14 days

Concentrated / Generalised

Disease, Death

Very High

No Immunity

Challenge model data available

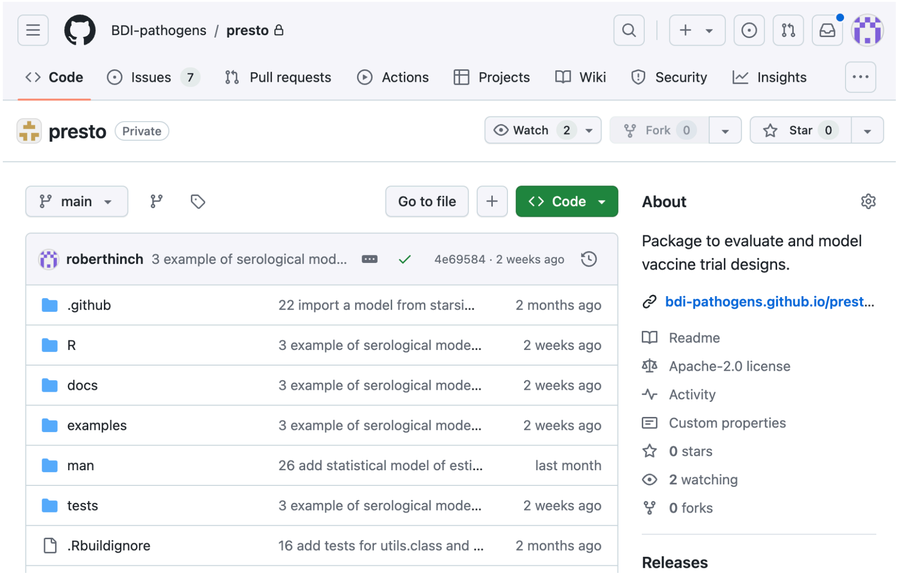
	iRCT	cRCT	2-stage	Ring
Sample size				
Duration				
In-trial deaths				
Endpoint				
Cost				
Score	15	17	18	70
Ranking	4	3	2	1

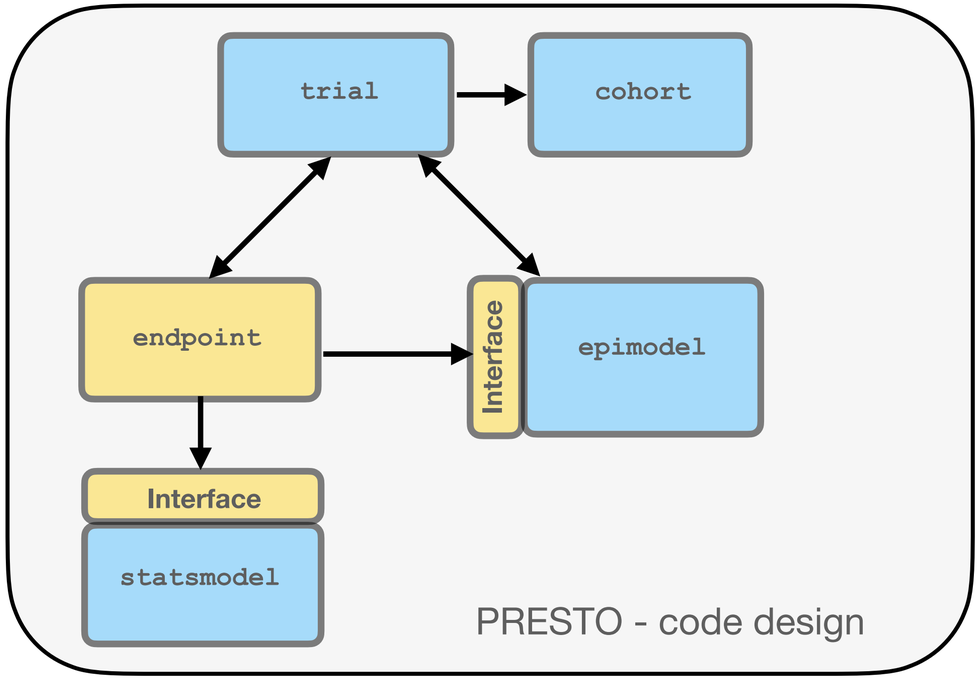
low medium high

PRESTO

Initial work

- **R package** on Github: https://github.com/BDI-pathogens/presto/
- **Modular -** enforced by use of interfaces on classes
- **Tested** - automated regression testing in Github
- **Documentation** - web-based including extensive examples
- **Trials implemented**
  - Trials - 1 (iRCT, cRCT)
  - End-points - 2 (e.g. total-case)
  - Epimodels - 4 (including external IDM model)
  - Statistical models - 3

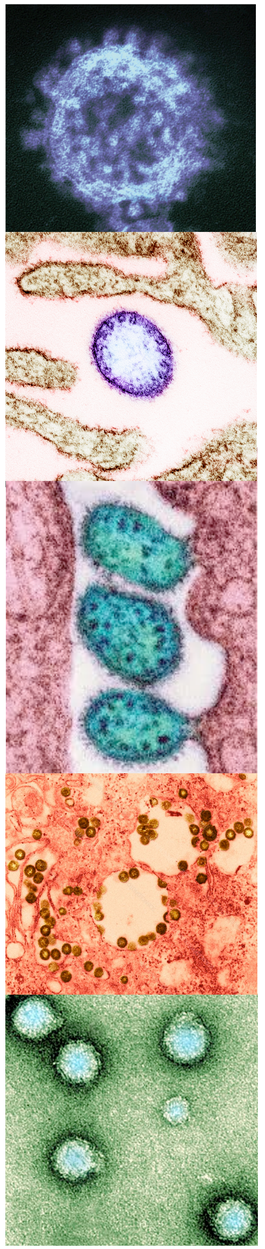




PRESTO

Areas for innovation / pushing boundaries

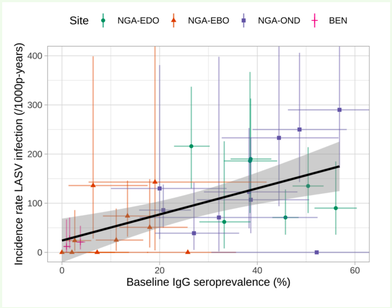
- Integrating vaccine evaluation into early operational response.
- Integrating newer approaches for correlates of protection.
- Estimating time since infection: before or after vaccine protection.
- Using digital approaches to measure exposure, and for digital ring trials.
- Integrating genomic & contact tracing for measuring VE_{total}.



PRESTO - Example

Lassa Vaccine Efficacy Trial (trial in an endemic region)

Data from Enable Study



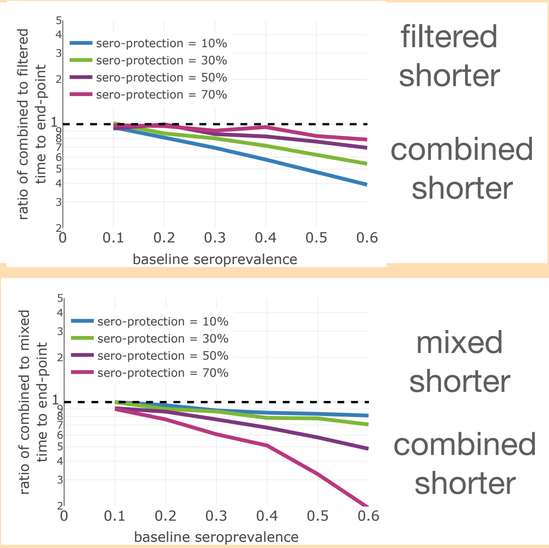
Trial

Individual randomised control trial

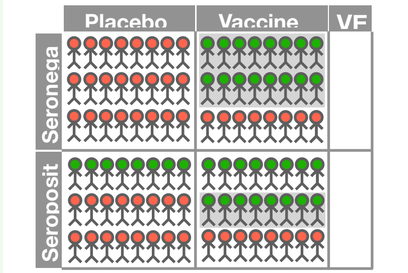
End-points

All participants
Baseline seronegative only
Baseline serostatus aware

Analysis of Trial Designs



Vaccine Efficacy on Baseline Seropositive



Epimodels

Multinomial models
Agent-based model

Statistical Models

Frequentist Binomial
Bayesian Combined

Panel discussion on planning for outbreak trials and pre-approved clinical trial protocols for vaccines

CEPI, Nina Wressnigg - Moderator

Paraguay, Pastor Perez Estigarribia (UNA)

EMA, Marco Cavaleri

Rwanda FDA, Alphonse Ndayambaje

Brazil, Maria Fernanda Thees (ANVISA)

Brazil, Jadher Precio (PNI/MOH)

The 2023 Chikungunya outbreak in Paraguay and the potential impact of a vaccine campaign

Pastor E Pérez-Estigarribia

2025

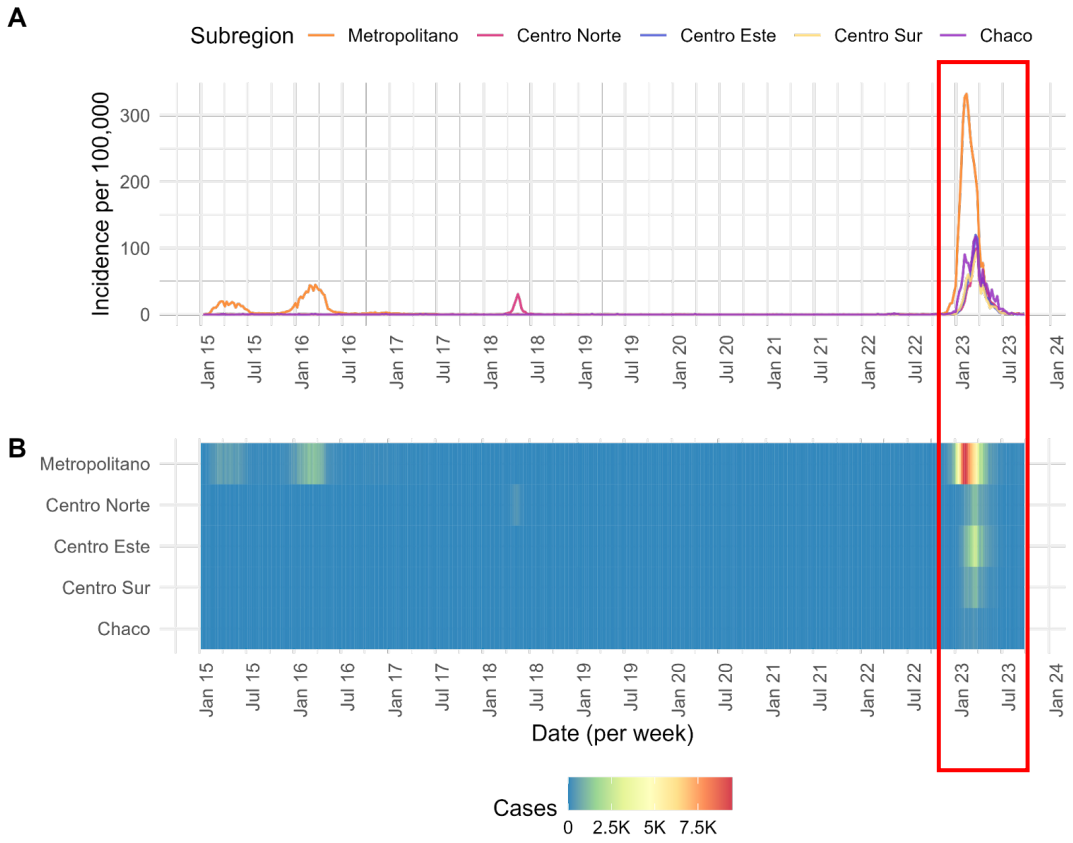
Profesor de postgrado – Facultad Politécnica

