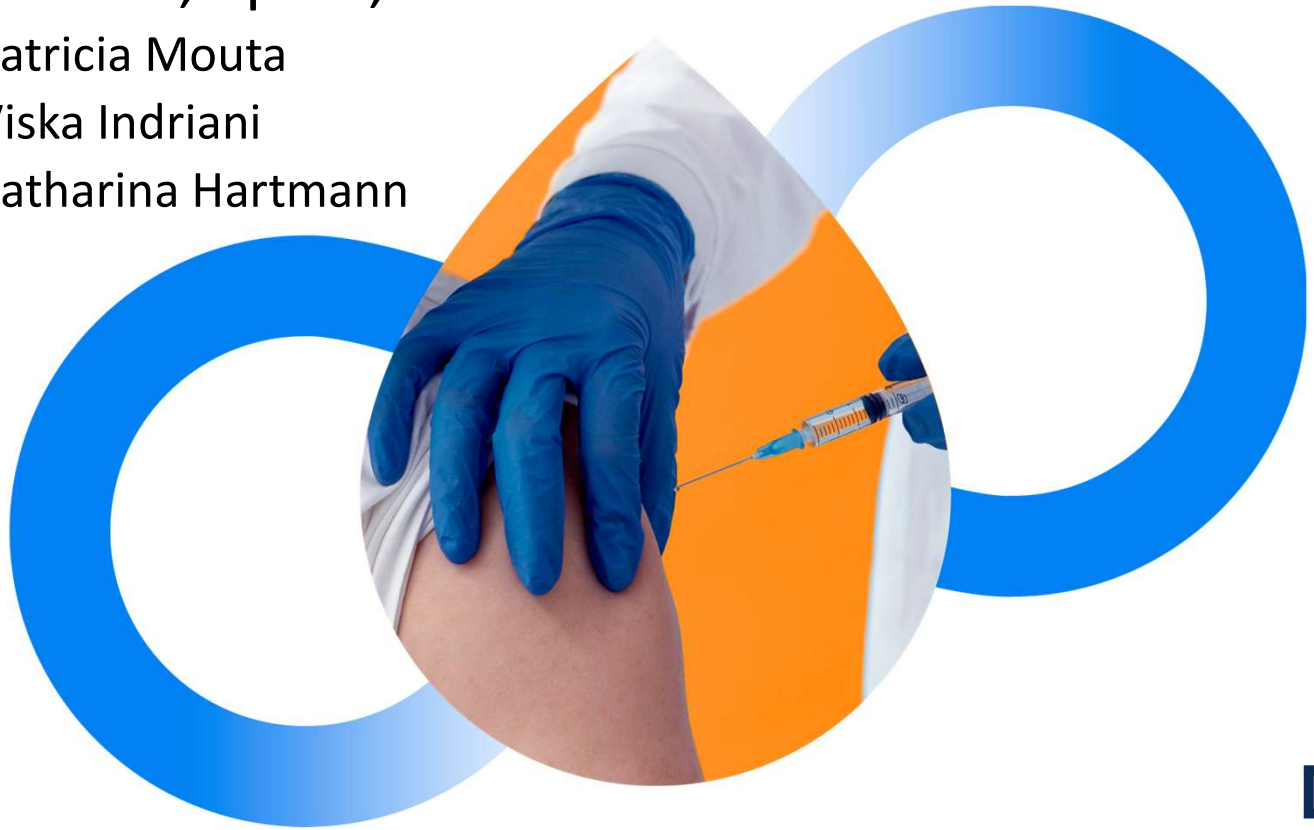
Barcelona, Spain, October 20th and 21st, 2023

Patricia Mouta
Viska Indriani
Katharina Hartmann



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How can AVSS help with vaccine safety issues?

Patricia Mouta
Katharina Hartmann

Session 1

Protecting people from global diseases since 2000.

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Vaccine Safety Surveillance in Post-Authorization

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Safety surveillance is a fundamental tool in Pharmacovigilance

Passive vaccine safety surveillance

- Spontaneous reporting of AEFIs by health care providers, immunization providers, consumers, or by other sources to the appropriate level in each country depending on its national PV reporting system (NRA) or to the Marketing Authorization Holder MAH.
- Collected data does not derive from a study or any other organized data collection.
- Is a relatively inexpensive strategy to cover large areas, but data quality and timeliness are difficult to control.

Active vaccine safety surveillance

- Data collection system that seeks to ascertain – as completely as possible – the number of AEFIs in a given population by a continuous organized process.
- Put in place to overcome the limitations and to complement passive systems – does not replace passive surveillance.
- Provides the most accurate and timely information, but it is an expensive strategy.

Vaccine Safety Surveillance in Post-Authorization Studies

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Post-Authorization Safety Studies PASS (EMA GVP VIII)

- Any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of the risk management measures (EMA GVP Annex I).
- May be an **interventional clinical trial (Phase IV) or an observational, non-interventional study.**
- May be aimed at collecting data to enable assessment of safety of medicinal products in everyday medical practice.

Post-Authorization Efficacy Studies PAES (EMA PAES Guidance)

- Studies conducted within the authorized therapeutic indication to complement available efficacy data in the light of well-reasoned scientific uncertainties on aspects of the evidence of benefits to be / or only can be addressed post-authorization (EMA Scientific Guidance of efficacy studies 2014).
- Although the term refers to “efficacy”, PAES collect data in a setting that reflects general clinical practice rather than a randomized clinical trial.
- PAES are providing rather «effectiveness» data than «efficacy» data.

vaccines

MDPI

Systematic Review

COVID-19 Vaccine Safety Monitoring Studies in Low- and Middle-Income Countries (LMICs)—A Systematic Review of Study Designs and Methods

Malede Mequanent Sisay [1,*], Camila Montesinos-Guevara [2], Alhadi Khogali Osman [1], Putri Widi Saraswati [1], Binyam Tilahun [3], Tadesse Awoke Ayele [4], Fariba Ahmadizar [1], Carlos E. Durán [1,5], Miriam C. J. M. Sturkenboom [1], Peter van de Ven [1] and Daniel Weibel [1]

Conclusions:
Published studies on COVID-19 vaccine safety surveillance in LMICs are limited in number and the methods used do not often address potential confounders. Active surveillance of vaccines in LMICs are needed to advocate vaccination programs. Implementing training programs in pharmacoepidemiology in LMICs is essential.

Key Points

- Active surveillance studies have been used to monitor COVID-19 vaccine safety in low- and middle-income countries.
- Most studies were **cross-sectional** with limited outcome validation and no temporal assessment.
- Major vaccination data sources were **medical charts or self-reported cases** based on clinical signs or symptoms.
- Only one-third of the studies employed parametric models, such as logistic regression (n = 17, 29.3%) and Cox regression (n = 3, 5.2%).

Study Designs

Table 1: Summary of Characteristics

Study Characteristics	Classification	Number (%)
Study Designs	Cross-Sectional Studies/Descriptive studies	41 (70.69)
	Cohort Studies	13 (22.41)
	Retrospective	2 (3.45)
	Both Cross-sectional and Cohort	1 (1.72)
	Cross-sectional—Sequential mixed-method	1 (1.72)
Country world bank classification	Low-income economies	4 (7.00)
	Lower-middle-income economies	26 (45.00)
	Upper-middle-income economies	28(48.00)
Data sources	Primary data	51 (87.93)
	Secondary data	5 (8.62)
	Mixed	2 (3.45)
Source of vaccination data	Spontaneous reporting	3 (5.17)
	Registry in Epidemiological Surveillance System	2 (3.45)
	Self-reported (Primary data collection)	52 (89.66)
	Active surveillance	1 (1.72)
Populations of interest	High-risk population (e.g., healthcare workers, immunocompromised hosts)	37 (63.79)
	Children	1 (1.72)
	Adults	15 (25.86)
	All group	5 (8.62)
Analysis method	Statistical tests (association)—No adjustment for confounder	47 (82.46)
	Advanced modeling (e.g., regression analysis)—Adjustment for confounders	10 (17.54)
Study type	Near real-time surveillance	57 (98.28)
	Phase IV observation study	1 (1.72)
Comparator for safety assessment (e.g., non-exposed, active comparator/vaccine)	Yes	2 (3.45)
	No	56 (96.55)

Sisay 2023

Vaccine 40 (2022) 3064–3071

Contents lists available at ScienceDirect

Vaccine

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

Dashboard development for near real-time visualization of COVID-19 vaccine safety surveillance data in the Vaccine Safety Datalink

Tat'Yana A. Kenigsberg [a,*], Anne M. Hause [a], Michael M. McNeil [a], Jennifer C. Nelson [b], Jo Ann Shoup [c], Kristin Goddard [d], Yingbo Lou [e], Kayla E. Hanson [f], Sungching C. Glenn [g], Eric S. Weintraub [a]

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Literature Examples of AVSS studies

What is the vaccine safety datalink?

Since 1990, the Vaccine Safety Datalink (VSD) monitors the safety of U.S. licensed vaccines by conducting surveillance and targeted research studies on rare, unusual adverse events following immunization, and provided critical, timely scientific information to the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP).

The Vaccine Safety Datalink (VSD) conducts active surveillance and vaccine safety research studies.

How did it help with the covid-19 vaccine?

Since the start of the U.S. COVID-19 vaccination program, the VSD has conducted near real-time safety surveillance of COVID-19 vaccines using Rapid Cycle Analysis.

Key metrics include population demographics, vaccine uptake, prespecified safety outcomes, sequential analyses results, and descriptive data on potential vaccine safety signals.

Dashboard visualizations are used to provide situational awareness on dynamic vaccination coverage and the status of multiple safety analyses conducted among the VSD population.

VSD includes the participation of healthcare systems that serve approximately 12 million persons annually, or 3.6% of the U.S. population, with all major demographic groups represented and no major differences in sex, race, ethnicity, and education attainment between the VSD and the 2010 US Census population.

Population under surveillance

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Methodology

VSD COVID-19 Vaccine Dashboard, which consolidates and visualizes summary coverage and safety data from eight of the nine VSD sites, was possible due to VSD's well established distributed data model (DDM) and dynamic data files(DDF).

Vaccination data are linked with health outcome data, both of which are captured during routine patient care visits.

Each site creates a standardized set of patient files with unique study identification numbers using their electronic health record (EHR) system, and CDC obtains relevant data from site files to create specific datasets for analyses.

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Inclusion

The vaccinated population consists of enrolled VSD members who are vaccinated and age-eligible to receive COVID-19 vaccination.

The age range of the population is adjusted when new age groups are authorized to receive COVID-19 vaccine.

Individuals must be enrolled in one of the VSD sites on the day of their COVID-19 vaccination to be included in the vaccinated population.

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How was the database Search?

The 23 pre-specified COVID-19 RCA vaccine safety outcomes (i.e., medically-attended outcomes) are identified using the International Classification of Diseases 10th Revision (ICD-10) diagnosis codes

Diagnosis codes for most pre-specified outcomes are restricted to those assigned in the emergency department and inpatient settings;

CLICK BELOW TO NAVIGATE

- HOME
- Outcomes List
- RCA
- OUTCOME SPECIFIC
- COVERAGE
- HOSPITALIZATIONS
- SIMULT. VACCINES
- DETAILED TABLES
- PREGNANCY
- BOOSTER DOSES

Vaccine Safety Datalink (VSD) Weekly COVID-19 Vaccine Dashboard: February 27, 2022 *

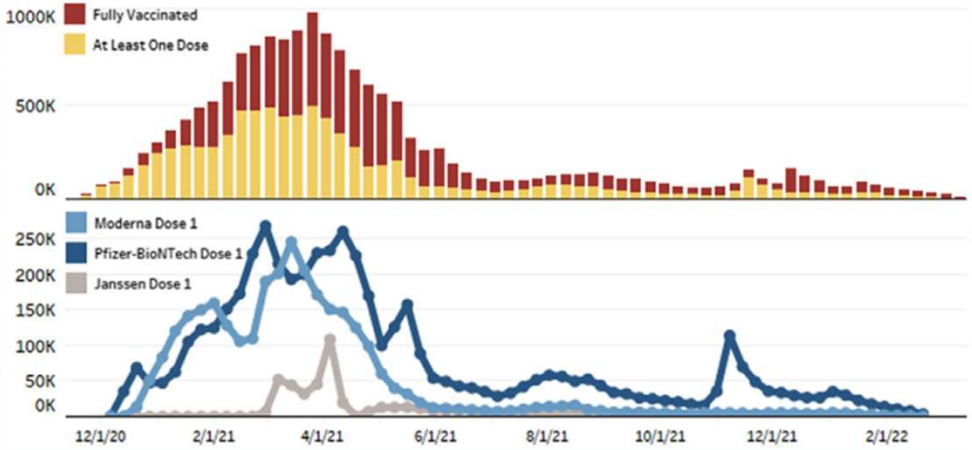
* Visualization published on February 27, 2022; data current as of previous Saturday. VSD population includes individuals 5 years of age and older.

Total Doses Administered	Total Doses Admin per 100K	# People Received At Least One Dose	# People Fully Vaccinated	Total Booster Doses Admin^
16,403,956	147,189	8,504,214	8,401,211	4,564,951

To date, 74.5% of the age eligible VSD population is fully vaccinated and 77.3% received at least one dose

^ Booster dose count includes anyone since 08/10/2021 who is fully vaccinated and received another COVID-19 vaccine >=4 months following mRNA series completion or >=2 months following receipt of Janssen vaccine.

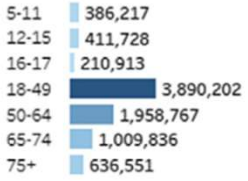
Number of people vaccinated with primary series & doses administered over time, by reporting week



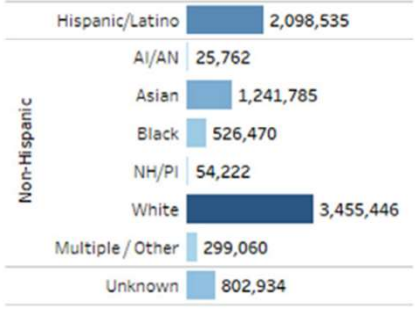
Demographic breakdown of people who received at least one primary series dose

By Sex

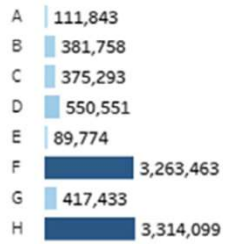
By Age Group



By Race/Ethnicity



By Site *



* There is a one week lag in data reported by SCK

Number of events in primary series by outcome *

	Janssen	Moderna		Pfizer-BioNTech		Total
	Dose 1	Dose 1	Dose 2	Dose 1	Dose 2	
ADEM				2	3	5
AMI	42	159	207	186	242	836
ANAPH	13	41	25	71	26	176
ANAPH2	3	29	10	31	6	79
APPND	47	196	204	397	397	1,241
ARDS	1	4	7	7	6	25
BP	43	161	174	190	193	761
CVST	1	4	8	8	3	24
DIC	2	7	12	11	17	49
ENCEPH		6	8	5	6	25
GBS	13	7	4	12	4	40
HSTK	9	73	56	82	92	312
ISTK	58	322	330	356	349	1,415
ITP	5	10	18	19	15	67
KD						
MISC/MISA				11	3	14
MYOC	8	33	70	62	150	323
NARC	2	5	9	9	11	36
PE	24	148	156	147	196	671
SZ	16	78	84	138	133	449
TM	2	2	2	2	7	15
TTP	3	2	3	4	2	14
TTS	7	29	21	22	19	98
VTE	37	185	170	201	246	839
Total	336	1,501	1,578	1,973	2,126	7,514

* Table displays outcomes with cases in the 1-21 day risk window (0-1 day for ANAPH & ANAPH2). ANAPH2 uses internal DXID's to identify anaphylaxis vs. ICD-10 codes used in ANAPH; ANAPH and ANAPH2 are not mutually exclusive.

Vaccinated concurrent comparator sequential analysis, signals to date

Outcome	Vaccine Type	Dose	Risk Interval	Signal this week?
MYOC	Both mRNA	Both doses	1-21	Yes
		Dose 2	1-21	Yes
	Pfizer- BioNTech	Both doses	1-21	Yes
		Dose 2	1-21	Yes

Analysis

- The observed number of pre-specified outcomes of interest in a defined risk window following COVID-19 vaccines are compared to the expected number;
- if the observed rate is significantly higher than the expected rate, this indicates a ‘‘statistical signal.”
- If such a signal is identified, additional analyses are conducted to determine if there is a true association, in which case a formal epidemiologic investigation may be undertaken.

Example of a safety study aiming a specific population, in this case Health professionals

Journal of Community Health (2022) 47:211–225
https://doi.org/10.1007/s10900-021-01039-3

ORIGINAL PAPER

Active Surveillance of Adverse Events in Healthcare Workers Recipients After Vaccination with COVID-19 BNT162b2 Vaccine (Pfizer-BioNTech, Comirnaty): A Cross-Sectional Study

Giancarlo Ripabelli[1,3] · Manuela Tamburro[1] · Nicandro Buccieri[2] · Carmen Adesso[3] · Valeria Caggiano[3] · Fabio Cannizzaro[3] · Michela Anna Di Palma[3] · Gloria Mantuano[3] · Valeria Giovanna Montemitro[3] · Anna Natale[3] · Leonardo Rodio[3] · Michela Lucia Sammarco[1]

Accepted: 1 October 2021 / Published online: 9 October 2021

REVISTA DO INSTITUTO DE MEDICINA TROPICAL DE SÃO PAULO

JOURNAL OF THE SÃO PAULO INSTITUTE OF TROPICAL MEDICINE

In this safety study a special population, the elderly, are the target

ORIGINAL ARTICLE

http://doi.org/10.1590/S1678-9946202264056

Adverse events following immunization of elderly with COVID-19 inactivated virus vaccine (CoronaVac) in Southeastern Brazil: an active surveillance study

Karina Takesaki Miyaji[1,2], Lucas Yuji Umesaki Itto[3], Lucas Caue Jacintho[3], Amanda Caroline Ribeiro Sales[1], Marcel Hiratsuka[4], Fabio Campos Leonel[4], Keila Tomoko Higa-Taniguchi[4], Camila Melo Picone[2], Amanda Nazareth Lara[1,2], Camila Cristina Martini Rodrigues[1,2], Marta Heloisa Lopes[1,2], Ana Marli Christovam Sartori[1,2]

Soltani *et al. BMC Public Health* (2023) 23:1415
https://doi.org/10.1186/s12889-023-16265-8

BMC Public Health

In this study the goal was to observe a change in the vaccine scheme, with use of diferente vacines as booster doses

STUDY PROTOCOL

Open Access

A prospective cohort study protocol: monitoring and surveillance of adverse events following heterologous booster doses of Oxford AstraZeneca COVID-19 vaccine in previous recipients of two doses of Sinopharm or Sputnik V vaccines in Iran

Shahin Soltani[1], Behzad Karami Matin[1,2], Mohammad Mehdi Gouya[3], Sayed Mohsen Zahraei[4], Ghobad Moradi[5], Omid Chehri[1], Moslem Soofi[2], Mehdi Moradinazar[6], Fatemeh Khosravi Shadmani[1], Mahsa Kalantari[1], Hamidreza Khajeha[7], Mohammad Hassan Emamian[7] and Farid Najafi[1*]

Vacunas

www.elsevier.es/vac

Original article

Adverse events following COVID-19 vaccination among pregnant women attending primary health centers: An active-surveillance study

In this example, another special population being evaluated, the pregnant women.

Narayana Goruntla[a,*], *Basappa Karisetty*[b], *Nandini Nandini*[b], *Bharadwaj Bhupasamudram*[b], *Himaja Reddy Gangireddy*[b], *Kasturi Vishwanathasetty Veerabhadrappa*[c], *Joseph Obiezu Chukwujekwu Ezeonwumelu*[a], *Vishnuvandana Bandaru*[d]

[a] Department of Clinical Pharmacy and Pharmacy Practice, School of Pharmacy, Kampala International University, Western Campus, Uganda
[b] Department of Pharmacy Practice, Raghavendra Institute of Pharmaceutical Education and Research (RIPER) – Autonomous, Anantapur, Andhra Pradesh, India
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[d] Department of Pharmaceutical Analysis, Balaji College of Pharmacy, Anantapur, Andhra Pradesh, India

Vaccine
Volume 31, Issue 49, 2 December 2013, Pages 5909-5914

Post-authorization safety surveillance of a liquid pentavalent vaccine in Guatemalan children

Edwin J. Asturias [a b d], Ingrid L. Contreras-Roldan [c], Malathi Ram [d], Ana J. Garcia-Melgar [e], Vilma Morales-Oquendo [e], Katharina Hartman [f], Martina Rauscher [f], Lawrence H. Moulton [d], Neal A. Halsey [d]

Methods: A prospective observational safety surveillance study of the incidence of important medical events (IME) and serious adverse events (SAE) was conducted in healthy children from two outpatient clinics at the Institute of Guatemalan Social Security (IGSS) who received pentavalent and oral polio vaccines at 2, 4 and 6 months of age. Parents were contacted by telephone 2 weeks after each dose and 6 weeks after the 3rd dose. All outpatient, emergency department visits, and hospitalizations were monitored. Each child was followed for a minimum of 5 months. SAEs were evaluated by a safety monitor and judged for relationship to the vaccine. A self-controlled analysis was conducted to determine if there was evidence of increased risk of SAEs following vaccines as compared to control time windows.