Universidad Nacional de Asunción

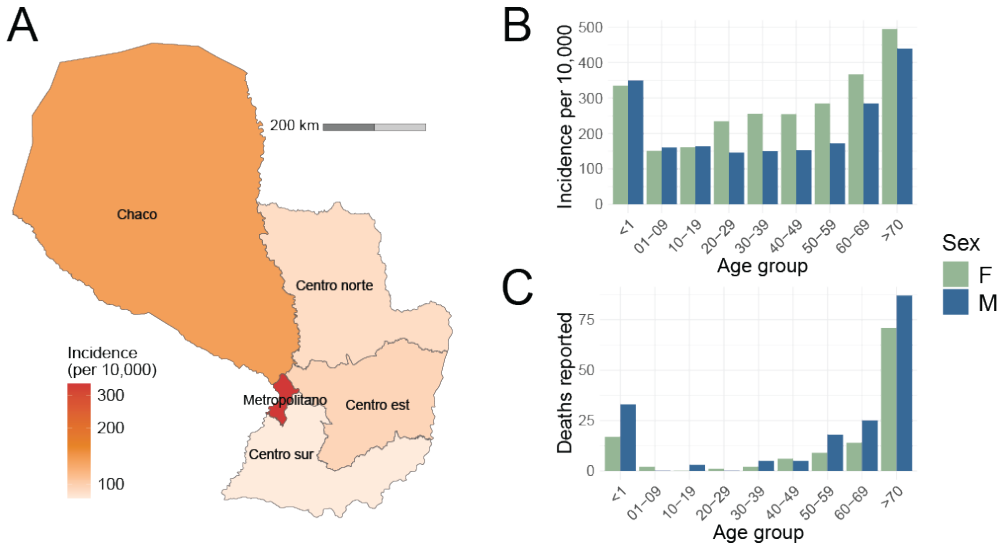
peperez.estigarribia@pol.una.py

LABORATORIO DE
ANÁLISIS Y MODELADO
BASADO EN DATOS

2023 outbreak in Paraguay

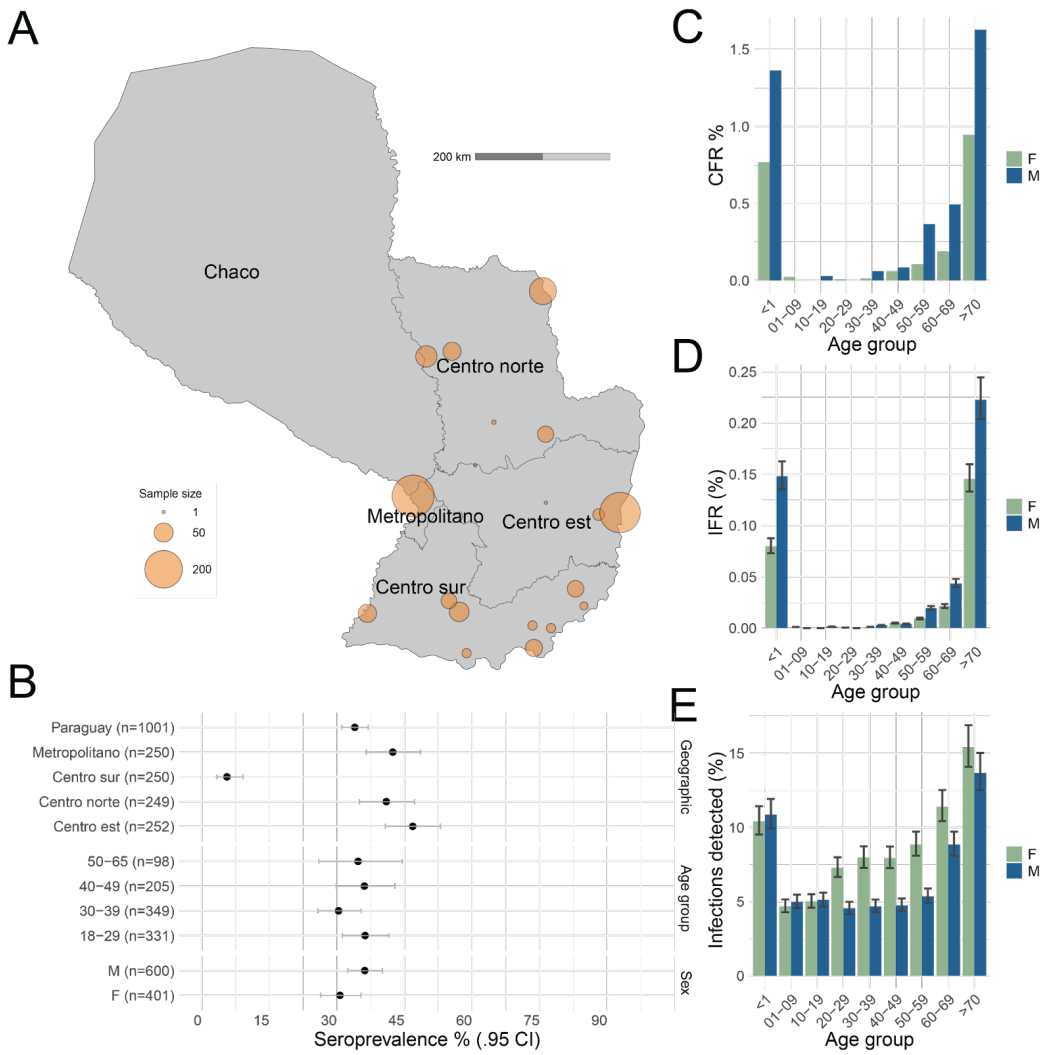


Chikungunya cases per week in Paraguay subregions between 2015-2023



- From Sep 2022 to Sep 2023, there were 142,412 chikungunya cases detected, with an average incidence of 208 cases per 10,000 people (2% clinical attack rate).
- Case incidence was 1.43 times higher in females than in males.
- fatal cases concentrated in the youngest (16.8% of deaths in infants <1y) and the oldest (53.0% of deaths in those >70y), 122 deaths were in females, and 176 deaths were in males.

Seroprevalence study and risk of severe disease



(A) Location of samples by subregion.

(B) Seroprevalence by location, age and sex with 95% confidence intervals derived from a binomial distribution with varying sample sizes (n).

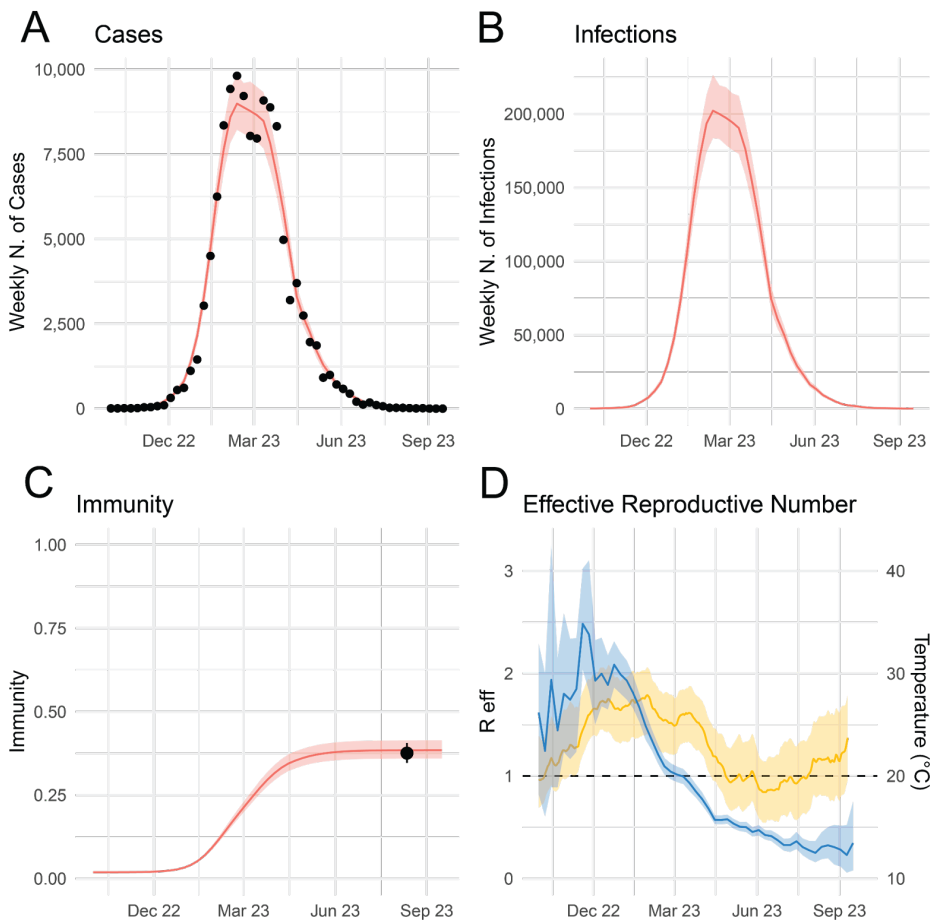
(C) Case fatality ratio by age and sex.

(D) Infection fatality ratio by age and sex.

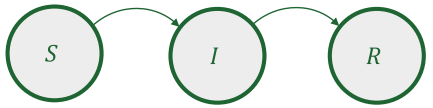
(E) Probability of severe disease (i.e., being detected by the surveillance system) by age and sex.

Error bars from (D) and (E) are derived from the 95% confidence interval of a binomial distribution (n = 1001)

Mathematical model of outbreak



We built an **SIR** transmission model in a Bayesian framework



The mean reproductive number (**R eff)** was **1.81** (95%CI: 1.35 - 2.34)

R eff. was highly correlated to **temperature** (Pearson 0.75)

(A) Weekly number of cases, black dots is case data from passive surveillance, red is model fit.

(B) Weekly number of infections inferred from the model.

(C) Evolution of nationwide levels immunity inferred by the model. Black dot is the result of seroprevalence study. Error bar is derived from the 95% confidence interval of a binomial distribution (n = 1,001)

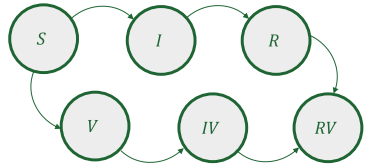
(D) Inferred effective reproductive number (blue) and average, minimum and maximum temperature (yellow).

For (A) (B) (C) and (D), 95% of all MCMC iterations are within the boundaries of the red or blue ribbons as a measure of uncertainty.

https://doi.org/10.1101/2024.12.02.24318291

Results of vaccine model

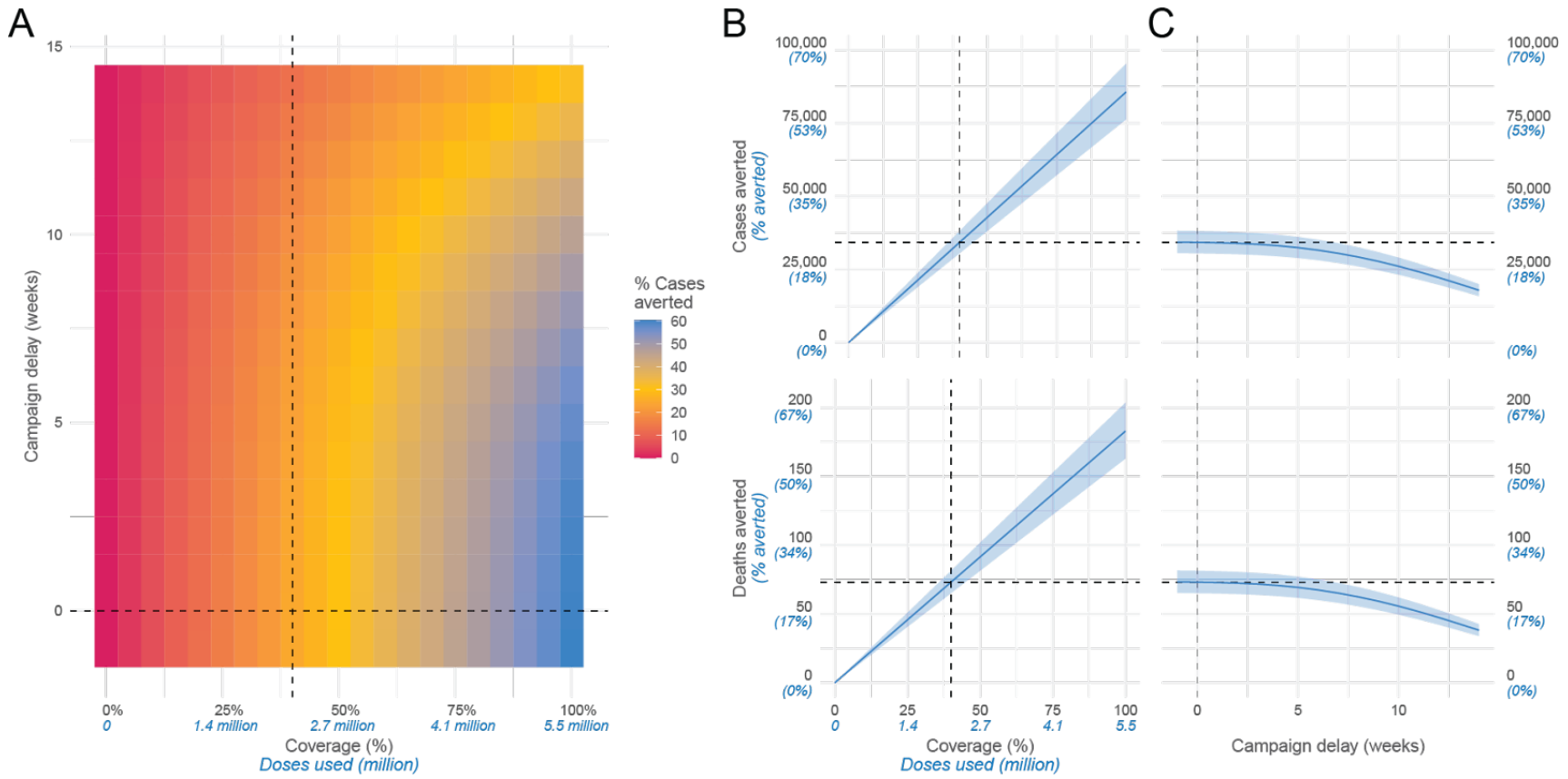
We built an **SIRV** simulation framework:



Vaccine characteristics :
75% vaccine efficacy
Doesn't block infection

Reactive vaccination campaign :
Deployed in **Oct. 2022**
Target population : **12> yo**
40% coverage over **3 months**

Estimated impact :
2.2 million doses used
34,200 (30,500 – 38,100) cases averted
73 (65-81) deaths averted



https://doi.org/10.1101/2024.12.02.24318291

Acknowledgements

Gabriel Ribeiro dos Santos*[,3,4], Simon Cauchemez[5], Cynthia Vazquez[6], Ana Karina Ibarrola-Vannucci[7], Guillermo Sequera[8], Shirley Villalba[6], María José Ortega[6], Jose Luis Di Fabio[9], Danny Scarponi[9], Christinah Mukandavire[9], Arminder Deol[9], Águeda Cabello[10,$], Elsi Vargas[11], Cyntia Fernández[11], Liz León[11], Henrik Salje[3]

Pathogen Dynamics Unit (Cambridge)

3.Department of Genetics, University of Cambridge, Cambridge, UK

4.Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, USA

5.Mathematical Modelling of Infectious Diseases Unit, Institut Pasteur, Université Paris Cité, UMR2000 CNRS, Paris, France

6.Departamento de Virología, Laboratorio Central de Salud Pública, Paraguay

7.Unidad de Proyectos, Convenios e Investigación, SENEPA- Ministerio de Salud Pública y Bienestar Social, Paraguay

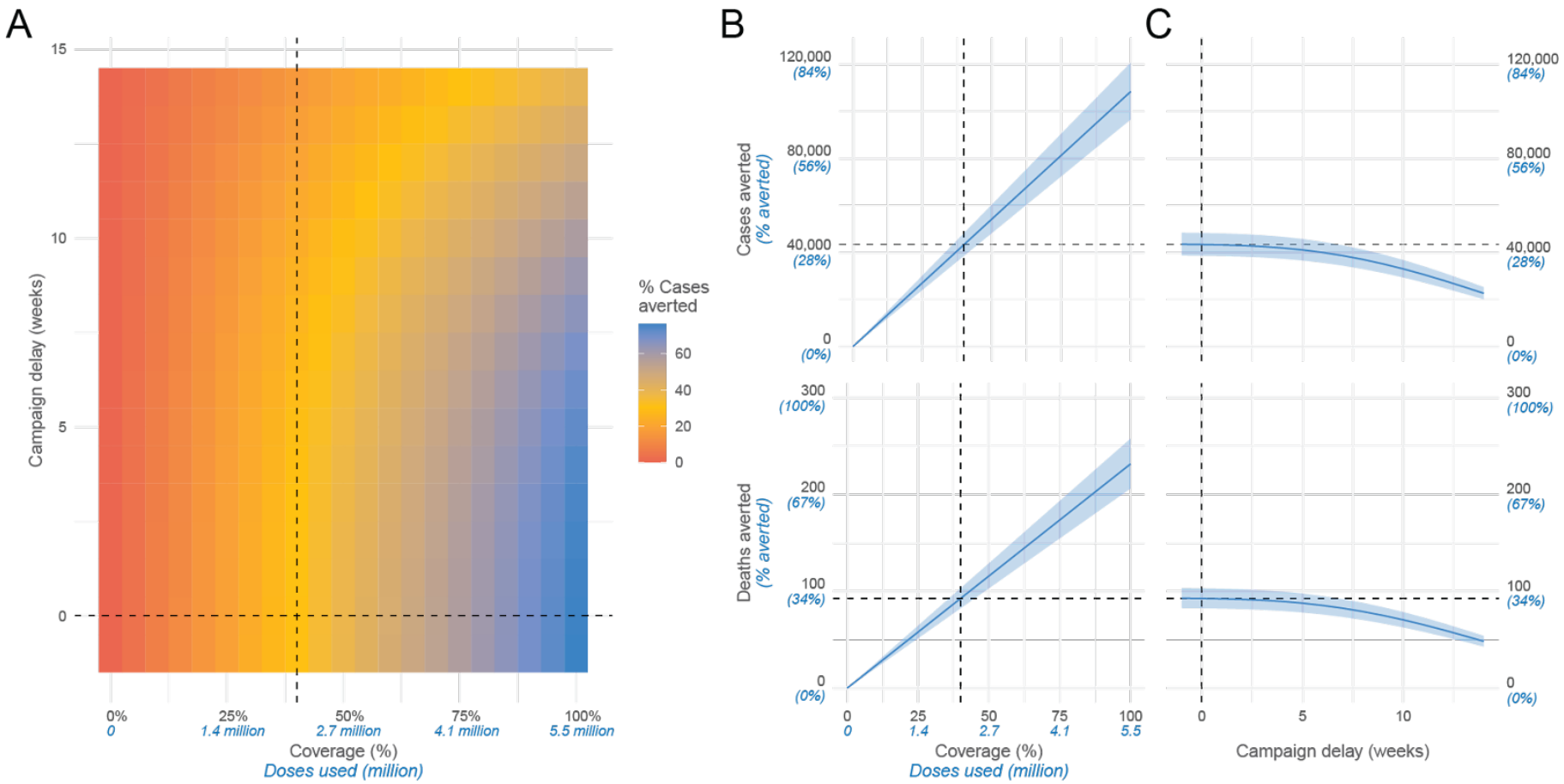
8.Cátedra de Salud Pública, Universidad Nacional de Asunción, Paraguay