Conclusion: The liquid pentavalent vaccine was associated with low rates of SAEs and not associated with increases in healthcare visits or hospitalizations. Systems can be set up in low to middle income countries to capture all health care visits to monitor the safety of new vaccines.

Study was designed within a RMP as a requirement of WHO PQ

Study Design

- Setting:
  - Guatemala City, Guatemala
  - 2 public health clinics from the Institute of Social Security (ISS) in Guatemala City will perform the primary immunization using the pentavalent vaccine Quinvaxem® only
- Design outline:
  - administration of 3 injections 1 month apart starting at 2 months of age according to the National Vaccination Program
  - active surveillance of clinically relevant adverse reactions after administration
  - group size: 3’000 (Quinvaxem®)
  - follow-up period:
    - active: until 1 month after third vaccination
    - passive: up to six months after last vaccination
  - 3’000 infants eligible for local EPI schedule enrolled over 1.5 years

Important Medical Events

Whenever a treating health care professional considers an event clinically relevant, the event must be reported.

- all serious (according to the ICH criteria) events
- sudden infant death (sudden unexplained death)
- hypotensive-hyporesponsive episodes (HHE-like symptoms)
- fever > 39.5°
- convulsions / seizures (incl. febrile convulsions)
- anaphylactic reactions / anaphylactic shock
- hypersensitivity reactions
- severe injection site reactions (e.g., cellulitis, swelling etc.)
- whole limb swelling
- thrombocytopenia
- persistent crying / abnormal crying
- encephalopathy and / or related signs and symptoms
- neurological disorders and / or related signs and symptoms
- serum sickness like disease
- unusual events

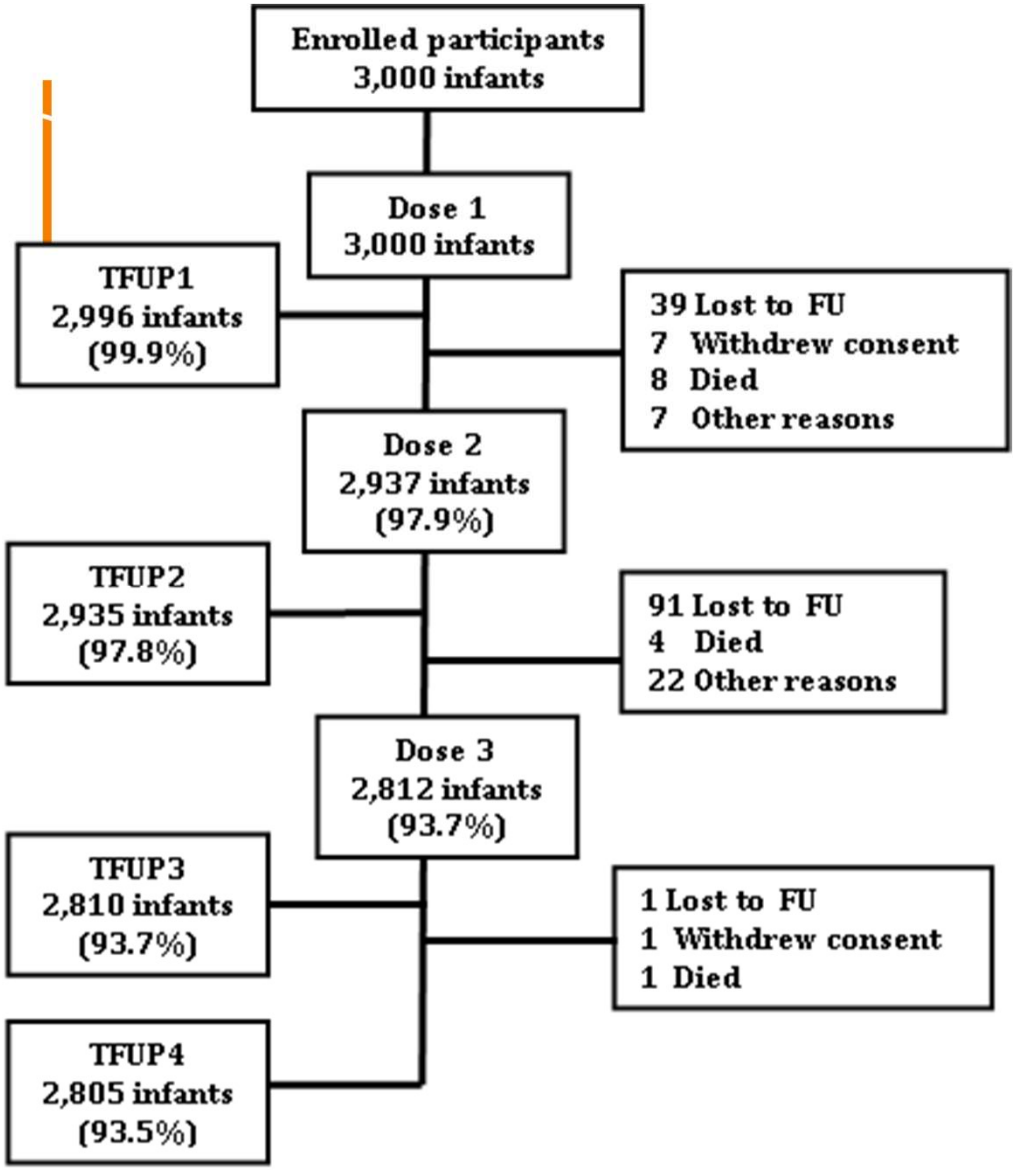
Inclusion / Exclusion Criteria

Inclusion criteria

- Infants eligible for the national routine childhood immunization schedule (local EPI schedule)
- Parent or legal guardian accessible by telephone (approximately 90-95% of families own a mobile phone in this population)
- Consent to medical information release obtained from parent or legal guardian of the subject

Exclusion criteria

- Known or presumed hypersensitivity to any component of the vaccine, or individuals with a history of allergy to products or mercury-containing compounds, such as sodium ethylmercurothio-salicylate (e.g.thiomersal)
- Children having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B, or Hib vaccines
- Children who have experienced an encephalopathy of unknown etiology after a previous vaccination with pertussis containing vaccine



Flowchart

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Relative risk and 95% CI of children having all causality IMEs, SAEs, or IMEs due to respiratory or diarrheal disease after the first dose of pentavalent vaccine according to the period post-vaccination

* p=<0.01

** p=<0.05

RR = rate ratio

Respiratory disease=any event presenting as upper or lower respiratory tract disease

Diarrhea=any event presenting as upper or lower gastrointestinal illness

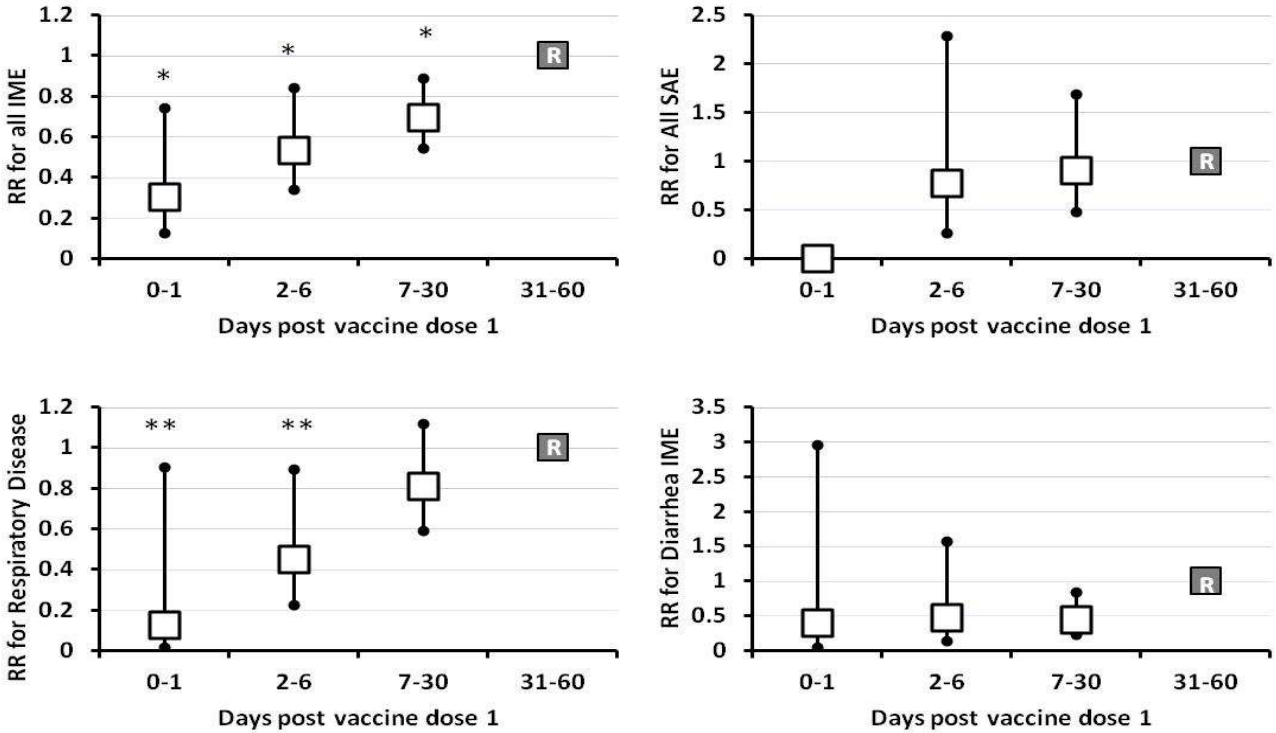
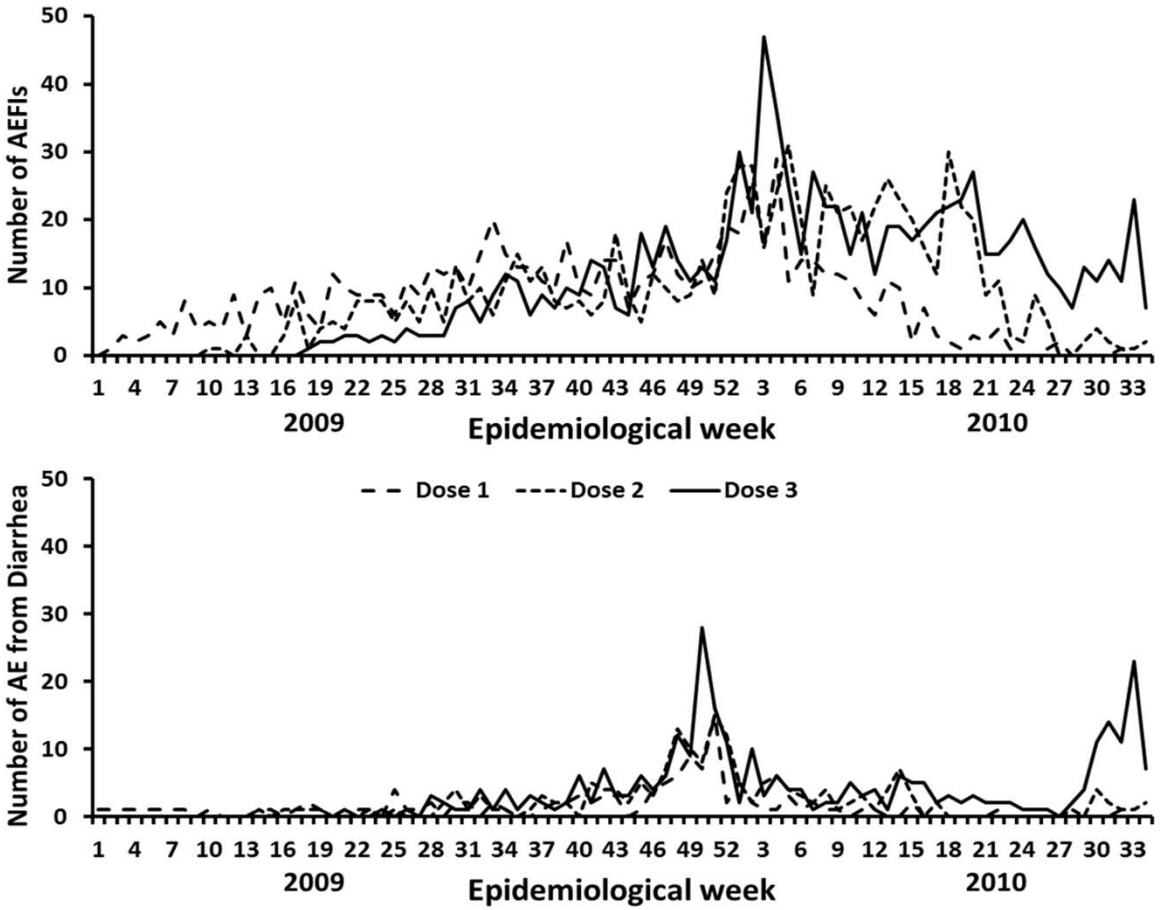


Figure 3. Incidence of all medically important and serious adverse events after each vaccine dose and those reported as diarrheal illness by epidemiological week in Guatemala City 12/2008-01/2010



Talking about AVSS – steps to define if AVSS can help

Patricia Mouta
Katharina Hartmann

Session 2

Protecting people from global diseases since 2000.

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Passive surveillance is the cornerstone of vaccine Pharmacovigilance.

Passive Vaccine Safety Surveillance
Strengths

Covers all medicinal products / vaccines during their whole life cycle

Covers the whole patient population, incl. special sub-groups ("real life")

Ability to detect AEFIs that are
- rare
- unexpected
- unknown
- clinically relevant
- serious

Early signal function

Signal generation function

"the tip of the iceberg"

Inexpensive and less labor - intensive strategy to cover a large population

Passive Vaccine Safety Surveillance
Limitations

No direct information on incidence

No information on vaccine exposure (no denominator)

Reporting rate not stable over time (risk of over- / underreporting)

Sensitive to selective reporting

Not representative (bias)

Clinical information often too limited in terms of quality and quantity

Case evaluation / causality assessment questionable

No control group(s)

Generated signal cannot be tested

Poor case identification

Possibility to fake AEFIs

KEY BACKGROUND CONCEPTS AND INTRODUCTION

Passive surveillance has a number of well-recognized limitations, including:

- underreporting;
- difficulty determining rates of AEFIs; and
- inability to properly characterize strength of association between vaccine exposure and adverse events.

Many countries, particularly in resource-limited settings, lack robust passive vaccine surveillance systems.

What is AVSS?

AVSS is a data collection system that seeks to ascertain as completely as possible the number of AEFIs in a given population via a continuous organized process.

CIOMS GUIDE TO ACTIVE VACCINE SAFETY SURVEILLANCE

AVSS KEY BACKGROUND CONCEPTS

AVSS can complement a passive surveillance, confirming or discarding the signals detected in the latter.

AVSS may also be of use to any resource-limited country lacking a sufficient passive system, or requiring vaccine safety information that is otherwise unavailable.

For example, an AVSS involving 30,000 patients can only identify events that occur at or more frequently than 1 in 10,000 (know as the “rule of 3”).[25]

A primary aim of AVSS systems is to estimate the risk of an AEFI in a population exposed to a vaccine. To evaluate if a vaccine increases the risk of a particular AE requires determination of relative risks. Usually, relative risk estimation involves the comparison with background rates

Active Vaccine Safety Surveillance
Non-Interventional study / Observational study

Features of Non-interventional / Observational Studies

- Interventions (e.g., vaccinations) are in accordance with the local clinical practice (e.g., national immunization scheme, EPI scheme)
- Investigator does not interfere with the choice of the intervention (e.g., vaccine)
- No assignment of the study participant to a pre-defined intervention (i.e., no randomization)
- No additional diagnostic or monitoring procedures applied to study participants
- Epidemiological methods used for analysis of the collected data

Sources of Observational Data (Real World Data)

- Vaccination / Immunization registries (patient registries)
- Hospital / medical chart reviews
- Data from hospital / sentinel sites
- Data from insurance claims databases
- Electronic health records
- Data from post-marketing safety studies

Post-Authorization Vaccine PV Approaches

	Passive Surveillance	Active Surveillance	
		Non-interventional	Interventional
Setting	• Spontaneous reporting • Stimulated reporting / enhanced passive reporting • Sentinel sites for enhanced passive surveillance	• Active case finding (e.g., field studies) • Registries • Large linked databases • Vaccine event monitoring systems	• Interventional Phase IV study
Data Analysis	Various AEFI analyses: • Case series • Disproportionality analyses (Data mining) • Observed / Expected (O/E Analysis)		
Key design		Observational study design: • Cross-sectional • Cohort • Case-control • Case only studies	Interventional study design: • Controlled / uncontrolled • Blinded / unblinded • Randomized / non-randomized

When AVSS can help?

1. Introduction of a novel vaccine for which only limited safety data are available from other countries;
2. Introduction of a well-established (i.e., in widespread use) vaccine into a new country for the first time; and
3. Evaluation of special populations or circumstances that could be involved.

When AVSS can help?

Each of the examples may prompt stakeholders (e.g., MAH NRA, NIP, MOH) to question whether passive surveillance is sufficient – or additional data is needed for assessment of the benefit / risk balance.

- Study included by the MAH in Part III of the RMP (Pharmacovigilance Plan).
- Study imposed by the NRA / NIP:
  - a condition for authorization of a new vaccine,
  - to establish safety in the own population when introducing a new or established vaccine into their jurisdiction,
  - change in the vaccination program (e.g., new dosing, new immunization schedule, etc.).
- To study a new identified safety issue (e.g., detected through signal management activities in passive surveillance)
- To study international or local safety concerns raised e.g., in the literature, by the media, etc.
- When extending the use of the vaccine to a new population or circumstances e.g., in an outbreak situation for timely impact assessment
- To study the safety profile of a new vaccine in LMICs with limited passive surveillance capacities (e.g., when introducing a new vaccine aimed at diseases of resource-limited countries).

Knowledge Gap – what is it?

'knowledge gap' refers to lack of available or easily accessible information on vaccines in countries which need the respective information in contexts such as:

- vaccine introduction,
- new safety issue,
- change in the nature of the vaccination program, or
- inadequate passive surveillance system.

Knowledge gaps are ideally addressed in the RMPs

This lack of information equals a research gap or question on some aspect of vaccine safety that has not been answered sufficiently.

If the knowledge gap has the potential to negatively influence the benefit-risk profile of the vaccine to such a degree that it could significantly affect the safety of those receiving vaccinations, it can be described as a "significant knowledge gap" (SKG).

An SKG may be specific to a particular country, region, or population subset (e.g. elderly, pregnant women).

Significant Knowledge Gap

It should be emphasized that even if a Significant Knowledge Gap (SKG) has been identified, that does not necessarily mean that AVSS is the best available tool.

Numerous tools for closing a SKG can be considered, and AVSS should only be undertaken if it is determined that this is the appropriate approach.

Vaccine Information source list

It creates a framework to find and organize available data, using source documents. The specific documents may vary depending on how the vaccine has been authorized in a particular country or region. By using the EVI, the stakeholder can determine whether information relevant to introduction in their country is known or if a gap is confirmed to exist.

Specific types of gaps: examples of potential gaps related to the vaccine or its usage

1.Related to the vaccine itself:

Novelty of the vaccine

Changes/differences in the vaccine product

2. Related to the population:

Related to the target population

Different age groups being targeted

Related to the target disease, or differences in local serotypes, mutations, or virulence factors

3. Related to the use of the vaccine:

Change in the use of the vaccine

Concomitant vaccine or other medication with the present vaccine

Related to the health care setting

Is the vaccination initiative part of a mass vaccination campaign?

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Confirm that the significant knowledge gap exists: How?

1.Reaching out to relevant experts in the field who may have insight into the issue;

2.Checking with other countries to confirm whether they have faced a similar gap, how it was closed, and even if they have initiated AVSS or other pharmacovigilance tools;

3.Discussing with the vaccine manufacturer/MAH to confirm that they are not aware of any additional data that may be relevant to the potential gap; and/or

4.Searching thoroughly through the literature for relevant published data. Once the stakeholder is confident that they have performed their due diligence and a true significant knowledge gap exists, they should proceed to determine which pharmacovigilance tool is most appropriate to close the gap.