9.Coalition for Epidemic Preparedness Innovations (CEPI), UK

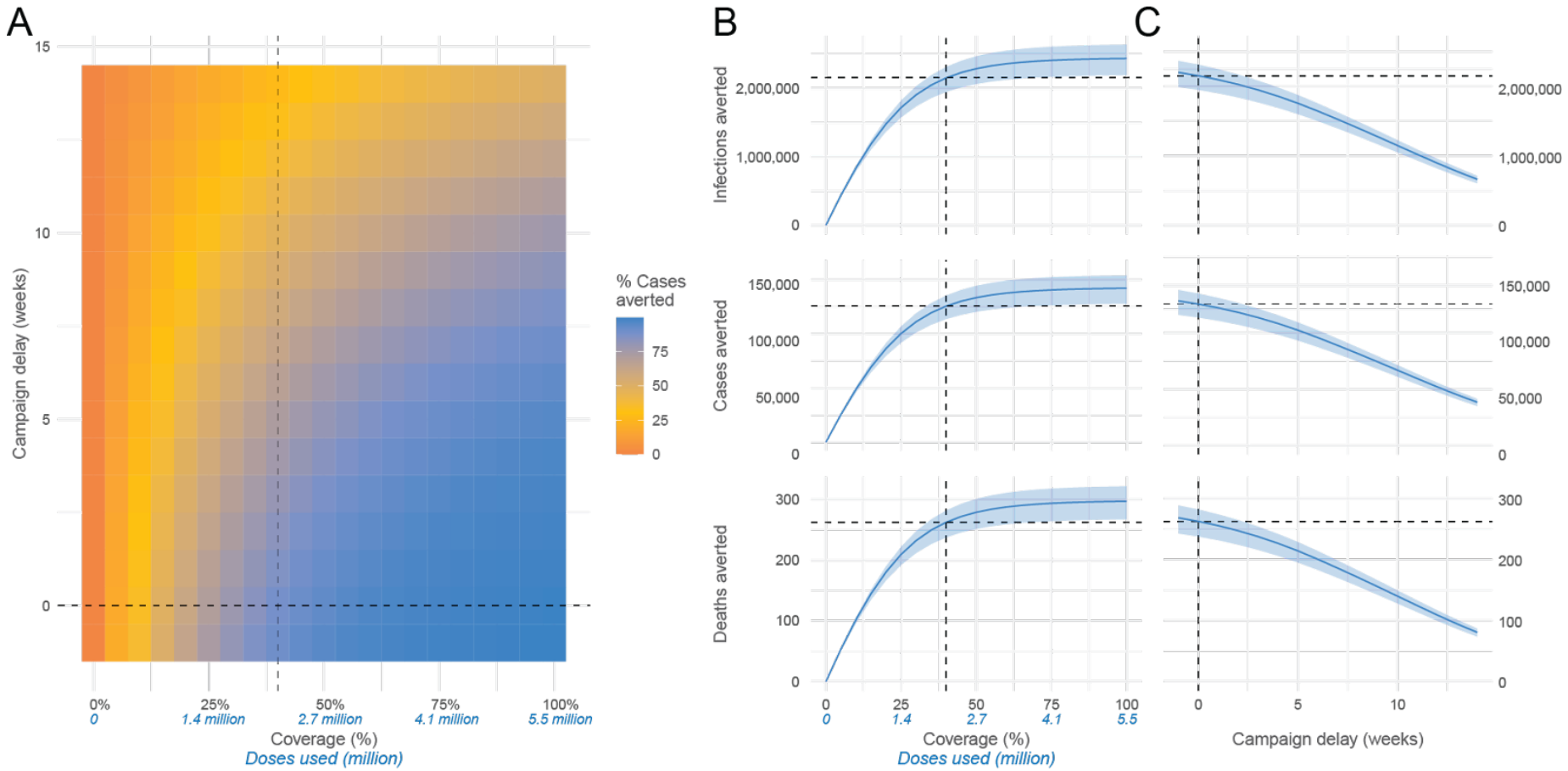
10.Ministerio de Salud Pública y Bienestar Social. Dirección General de Vigilancia de la Salud. Asunción, Paraguay

11.Centro Nacional de Servicios de Sangre (CENSSA), Asunción, Paraguay

Supplementary



Results of vaccine model - sensitivity with a 98% vaccine efficacy. (A) Proportion of cases averted for different values of coverage and delay. The dashed black line shows the base case scenario of 40% coverage with no delay between outbreak start and campaign vaccination. **(B)** Infections (top row), cases (middle row) and deaths (bottom row) averted when varying coverage and delay are fixed at 0 weeks. **(C)** Infections (top row), cases (middle row) and deaths (bottom row) averted when varying the delay between the detection of the outbreak and the start of the vaccine campaign, fixing coverage at 40%.



Results of vaccine model - sensitivity with infection-blocking vaccine. (A) Proportion of cases averted for different values of coverage and delay. The dashed black line shows the base case scenario of 40% coverage with no delay between outbreak start and campaign vaccination. **(B)** Infections (top row), cases (middle row) and deaths (bottom row) averted when varying coverage and delay are fixed at 0 weeks. **(C)** Infections (top row), cases (middle row) and deaths (bottom row) averted when varying the delay between the detection of the outbreak and the start of the vaccine campaign, fixing coverage at 40%.

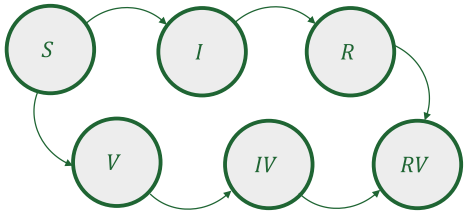
The likelihood of observing c_obs(t) incident cases on week t given the expected number of infections i_exp(t) for that week is given by the density of a Negative Binomial distribution :

$$P(c\_obs(t)|\ i\_exp(t)) = dNegBin(c\_obs(t)\ ,\ i\_exp(t) \cdot \rho,\ shape)$$

where ρ is the detection probability and shape is the overdispersion parameter of the negative binomial distribution.

The likelihood of observing n_pos(t) positive samples out of n_tot(t) on week t given the expected proportion of susceptible individuals in the population s(t) for that week is given by the density of a Binomial distribution :

$$P(n\_pos(t)|n\_tot(t),s(t)) = dBin(n\_tot(t),\ 1\text{-}s(t))$$



$$\frac{dS_a}{dt} = -StI_a - StV_a$$
$$\frac{dV_a}{dt} = StV_a - VtIV_a$$
$$\frac{I_a}{dt} = StI_a - ItR_a$$
$$\frac{dIV_a}{dt} = VtIV_a - IVtRV_a$$
$$\frac{dR_a}{dt} = ItR_a - RtRV_a$$
$$\frac{dRV_a}{dt} = IVtRV_a + RtRV_a$$

With :

- $StI_a = \beta_t * \frac{I_{tot}}{N} * S_a$
- $VtIV_a = \beta_t * (1 - v_{ei}) * \frac{I_{tot}}{N} * V_a$
- $ItR_a = \sigma * I_a$
- $IVtRV_a = \sigma * IV_a$
- StV_a and $RtRV_a$ being dictated by the daily rates of vaccination from the campaign
- $I_{tot} = \sum_a \quad (I_a + IV_a)$, the total number of infected individuals.
- $N = \sum_a \quad (S_a + V_a + I_a + IV_a + R_a + RV_a)$, the total population size
- v_{ei} the vaccine-induced protection against infection
- $1/\sigma$ is the mean duration of infectiousness
- β_t is the transmission rate estimated at time t

Use of Chikungunya Vaccines

Purpose: A session will be held with potential users of the vaccine, representatives from National Immunization Programs, and advisors to NITAGs and RITAGs, where it is expected that they will reflect on the properties of the vaccines, risk-benefit and country and regional priorities.

The probability of recommending use of Chikungunya vaccines with data available

CEPI, Gina Antaki – Moderator
Brazil - Jadher Percio, PNI/MOH
Colombia - Fernando de la Hoz, UNC
Kenya - George Warimwe, KWTRP & University of Oxford
Thailand – Wichan Bhunyakitikorn, DDC/MOH

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Use of CHIKUNGUNYA vaccines by Brazil

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SUS

MINISTÉRIO DA SAÚDE

GOVERNO FEDERAL
BRASIL
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Decision-making process for introducing new vaccines

Technical and political factors

Political and public health priority

Burden of disease

Product safety, efficacy and quality

Comparison with other interventions

Economic and financial criteria

Registration for use

Feasibility and Programming

Availability of the vaccine by the producing laboratory

Product features and presentation

Organization and adequacy of the cold chain

Vaccination Program Performance

Post-marketing pharmacovigilance

National Commission for the Incorporation of Technologies into the Unified Health System – Conitec

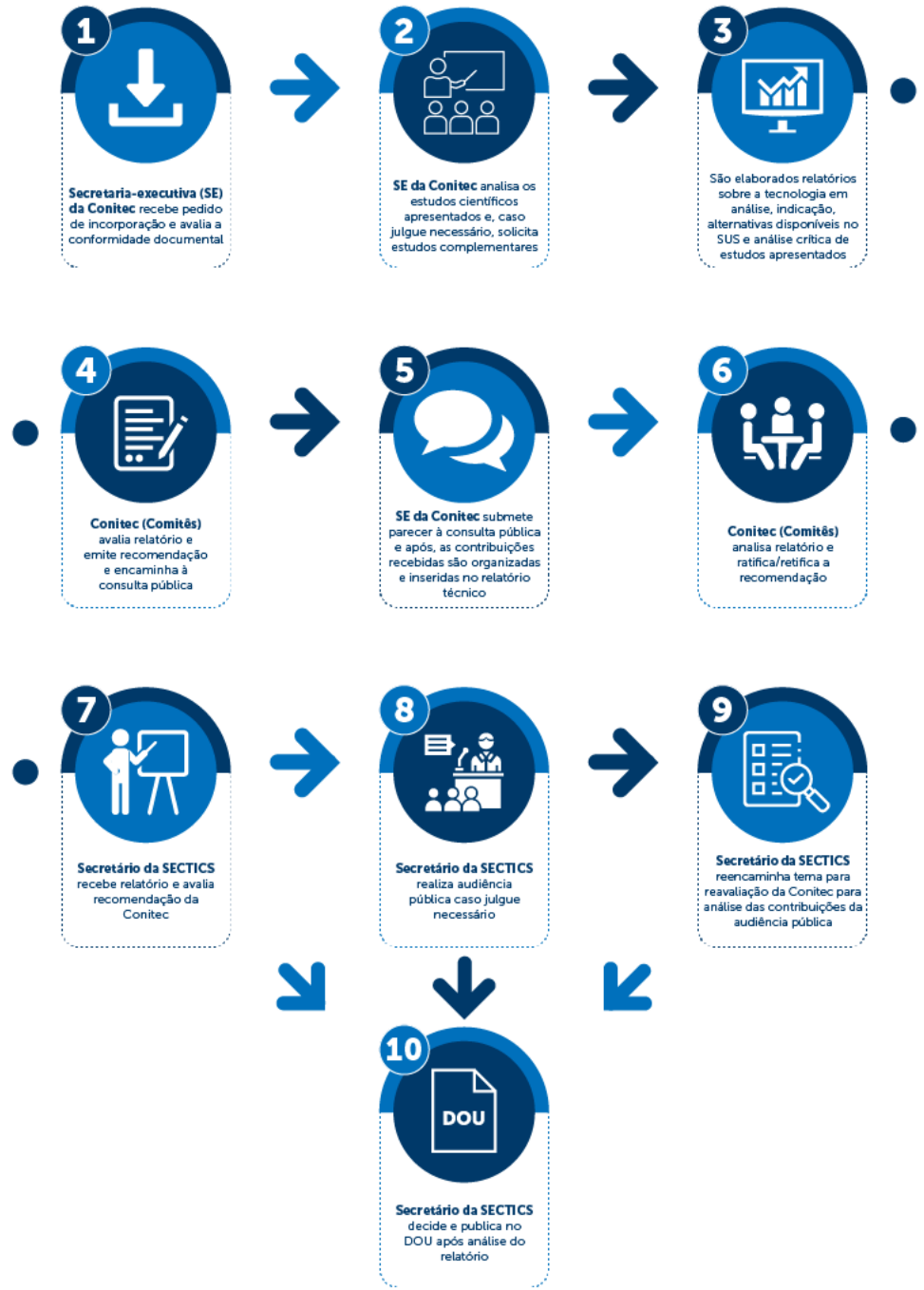
Objectives : to advise the Ministry of Health - MS on the attributions related to the incorporation, exclusion or alteration of health technologies by the SUS - Law No. 12,401/2011 and Decree No. 7,646/2011

Composition :

- Executive Secretariat: Department of Management and Incorporation of Health Technologies – DGITS/SECTICS/MS
- 3 committees (15 institutions): 1) drugs, 2) products and procedures and 3) clinical protocols and therapeutic guidelines
- Social participation
- National Council of Justice, the National Council of the Public Prosecutor's Office and the Superior Council of the Public Defender's Office

Deadlines :

- Decision making: 180 days (extendable for another 90 days)
- Incorporation into the SUS: 6 months



Source : Ministry of Health (https://www.gov.br/conitec/pt-br/assuntos/a-comissao/conheca-a-conitec)

RESOLUÇÃO - RDC Nº 203, DE 26 DE DEZEMBRO DE 2017(*)

Dispõe sobre os critérios e procedimentos para importação, em caráter de excepcionalidade, de produtos sujeitos à vigilância sanitária sem registro na Anvisa.

A Diretoria Colegiada da Agência Nacional de Vigilância Sanitária, no uso da atribuição que lhe conferem o art. 15, III e IV aliado ao art. 7º, III, e IV, da Lei nº 9.782, de 26 de janeiro de 1999, o art. 53, V, §§ 1º e 3º do Regimento Interno aprovado nos termos do Anexo I da Resolução da Diretoria Colegiada - RDC nº 61, de 3 de fevereiro de 2016, resolve adotar a seguinte Resolução da Diretoria Colegiada, conforme deliberado em reunião realizada em 12 de dezembro de 2017, e eu, Diretor-Presidente Substituto, determino a sua publicação.

Art. 1º Esta Resolução estabelece os critérios e os procedimentos para a importação, em caráter de excepcionalidade, de produtos sujeitos à vigilância sanitária sem registro na Anvisa, nos termos do § 5º, do art. 8º da Lei nº 9.782, de 1999, e do § 5º do art. 7º do Decreto nº 8.077, de 2013, destinados exclusivamente para uso em programas de saúde pública pelo Ministério da Saúde e suas entidades vinculadas.

Art. 2º Enquadram-se nos dispositivos desta Resolução os produtos sujeitos à vigilância sanitária a serem adquiridos por intermédio de organismos multilaterais internacionais.

Art. 3º Poderão ser autorizados para importação, em caráter de excepcionalidade, os produtos sujeitos à vigilância sanitária cujo fármaco e/ou tecnologia se enquadrem em, pelo menos, uma das seguintes situações:

I - indisponibilidade no mercado nacional, bem como de suas alternativas terapêuticas ou produtos usados para a mesma finalidade devidamente registrados, quando existirem;

II - emergência de saúde pública de importância nacional, nos termos do Decreto nº 7.616, de 2011, ou de importância internacional (ESPII), conforme o Regulamento Sanitário Internacional;

III - imunobiológicos integrantes do Programa Nacional de Imunização, adquiridos por meio do Fundo Rotatório para Aquisições de Imunobiológicos da Organização Pan-americana da Saúde (Opas)/Organização Mundial de Saúde (OMS); ou

IV - doações oriundas de organismos internacionais multilaterais ou agências oficiais de cooperação estrangeira.

§ 1º Para fins desta Resolução, a indisponibilidade no mercado nacional é caracterizada pela incapacidade, temporária ou definitiva, de atendimento à demanda do Sistema Único de Saúde por detentores de registro devidamente regularizados no país.

§ 2º As aquisições de produtos sujeitos à vigilância sanitária para atendimento às situações do inciso II deste artigo poderão ser autorizadas mesmo quando não realizadas por intermédio de organismos multilaterais internacionais.

Art. 4º Os produtos a serem importados em caráter de excepcionalidade devem ser pré-qualificados pela Organização Mundial de Saúde (OMS).

Emergency use authorization by Anvisa

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Exceptional and temporary exemption from registration and requirements for exceptional authorization to import medicines and vaccines due to public health emergencies

Responsibilities of the Ministry of Health:

- Establish vaccination strategies
- Maintain ongoing assessment of the benefit-risk of vaccination
- Ensure that all batches of vaccines have been analyzed by the Institute for Quality Control in Health (INCQS/Fiocruz)
- Adopt risk mitigation and patient safety measures
- Carry out health education actions
- Intensify post-marketing pharmacovigilance and quality deviations
- Communicate risks and adopt risk minimization measures in case of safety signals

Source : Anvisa (https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2023/pedidos-de-autorizacao-de-importacao-em-carater-excepcional-confira-as-mudancas)

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Technical Advisory Board on Immunization - CTAI

Linked to the Ministry of Health, created to offer technical and scientific advice to the National Immunization Program (PNI) - Ordinance GM/MS No. 470, of April 13, 2023

Source : Ministry of Health (https://www.gov.br/saude/pt-br/vacinacao/ctai)

Vaccination strategies in Brazil

- Routine
- Network of Immunobiologicals for People in Special Situations (RIE)
- Scan
- Vaccination
- Emergency
- Vaccine
- Vaccination
- Vaccination Strategies - SEM
- Rescue of Unvaccinated People Against HPV4
- Border
- Operation Drop
- Dengue vaccination (teenagers between 10 and 14 years old)
- Vaccination against COVID-19 (special groups)
- Influenza
- School

Source : Ministry of Health
(https://www.gov.br/saude/pt-br/vacinacao)

Microplanning and its steps

1. Analysis of the situation

Characterization, measurement and understanding of the health-disease profile of the population, the distribution of this same population throughout the territory

2. Planning and scheduling

Calculation of needs and operationalization of activities of this same population throughout the territory

3. Monitoring and supervision

Assessment of the progress of actions by comparing the indicators achieved with the expected parameters

4. Evaluation and monitoring

Monitoring and evaluation of the entire process (*before, during and after):* preparation of evidence reports

Source : Ministry of Health (https://www.gov.br/saude/pt-br/vacinacao)

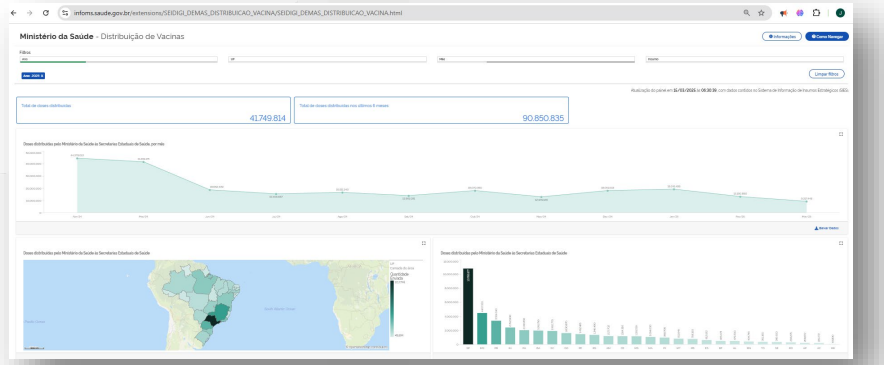
Information systems: flows and integration

SIPNI

Own/proprietary systems

RNDS
REDE NACIONAL DE DADOS EM SAÚDE

LocalizaSUS



PEC

SAÚDE ATENÇÃO PRIMÁRIA e-SUS

Source : Ministry of Health (https://infoms.saude.gov.br/extensions/SEIDIGI_DEMAS_DISTRIBUICAO_VACINA/SEIDIGI_DEMAS_DISTRIBUICAO_VACINA.html)

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Post-marketing pharmacovigilance

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Passive surveillance

Qualitative and quantitative analysis
Data Mining

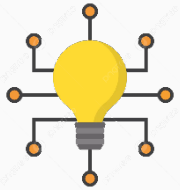
Implement active surveillance – CIOMS

Bigdata (linkage)

Sentinel units

Strengthening CIFAVI/CEFAVI*

Research



Continuing education

Communication

CIFAVI = Committee Interinstitutional Pharmacovigilance Committee for Vaccines and other Immunobiologicals
CEFAVI = State Committee for Pharmacovigilance of Vaccines and other Immunobiologicals
Source: Ministry of Health (https:// www.gov.br/saude/pt-br/vacinacao/esavi)

SUS

MINISTÉRIO DA SAÚDE

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BRASIL
UNIÃO E RECONSTRUÇÃO

Final considerations

01

Decision-making process

Evidence - based techniques, scientific economic and financial

Rules and legislation suitable to ensure speed, transparency and efficiency in health actions public

02

Key challenges

Availability of sufficient and timely doses – laboratory producer

Differences geopolitical and sociocultural – access to the services and to vaccines and trust in health actions public

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UNIÃO E RECONSTRUÇÃO

Is Colombia likely to incorporate CHKV vaccines in regular vaccination programs.

FERNANDO DE LA HOZ RESTREPO. MD MSc PhD

Universidad Nacional de Colombia-School of Medicine

Department of Public Health

Phase IV post-approval studies in the context of vaccines approved through accelerated procedures: Case study, CHIKUNGUNYA vaccines.

Sao Paulo, Marzo 19 y 20 2025

Content

- Policy
    - Public and political concern.
    - Who should get vaccinated.
    - How many people need to be vaccinated.
    - Challenges to adult vaccination.
- Financing
    - Sources of financing.
    - Challenges for making a decision on CHKV vaccines
    - How much is right to pay.
- Summary and recommendations

Policy

- Public concern:
  - Low?
- Political concern:
  - Low?
- Prevention / control alternatives:
  - Not too many.
  - Failure or low effectiveness of traditional measures against urban vectors like A aegyptii/Anopheles/others.

Chikungunya

Tomás Montalvo, biólogo: "Ya no podemos evitar que haya brotes de dengue en España, el objetivo es que no sean muy grandes"

Este experto considera necesario estrechar la vigilancia del mosquito tigre para contener el auge de la enfermedad, que este año ha registrado un máximo histórico en Europa y ha causado por primera vez contagios locales en latitudes tan al norte como la de París

En fotos: combatir el dengue, el zika y la chikungunya con un ejército de mosquitos

Médicos Sin Fronteras promueve en Honduras un programa en alianza con las autoridades locales y las comunidades locales para reducir las enfermedades causadas por arbovirus

Los hospitales españoles detectan un súbito aumento de viajeros con enfermedades tropicales

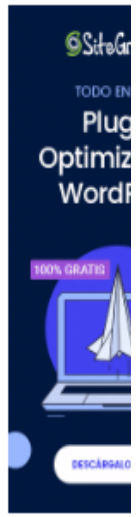
La elevada incidencia de chikungunya y dengue en los países donde son endémicas eleva el riesgo de contagios en las zonas europeas con mosquito tigre como España, según alerta la UE

Dengue en América Latina: cómo se transmite, cuántos casos existen en la región y cómo evitarlo

De México a Brasil, el dengue es una enfermedad en aumento y ha provocado una epidemia en la región por factores climatológicos que facilitan su proliferación

Argentina registra el brote de dengue más letal de su historia, con al menos 39 muertos

Más de 50.000 personas han contraído este año la enfermedad transmitida por la picadura del mosquito 'Aedes aegypti' en el país sudamericano



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El Comercio

TAG
Chikungunya

05/06/2023 22:39
Dengue: disponen clases virtuales en las instituciones educativas de la región Piura
Redacción EC

21/03/2023 20:57
El dengue avanza con los huaicos: casos superan en un 70% a los del año pasado tras lluvias intensas, ¿cómo protegernos?
Hernán Medrano Marín

23/10/2019 15:51
Zika: casos aumentaron en 45% respecto a todos los registrados el año pasado
Ralph Zapata

18/07/2019 12:01
Científicos logran eliminar el mosquito transmisor del dengue y chikungunya
Redacción EC

13/02/2019 12:27
México | Científicos buscan diseñar anticuerpos contra la chikunguña
Redacción EC

14/02/2018 19:03
Aumentan a cuatro los casos autóctonos de chikungunya en Piura

14/02/2018 16:29
Piura: suben a 4 los casos autóctonos de chikungunya

14/02/2018 08:45
Piura: confirman el primer caso autóctono de chikungunya

EL TIEMPO

chikungunya

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Se encontraron 296 resultados por chikungunya

SALUD NOVIEMBRE 15 DE 2023
Aprueban primera vacuna contra el virus chikungunya en los Estados Unidos: así funciona
La FDA aprobó una única dosis para personas mayores de 18 años con alto riesgo de infección.