Steps	Steps in determining if there is a gap and how to close it	Responsible and/ or accountable	Consulted and/ or informed of decision
Pre	Is there a reason to consider AVSS?	WHO, NRA/NIP, MAH	PvC, medical communities, appropriate expert advisory and other relevant organizations.
1	Is there a significant knowledge gap?	WHO, NRA/NIP, MAH	PvC, MAH, other NRAs, WHO, NGO, MO, payers, academia
2	Is it confirmed the gap actually exists after further research?	WHO, NRA/NIP, MAH	PvC, MAH, other NRAs, WHO, NGO, MO, payers, academia
3	Can the knowledge gap be closed with existing passive surveillance (including enhanced passive surveillance)?	NRA/NIP, MOH MAH	PvC, MAH, other NRAs, WHO, NGO, MO, academia
4	Confirm: is AVSS the right tool to close the significant knowledge gap?	NRA/NIP, MOH MAH	PvC, MAH, other NRAs, WHO, academia
5	Choose the right type of AVSS.	NRA/NIP,MAH	PvC, MAH, other NRAs, WHO, NGO, MO, academia
6	Consider practical aspects of implementation.	NRA/NIP	NECs, PvC, MAH, other NRAs, WHO, NGO, MO
Post	Who determines action based on results?	NRA/NIP	MAH, donors, PvC, other NRAs, WHO, NGO, MO

Step 1: Is there a significant knowledge gap

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1. What are the circumstances in which AVSS may be initiated for a vaccine?
2. How do we determine if there is a significant knowledge gap for a particular vaccine?
3. What factors contribute to the existence of a significant knowledge gap?
4. How can we assess the novelty of a vaccine and its impact on the need for AVSS?

Step 2: Is it confirmed that the gap actually exists after further research?

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5. What is the Essential Vaccine Information (EVI) source list, and how can it be used to assess data needs?

6. What are the steps involved in confirming the existence of a significant knowledge gap?

7. How can stakeholders access all relevant documents and data sources for validation?

8. What are the benefits of confirming a significant knowledge gap before proceeding with AVSS?

Step 3: Can the knowledge gap be closed with existing passive surveillance?

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9. When is it appropriate to consider using passive surveillance to address a knowledge gap?

10. How can we determine if local passive surveillance systems are adequate for addressing the issue?

11. What factors should be considered when deciding between passive surveillance and AVSS?

12. What resources are available for passive surveillance, and how can they be leveraged effectively?

Step 4: Confirm AVSS is the appropriate tool to close the SKG

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13. What are the key differences between passive surveillance and AVSS?

14. When should stakeholders consider enhanced passive surveillance as an alternative to AVSS?

15. How can stakeholders determine if AVSS is the right tool to close a specific knowledge gap?

16. What are the ethical considerations in choosing AVSS as the tool for vaccine safety assessment?

Steps 5 and 6: Moving forward with AVSS: choosing the right type of AVSS and practical implementation issues

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17. What are the various forms of AVSS discussed in Chapter 3, and when should each be selected?

18. Can you provide examples of when different forms of AVSS might be appropriate?

19. What are the fundamental technical considerations for designing, implementing, and analyzing AVSS data?

20. How can stakeholders foster dialogue and partnerships among vaccine stakeholders to ensure successful AVSS activities?

Data collection strategies in AVSS

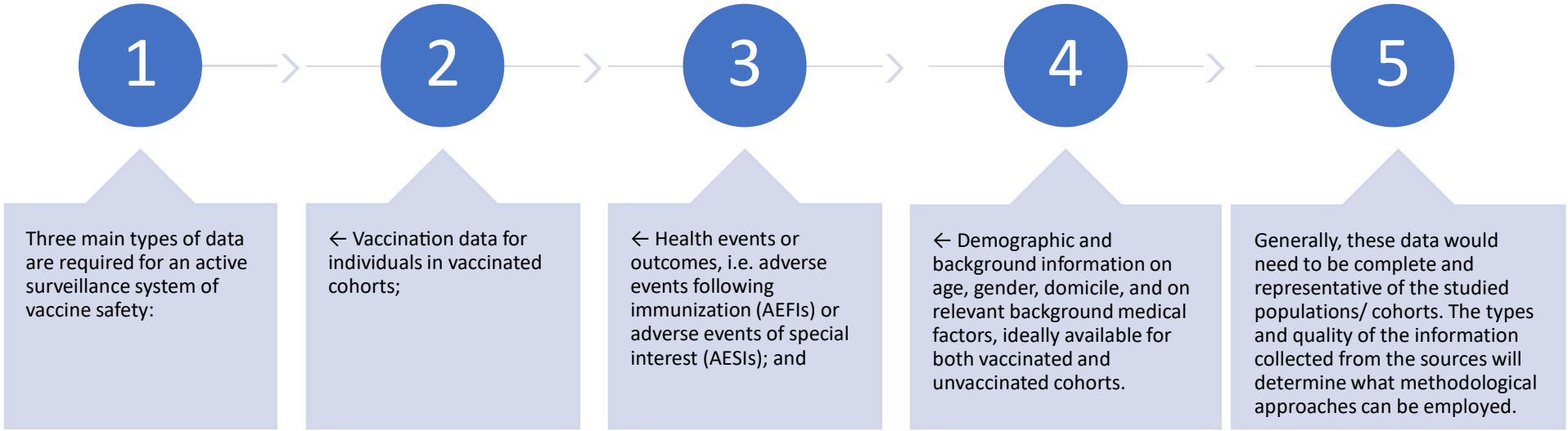
Primary Data Collection – Field Study

- Information collected specifically for the research in the «field»,
  - ✓ e.g., sentinel surveillance, prospective observational studies not using information already recorded in databases / registries.

Secondary Data Collection – Databases / Registries

- Information collected in a record system / database, collected for other reasons , not associated with the specific research study.
  - ✓E.g., automated healthcare databases / health administrative databases, population / vaccination registries, hospital or primary care clinic registries, etc.
  - ✓Record Linkage strategies
- Identification of the secondary data source if «fit for purpose», reliable and relevant to the study research question / meets the needs of the study (structured feasibility assessment of the data source).
- Data access consideration (accessibility of the data, contracting logistics. etc.).

Type of data needed for establishing AVSS



Individual Data

AVSS system would benefit from access to readily-retrievable, documented data on every individual vaccinated concerning:

- Individual identifier
- Place of vaccination
- Vaccine type
- Vaccine presentation, single or multiple dose
- Manufacturer
- Lot number (of vaccine and any dilutents)
- Date of vaccination (and perhaps time)
- Vaccine injection site
- Number of dose

Individual Data

Ideally, vaccination data for exposed individuals should be maintained in a computerized database or registry.

With new vaccines being deployed, the higher costs associated with these databases and software may be obviated by their ability to yield required information quickly and efficiently without the need for laborious data collection each time a new vaccine is being introduced.

Health events/ outcomes data

For information on health events or outcomes, the source of data to be used will depend on the type and severity of the health event (AEFI/AESI) of interest .

Generally, serious events that require medical care would be better suited for AVSS, since the events have a greater chance of being recorded in medical institutions.

- ✓ Patient identifier (to allow for linkage to other data)
- ✓ Place of care
- ✓ Diagnosis(es) (ideally standardized)
- ✓ Date (and time) of onset of first symptom of the event
- ✓ Other relevant medical information (e.g. clinical details and treatment outcomes)

Sources of Observational / Real World Data

- Vaccination / Immunization registries (patient registries)
- Hospital / medical chart reviews
- Data from hospital / sentinel sites
- Data from insurance claims databases
- Electronic health records
- Data from post-marketing safety studies

Observational / real world data are subject to **bias and confounding**

Bias and Confounders
Some explanations

- Confounder / Confounding:
  - Term used to describe a co-variate that is related to the outcome measure and to a possible prognostic factor
  - Confounding by indication: Patients with underlying chronic disease more likely to be vaccinated as compared to a healthy study participant
- Bias:
  - Systematic error in design, implementation, analysis of a study resulting in an estimate that differs from the truth
    - Information bias: misclassification, recall, reporting, surveillance
    - Selection bias e.g., Berkson's bias: hospitalization rates for individuals with the target disease will differ from the rates of those with the control condition)
    - Lead-time bias: difference in time between the date of diagnosis with screening and the date of diagnosis without screening
    - Healthy vaccinee bias: Patients / study participants who are in better health more likely to adhere to vaccination (opposite of confounding by indication)

Basic Questions

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What is he Research Question?

Which research design is most appropriate to answer the question ?

- What is the most appropriate methodological approach?
- How is the feasibility of the planned and designed study?
  - Scientific feasibility?
  - Operational feasibility?

Importance of feasibility assessments before implementing non-interventional pharmaco-epidemiological studies of vaccines

Willame et al 2016

Example: Mosquirix

Study (exposure, outcome)	Design criteria	Feasibility assessment outputs: What was known before the feasibility assessment?	Feasibility assessment outputs: What was found by conducting the feasibility assessment?
Study #5 (Malaria vaccine, autoimmune disease, KD, meningitis)	Population and setting information	-Theoretical risk of autoimmune diseases with novel adjuvanted vaccine. -Pivotal clinical trial data showed a potential risk of meningitis. -Literature reviews show scarcity of background rates for adverse events in SSA. -No existing databases in SSA thus need for prospective data collection.	-Comprehensive literature review conducted to reinforce background incidence data. -Positive scientific opinion by experts or health agency on the proposed study protocol. -Identified need for partnership with specialized agency (HDSS). -Identified need for capacity building, for example know-how in pharmacovigilance systems, medical diagnosis, laboratory capacities.
	Exposure	NA	NA
	Outcome	-Multiple outcomes (AEs) of interest	-Support of an expert panel for case ascertainment.

AE: Adverse Event; CPRD: Clinical Practice Research Datalink; GP: General Practice; HDSS: Health and Demographic Surveillance Sites; HES: Hospital Episode Statistics; HPV: human papillomavirus; KD: Kawasaki Disease; NA: Not Applicable; PPV: Positive Predictive Value; SSA: Sub-Saharan Africa; UK: United Kingdom.

Study #5 *(Exposure: Malaria vaccine, Outcome: autoimmune diseases, Kawasaki disease, intussusception, meningitis, and other pre-defined diseases).* The feasibility assessment performed in Sub-Saharan Africa confirmed that a field study could be implemented through an existing network of health and demographic surveillance systems (HDSS) in African regions with low to moderate malaria endemicity. Missing key elements such as laboratory capacity, know-how in pharmacovigilance and a need for an expert panel for case ascertainment for some of the endpoints were identified.

Scientific Feasibility Questions

- What is the most appropriate study design - prospective / retrospective; type of specific design?
- What is the most appropriate data collection strategy - primary (field study) or secondary (large healthcare databases)?
- What is the adequate risk period?
- Is a comparator required – if so, what is an adequate control group?
- What is the required sample size?
- What are the most appropriate statistical methods to control for bias, confounding, missing data?
- What are the inclusion / exclusion criteria?
- What are the expected limitations of the study?

Operational Feasibility Questions

Governance

- What are the ethical requirements (Ethics / Scientific Committee submissions)?
- What are the regulatory submission requirements?
- What are the Data Protection Directives in the respective county / region?
- Is there a need for Informed Consent?
- Is there a need to collect and report serious adverse events ? If yes - how will this be performed?

Vaccine manufacturers constraints

- What are the timelines for delivering results according to regulatory requirements / expectations?
- Are the level of resources and budget for the study acceptable?

Partnership / Collaborations

- How can the company / sponsor get access to the data?
- What kind of study to implement (e.g., industry – sponsored, collaboration, outsourced, etc.)?
- Which types of collaborations are needed?
  - ✓External collaborators (e.g., coordinators, etc.) required?
  - ✓Can the Principal Investigator be identified?
  - ✓How can the experts be identified?

Which AVSS Methodology?

Data Type			Methods
Vaccine	Health Event	Population/ Demographic*	
Available	Available	Available	Cohort Case-control Self-control
Available	Available	Not available	Self-control
Available	Not available	+/- Available	none
Not available	+/- Available	+/- Available	none

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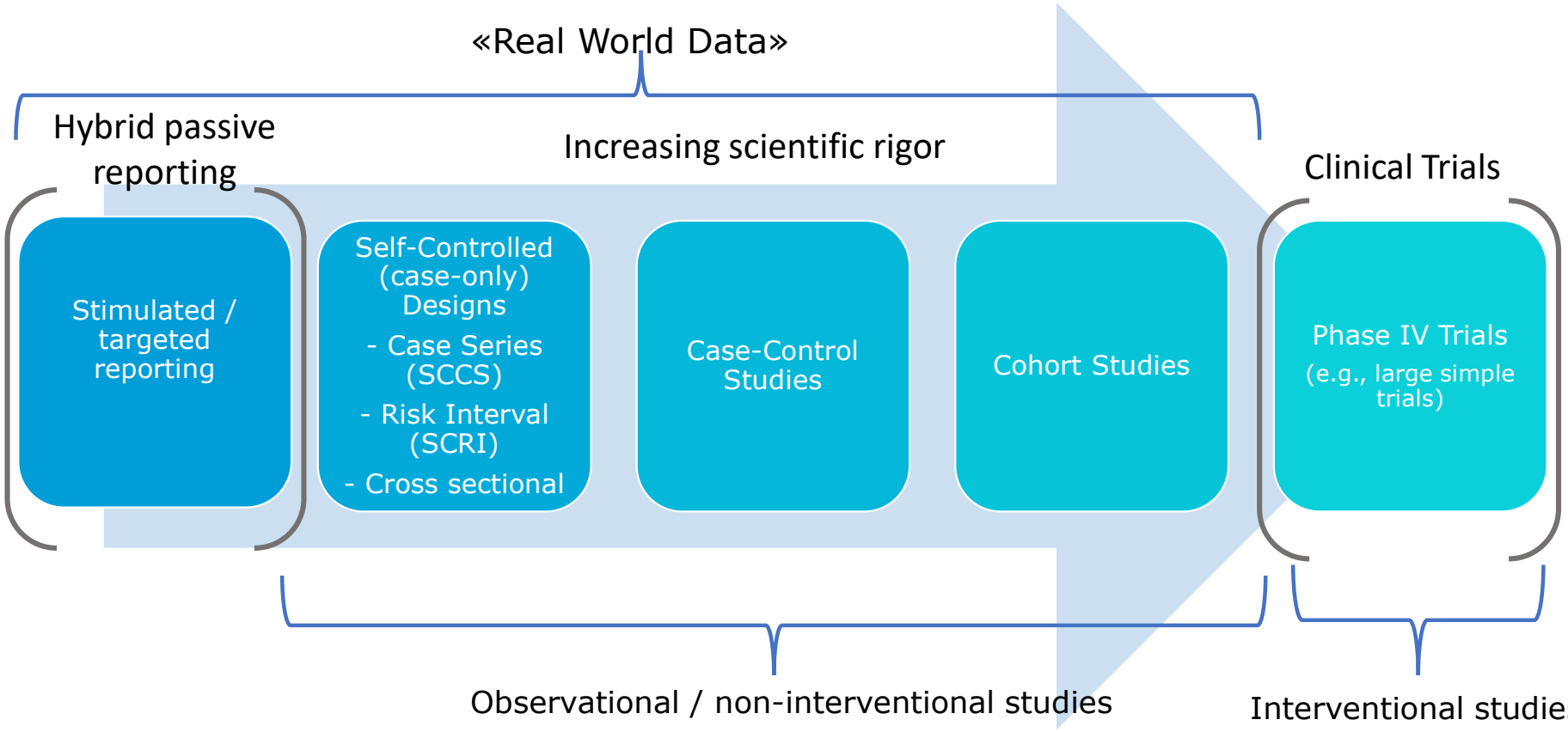
Types of Common Study Designs in AVSS



Hybrid Passive Vaccine Safety Surveillance Stimulated / Targeted Reporting

Public information campaign to increase reporting during a mass vaccination

Encourage and facilitate reporting in specific situations, e.g., for new vaccines during a limited time period

Stimulation strategy focused on AEFI of special interest (AESI)

Resources and efforts more effective by limiting stimulated reporting to few sentinel sites

Various methods to enhance passive surveillance:

- Telephone / online reporting / Apps
- Systematic stimulation via e-mail reminders, personal visits etc.
- Additional training to healthcare providers (short-term effect to increase data quality)

Practical Aspects when conducting AVSS Studies
Basic questions

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Who will finance the study?

- MAH / Manufacturer?
- Public partner, such as Governmental Bodies (e.g., MOH, NRA, NIP, BARDA, CEPI etc.)
- Funding organizations (e.g., BMGF, GAVI, Welcome Trust, others)
- Consortia including different public and private partners
- Others

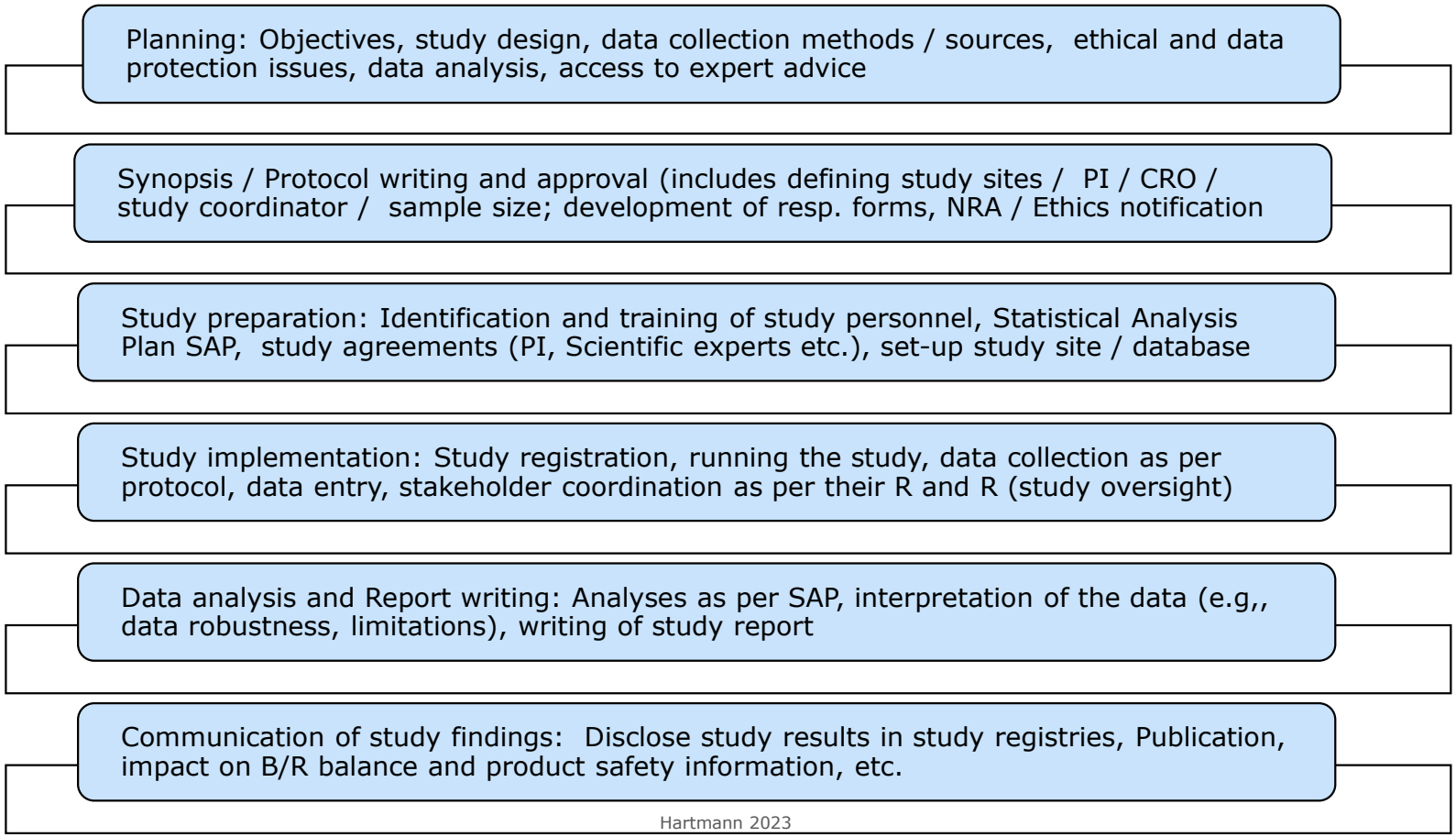
Who is responsible for the study / Who runs the study?

- Outsourced to CRO / academia / MAH / other?
- Private organization (e.g., MAH, CRO)?
- Public organization (e.g., governmental body)?
- Who is the Principal Investigator?
- Who is the Sponsor?
- Who oversees the study team?

What approvals are needed?

The answers to the questions determine the roles and responsibilities of each party.