SALUD NOVIEMBRE 11 DE 2023
Se aprueba la primera vacuna contra el Chikungunña en Estados Unidos
Se autorizó para aplicar a personas mayores de 18 años.

NEW YORK TIMES INTERNATIONAL WEEKLY OCTUBRE 5 DE 2023
SUSCRIPTORES
Los mosquitos son cada vez más resistentes y mortales para los humanos: 'Están ganando'
Los insecticidas utilizados desde la década de 1970 se han vuelto mucho menos eficaces. ¿Qué hacer?

OTRAS CIUDADES SEPTIEMBRE 13 DE 2023
El Dengue no da tregua en Cartagena: 39 nuevos casos
Según el Departamento de Salud, Dadis, casos han aumentado un 114%, y llegan a 1.885 casos.

COLUMNISTAS SEPTIEMBRE 2 DE 2023
Un país de ojos rojos
Si se angustia uno cuando un hijo se demora, ¿cómo será cuando pase un día, un mes, 10 o 20 años?

SALUD AGOSTO 28 DE 2023
Dengue y otras enfermedades infecciosas transmitidas por el arbovirus
Los arbovirus son virus que se transmiten al humano o a otros vertebrados por ciertos artrópodos.

TECNOLOGÍA AGOSTO 28 DE 2023
¿Una cédula única para todos los ciudadanos del mundo? El nuevo proyecto de Bill Gates
El software permitiría reconocer la identidad de las personas sin necesidad de un documento.

- Children:
  - < 15 yrs?.
  - Newborns?

- Adults?
  - Adults living in crowded environments and potentially at risk of outbreaks?
  - Jails?
  - Army?
  - Schools?
  - All adults above 18?

- People at risk:
  - Immunosuppression?
  - Health workers? Public Workers?

Who should be vaccinated

- Adults may be a valid target for vaccination.

- Vaccinating adults is challenging.
  - In this case, there is no data on clinical efficacy and small number of participants in trials may not detect side effects (>1 case per 5,000 people).

- Covid vaccination, which caused much more concern, was below expectative.

- Flu vaccination in adults is consistently lower than coverage for children's vaccines.

Who will finance the vaccine?

- In Colombia, the Ministry of Health make the decision previous analysis and recommendation from the NITAG.
  - Assessment of burden of disease
  - Assessment of costs of disease, costs of vaccination, costs of alternatives
  - Assessment of cost utility
  - Threshold 1 PIB per capita

Who will finance the vaccine?

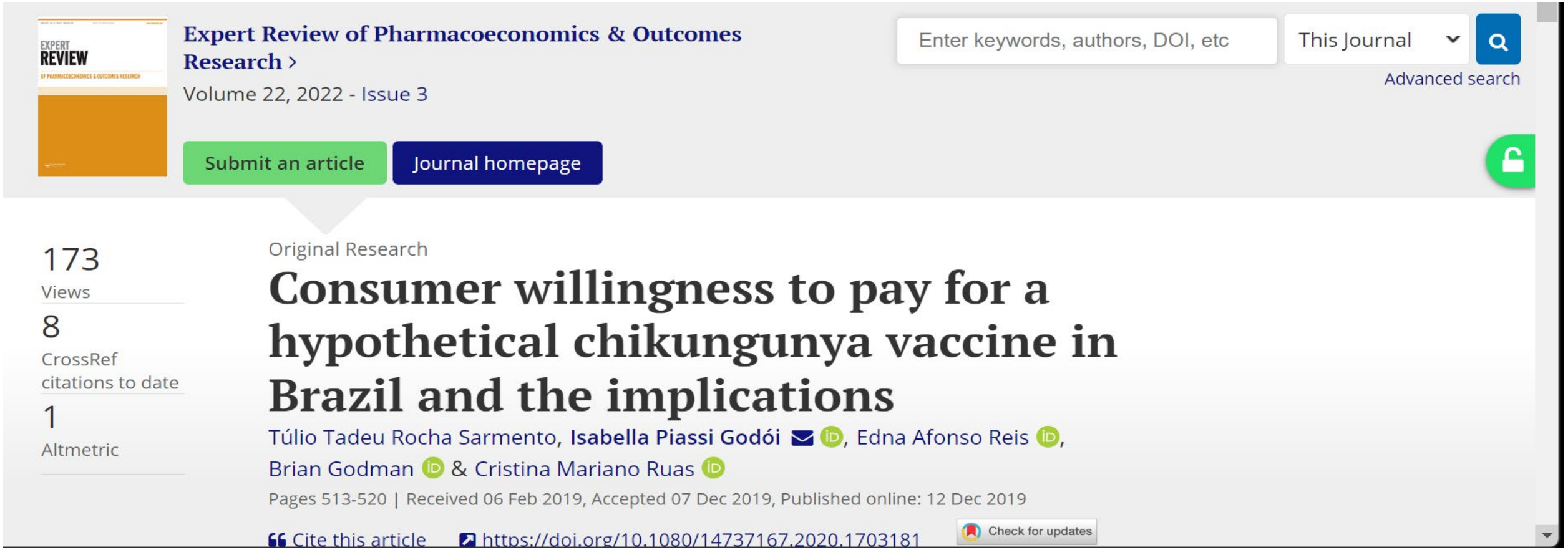
- Challenges to make a positive decision on CHKV vaccine:
  - Quality of surveillance data
  - Low public and political concern about impact of clinical CHKV
  - Competing interest with vaccines for high profile diseases like dengue, RSV, meningococcal diseases.
  - Lack of data clinical efficacy.

Who will finance the vaccine?

- In Colombia, the Ministry of Health have to get clearance from the Ministry of the Treasury.

- Colombia and other countries have laws to finance the introduction of new vaccines but assessments have to be done first.

Who will finance the vaccine?



Expert Review of Pharmacoeconomics & Outcomes Research >
Volume 22, 2022 - Issue 3

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Original Research

Consumer willingness to pay for a hypothetical chikungunya vaccine in Brazil and the implications

Túlio Tadeu Rocha Sarmento, **Isabella Piassi Godói**, Edna Afonso Reis, Brian Godman & Cristina Mariano Ruas

Pages 513-520 | Received 06 Feb 2019, Accepted 07 Dec 2019, Published online: 12 Dec 2019

Cite this article https://doi.org/10.1080/14737167.2020.1703181 Check for updates

USD$ 32.00

What do we like to know before taking a decision?

- Epidemiology
  - Better knowledge of current infections and its relationship with other viruses
  - Cyclic and Seasonal trends
  - Population at risk after the first wave.
  - Better knowledge of clinical characteristics on non typical cases

- Vaccine:
  - Clinical efficacy and safety in adults
  - Efficacy and safety in Children
  - Costs

Summary

- CHKV may be a cause for a large share of febrile and severe cases in LATAM
- Surveillance need to be adjusted to improve laboratory based diagnosis of CHKV and other arboviruses especially in low transmission periods.
- Lack of public and political awareness may be an important barrier for vaccine introduction as well as lack of clinical efficacy data in older adults and young children.
- Small pilot studies may contribute to pave the way for CHKV vaccines to get their way into the public agenda.
- Novel designs and endpoints may be used: Clinical definition of CHKV? Stepped wedge trials?

Use of chikungunya vaccines

George Warimwe

Professor of Vaccinology

UNIVERSITY OF OXFORD

KEMRI | Wellcome Trust

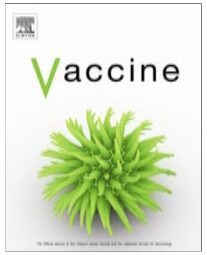
Factors are taken into consideration when determining new vaccine introduction

	Epidemiological landscape	Financial factor	Programmatic/ Health system	Regulatory framework
Goal	• Will vaccine significantly reduce mortality and morbidity by vaccine introduction	• Financial feasibility of introducing the vaccine. • Critical as Government funding is increasing	• Human resource capacity, Cold chain capacity and supply chain capacity to introduce vaccine	• The Pharmacy and poison board determines the registration of all vaccines.
Process	• Guidance from KENITAG, MoH and technical partners helps to prioritize impact of vaccines	• This is led by MoH and Treasury together with guidance and advice such as Gavi and UNICEF. • Final decisions is by GoK	• This is led by NVIP and involves wide collaboration with counties governments, partners and different departments in MoH	• Approval of vaccines is by PPB • Vaccine Adverse event following immunization is a collaborative process between NVIP and PPB with partner support

9

Case study

er.com/locate/vaccine



Developing a seasonal influenza vaccine recommendation in Kenya: Process and challenges faced by the National Immunization Technical Advisory Group (NITAG)

Safety	Type, consequences and frequency of short and long-term adverse events following vaccination including adverse effects on foetus and new born, and Guillian Barre Syndrome	Critical	No Kenyan data available. Used studies from outside Kenya
	Risk groups or risk factors for adverse events	Critical	No Kenyan data available. Used studies from outside Kenya
	Contraindications	Critical	No Kenyan data available. Used studies from outside Kenya
Efficacy and effectiveness	Efficacy worldwide	Critical	Used data from Kenya and Africa studies.
	Efficacy against strains circulating in Kenya	Critical	Used data from Kenya and Africa studies.
	Duration of protection and waning of immunity in general and risk groups	Critical	Used data from Kenya and Africa studies.
	Impact on incidence of severe pneumonia, admissions, outpatient attendance, mortality	Critical	Used data from Kenya and Africa studies.

3. Economic and operational considerations	Vaccine related costs and resource use	Local data on the direct and indirect costs to administer the vaccine as they compare to those of other existing vaccines or other prevention or control measures	Important	No data obtained
	Vaccine availability	Local data on cost to the government	Important	No data obtained
		Local data on sources of funding	Critical	No data obtained
		Availability in private sector	Non - critical	No data obtained
	Economic impact of intervention on immunization program as well as health sector	Cost benefit, cost effectiveness, DALY, QALY,	Important	No Kenyan data available. Used studies from outside Kenya
4. Health policy and programmatic issues	Feasibility	Local data on accessibility of target population and risk groups, no. of individuals in target pop and risk groups	Important	No local data obtained
		Local data on human, technical and financial requirements i.e. cold chain, supply chain requirements	Important	No local data obtained
		Local data on possibility of inclusion into regular immunization schedule	Important	No local data obtained
	Ability to evaluate	Reliability and sustainability of surveillance system for disease	Critical	Local data available
		Adverse events following immunization (AEFI) monitoring	Critical	No local data obtained
		Local data on availability of information systems to measure coverage and vaccine utilization	Important	No local data obtained
	Acceptability	Perception of the public and medical community about the flu and the vaccine	Critical	Some local data available
		Health seeking behaviour	Critical	Some local data available
	Equity	Accessibility for all the inhabitants in the country	Important	No local data obtained

กรมควบคุมโรค

Department of Disease Control

Prioritization and process of introducing a new vaccine in Thailand

Department of Disease Control,
Thailand's Ministry of Public Health

Use of the Chikungunya vaccine

Chikungunya Incidence and Significance in Thailand

Historical Incidence:

- **1958:** First reported outbreak in Bangkok.
- **2008–2009:** Significant outbreak in southern Thailand, with over 50,000 cases.
- **2018–2020:** Re-emergence with approximately 15,000 cases across 60 provinces
- **2024:** As of April, 208 cases reported.