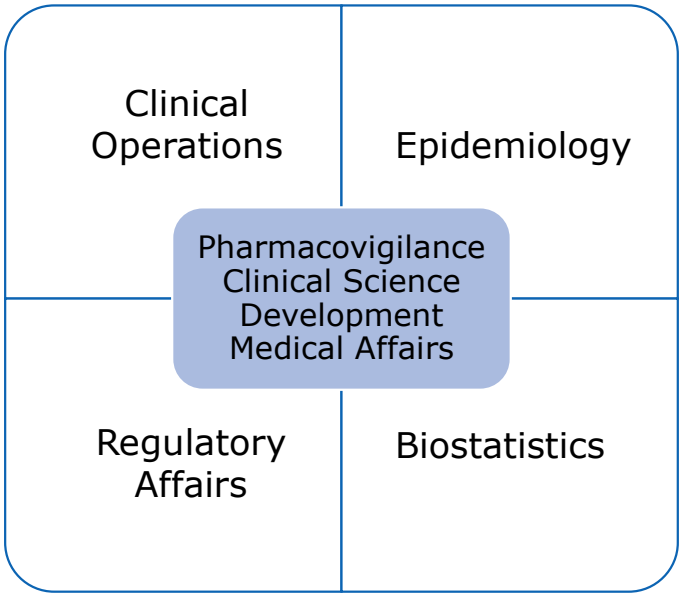
AVSS Practical Aspects
Six basic steps



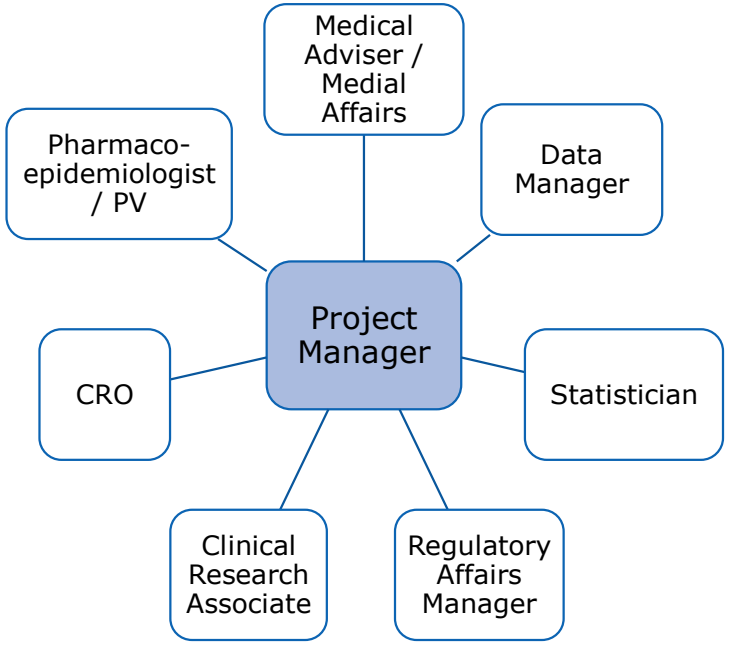
Hartmann 2023

Company Functions involved in AVSS
Company-sponsored study

Matrix Organization
Scientific Study Team



Matrix Organization
Operational Study Team



Project Documentation:

- ✓ Project Plan
- ✓ Who does What
  (Roles and Responsibilities)
- ✓ Tasklist
  (e.g., Gantt Chart)
- ✓ Workload Analysis
- ✓ Milestones
- ✓ Budget / Funding

AVSS Practical Aspects

STEPS	ACTIVITIES	RESOURCES
Protocol writing	- Writing of the study protocol (including sample size, study site(s), data to be collected, principal investigator/ study coordinator); - Application for ethical clearance and other study permit, according to the regulation of each country; - Notification to NRA/other RA as applicable.	← National Immunization Programme ← NRA ←Pharmacovigilance centres ← Academia ← Manufacturers ← Study site(s) ← Other research centre(s) according to institution involved in the study.
Study preparation	- Identification of personnel with expertise for the study; implementation, analysis and interpretation of the results; - Identification and training of the study team and other partners; - Agreement (together with scientific committee and field investigators) on feasibility and practicalities; - Public communication.	← Study site(s) ← Other research centre(s) according to institution involved in the study.
Study implementation	- Running of the active surveillance study; - Collection of the data according to the protocol; - Entering the data into the analysis program; - Cooperation with stakeholders.	← Study site(s) ← Monitoring centre ← Other research centre(s) according to institution involved in the study.
Data analysis and report	- Strategies for analyses, including statistical analysis plan; - Analysis of the data according to the protocol; - Writing of the report; - Publication.	← Study site(s) ← Monitoring centre ← Other research centre(s) according to institution involved in the study. ← NRA ← Manufacturers

Considerations on Sample Size Estimation /1

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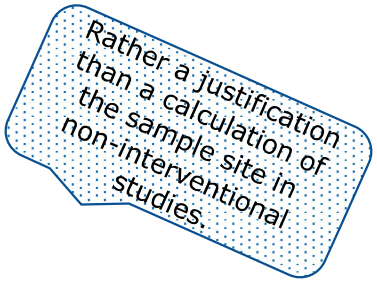
Calculation of sample size is a critical part of the study design

- Involves statistical and clinical informed judgement.
- The values placed into the formula are chosen by the sponsor and needs involvement of statisticians.
  - ✓Approaches differ depending on the type of a AVSS study design and the specific study objectives.
  - ✓Statistical methods used in the various study designs developed in AVSS are under continuous development by statisticians.
- Imperative to estimate a reasonable sample size based on best evidence available at the time to be able to give a correct answer to the research question.
- Some values are typically chosen from a standard set of possibilities, others are estimated based on literature or earlier trials.
  - ✓Researcher decides which of the several general acceptable values are best suited for the intention of the study.
  - ✓Deciding on sample size is a balancing act with several factors to be considered.

Considerations on Sample Size Estimation /2

Sample size determined by four factors



- *Variability of the out-come measurement (end-point) of the study:*
  - ✓Imprecise measurements are invariably encountered with clinical data.
  - ✓The higher the variability of the outcome measure (expressed as the standard deviation) the larger the sample size.
  - ✓The more precisely the endpoint can be measured / determined, the fewer subjects require.
- *Magnitude of response under investigation:*
  - ✓What is the clinically relevant and biologically plausible difference between the groups that the test is required to detect?
  - ✓The smaller the difference the larger the sample size.
- *Power to reach a true conclusion:*
  - ✓Probability to avoid type II error (β) / probability to get the right answer and avoid false-negative conclusion.
  - ✓Power (1-β) should be minimally 80%, often 90-95% to detect a particular clinical effect.
  - ✓The smaller the power, the less subjects required with the consequence of false-negative conclusions.
- *Statistical significance:*
  - ✓Probability of a type I error (α), acceptance to come to a false positive conclusion, usually 5% or 1%.
  - ✓The smaller α, the more certainty and the more subjects required.

Considerations on Sample Size Estimation /3
Information needed in Cohort and Case-Control Studies

Type I error (α) considered tolerable and whether one- or two-sided	▪ The less willing to accept a type I error the larger the sample size.
Type II error (β) considered tolerable	▪ The larger type II error is acceptable, the smaller the required sample size, and the smaller the power (1- β).
Minimum relative risk to be detected	▪ The smaller the relative risk to be detected the larger the sample size.
Cohort study: Incidence of the disease (AESI) in the unexposed control group Case-Control study: Prevalence of exposure in the diseased control group	▪ The rarer the AEFI (cohort study) / vaccine exposure (CCS) of interest, the larger the sample size.
Cohort study: Ratio of unexposed controls to exposed study subjects Case-control study: Ratio of undiseased controls to diseased study subjects	▪ Most statistical power for a given number of study subjects if number of controls is the same as exposed subject. ▪ Increasing the number of controls for each exposed subject increases power but only with progressively smaller gains in statistical power

- Mathematical formula in the literature / textbooks to calculate sample sizes focus mainly on randomized clinical trials RCTs and need adaptions for study designs used in AVSS.
- In AVSS studies the sample calculation is troubled by a large amount of imprecision and variability of the data (e.g., adjusting for bias, confounders and missing data).
- The choice of the 4 parameters apply also for AVSS study designs: The sample size is very sensitive to
  - Variability (SD)
  - Relevant clinical difference between the study groups
  - Power (1-β)
  - Statistical evidence (α)

Sample Size Estimation /4

Simple Guide „Rule of three"

Without consideration of background incidence

Expected ADR frequency	Required number of subjects Adverse reactions		
	1	**2**	**3**
1 in 100	300	480	650
1 in 200	600	960	1'300
1 in 1'000	3'000	4'800	6'500
1 in 2'000	6'000	9'600	13'000
1 in 10'000	30'000	48'000	65'000

With consideration of background incidence

Control group	Basic ADR risk	Additional risk of an ADR		
		1 in 100	1 in 1'000	1 in 10'000
unlimited (background risk known)	1 in 10	10'000	980'000	98'000'000
	1 in 100	1'600	110'000	11'000'000
	1 in 1'000	500	16'000	1'100'000
5 x treatment group	1 in 10	12'000	1'200'000	120'000'000
	1 in 100	1'900	130'000	13'000'000
	1 in 1'000	700	19'000	1'400'000
Equal to treatment group	1 in 10	20'000	2'000'000	200'000'000
	1 in 100	3'200	220'000	22'000'000
	1 in 1'000	1'300	32'000	2'300'000

J.A. Lewis 1981

Many Tables available in Statistical Textbooks and different software programs are available to calculate the sample sizes needed; e.g., to detect different relative risks (from 0.2 -50), based on $\alpha = 0.05$ two-tailed (type I error 95%), $\beta = 0.10$ (power = 90%) and control : exposed ratio = 1:1 (up to ratios 4:1).

Toolbox /1
Supportive Forms, Checklists and Guidance

- Observational Studies - Planning & Startup (nih.gov)
- ENCePP Home Page
- CIOMS Guide to Active Vaccine Safety Surveillance – CIOMS
- Guideline on good pharmacovigilance practices (GVP) - Module VIII – Post-authorisation safety studies (Rev 3) (europa.eu)
- GVP Module VIII Addendum I Rev 3 - Final published (europa.eu)
- Protocol template to be used as template for observational study protocols: sentinel surveillance of adverse events of special interest (AESIs) after vaccination with COVID-19 vaccines (who.int)
- Protocol template to be used as template for observational study protocols: cohort event monitoring (CEM) for safety signal detection after vaccination with COVID-19 vaccines (who.int)
- Protocol_ACCESS_COVID-19 EHR Vaccine Effectiveness Protocol Template.docx (vac4eu.org)

Toolbox / 2
Supportive Forms, Checklists and Guidance

- ENCePPChecklistforStudyProtocols.doc (live.com)
- nidcr-observational-protocol-template.docx (live.com)
- Checklists - STROBE (strobe-statement.org)
- Characterizing RWD Quality and Relevancy for Regulatory Purposes (duke.edu)
- A Framework for Regulatory Use of Real-World Evidence (duke.edu)
- Special Task force on Real World Evidence in Health Care Decision Making.pdf
- ICH M14_ConceptPaper_2022_0405 (ich.org)
- Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products | FDA
- Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry | FDA
- EMA Guideline on registry-based studies (europa.eu)
- About | ViewHub (view-hub.org)

Group Activity

Patrica Mouta
Viska Indriani
Katharina Hartmann

Session 3

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people from
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Manufacturers Network International

Study Protocol

Format and content as per GVP Module VIII.B.3.1.

Study Title
Marketing Authorization Holder
Responsible Parties
Abstract
Amendments and updates
Milestones
Rational and Background
Research question and objectives
Research methods
Protection of human rights
Management and reporting of AEFIs
Plans for disseminating and communicating study results
References

Research Methods:
- Study design
- Setting
- Variables
- Data sources
- Study size
- Data management
- Data analysis
- Quality control
- Study limitations

Checklists for Study Protocols:

- EU / ENCePP:
  - ENCePPChecklistforStudyProtocols.doc (live.com)
  - Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies (europa.eu)
- STROBE*:
  - Checklists - STROBE (strobe-statement.org)
- NIH Observational Study toolbox:
  - nidcr-observational-protocol-template.docx (live.com)

*Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

Checklist for a Study Protocol

- Milestones
- Research Question
- Study Design
- Source and Study Populations
- Exposure Definition and Measurement
- Outcome Definition and Measurement
- Bias and Confounders
- Data Sources
- Analysis Plan
- Data Management and Quality Control
- Limitations
- Ethical / Data Protection Issues
- Amendments and Deviations
- References
- Plans for Communication of Study Results

Research Question

The research question and the objectives of the study must be clearly formulated:

- Why then study is conducted, e.g.:
  - To address an important public health concern.
  - To address a risk identified in the RMP
  - To close a research gap
  - To identify a potential or emerging safety issue
- The objectives of the study
- The target population (population or subgroup to whom the study results are intended to be generalized)

Study Design

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- Describe the study design clearly (e.g., cohort, case-control, cross-sectional, case only, other design)?
- Specify whether the study is based on primary, secondary or combined data collection.
- Describe the approach for the collection and reporting of adverse events / adverse reactions / adverse events of special interest (e.g., AEs that will not be collected in a primary collection setting)
- Specify measures of the occurrence (e.g., rates, risk, prevalence), if applicable
- Describe outcome and measures of association (e.g., risks, OR, excess risk, etc.), if applicable

Bias and Confounders:

- Consider e.g., healthy vaccinee effect, exposure and outcome misclassifications, time-related bias, etc.

Study Population

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- Describe and define the study population:
  - Study time period
  - Age and sex
  - Country of origin
  - Indication
  - Duration of follow-up
  - Eligibility, inclusion / exclusion criteria
- Describe the data sources:
  - How will the exposure data be collected?
  - How will the outcome data be collected?
  - Coding System used?

Example 1 : Rotavirus vaccine introduction in NIP

Patricia Mouta
Viska Indriani

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Rotavirus disease

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Rotavirus is a double-stranded RNA virus of the family Reoviridae.

The virus is composed of three concentric shells that enclose 11 gene segments. The outermost shell contains two important proteins: VP7, or G-protein, and VP4, or P-protein. VP7 and VP4 induce neutralizing antibodies that are believed to be involved in immune protection.

From 1996 through 2005, five genotypes of rotavirus (G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8]) accounted for 90% of strains isolated from children younger than age 5 years in the United States. Of these, genotype G1P[8] accounted for more than 75% of strains. In the recent past, G12P[8] has become the most common genotype identified in the United States.

Rotavirus is very stable and may remain viable in the environment for weeks or months if disinfection does not occur.

https://www.cdc.gov/vaccines/pubs/pinkbook/rota.html#rotavirus

Rotavirus disease

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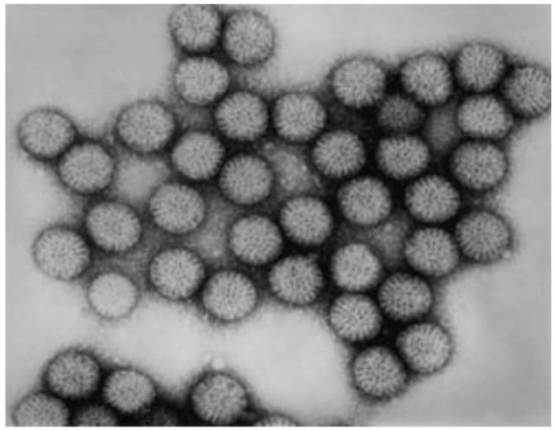
Rotavirus Pathogenesis

- Entry through mouth
- Replication in epithelium of small intestine
- In severe infections-rotavirus antigen can be detectable in serum
- Infection leads to isotonic diarrhea



https://www.cdc.gov/vaccines/pubs/pinkbook/rota.html#rotavirus

Infection may result in decreased intestinal absorption of sodium, glucose, and water, and decreased levels of intestinal lactase, alkaline phosphatase, and sucrase activity, and may lead to isotonic diarrhea.
The immune correlates of protection from rotavirus are not fully understood. Serum and mucosal antibodies against VP7 and VP4 are probably important for protection from disease. Cell-mediated immunity probably plays a role in protection and in recovery from infection.

Rotavirus disease

Protecting people from global diseases since 2000.

Clinical Features

The incubation period for rotavirus diarrhea is short, usually less than 48 hours.

The clinical manifestations of infection vary and depend on whether it is the first infection or reinfection.

Infection may be asymptomatic, cause self-limited watery diarrhea, or may result in severe dehydrating diarrhea with fever and vomiting.

Up to one-third of infected children may have a temperature greater than 39°C (102°F).

The first infection after 3 months of age is generally the most severe. The gastrointestinal symptoms generally resolve in 3 to 7 days.

https://www.cdc.gov/vaccines/pubs/pinkbook/rota.html#rotavirus

Rotavirus disease

Protecting people from global diseases since 2000.

Rotavirus Complications

- Severe diarrhea
- Dehydration
- Electrolyte imbalance
- Metabolic acidosis
- Children who are immunocompromised may have more severe or persistent disease

https://www.cdc.gov/vaccines/pubs/pinkbook/rota.html#rotavirus

Rotavirus Secular Trends in the United States

Prevaccine era:

- Estimated 2.7 million cases per year
- 95% of children infected by 5 years of age

Following the introduction of rotavirus vaccine:

- Annually averted:
  - 280,000 clinic visits
  - 62,000 emergency department visits
  - 45,000 hospitalizations

Rotavirus vaccine schedule

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Rotavirus Vaccine Schedule

- Routine vaccination of all infants without a contraindication
- 2-dose series for RV1 vaccine (at age 2 and 4 months)
- 3-dose series for RV5 vaccine (at age 2, 4, and 6 months)
- For both rotavirus vaccines
  - May be started as early as age 6 weeks
  - Maximum age for first dose is 14 weeks 6 days*
  - Minimum interval between doses is 4 weeks
- ACIP did not define a maximum interval between doses
- No rotavirus vaccine should be administered to infants older than 8 months 0 days*

https://www.cdc.gov/vaccines/pubs/pinkbook/rota.html#rotavirus

Rotavirus vaccine

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Rotavirus Vaccine Contraindications and Precautions

- **Contraindication**
  - Severe allergic reaction to a vaccine component or following a prior dose of vaccine
  - History of intussusception
  - Severe combined immunodeficiency (SCID)

- **Precaution**
  - Moderate or severe acute illnesses, including gastroenteritis (defer until symptoms improve)
  - Altered immunocompetence (SCID is a contraindication)
  - Limited data do not indicate a different safety profile in HIV-infected versus HIV-uninfected infants
  - Chronic gastrointestinal disease (data regarding the safety of rotavirus vaccine for infants with preexisting chronic gastrointestinal conditions are lacking)

https://www.cdc.gov/vaccines/pubs/pinkbook/rota.html#rotavirus

Rotavirus Vaccine Safety

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Rotavirus Vaccine Safety

- **RV5**
  - Diarrhea 18.1%
  - Vomiting 11.6%
  - Also greater rates of otitis media, nasopharyngitis, and bronchospasm
- **RV1**
  - Irritability 11.4%
  - Cough or runny nose 3.6%
  - Flatulence 2.2%
- **Intussusception**
  - Postlicensure-evaluation of RV1 and/or RV5 identified low level risk of intussusception; 1 excess case per 20,000 to 100,000 in the U.S.

https://www.cdc.gov/vaccines/pubs/pinkbook/rota.html#rotavirus

Rotavirus Vaccine History

Protecting people from global diseases since 2000.

1990s the first licensed vaccine, Rotashield (Wyeth Labora tories,USA), an attenuated simian and three simian human reassortant strains of the virus, showed that good efficacy .

However,intestinal intussusception ocurred in about one in11.000 children vaccinated, leading to its withdrawal an d posing a large challenge for new candidate vaccines

because future trials needed to include 60000 children to reasonably assure safety.

https://www.who.int/teams/immunization-vaccines-and-biologicals/diseases/rotavirus#:~:text=Four%20oral%2C%20live%2C%20attenuated%20rotavirus,G1%2C%20G2%2C%20G3%20and%20G4

Available Vaccines

Protecting people from global diseases since 2000.

Four oral, live, attenuated rotavirus vacines:

- Rotarix™ (derived from a single common strain of human rotavirus);
- RotaTeq™ (a reassorted bovine-human rotavirus);
- Rotavac™ (naturally occurring bovine-human reassortant neonatal G9P, also called 116E);
- RotaSiil™ (bovine-human reassortant with human G1, G2, G3 and G4 bovine UK G6P[5] backbone)

https://www.who.int/teams/immunization-vaccines-and-biologicals/diseases/rotavirus#:~:text=Four%20oral%2C%20live%2C%20attenuated%20rotavirus,G1%2C%20G2%2C%20G3%20and%20G4

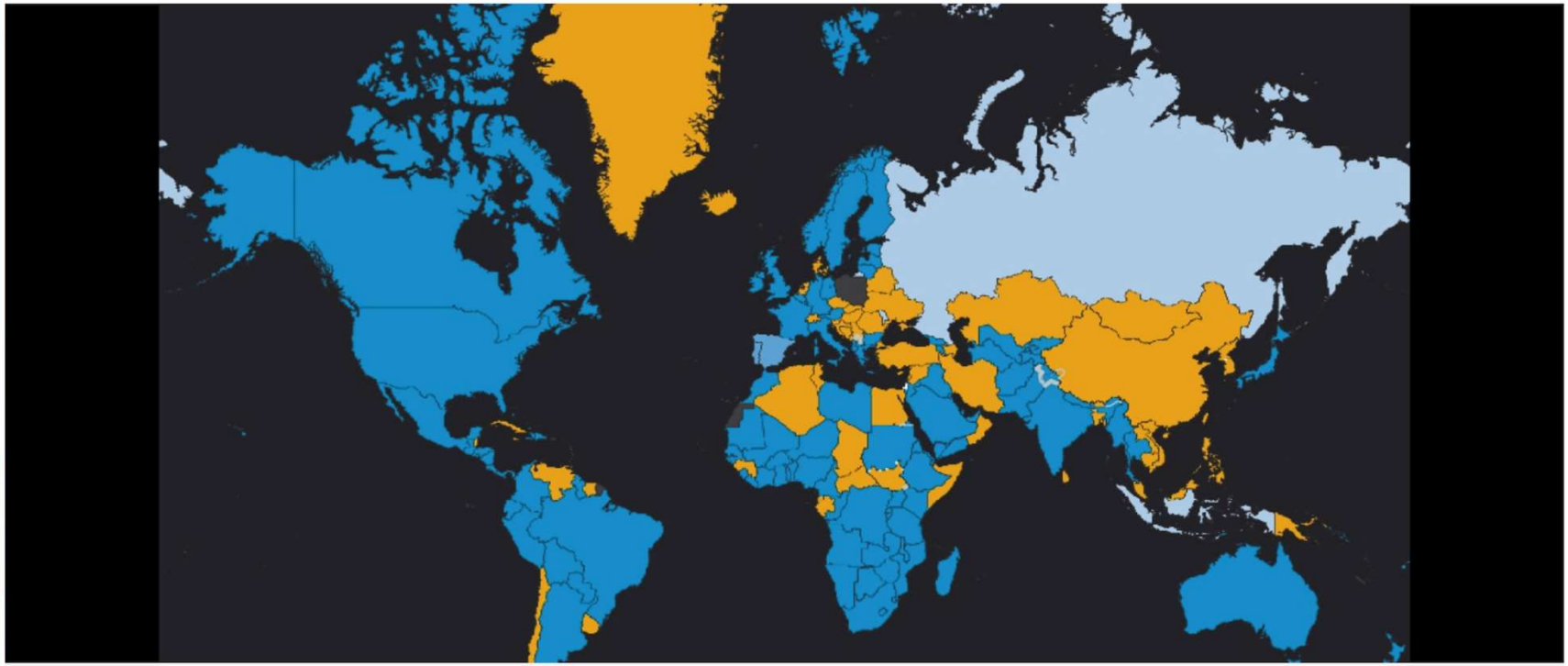
Available Vaccines

Protecting people from global diseases since 2000.

- Available internationally and WHO prequalified;
- All four vaccines are considered highly effective in preventing severe gastrointestinal disease.
- In low income countries, vaccine efficacy can be lower than in industrialized settings, similar to other live oral vaccines. Even with this lower efficacy, a greater reduction in absolute numbers of severe gastroenteritis and death was seen, due to the higher background rotavirus disease incidence.

https://www.who.int/teams/immunization-vaccines-and-biologicals/diseases/rotavirus#:~:text=Four%20oral%2C%20live%2C%20attenuated%20rotavirus,G1%2C%20G2%2C%20G3%20and%20G4

World Health Organization



https://immunizationdata.who.int/pages/vaccine-intro-by-antigen/rotavirus.html?ISO_3_CODE=&YEAR=

https://www.who.int/teams/immunization-vaccines-and-biologicals/diseases/rotavirus#:~:text=Four%20oral%2C%20live%2C%20attenuated%20rotavirus,G1%2C%20G2%2C%20G3%20and%20G4

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SOCIEDADE BRASILEIRA DE PEDIATRIA

Jornal de Pediatria

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ORIGINAL ARTICLE

Hospital-based surveillance of intussusception among infants☆

Eder Gatti Fernandes[a,*], Eyal Leshem[b], Manish Patel[c], Brendan Flannery[d], Alessandra Cristina Guedes Pellini[e], Maria Amelia Veras[f], Helena Keico Sato[g]

Objective: The study was initiated to monitor intussusception after the nationwide introduction of the live attenuated monovalent rotavirus vaccine (RV1). The main goal was to assess the epidemiology of intussusception and compare the number of cases before and after the introduction of the rotavirus vaccine.
Methods:
•Cases of intussusception between March 2006 and January 2008 were identified through a prospective enhanced passive surveillance system in sentinel state hospitals.
•Retrospective review of medical records was used to identify cases from January 2001 to February 2006.
Results:
•From 2001 to 2008, 331 intussusception cases were identified.
•59.5% of the cases were male, with the highest incidence among those aged 18-24 weeks.
•Less than 10% of cases were among infants aged 6-14 weeks (when the first dose of RV1 is administered).
•Common symptoms included vomiting (89.4%), bloody stool (75.5%), and abdominal distention (71.8%).
•92.1% of the patients required surgical treatment; 31.8% of those needed bowel resection, and 13 (3.9%) died.
•The number of intussusception events during 2007 and 2008 was not greater than the average annual number during the baseline years 2001-2005.
Conclusions: The analysis did not identify an increase in intussusception cases during the two years after RV1 introduction. However, the results highlight the need for special epidemiologic methods to assess the potential link between the rotavirus vaccine and this rare adverse event.

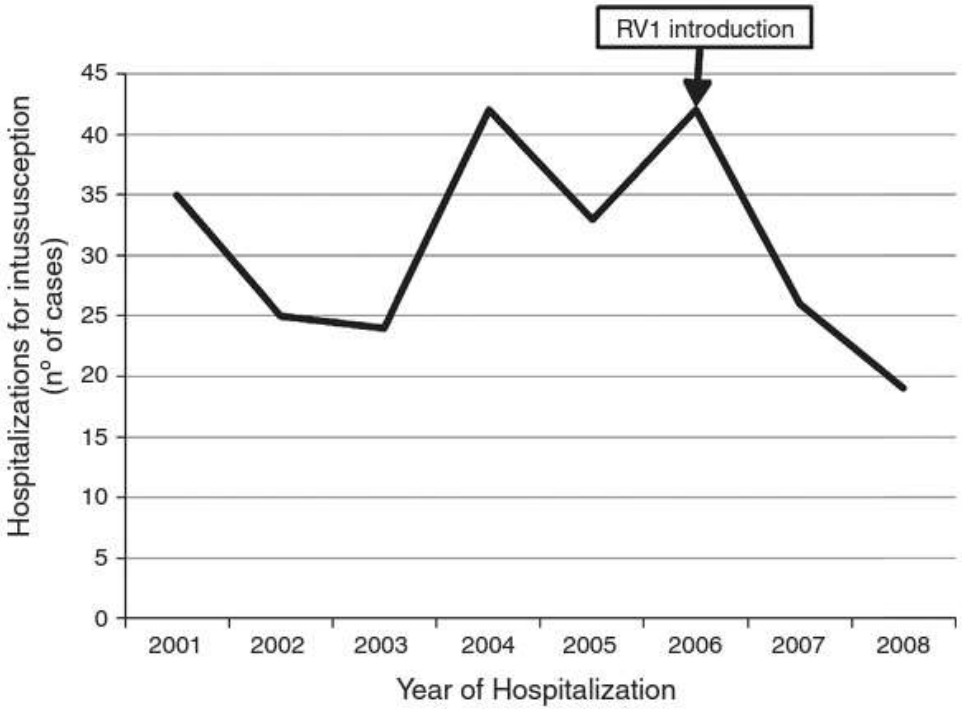

Figure 3 Trends in yearly intussusception hospitalizations among infants aged <12 months between 2001 and 2008. Data are from 21 sentinel hospitals of the hospital-based intussusception surveillance of São Paulo State, Brazil ($n = 246$).

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Intussusception Risk and Health Benefits of Rotavirus Vaccination in Mexico and Brazil

Manish M. Patel, Vesta Richardson López-Collada, Marília Mattos Bulhões, Lucia Helena De Oliveira, Aurora Bautista Márquez, Brendan Flannery, Marcelino Esparza-Aguilar, Ernesto Isaac Montenegro Renoiner, María Edilia Luna-Cruz, Helena Keico Sato, Luz del Carmen Hernández-Hernández, Gerardo Toledo-Cortina, Magdalena Cerón-Rodríguez, Neydi Osnaya-Romero, Mario Martínez-Alcazar, Rocío Gabriela Aguinaga-Villasenor, Arturo Plascencia-Hernández, Francisco Fojaco-González, Guillermo Hernández-Peredo Rezk, Sixto Fortino Gutierrez-Ramírez, Roberto Dorame-Castillo, Rogelio Tinajero-Pizano, Bernice Mercado-Villegas, Marilia Reichelt Barbosa, Eliane Mara Cesário Maluf, Lucimar Bozza Ferreira, Francisca Maria de Carvalho, Ana Rosa dos Santos, Eduardo Dolabella Cesar, Maria Elisa Paula de Oliveira, Carmem Lúcia Osterno Silva, Maria de los Angeles Cortes, Cuauhtemoc Ruiz Matus, Jacqueline Tate, Paul Gargiullo, and Umesh D. Parashar*

Because postlicensure surveillance determined that a previous rotavirus vaccine, RotaShield, caused intussusception in 1 of every 10,000 recipients, we assessed the association of the new monovalent rotavirus vaccine (RV1) with intussusception after routine immunization of infants in Mexico and Brazil.

- **Results**:
- **Study Enrollment**: 615 infants with intussusception (285 in Mexico and 330 in Brazil) and 2050 controls were enrolled.
- **Vaccination History**: 594 case patients (97%) and 2033 controls (99%) had a confirmed history of vaccination.
- **Intussusception Post-Vaccination**:
  - In Mexico, a higher proportion of intussusception cases occurred within 1 to 7 days after the first dose of RV1 vaccination.
  - In Brazil, no significant risk was observed after the first dose, but a small elevated risk was noted 1 to 7 days after the second dose.
- **Incidence Ratios**:
  - Mexico: After the first dose, the rate of intussusception was significantly higher 1 to 7 days post-vaccination.
  - Brazil: A small but significantly elevated rate was noted 1 to 7 days after the second dose.
- **Benefit-Risk Analysis**:
  - RV1 vaccination program would prevent numerous deaths and hospitalizations due to rotavirus disease in both Mexico and Brazil.
  - However, the program might cause a few excess hospitalizations and deaths due to intussusception in both countries

- **Discussion**:
- **Causal Link in Mexico**: Evidence suggests a causal link between intussusception and the first dose of RV1 vaccination among infants in Mexico.
- **Comparison with RotaShield**: Similar to the experience with RotaShield, the increased risk of intussusception after RV1 occurred primarily in the first week after the first dose.
- **Potential Bias**: There might be a detection bias related to heightened awareness of the association between intussusception and rotavirus vaccination. However, such a bias wouldn't cause clustering on specific days after only one of the two vaccine doses.
- **Conclusion**: The absolute number of deaths and hospitalizations averted due to vaccination far exceeded the number of intussusception cases that might have been associated with vaccination.

Mexico

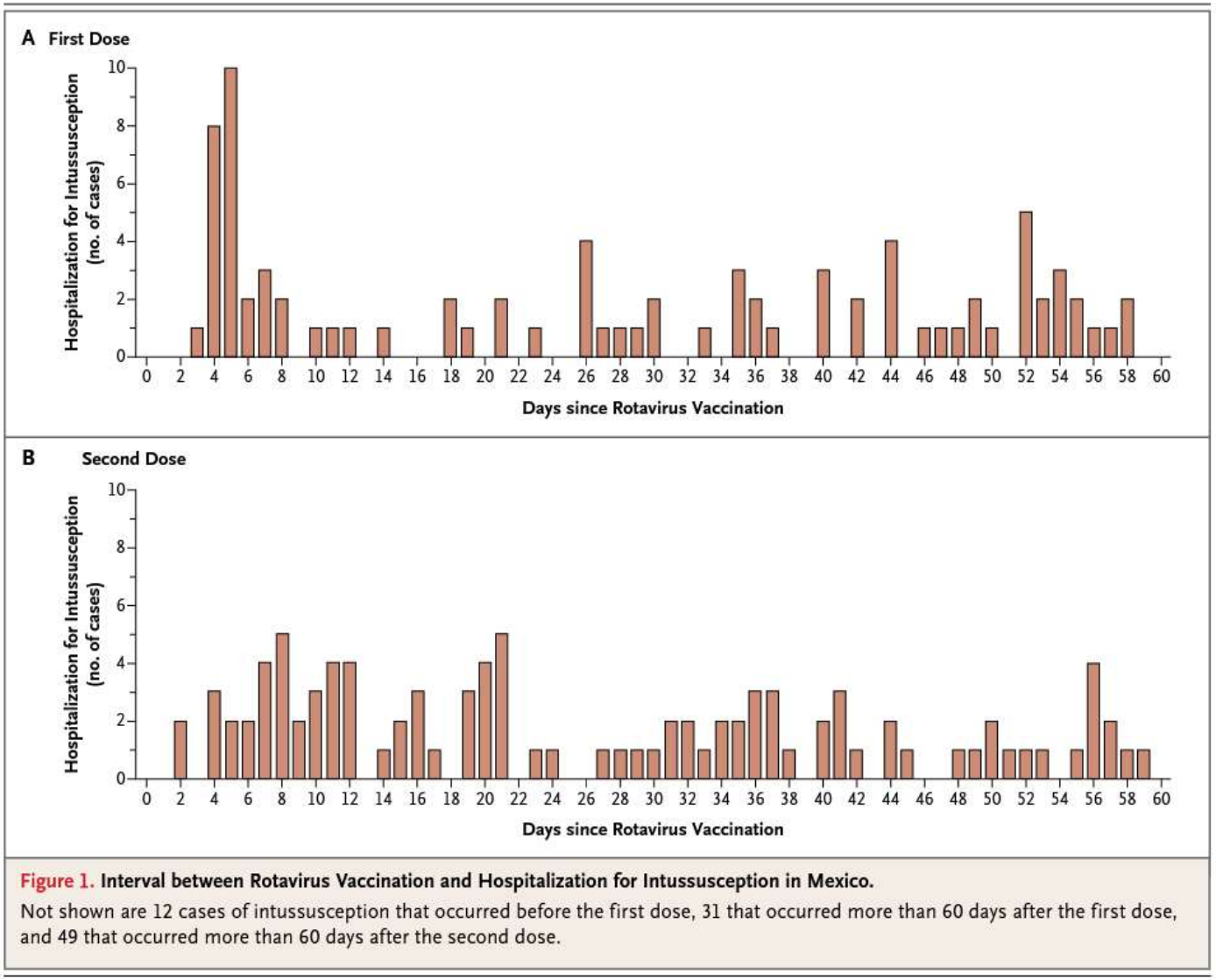

Figure 1. Interval between Rotavirus Vaccination and Hospitalization for Intussusception in Mexico.

Not shown are 12 cases of intussusception that occurred before the first dose, 31 that occurred more than 60 days after the first dose, and 49 that occurred more than 60 days after the second dose.

Brazil

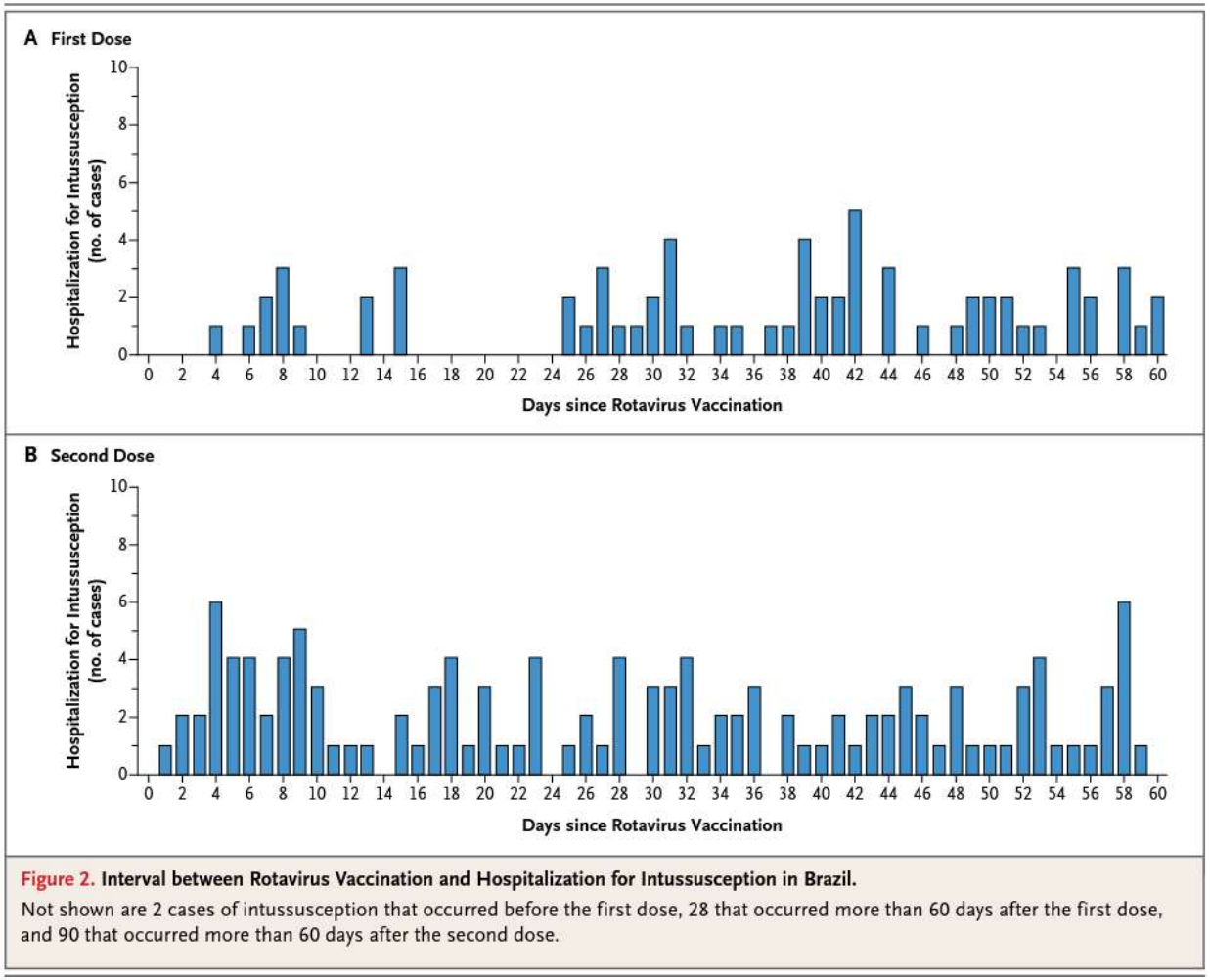

Figure 2. Interval between Rotavirus Vaccination and Hospitalization for Intussusception in Brazil.

Not shown are 2 cases of intussusception that occurred before the first dose, 28 that occurred more than 60 days after the first dose, and 90 that occurred more than 60 days after the second dose.

Results

Table 2. Association between Rotavirus Vaccination and Intussusception in Mexico and Brazil, According to Case-Series and Case–Control Analyses.

Dose and Risk Period*	Case Patients	Controls	Case-Series Analysis†	Case–Control Analysis‡
	no./total no. (%)		Incidence Ratio (95% CI)	Odds Ratio (95% CI)
Mexico§				
Either dose, any time before reference date	260/285 (91)	672/739 (91)	—	1.0 (0.6–1.7)
First dose				
1–7 days	24/274 (9)	17/701 (2)	5.3 (3.0–9.3)	5.8 (2.6–13.0)
8–14 days	6/256 (2)	17/701 (2)	1.1 (0.5–2.7)	1.0 (0.4–2.9)
15–21 days	5/255 (2)	21/705 (3)	0.9 (0.3–2.2)	0.8 (0.3–2.1)
Second dose				
1–7 days	13/248 (5)	34/689 (5)	1.8 (0.9–3.8)	1.1 (0.6–2.2)
8–14 days	19/254 (7)	24/679 (4)	2.2 (1.1–4.2)	2.3 (1.2–4.4)
15–21 days	18/253 (7)	26/681 (4)	2.2 (1.2–4.0)	2.0 (1.0–3.8)
Brazil				
Either dose, any time before reference date	312/330 (95)	1264/1311 (96)	—	1.7 (0.9–2.9)
First dose				
1–7 days	4/321 (1)	13/1271 (1)	1.1 (0.3–3.3)	1.4 (0.4–4.8)
8–14 days	6/323 (2)	19/1277 (1)	1.3 (0.5–3.4)	1.6 (0.5–4.7)
15–21 days	3/320 (1)	21/1279 (2)	0.2 (0.0–1.4)	0.6 (0.1–2.2)
Second dose				
1–7 days	21/300 (7)	50/1169 (4)	2.6 (1.3–5.2)	1.9 (1.1–3.4)
8–14 days	15/294 (5)	70/1189 (6)	1.4 (0.7–3.0)	0.9 (0.5–1.8)
15–21 days	15/294 (5)	72/1191 (6)	0.9 (0.4–2.0)	0.8 (0.4–1.6)

* The risk period is the interval before the reference date (the date of hospitalization of infants with intussusception or the date on which the matched control was the same age as the infant with intussusception at the time of hospitalization). The denominators for each risk period include infants who were never vaccinated with RV1 and those who were vaccinated with RV1 either during the risk period of interest or outside the 21-day risk period for the respective dose.