Public Health Importance:

- **Economic Impact:** High healthcare costs and reduced workforce productivity during outbreaks.
- **Tourism:** Outbreaks can deter tourists, affecting the economy.
- **Healthcare System:** Strain due to increased patient load during outbreaks.

Current Status:

- As of March 2025, Thailand is among countries with recent chikungunya cases, highlighting the need for continued surveillance and preventive measures.

Use of the Chikungunya vaccine

Vaccine Development Progress

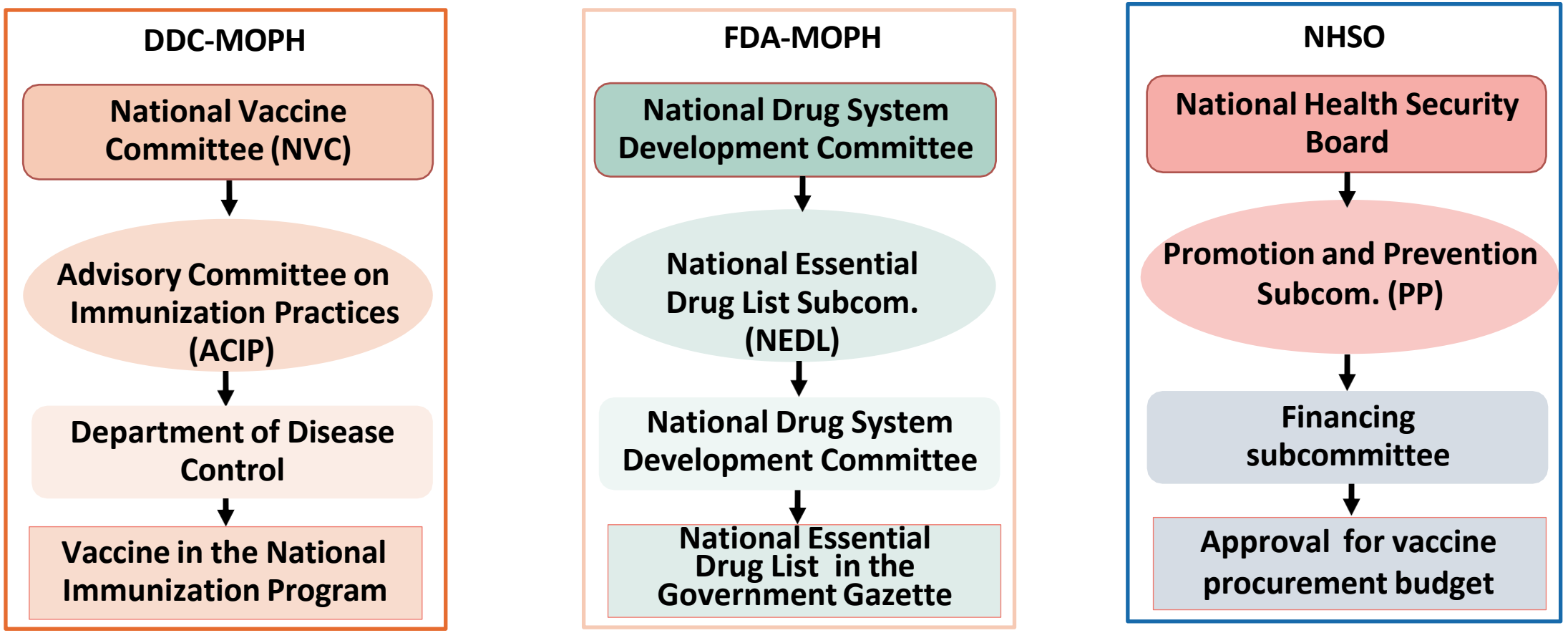
As of March 2025, significant advancements have been made in chikungunya vaccine development:

- **IXCHIQ Vaccine:** Developed by Valneva SE, IXCHIQ is the world's first and only licensed chikungunya vaccine. It has received approvals in the United States, Europe, and Canada for individuals aged 18 and older. The vaccine is administered as a single intramuscular dose. Clinical trials have demonstrated strong immunogenicity, with seroresponse rates of 98% observed 22 days post-vaccination
- **Expanded Approvals:** In February 2025, the U.S. Food and Drug Administration (FDA) approved IXCHIQ for individuals aged 12 and older, following successful Phase 3 trials that met primary endpoints.
- **Pediatric Trials:** A pivotal Phase 3 study in children is planned for the fourth quarter of 2025, aiming to extend the vaccine's availability to younger populations.

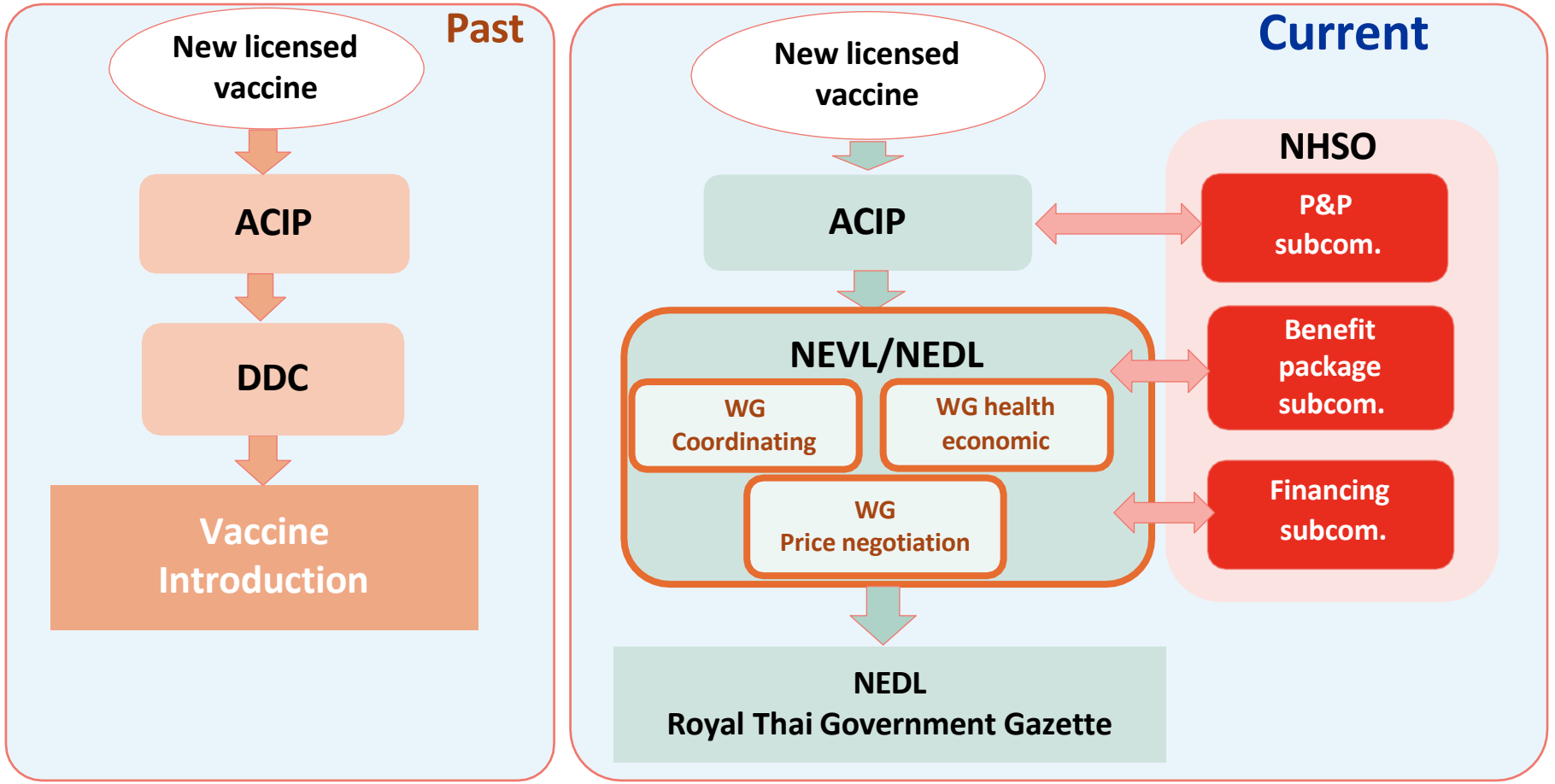
Introducing the Chikungunya vaccine in Thailand

- The use of the Chikungunya vaccine in Thailand depends on several considerations, including the number of case incidences, vaccine safety, cost-effectiveness including Thai FDA Registration Process, which must go through an appropriate evaluation process