† Conditional Poisson regression was used to calculate incidence ratios (the ratio of the incidence of intussusception within each risk period to the incidence outside all risk periods, adjusted for age in 14-day intervals).

‡ Conditional logistic regression was used to calculate odds ratios (the odds of vaccination during the risk period in case patients as compared with controls, adjusted for the age of the infant).

§ In Mexico, 285 case patients were included in the case-series analysis; 44 of the 285 had no age-matched controls and were not included in the case–control analysis.

Results

Table 3. Effect of a Rotavirus Vaccination Program, as Compared with No Rotavirus Vaccination Program, on Deaths and Hospitalizations Associated with Diarrhea and Intussusception in Mexico and Brazil.*

Event	Without Vaccination Program	With Vaccination Program	No. of Events Averted or Caused	No. of Vaccinated Infants per Event Averted or Caused†
	no. of events			
Mexico				
Deaths				
Rotavirus diarrhea	923	260	663 averted	3,164
Intussusception	61	63	2 caused	1,026,737
Hospitalizations				
Rotavirus diarrhea	16,086	4,535	11,551 averted	182
Intussusception	1,215	1,256	41 caused	51,337
Brazil				
Deaths				
Rotavirus diarrhea	850	210	640 averted	5,789
Intussusception	107	110	3 caused	1,354,737
Hospitalizations				
Rotavirus diarrhea	92,453	22,881	69,572 averted	53
Intussusception	2,146	2,200	55 caused	67,737

* Details of the model used in this analysis are provided in the Supplementary Appendix.
† These values were obtained by taking the number of events averted or caused, dividing it by the respective country's birth cohort, and then calculating the inverse.

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RESEARCH PAPER

Impact of polio vaccines (oral polio vaccine - OPV or inactivated polio vaccine - IPV) on rotavirus vaccine-associated intussusception

Camila Cristina Martini Rodrigues [a], Eder Gatti Fernandes [b], Paulo Piva dos Santos [c], Renato Yoshio Eguti [c], Antonio Carlos Pedroso-de-Lima [c], Gisela Tunes da Silva [c], and Ana Marli Christovam Sartori [a]

[a]Parasitarias, Faculdade de Medicina, Universidade de Sao Paulo (USP)Departamento de Molestias Infecciosas e , Sao Paulo, Brazil; [b]Divisao de Imunizacoes, Centro de Vigilancia Epidemiologica, Centro de Controle de Doenças, Secretaria de Estado da Saude de Sao Paulo, Sao Paulo, Brazil; [c]Estatistica, USPDepartamento de Estatistica, Instituto de Matematica e , Sao Paulo, Brazil

In Brazil, after the oral human rotavirus vaccine (OHRV) introduction in the childhood immunization, in 2006, increased intussusception risk was identified after the second OHRV dose, whereas in other countries, higher risk was associated to the first vaccine dose. It was hypothesized that the concomitant use of oral poliovirus vaccine (OPV) in Brazil might explain this difference.

Study Design and Periods

Retrospective analysis of intussusception cases in children aged six weeks to 11 months and 29 days.
Study conducted in Sao Paulo state, Brazil, from March 2006 to December 2017.
Two periods based on vaccine type: OPV period (March 2006 to June 2012) and IPV period (October 2012 to December 2017).
July to September 2012 was a transition period.

Vaccination in Brazil

OPV to IPV vaccine replacement occurred in August 2012.
Ministry of Health in Brazil centralizes vaccine purchase and distribution.
Most childhood vaccinations are done at public Unified Health System (SUS) facilities.
Both polio and rotavirus vaccines had high coverage during the study period.
Polio vaccine third dose coverage was below 95% in three years.
Rotavirus vaccine coverage was initially lower than polio but increased over time.

Data Sources

Intussusception cases data were collected from the Surveillance System databases.
Reporting of Adverse events following immunization (AEFI) is mandatory in Brazil since 2005.
AEFI includes symptoms, signs, vaccine details, diagnostic findings, healthcare provided, and outcomes.
Serious AEFI reports are followed up for more information.
In March 2006, a passive hospital-based sentinel surveillance of intussusception was established.
From August 2008 to January 2010, a multi-center study of OHRV safety was conducted, supported by GAVI, PAHO, and CDC.
All three surveillance systems in Sao Paulo state used the same reporting form and definitions for intussusception cases.

Surveillance and Reporting

Sao Paulo state had a passive hospital-based sentinel surveillance system for intussusception.
Sentinel hospital staff were trained to identify, investigate, and report cases.
The state also participated in a multi-center study on OHRV safety.
All surveillance systems in Sao Paulo used the Brighton Collaborative Group's definition for intussusception.
Data on Live Births:Data on live births in Sao Paulo was sourced from the Unified Health System Department of Informatics (DATASUS).This data was used to estimate the annual rates of intussusception.

Table 1. Characteristics of confirmed cases of intussusception in infants reported to the surveillance systems. Sao Paulo State, Brazil, 2006 to 2017.

Characteristics	All cases (n= 325)	Cases with history of rotavirus vaccination (n= 296)	Cases occurring within 30 days after rotavirus vaccination (n= 164)
Male sex n (%)	194 (59.9)	177 (60)	96 (58.5)
Age (weeks)			
Median	22	21	19
Min-Max	8-51	8-51	8-34
Type of feeding (%)	n = 162	n = 141	n = 53
Breastfeeding	116 (71.6)	99 (70.2)	35 (66)
Artificial feeding	46 (28.4)	42 (29.8)	18 (34)
Duration of symptoms up to medical care (days)	n = 325	n = 296	n = 164
Median	1	1	1
Min-Max	0-55	0-55	0-55
Diagnostic method (%)	n = 230	n = 201	n = 102
Radiology	32 (13.9)	29 (14.9)	18 (17.6)
Surgery	197 (85.7)	165 (84.6)	84 (82.4)
Autopsy	1 (.4)	1 (.5)	0
Surgical treatment (%)	n = 229	n = 200	n = 101
	209 (91.3)	181 (90.5)	101 (90.1)
Duration of hospitalization (days)	n = 172	n = 157	n = 79
Median	7	5	5
Min-Max	0-52	0-52	0-35
Deaths (%)	n = 222	n = 195	n = 101
	8 (3.6)	7 (3.6)	4 (4)
Cases after the 1st rotavirus vaccine dose	95	95	54
Interval between the 1st rotavirus vaccine dose and symptoms (%)		n = 95	n = 54
1–7 days		30 (31.6)	30 (55.5)
8–14 days		7 (7.4)	7 (13)
15–21 days		6 (6.3)	6 (11.1)
22–30 days		11 (11.6)	11 (20.4)
>30 days		41 (43.2)	
Cases after the 2nd rotavirus vaccine dose	198	198	108
Interval between the 2nd rotavirus vaccine dose and symptoms (%)		n = 198	n = 108
1–7 days		47 (23.7)	47 (43.5)
8–14 days		20 (10.1)	20 (18.5)
15–21 days		17 (8.6)	17 (15.7)
22–30 days		24 (12.1)	24 (22.2)
> 30 days		90 (45.5)	
Cases after the 3rd rotavirus vaccine dose		3	2

Sources: Information System of Adverse Events Following Immunization (SI-EAPV); Sentinel Surveillance of Intussusception (SVSII).

Reported Cases

From 2006 to 2017, 325 intussusception cases in children aged 6 weeks to 11 months and 29 days were reported in Sao Paulo State.

Of these, 296 (91.1%) had a history of rotavirus vaccination.
164 of these cases occurred within 30 days post-vaccination and might be associated with the rotavirus vaccine.

Epidemiological and Clinical Characteristics

Vomiting was the most common symptom (92.3% of 209 records).
"Strawberry jelly" feces was reported in 80.8% of 182 records.
Surgery was the primary diagnostic and treatment method in 85.7% of 197 cases.
Case-fatality rate was 3.6% based on 222 cases with reported outcomes.

Vaccination Details

Most of the 164 cases post-rotavirus vaccination (within 30 days) were associated with the second vaccine dose (108 cases or 65.9%).
Three infants received the first vaccine dose after the maximum recommended age.

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>30 days		41 (43.2)	
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22–30 days		24 (12.1)	24 (22.2)
> 30 days		90 (45.5)	
Cases after the 3rd rotavirus vaccine dose		3	2

Sources: Information System of Adverse Events Following Immunization (SI-EAPV); Sentinel Surveillance of Intussusception (SVSII).

Analysis of Polio Vaccines and Intussusception

11 of the 296 cases with a history of rotavirus vaccination were excluded for various reasons.
Of the remaining 285 cases, 221 that occurred within the first 60 days post rotavirus vaccination were included in the SCCS analyses.
159 cases were from the OPV period, and 62 from the IPV period.

SCCS Analysis Results

In the 7-day risk period post rotavirus vaccination, a higher relative incidence of intussusception was found for both the first and second doses in both OPV and IPV periods.

A similar pattern was seen in the 21-day risk period, but the relative incidences were lower.

When analyzing the entire study period, the relative incidence of intussusception was higher in the 7-day risk period compared to the 21-day risk period.

The standard SCCS analysis showed statistically significant higher relative incidence after the first and second rotavirus vaccine doses in both OPV and IPV periods.

Table 2. Relative incidence (RI) of intussusception and respective 95% confidence Iinterval (95%IC), according to risk period (7- and 21-days post-vaccination), rotavirus vaccine dose, and study period (OPV-, IPV- or the entire study period) in the SCCS with event-dependent exposure model. Sao Paulo State, Brazil. March 2006 to December 2017.

	OPV period		IPV period		Entire study period	
Risk period and rotavirus vaccine dose	RI (95% CI)	p value	RI (95% CI)	p value	RI (95% CI)	p value
7-day risk period*						
1st dose, 1-7 days	4.4 (2.7 – 7.1)	<0.001	4.2 (1.9 - 9)	<0.001	4.3 (2.8 – 6.5)	<0.001
1st dose 1, 8-30 days	0.6 (0.3 – 1.1)	0.101	1 (0.5 – 2.2)	0.921	0.7 (0.5 – 1.2)	0.194
2nd dose, 1-7 days	4.1 (2.5 – 6.6)	<0.001	4.6 (1.7 – 12.2)	0.002	4.2 (2.7 – 6.4)	<0.001
2nd dose, 8-30 days	1.6 (1 – 2.4)	0.049	2.8 (1.2 – 6.7)	0.017	1.8 (1.2 – 2.6)	0.003
21-day risk period**						
1st dose, 1-21 days	1.6 (1 – 2.5)	0.033	2.1 (1.1 - 4)	0.019	1.8 (1.2 – 2.5)	<0.001
1st dose, 22-30 days	0.8 (0.4 – 1.6)	0.506	0.7 (0.2 – 2.5)	0.638	0.8 (0.4 – 1.4)	0.408
2nd dose, 1-21 days	2.4 (1.5 – 3.6)	<0.001	3.7 (1.6 – 8.6)	0.002	2.6 (1.8 – 3.8)	<0.001
2nd dose, 22-30 days	1.7 (1 - 3)	0.06	2.2 (0.7 – 6.7)	0.174	1.8 (1.1 – 3)	0.022

OPV=oral polio vaccine; IPV=inactivated polio vaccine.
Chi-square test was used to compare the OPV and IPV periods: *7-day risk period: p = .606; **21-day risk period: p = .811.

Example 2 : Chikungunya vaccine

Katharina Hartmann

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DCVMN INTERNATIONAL
Developing Countries Vaccine Manufacturers Network International

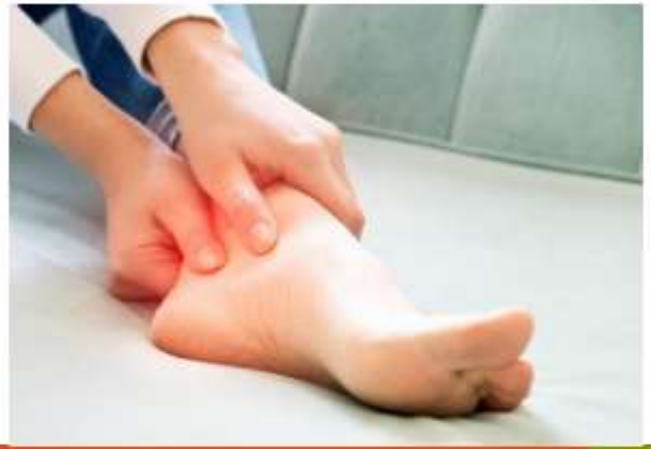
Chikungunya virus disease

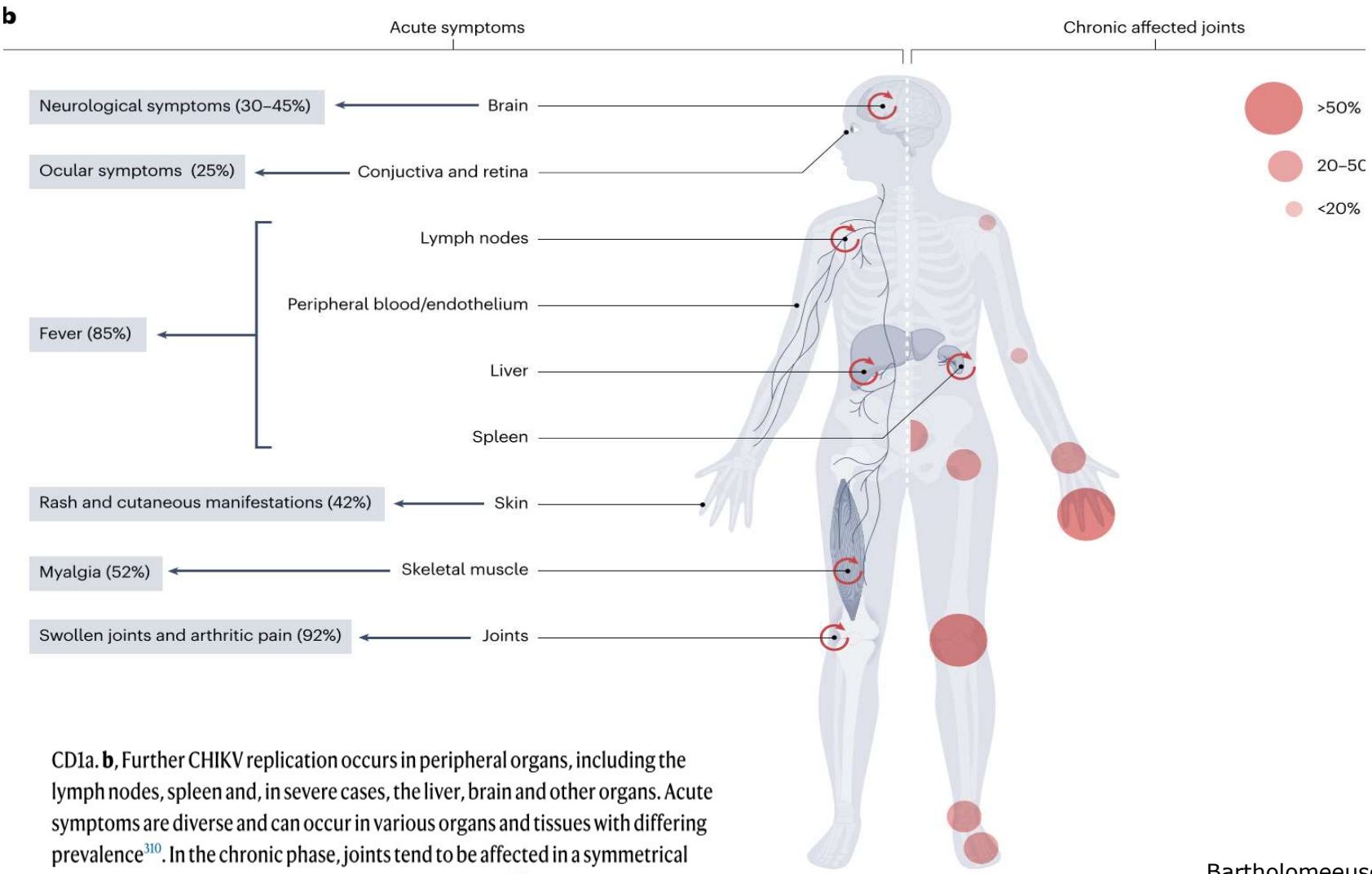
- Mosquito-borne disease caused by an alphavirus
- Clinically characterized by acute onset of fever and often severe polyarthralgia
- Has caused large outbreaks with high attack rates
- Outbreaks have occurred in Africa, Asia, Europe, Americas, and islands in the Indian and Pacific Oceans

Source: PAHO, 2011. www.paho.org

Clinical features of chikungunya

- Incubation period: 3–7 days
- Febrile illness with often severe arthralgia
- Multiple joints involved, typically bilaterally and symmetrically
- Arthralgia most common in hands and feet, can involve more proximal joints
- No specific antiviral treatment

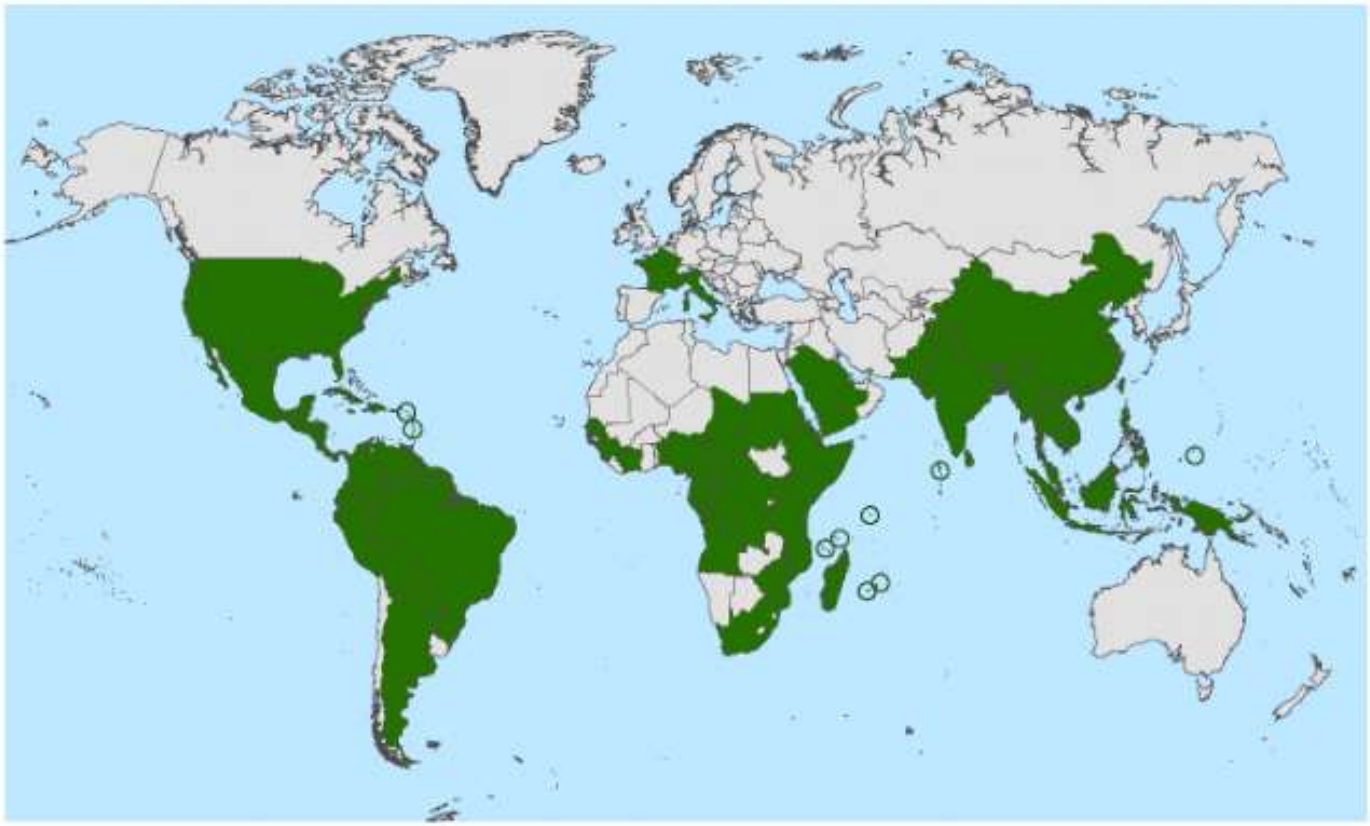
CD1a. **b**, Further CHIKV replication occurs in peripheral organs, including the lymph nodes, spleen and, in severe cases, the liver, brain and other organs. Acute symptoms are diverse and can occur in various organs and tissues with differing prevalence[310]. In the chronic phase, joints tend to be affected in a symmetrical manner, with the highest prevalence in peripheral joints[118].

Bartholomeeusen, 2023

Risk factors for severe disease

- Age >65 years
- Underlying medical conditions (e.g., hypertension, diabetes, heart disease)
- Intrapartum transmission
  - Neonatal complications can include neurologic, myocardial, hemorrhagic symptoms

Countries and territories with past or current transmission of chikungunya virus, 2023



https://www.cdc.gov/chikungunya/geo/index.html

General features of chikungunya virus transmission

- Occurs in tropical and subtropical regions
  - Rare outbreaks in temperate areas
- Often seen in areas with similar vector-borne diseases (e.g., dengue, Zika)
- Transmission impacted by several factors including weather, environmental factors, pre-existing population immunity, population density, local vectors

Patterns for chikungunya virus transmission vary

- Ongoing low-level transmission with periodic outbreak activity in Africa, Asia, Central America, and South America
  - Immunologically susceptible individuals continue to acquire infection and propagate human-mosquito-human cycles
  - Outbreaks are unpredictable in terms of timing and size

- Cessation of transmission after outbreaks is common in island nations
  - Apparent interruption in Pacific Island and most of Caribbean countries and territories
  - Risk for reintroduction will increase over time as population immunity decreases

Limited data sources for understanding current patterns of chikungunya virus transmission

Cases among travelers

ArboNET

National Arbovirus Surveillance System

Features of chikungunya outbreaks

- More likely in regions with no or mild outbreaks in recent past
- Can be localized or widespread

- Often rapid increase in size
- 30%–60% population infected within few months
- Huge outbreaks, like 2014–2016 in Americas, unlikely in future
- Continued reporting of large outbreaks likely

- Many commence during tropical rainy season
- Can occur in dry season
- Period of intense transmission typically short, often 3–6 months

Interval between outbreaks

- Unpredictable and variable, can be >20 years
- Related to factors including pre-existing population immunity, build-up of non-immune population, environmental factors
- Some countries report outbreaks regularly, but typically in different locations

Summary

- Mainly tropical and subtropical areas
- Currently, most countries with chikungunya virus activity have low-level transmission
- Outbreak-prone disease
- Important impact when outbreaks occur as often intense, although generally short-lived, transmission

Chikungunya Vaccines in development

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Table 2 | Chikungunya virus vaccine candidates

Vaccine	Type	Chikungunya virus lineage	Chikungunya virus strain	Advantages	Limitations	Status	Refs.
VLA1553	Live-attenuated virus	East Central South African	La Réunion Island, 2006	Rapid immune response (<14 days); single dose	Transient arthralgia and fever; cannot use in pregnancy or immunocompromised; durability >1 year unknown	Phase III study, complete; FDA license application started August 2022	Wressnigg et al.[201], Roques et al.[202]
PXVX0317	Virus-like particle plus adjuvant	West African	Senegal, 1983	Rapid immune response (<14 days); durable immune response (2 years); thermostable; single dose; platform safe in pregnancy and immunocompromised	Requires an adjuvant	Phase III study, ongoing	Chang et al.[204], Goo et al.[205], Bennett et al.[206]
V184	Measles vector	East Central South African	La Réunion Island, 2006	Platform based on the highly safe, effective and durable measles vaccine; also boosts measles immunity	May require 2 doses; durability >224 days unknown; cannot use in pregnancy or immunocompromised	Phase III study, not started	Reisinger et al.[209], Ramsauer et al.[210]
BBV87	Inactivated virus plus adjuvant	East Central South African	India, 2006	Thermostable; platform safe in pregnancy and immunocompromised	Phase I data not published yet; requires 2 doses; requires an adjuvant	Phase II/III study, ongoing	CEPI press release[220]

Chikungunya vaccines (Phase III clinical trials)

Manufacturer	Type	Schedule and administration	Status	Notes
Valneva	Live attenuated	1 dose IM	- Phase III in adults ≥18 years completed - Phase III in adolescents (12–17 years) commenced January 2022 - Lot-to-lot consistency completed	CEPI co-funding
Emergent BioSolutions	Virus-like particle	1 dose IM	- Phase III in 12–65 years commenced October 2021 - Phase III in ≥65 years commenced May 2022	

Abbreviations: IM-Intramuscular; BLA-Biologics License Application; FDA-Food & Drug Administration; CEPI-Coalition for Epidemic Preparedness Innovations

Other chikungunya vaccines with support from CEPI

Manufacturer	Type	Schedule and admin		Status	Notes
Merck	Live attenuated measles-vectored	1 dose + booster	-	Phase II completed	CEPI co-funding
International Vaccine Institute/ Bharat Biotech	Inactivated whole virus	2-dose	-	Phase II/III commenced August 2021	CEPI co-funding

Abbreviations: CEPI - Coalition for Epidemic Preparedness Innovations

Valneva's chikungunya vaccine

- Rolling BLA submission to FDA initiated August 2022
- FDA has given Breakthrough Therapy designation which allows request for priority review
- Licensure expected during 2023
  - Initial indication for ages ≥18 years

Safety and immunogenicity of a single-shot live-attenuated chikungunya vaccine: a double-blind, multicentre, randomised, placebo-controlled, phase 3 trial

Martina Schneider, Marivic Narciso-Abraham, Sandra Hadl, Robert McMahon, Sebastian Toepfer, Ulrike Fuchs, Romana Hochreiter, Annegret Bitzer, Karin Kosulin, Julian Larcher-Senn, Robert Mader, Katrin Dubischar, Oliver Zoihsl, Juan-Carlos Jaramillo, Susanne Eder-Lingelbach, Vera Buerger, Nina Wressnigg

https://pubmed.ncbi.nlm.nih.gov/37321235/

CHIKV Candidate VLA1553

Summary

Background VLA1553 is a live-attenuated vaccine candidate for active immunisation and prevention of disease caused by chikungunya virus. We report safety and immunogenicity data up to day 180 after vaccination with VLA1553.

Methods This double-blind, multicentre, randomised, phase 3 trial was done in 43 professional vaccine trial sites in the USA. Eligible participants were healthy volunteers aged 18 years and older. Patients were excluded if they had history of chikungunya virus infection or immune-mediated or chronic arthritis or arthralgia, known or suspected defect of the immune system, any inactivated vaccine received within 2 weeks before vaccination with VLA1553, or any live vaccine received within 4 weeks before vaccination with VLA1553. Participants were randomised (3:1) to receive VLA1553 or placebo. The primary endpoint was the proportion of baseline negative participants with a seroprotective chikungunya virus antibody level defined as 50% plaque reduction in a micro plaque reduction neutralisation test (µPRNT) with a $\mu PRNT_{50}$ titre of at least 150, 28 days after vaccination. The safety analysis included all individuals who received vaccination. Immunogenicity analyses were done in a subset of participants at 12 pre-selected study sites. These participants were required to have no major protocol deviations to be included in the per-protocol population for immunogenicity analyses. This trial is registered at ClinicalTrials.gov, NCT04546724.

Findings Between Sept 17, 2020 and April 10, 2021, 6100 people were screened for eligibility. 1972 people were excluded and 4128 participants were enrolled and randomised (3093 to VLA1553 and 1035 to placebo). 358 participants in the VLA1553 group and 133 participants in the placebo group discontinued before trial end. The per-protocol population for immunogenicity analysis comprised 362 participants (266 in the VLA1553 group and 96 in the placebo group). After a single vaccination, VLA1553 induced seroprotective chikungunya virus neutralising antibody levels in 263 (98·9%) of 266 participants in the VLA1553 group (95% CI 96·7–99·8; $p<0·0001$) 28 days post-vaccination, independent of age. VLA1553 was generally safe with an adverse event profile similar to other licensed vaccines and equally well tolerated in younger and older adults. Serious adverse events were reported in 46 (1·5%) of 3082 participants exposed to VLA1553 and eight (0·8%) of 1033 participants in the placebo arm. Only two serious adverse events were considered related to VLA1553 treatment (one mild myalgia and one syndrome of inappropriate antidiuretic hormone secretion). Both participants recovered fully.

Interpretation The strong immune response and the generation of seroprotective titres in almost all vaccinated participants suggests that VLA1553 is an excellent candidate for the prevention of disease caused by chikungunya virus.

Overview of clinical studies

Three clinical trials provide data for initial licensure

Phase 1:

- **Phase 1 study[1]:**
  - **120 healthy adults** aged 18-45 years
  - **Three dose levels** of vaccine studied
  - Included a **re-vaccination** as homologous viral challenge
  - Study generated **safety, immunogenicity, and viremia[2]** data

Phase 3:

- **Pivotal Phase 3 study:**
  - **4,115 participants** aged ≥18 years
  - RCT comparing **VLA1553 to placebo**
  - Study generated **safety and immunogenicity** data
- **Lot-to-Lot consistency study:**
  - **408 participants** aged **18-45 years**
  - RCT comparing **3 lots of VLA1553**

1 Wressnigg et al. 2020; Lancet Infect Dis 20:1193-1203.
2 Viremia tested by RT-qPCR, readout: CHIKV genome copy equivalents (GCE) detected per 1mL of initial specimen.

Demographic Data (VLA1553-301)

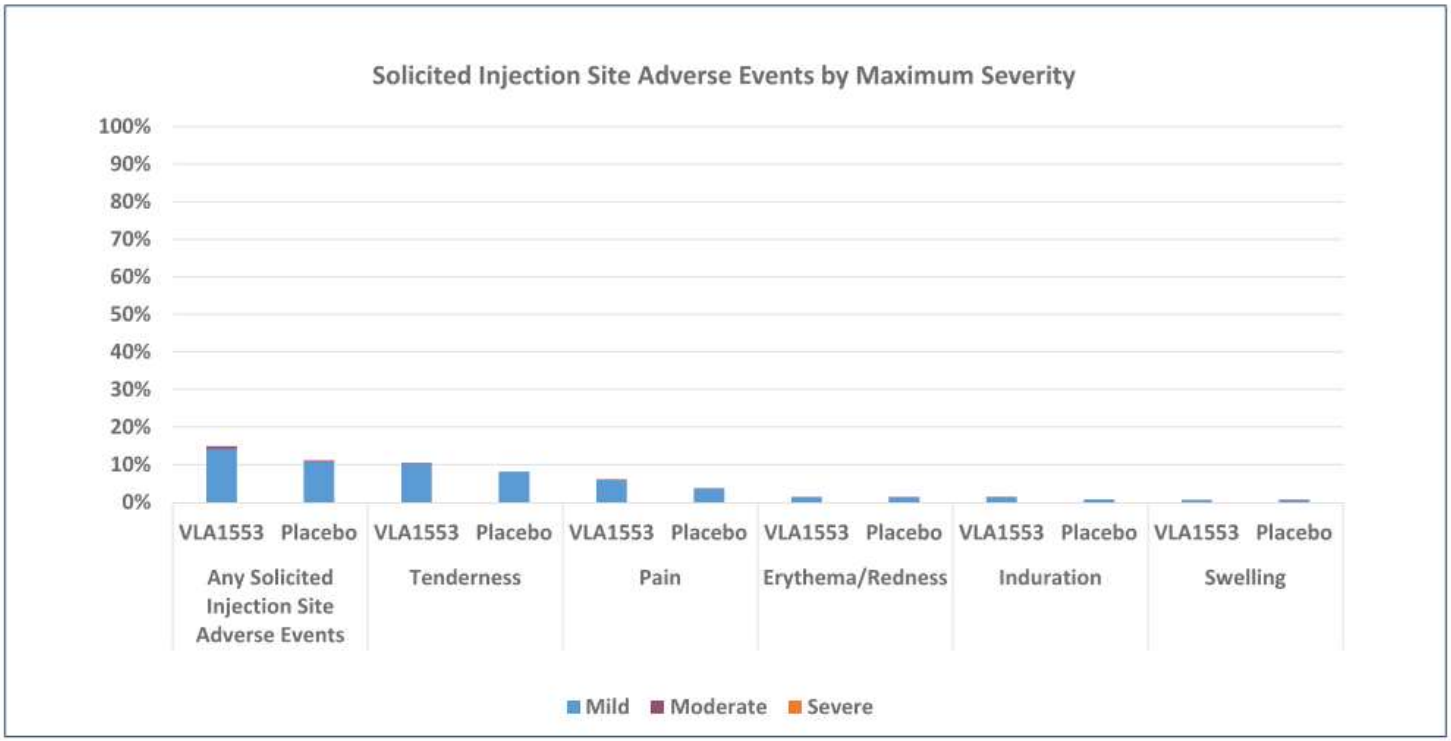
Similar baseline characteristics between VLA1553 group and Placebo

	VLA1553 N=3,082	Placebo N=1,033
Gender n (%)		
Female	1682 (54.6)	569 (55.1)
Male	1400 (45.4)	464 (44.9)
Race n (%)		
American Indian or Alaskan Native	27 (0.9)	5 (0.5)
Asian	51 (1.7)	17 (1.6)
Black or African American	451 (14.6)	122 (11.8)
Native Hawaiian or Other Pacific Islander	13 (0.4)	5 (0.5)
White	2456 (79.7)	853 (82.6)
Other	84 (2.7)	31 (3.0)
Age at screening (years)		
Mean	45.1	45.0
(Min/Max)	18, 88	18, 94
Age Group n (%)		
18 years - 64 years	2736 (88.8)	916 (88.7)
≥ 65 years	346 (11.2)	117 (11.3)

Safety Population

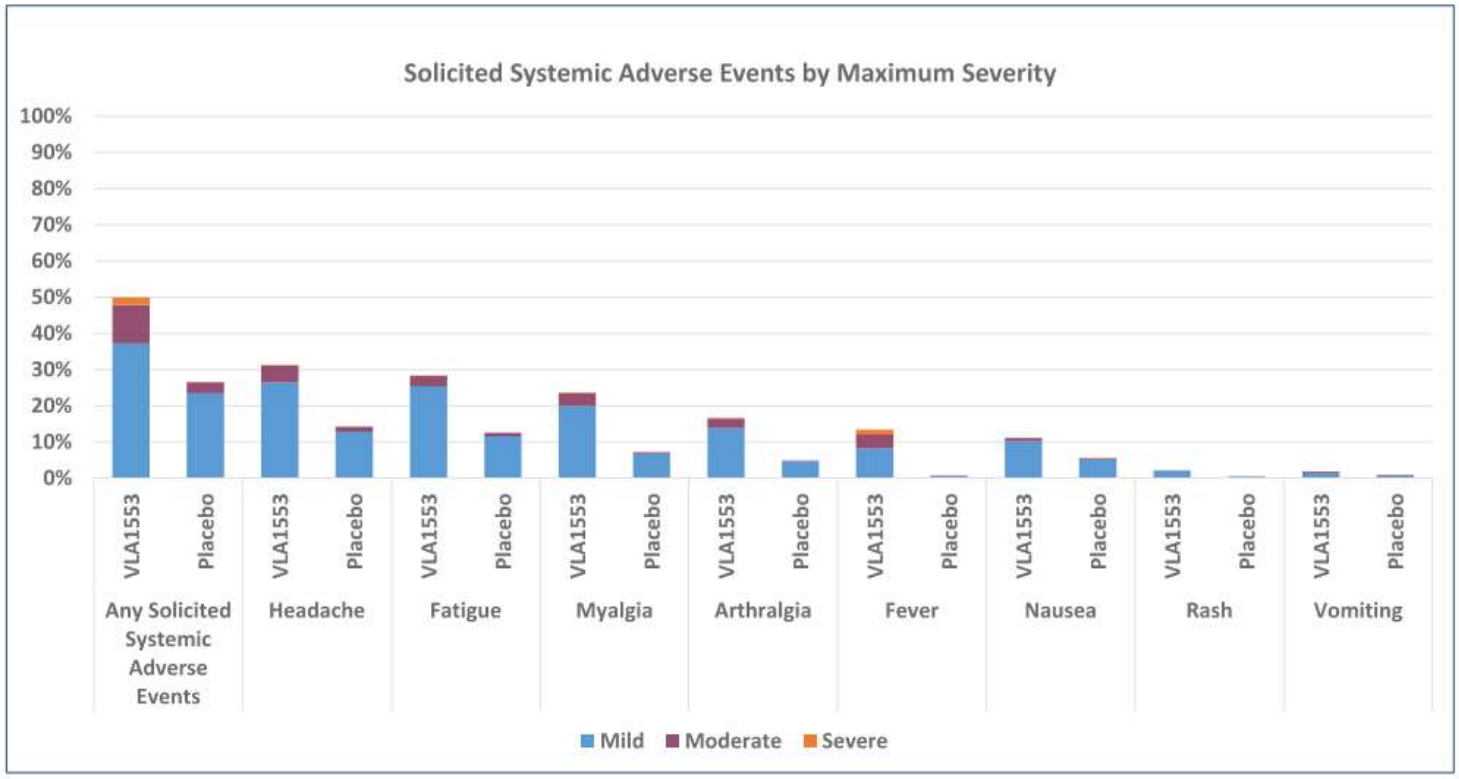
Pivotal Phase 3 Solicited Local AE Within 10 Days After Vaccination (VLA1553-301)

Local AEs in 15% of participants, majority of AEs mild-moderate



Pivotal Phase 3 Solicited Systemic AE Within 10 Days After Vaccination (VLA1553-301)

Generally well tolerated, majority of AEs mild-moderate



Pivotal Phase 3: Serious Adverse Events (VLA1553-301)

Two related serious adverse events, fully recovered

	VLA1553 N=3,082 n (%)	Placebo N=1,033 n (%)
Any SAE [95% CI] p-value	**46 (1.5)** [1.1, 2.0]	**8 (0.8)** [0.3, 1.5] 0.0835
Any related SAE [95% CI] p-value	**2 (0.1)** [0.0, 0.2]	**0** [0.0, 0.4] >0.9999

Case #1, 58-year-old female

- **Event:** Myalgia
- **Vaccination:** VLA1553 03 NOV 2020
- **Onset:** 04 NOV
- **Hospitalization:** 06 NOV – 11 NOV
- **Outcome:** recovered 03 DEC
  - Participant has a history of fibromyalgia
  - No other trigger for myalgia could be identified

Case #2, 66-year-old male

- **Event:** Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- **Vaccination:** VLA1553 17 NOV 2020
- **Onset:** 27 NOV
- **Hospitalization:** 27 NOV – 30 NOV
- **Outcome:** recovered 10 DEC
  - Appeared to be related to prolonged fever/symptoms post-vaccination

Pivotal Phase 3: Adverse Events Rates by Age (VLA1553-301)

Similar AE profile in participants 18-64 or ≥65 years

	18-64 years		≥ 65 years	
AE Category	**VLA1553** (N=2,736) n (%)	**Placebo** (N=916) n (%)	**VLA1553** (N=346) n (%)	**Placebo** (N=117) n (%)
Any AE	**1708 (62.4)**	407 (44.4)	**218 (63.0)**	56 (47.9)
Any Related AE	**1415 (51.7)**	292 (31.9)	**160 (46.2)**	30 (25.6)
Any Severe[a] AE	**94 (3.4)**	10 (1.1)	**10 (2.9)**	4 (3.4)
Any Related Severe[a] AE	**58 (2.1)**	1 (0.1)	**4 (1.2)**	0

a Severe (grade 3): incapable of work or usual activity and requiring medical intervention. Injection site AEs and systemic AEs were rated based on the FDA Guidance on Toxicity Grading Scales

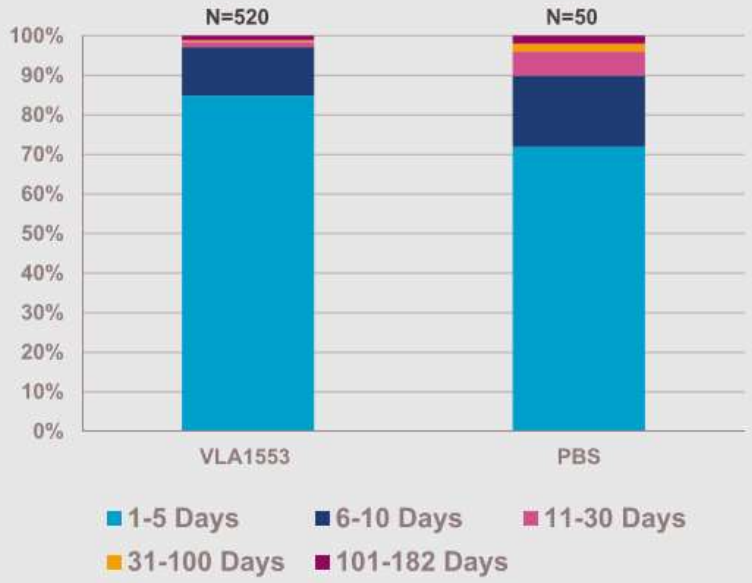
Details on Post-Vaccination Arthralgia (VLA1553-301)

Similar duration of arthralgia with VLA1553 and placebo

Arthralgia Rates

- VLA1553:
  - 17% (n=520) any arthralgia
  - 0.5% (n=15) duration >11 days
  - Longest duration: 182 days
- Placebo:
  - 5% (n=50) any arthralgia
  - 0.5% (n=5) duration >11 days
  - Longest duration: 180 days

Relative Frequency of Arthralgia Duration



Solicited Arthralgia ie onset within 10 days post-vaccination

Arthralgia after vaccination

- Reported by 17% (N=514) vaccine recipients vs 5% placebo recipients

- Severity of arthralgia (N=514)
  - Mild: 83%
  - Moderate:16%
  - Severe: 2%

- Duration until resolution of arthralgia (N=514)
  - 1–5 days: 85%
  - 6–15 days: 13%
  - >15 days: 2% (maximum 182 days)