The Three Mechanisms for New Vaccine Decision Making in Thailand

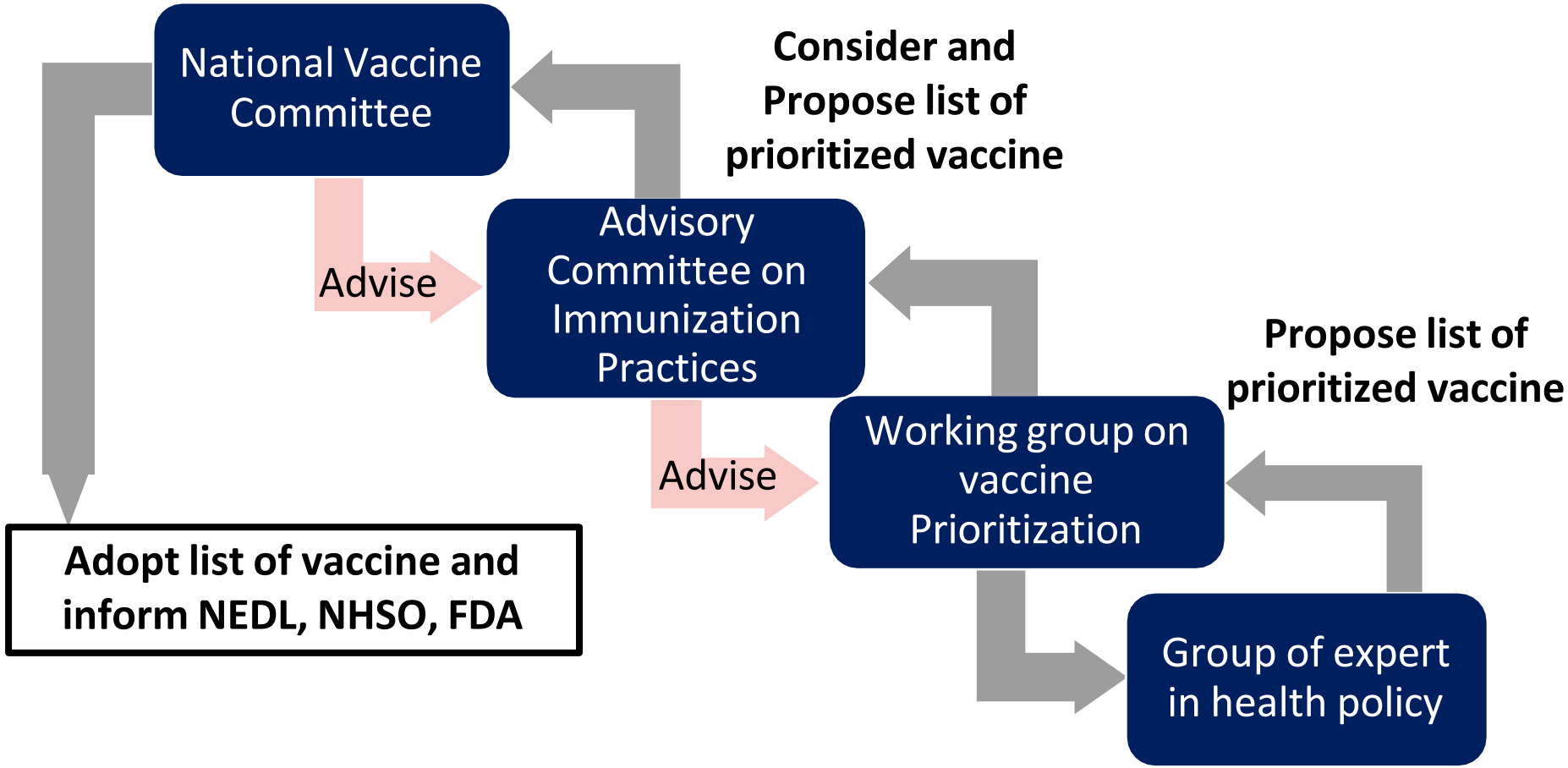


New Vaccine Decision Making Mechanism in Thailand



Overview of the prioritization process

Vaccine Prioritization-Thailand



Working Group on Vaccine Prioritization

Consultant : Senior expert in Immunization, Senior pediatrician

Secretariat : EPI manager

Members: Senior expert in immunization / Pediatrician (Infectious dis.) / Pediatrician (Vaccinologist) / Virologist / Infectious medicine (Vaccinologist) / Epidemiologist / Health economist / NHSO / NVI

Established in 2023 under National Immunization Technical Advisory Group

To ensure equitable access to vaccines for all Thai citizens, excluding supplementary immunization activities:

1. **Advocate for new vaccines not yet included in the National List of Essential Medicines.**
2. **Advocate for vaccines already listed in the National List of Essential Medicines to be provided to all target groups according to their benefit entitlements, and to update the scope of health services to align with current scientific evidence.**

Criteria - Weighting and scoring

Measurable criterion

1. Incidence (per 100,000 person)
2. Severity of disease (case fatality rate, %)
3. Efficacy/Effectiveness (% prevention in target population)
4. Estimated budget
5. Capacity of local production

Non-measurable criterion

1. Econ burden of disease (THB)
2. CEA (Cost Effectiveness Analysis)
3. Alternative
4. Social cons.
5. Policy cons.

Criteria - Weighting and scoring

Scoring for Measurable Criterion

Criterion	5	4	3	2	1
Incidence (per 100,000 person)	100	76-100	51-75	26-50	<25
Severity of disease (case fatality rate, %)	>10%	5-10%	1-4.9%	0.1-0.9%	<0.1%
Efficacy/ Effectiveness	> 90%	71-90%	61-70%	50-60%	≤ 50%
Estimated budget*	< 300 MB	300-499 MB	500-799 MB	800-1,599 MB	≥ 1,600 MB
Capacity of local production	There are domestic vaccine manufacturing from the upstream level.	There are domestic vaccine manufacturing from the mid-level.	There are domestic vaccine manufacturing from the down stream level.	Imported vaccines > 1 case	Imported vaccines only 1 case

Potential vaccines

Children and Teenager (<18 years old)

Vaccine	Target
DTwP-HB-Hib-IPV	2, 4, 6 month (Not registered in Thailand)
DTaP-HB-Hib-IPV	2, 4, 6 month
DTaP-HB-Hib	< 5 years old (No data found)
Rabies (pre-exposure)	5 years old
EV 71	1 years old
HPV at least 4 species	Male, 11 years old
Dengue	10 years old
Varicella	1 years old
Hepatitis A	1 years old
Tdap	12 years old

Adult (≥18 years old)

Vaccine	Target
HPV	Female, 21 years old
Dengue	35 or 45 years old (Reduce morbidity rate), 60 years old (Reduce case fatality rate)
Varicella	20 years old
Hepatitis A	40 years old
Hepatitis B	40 years old
Tdap	20 years old
Zoster	Elderly, 65 years old
PCV / PPSV	Elderly, 65 years old

Specific Target Group

Vaccine	Target
Varicella	Medical Personnel, 20 years old
MR	Medical Personnel
Hepatitis B	Medical Personnel, Born before and after 1992
Tdap	Medical Personnel
MR	Risk Group (Prisoner, Correctional officer, Conscript)

Evidence Assessment

- **Review of Scientific Data:**
  - ✓ the latest clinical trials
  - ✓ epidemiological studies
  - ✓ real-world evidence on new vaccines and their effectiveness against evolving disease strains.
  - ✓ Health economics study
- **Evidence:**
  - ✓ The Ministry of Public Health including D506 (DDC), Drug and Medical Supply Information Center, HDC etc.
  - ✓ National vaccine institute (NVI)
  - ✓ Department of Provincial Administration, Ministry of Interior
  - ✓ World Health Organization (WHO)
  - ✓ Pan American Health Organization (PAHO)

Challenges and mitigation

Challenges	Mitigation
Applying international economic data (such as cost-effectiveness ratios) directly to Thailand's context may lead to inaccurate assessments due to differences in healthcare infrastructure, disease burden, and vaccine prices between countries.	• Perform country-specific studies to gather accurate data on disease prevalence, vaccine pricing, and cost-effectiveness in Thailand’s context. • Ensure that affordability and budget impact are evaluated with local economic realities in mind, considering factors like the National Immunization Program's budget and public health priorities.
Some vaccines may be needed urgently, while others may be critical in the long term. Balancing immediate needs (e.g., for emerging diseases) with long-term vaccination goals (e.g., herd immunity, control of endemic diseases) can be difficult.	• Continuous monitoring of disease trends, vaccine availability, and emerging public health needs can help adjust prioritization over time. Flexible criteria should be used to accommodate urgent vaccination needs while still planning for long-term goals.

Lessons learned and conclusions

- Vaccine prioritization should not be a one-time event. It requires an ongoing, flexible process that incorporates new evidence, public health shifts, and emerging global health challenges.
- Thailand’s experience demonstrates that a successful vaccine prioritization strategy requires a multifaceted approach that integrates scientific data, economic evaluations, and ethical considerations.
- Success in vaccine prioritization depends on close cooperation between various stakeholders, including health authorities, academia, and government bodies.
- Thailand should invest in local research to ensure the cost-effectiveness analyses reflect the country’s unique healthcare system and disease burden.

THANK YOU!


กระทรวงสาธารณสุข
MINISTRY OF PUBLIC HEALTH
กรมควบคุมโรค
Department of Disease Control

Recommendations & Conclusions

Danielle Craig, CEPI

Recommendations and conclusion

Workshop Conclusions & Recommendations (1/5)

- The amount, type, and quality of data on ChikV disease manifestations and epidemiology is growing exponentially, but gaps in coverage of data remain
- Modeling techniques are a tool that should be further used to identify and explore regional and subregional differences in disease epidemiology
- Major burdens to the feasibility of clinical efficacy trials for ChikV vaccines remain, which continues to support the use of correlates of protection for the licensure of vaccines in new markets
- Lack of feasibility for conducting efficacy trials is driven by different factors in each region, which also means that the disease end points typically used for diagnosis may confound effectiveness analyses in the global post-marketing environment

Workshop Conclusions & Recommendations (2/5)

- Regulators from the Americas, Africa, the Asia Pacific regions all confirmed that they have regulations or other regulatory frameworks that will allow licensure of ChikV vaccines using correlates of protection data instead of clinical efficacy
- These same regulators shared potential paths to accelerate licensure of ChikV vaccines, such as reliance mechanisms and expedited reviews supported by the prior approval of the vaccines by WLA regulatory agencies
- Regulators shared that well designed Risk Management Plans, taking to account the country contexts, will be an important component of approvals, in conjunction with post-marketing studies and Real World Evidence (RWE) and Real World Data (RWD)
- The need and desire for continued, formal engagement with global regulators throughout the product development life cycle was highlighted, both to accelerate paths to approval and to allow regulators to put into practice the regulatory flexibilities they already have

Workshop Conclusions & Recommendations (3/5)

- Differing requirements and frameworks for approval of products received by technology transfer were also discussed
- Regulators shared that they have frameworks and guidelines describing the requirements of RWE and RWD studies to be used for regulatory decision-making
- EMA and FDA reinforced that generation of post-marketing effectiveness and expanded safety data are generally expected for vaccines. For the ChikV vaccines:
    - In the US context, demonstration of effectiveness is a post-marketing requirement by the law for accelerated approval. However, there are flexibilities to renegotiate the terms of the requirement if the conduct of the agreed studies remains unfeasible at the readiness milestone date
    - In the EU context, post-marketing effectiveness is requested to support confirming the clinical benefit predicted by the CoP data that underlies the approval

Workshop Conclusions & Recommendations (4/5)

- The Regulator panel emphasized that discussions on the designs of RWE studies (e.g. negative case control designs) and approval of RWE protocols should continue in parallel with the current committed/required pragmatic trials, as the RWE may fulfill the effectiveness data ask
- The use of conference reports to consolidate recommendations on the integration of RWE studies into the end-to-end product development for vaccines that will use CoP approaches for primary data will be faster than possible development of formal regulatory guidelines
    - Input from stakeholders who will support vaccine uptake, such as MOH and Immunization Programs, must be included

Workshop Conclusions & Recommendations (5/5)

- EMA shared ongoing work to develop frameworks for streamlining clinical response timelines in emergencies, including concepts of pre-approved protocols submitted with data for at least one investigational product, reduced number and types of documents to submit, parallel and joint regulator and ethics reviews, and agreed rapid timelines
  - A similar global approach is being discussed at WHO
  - The Regulators panel support establishing these types of frameworks, but emphasized that a final benefit-risk cannot be made until the emergency is characterized
  - Establishment of scientific technical committees and ongoing engagement with regulators and other public health stakeholders in 'peacetime' to inform on the characteristics and epidemiological changes of different diseases would be beneficial
- The Regulator panel felt that pre-approved outbreak protocols for ChikV could have a role to play, even given the approval of the vaccines

CHIKUNGUNYA
Phase IV

São Paulo, Brazil March 2025

CEPI

ANVISA
Agência Nacional de Vigilância Sanitária