CHIKV Candidate VLA1553 Phase 3 Overall Safety Data

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	VLA1553 (n=3082)	Placebo (n=1033)	Total (n=4115)
Any adverse events	1926 (62·5%, 60·8–64·2) 6415	463 (44·8%, 41·8–47·9) 1071	2389 (58·1%, 56·5–59·6) 7486
Any related adverse events	1575 (51·1%, 49·3–52·9) 4621	322 (31·2%, 28·4–34·1) 647	1897 (46·1%, 44·6–47·6) 5268
Any related severe adverse events	62 (2·0%, 1·5–2·6) 70	1 (0·1%, 0·0–0·5) 3	63 (1·5%, 1·2–2·0) 73
Any serious adverse events	46 (1·5%, 1·1–2·0) 73	8 (0·8%, 0·3–1·5) 10	54 (1·3%, 1·0–1·7) 83
Any related serious adverse events	2 (0·1%, 0·0–0·2) 2	0 (0%, 0·0–0·4) 0	2 (0·0%, 0·0–0·2) 2
Any adverse events of special interest	10 (0·3%, 0·2–0·6) 26	1 (0·1%, 0·0–0·5) 2	11 (0·3%, 0·1–0·5) 28
Any adverse event with a frequency ≥10% in at least one study arm			
Headache	986 (32·0%, 30·3–33·7) 1028	160 (15·5%, 13·3–17·8) 178	1146 (27·8%, 26·5–29·2) 1206
Fatigue	886 (28·7%, 27·2–30·4) 893	137 (13·3%, 11·3–15·5) 139	1023 (24·9%, 23·5–26·2) 1032
Myalgia	750 (24·3%, 22·8–25·9) 758	82 (7·9%, 6·4–9·8) 84	832 (20·2%, 19·0–21·5) 842
Arthralgia	554 (18·0%, 16·6–19·4) 589	63 (6·1%, 4·7–7·7) 70	617 (15·0%, 13·9–16·1) 659
Injection site pain	413 (13·4%, 12·2–14·7) 519	101 (9·8%, 8·0–11·8) 122	514 (12·5%, 11·5–13·5) 641
Pyrexia	427 (13·9%, 12·7–15·1) 429	13 (1·3%, 0·7–2·1) 13	440 (10·7%, 9·8–11·7) 442
Nausea	359 (11·6%, 10·5–12·8) 364	63 (6·1%, 4·7–7·7) 64	422 (10·3%, 9·3–11·2) 428
Any serious adverse event with a frequency ≥0·2% in at least one study arm by system organ class			
Infections and infestations	9 (0·3%, 0·1–0·6) 9	3 (0·3%, 0·1–0·8) 3	12 (0·3%, 0·2–0·5) 12
Injury, poisoning, and procedural complications	8 (0·3%, 0·1–0·5) 15	1 (0·1%, 0·0–0·5) 1	9 (0·2%, 0·1–0·4) 16
Psychiatric disorders	7 (0·2%, 0·1–0·5) 8	2 (0·2%, 0·0–0·7) 4	9 (0·2%, 0·1–0·4) 12
Cardiac disorders	5 (0·2%, 0·1–0·4) 7	0 (0%, 0·0–0·4) 0	5 (0·1%, 0·0–0·3) 7

Data are n (%, 95% CI) N. For each category, participants were included only once, even if they experienced multiple events in that category. Related adverse events are those recorded as probably related or possibly related on the eCRF. Adverse events of special interest counts are for the overall event and the adverse event of special interest symptom count includes a count of all symptoms contributing to the event. Two-sided exact Clopper-Pearson 95% CIs are presented. eCRF=electronic case report form. n=number of participants. N=number of events.

Table 3: **Overall summary of adverse events (safety population)**

Work Group Summary: Safety

- Available data for 3,490 adults in two Phase 3 trials
- Overall, AEs and severe AEs occurred at significantly higher rates in vaccine vs placebo recipients
- Solicited local AEs reported at low rate
- Solicited systemic AEs reported by 50% of vaccinated subjects
  - Arthralgia reported by 17% vaccine recipients
- Insufficient number of subjects to detect rare SAEs
- Work Group will be reviewing data more fully during GRADE assessment

Missing data on long-term safety not mentioned

VLA1553 Chikungunya Vaccine Candidate
Summary

- **VLA1553 met primary endpoint in a pivotal immunogenicity phase 3 study**
  - Serological endpoint, $\mu PRNT_{50}$ titer ≥150, agreed by FDA to support accelerated approval
  - **Single dose induced seroresponse in 98.9%** of participants at Day 29
  - Seroresponse was **sustained in 96.3%** of participants at **Day 180**
  - Similar GMT and SRR induced in participants aged 18-64 or ≥65 years of age
- **VLA1553 was generally well tolerated across age groups**
  - Independent DSMB did not identify any safety concern
  - **Majority of AEs mild or moderate** and resolved within 3 days, 2.1% severe solicited AEs (most commonly fever)
- **Safety profile comparable with other licensed vaccines[1]**
- **BLA Submission to FDA initiated**

VLA1553 is an investigational chikungunya vaccine candidate and is not approved for use in the United States or any other jurisdiction

1 E.g. compare FDA prescribing information Comirnaty, Bexsero, Shingrix, YF-VAX, all accelable at https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states

Contents lists available at ScienceDirect

Vaccine

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

A Brighton Collaboration standardized template with key considerations for a benefit/risk assessment for an inactivated viral vaccine against Chikungunya virus

Libia Milena Hernandez [a], K. Sumathy [b], Sushant Sahastrabuddhe [a], Jean-Louis Excler [a], Sonali Kochhar [c,e], Emily R. Smith [d,*], Marc Gurwith [d], Robert T. Chen [d], For theBenefit-Risk Assessment of VAccines by TechnolOgy Working Group (BRAVATO, ex-V3SWG)[1]

[a] International Vaccine Institute (IVI), Seoul, Republic of Korea
[b] Bharat Biotech International Limited (BBIL), Hyderabad, Telangana, India
[c] Global Healthcare Consulting, New Delhi, India
[d] Brighton Collaboration, A Program of the Task Force for Global Health, Decatur, GA, USA
[e] University of Washington, Seattle, USA

A Brighton Collaboration standardized template with key considerations for a benefit/risk assessment for an inactivated viral vaccine against Chikungunya virus - ScienceDirect

Inactivated whole virion CHIKV vaccine

The inactivated whole CHIKV vaccine was cultured on Vero cells and inactivated by ß-propiolactone. This provides an effective, flexible system for high-yield manufacturing. The inactivated whole CHIKV vaccinehasfavorablethermostabilityprofiles,compatiblewithvaccinesupplychains.

Safety data are compiled in the current inactivated whole CHIKV vaccine safety database with unblinded data from the ongoing studies: 850 participants from phase II study (parts A and B) outside of India, and 600 participants from ongoing phase II study in India, and completed phase I clinical studies for 60 subjects. Overall, the inactivated whole CHIKV vaccine has been well tolerated, with no significant safety issues identified. Evaluation of the inactivated whole CHIKV vaccine is continuing, with 1410 participants vaccinated as of 20 April 2022. Extensive evaluation of immunogenicity in humans shows strong,durablehumoralimmuneresponses.

11. Overall Risk Assessment	Information
11.1 Please summarize key safety issues of concern identified to date, if any:	None
● how should they be addressed going forward	
11.2 What is the potential for causing serious unwanted effects and toxicities in:	**Describe the toxicities**
● healthy humans?	None
● immunocompromised humans?	None
● human neonates, infants, children?	None
● pregnancy and in the fetus in humans?	None
● elderly?	None
● in any other special populations (e.g., institutionalized populations, individuals with associated chronic comorbidity)?	None

Chikungunya Fever ACIP Meeting Links

Protecting people from global diseases since 2000.

ACIP Meetings on Chikungunya vaccine
October 19, 2022 and February 23, 2023

Overview of Chikungunya and Chicungunya vaccines (cdc.gov)

VLA1553 ACIP Presentation_2022_10_19 (cdc.gov)

Work Group interpretation of vaccine data and Work Group plans and timelines (cdc.gov)

Global Epidemiology of Chikungunya (cdc.gov)

Chronic Arthralgia after Chikungunya CDC Presentation

Chikungunya Fever Links

Protecting people from global diseases since 2000.

Chikungunya Virus: Background, Pathophysiology, Etiology (medscape.com)

Chikungunya fact sheet (who.int)

Chikungunya Virus Clinical Presentation: History, Physical Examination, Diagnostic Criteria for Chikungunya Fever (medscape.com)

Chikungunya fever | Nature Reviews Disease Primers (Bartholomeeusen 2023)

The research progress of Chikungunya fever - PubMed (nih.gov)

Safety and immunogenicity of a single-shot live-attenuated chikungunya vaccine: a double-blind, multicentre, randomised, placebo-controlled, phase 3 trial - PubMed (nih.gov)

Live-attenuated Chikungunya vaccine: a possible new era - The Lancet

Strategic considerations on developing a CHIKV vaccine and ensuring equitable access for countries in need | npj Vaccines (nature.com)

Chikungunya Vaccine Candidates: Current Landscape and Future Prospects - PMC (nih.gov)

https://www.sciencedirect.com/science/article/abs/pii/S0264410X17309738

https://www.nature.com/articles/s41598-018-20305-4.pdf

Phase IV of the AVSS Project

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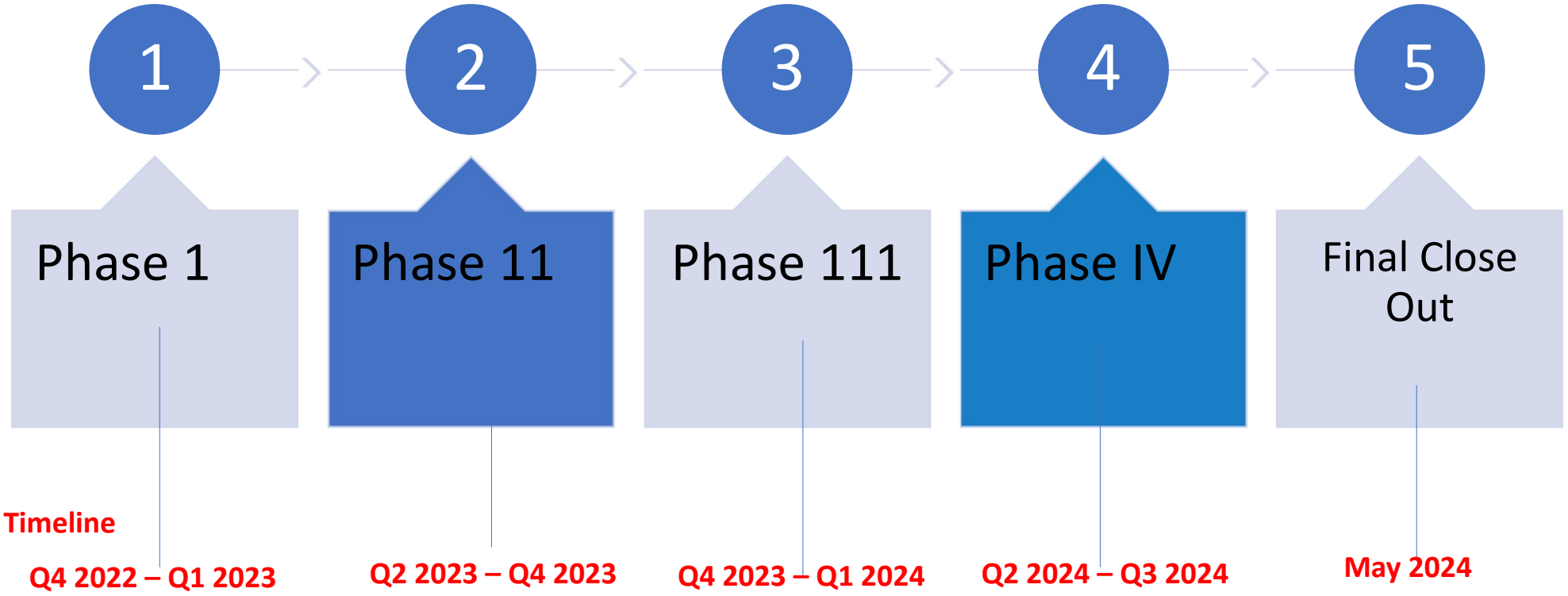
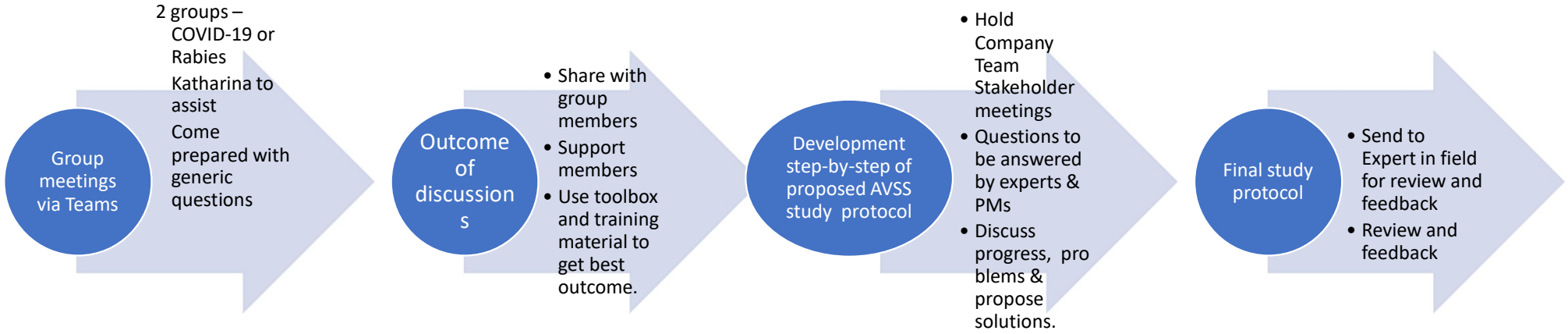
Protecting people from global diseases since 2000.

DCVMN INTERNATIONAL
Developing Countries Vaccine Manufacturers Network International

Phases of AVSS Project with timelines



Kickoff Webinar & Rollout - Workflows



Confidentiality requirements –

- do NDAs need to be signed with Experts and/or DCVMN PMs ?
- how are we going to deal with this ?
- Should each company use a code name for their vaccine instead of using generic vaccine name to bolster confidentiality ?

Conflict of interest –

- how to address sensitive issues (one to one meeting ?)
- Experts - How many experts do we need and do we need to contact them now to book them and cost?

Phase IV – final study protocol, timelines and review

Protocol

- Completion of the development of the protocols/synopses is expected by the end of February 2024;
- These protocols / synopses will be submitted to DCVMN project managers, who will facilitate a critical review by independent experts with experience in AVSS.

Progress

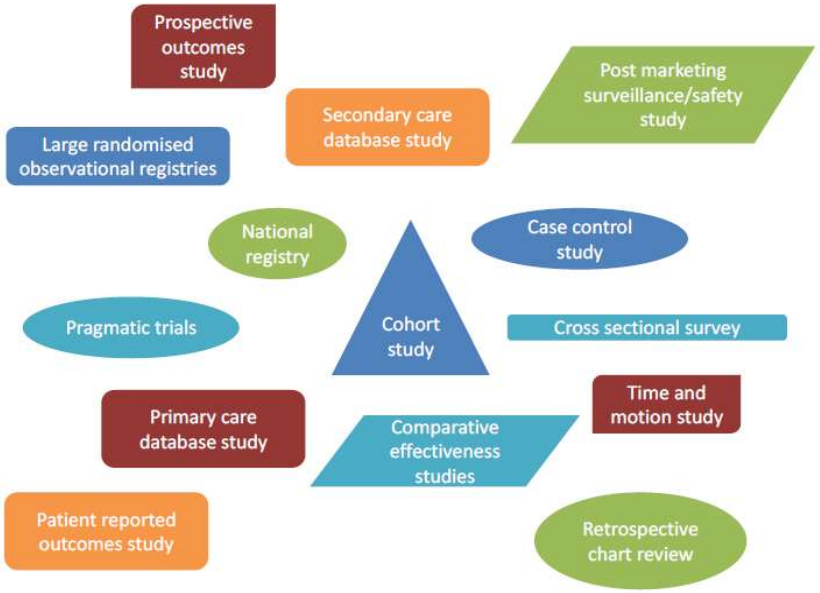
- Feedback from reviewers is expected within two months.
- Opportunities for monitoring progress. To discuss Individual monitoring via e-mail or telephone calls? Companies not able to meet the timelines?

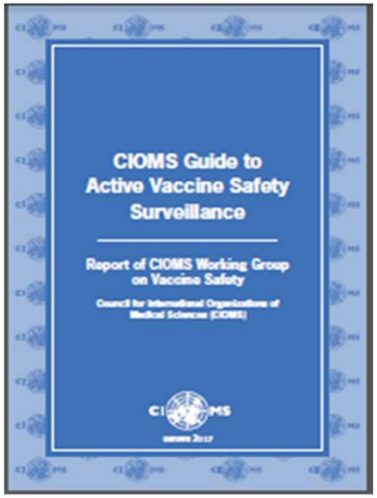
Close out

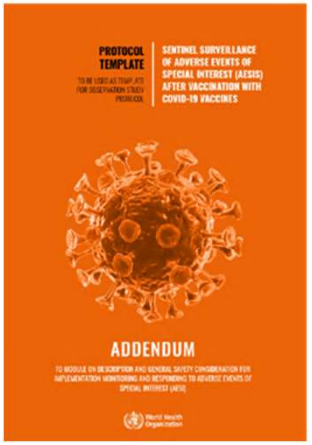
- The project should be completed by the end of April 2024, and a final close-out meeting / workshop is planned in May 2024.
- Based on the report findings, the conclusions will be published in Q2 2024.

Questions - Comments?

Confusing Real-World Studies….







Over the lifecycle, data from continuous safety monitoring strategies provide complementary insights in vaccine profile.

Hartmann 2023

SWOT of PV activities in DCVMN

Strenghts

1-Analytical skills and knowledge of regulation, Regulatory expectations
2- Some have experience in AVSS studies
3- New perspectives, Enhanced learning through sharing
4- Diverse Regulatory experience from diferente countries
5-

Weakness

1- We don't have experience in all the methodologies
2- Sample size calculation
3- Limited budget
4- Need to improve interaction and communicaton between cross-functional teams (PV, Reg, CD)
5- Most DC do not have centralized databais
6-

Opportunities

1- COVID pandemic opened some doors for collaboration in PV activities
2- All LMICs are sensitive to the importance of PV activities
3- AI can help us perform certain opportunites (data mining)
4- AVSS is more cost effective than clinical trials. LMICs have Advantage of cost effectiveness in conducting studies.
5- AVSS can help improve hospital information system
6- Regional AVSS studies can help save resources
7- Development of data security using block chain technology

Threats

1- Not easy to receive guidance from the NRA on NIP
2- We still need training on PV in order to teach AI to function propperly
3- We need to start regulating AI
4- Most NRAs in DC do not share information with the manufacturers
5- Background information is sometimes not linked to vaccination information, AE, deaths, hospitalizations, etc.
6- Information of DC does not flow to WHO digibase
7- Poor communication of safety data of vaccines increases vaccination hesitancy
8- Data security can lead to competitive disadvantage

What process improvements can we propose to mitigate manufacturers' challenges?

1- DCVMN could advocate with WHO, UNICEF, PAHO and NRAs that manufacturers need to have access to full data locally regarding their products (Create slides with scenario for RS to make this presentation- evaluate pros and cons on why they are not giving this data- Challenges, issues, and how it is impacting the industry, mention what is available, what is the tap and how to bridge)

2- Explore the possibility of receiving the signal detection test by WHO/NRA on a periodic basis for own products

3- Create a Teams group for Knowledge sharing and crisis management (no confidential information) and seeking advice from PV colleagues

4- Create a combined (PV, Reg, Clinical data) WG meeting for Feb- March next year for improving intra functional communication

WRAP-UP – PRINCIPAL OUTCOMES/ENDPOINTS

Principal dificulties pointed out by companies regarding AVSS execution:

-Regarding data acess and quality – need more robust data and linkage of databases (NIP,NRA,etc) to allow MAH to access the safety information available in the countries. It is important to real time surveillance and to allow AVSS protocols execution.

- Need to have access to local epidemiological data to allow AVSS study desing to be more robust.

- Communication – companies pointed out the need to stakeholders to collaborate and communicate more closely allowing more effetive actions regarding PV.

WRAP-UP – PRINCIPAL OUTCOMES/ENDPOINTS

- Stakeholders – important to talk with NRA/NIP previous to vaccine launch in order to align the possible safety surveillance requests, allowing MAH to be prepared and planned for it;
- Companies estabilish standardized process of safety issues evaluation, that will help to establish AVSS needs ;
- Clinical development teams and PV teams need to be alligned ;
- PV needs to participate since the beginning of clinical development;
- Clinical development database and PV database needs to be integrated;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