Considerations for Vaccine Safety Assessment

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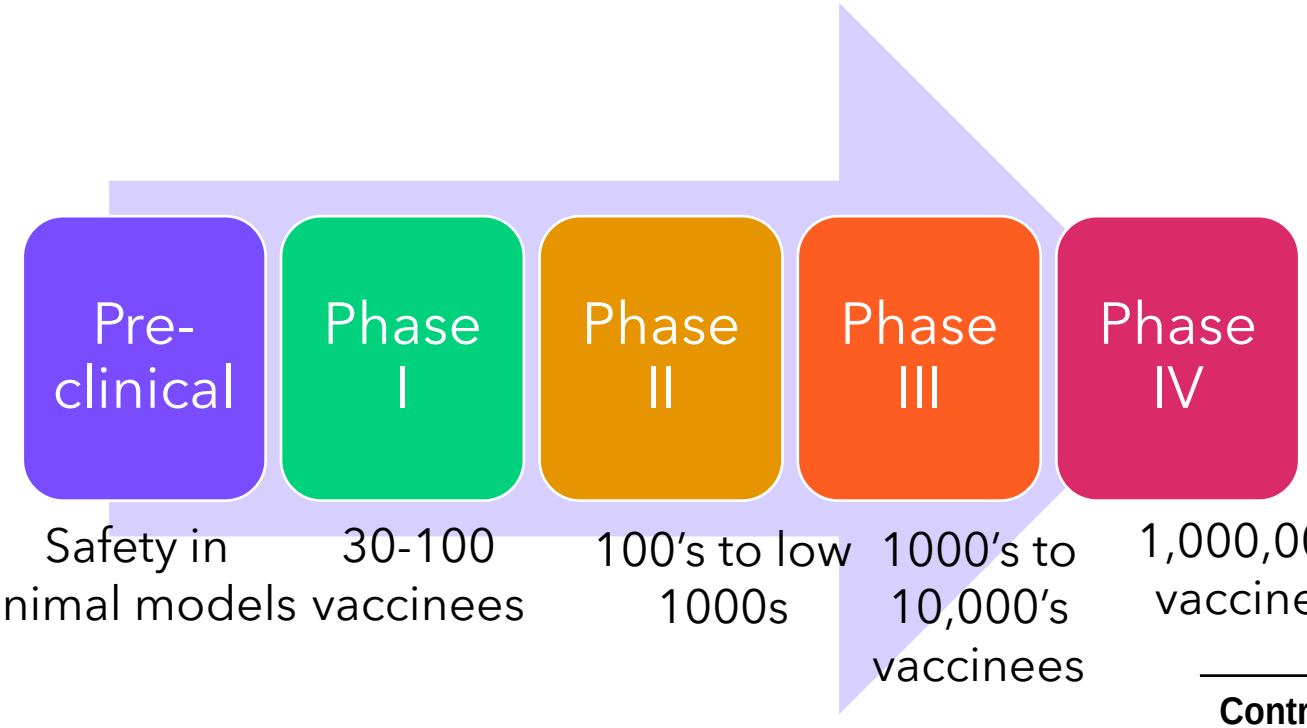
The complexity of assessing vaccine safety

- Efficacy or effectiveness is assessed by measurement of one or more **pre-defined** outcomes in the study population or vaccine recipients.
- Vaccine safety is determined by the **absence** or a low level of events many of which may not be known before the vaccine assessment begins.
- So, while there is a refined statistical definition of efficacy, one does not exist for safety.

Setting Appropriate Expectations



Even very rare events are important as they impact vaccine confidence and vaccine acceptance

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

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

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

Approaches to vaccine safety surveillance

Passive surveillance

- Relies on spontaneous reporting by individual or practitioner
- Primarily for signal detection
- Detects unexpected events
- Inconsistent data quality
- Reporting bias

Active surveillance

- Captures all adverse events of a certain type in a population
- Signal detection & evaluation
- More difficult to detect unexpected events
- Systematic data collection
- Less bias
- Resource-intensive
- Active surveillance in a defined sub-population can be more useful than passive surveillance in a larger population.

Rosenthal & Chen, *Am J Pub Health, 1995*
Singleton, et al., Vaccine 1999
Scheifele, Semin Pediatr Infect Dis, 2003

Approaches for assessing vaccine safety

- **For local and systemic reactions in Clinical Trials**
  - Diary cards that are collected by study personnel
  - Scripted telephone interviews or cohort event monitoring using telephone apps at pre-defined intervals
- **For more rare and serious adverse events in clinical trials**
  - Scripted interactions at defined intervals with trial personnel
  - CEM using Mobile apps has been proposed and was used in several COVID trials in HIC
- **Post introduction**
  - CEM monitoring was used in HIC (but did not pick up myocarditis) and was very useful for assessment in special populations not assessed in trials such as pregnant women as well as in health care workers in Nigeria. .
  - Passive reporting has been used widely globally including in LMIC but it has limitations:
    - Reporting bias, Underreporting especially in LMIC, Lack of ability to assess causality or assign attributable risk.
  - Active surveillance of hospital utilization is a key component of surveillance in HIC but is now finding application in LMIC.

SPEAC Tools to Facilitate Vaccine Safety Assessment in RCTs & Post introduction

- SPEAC Landscape Analyses identify possible AESIs because they are a:
  - **Known association with immunization in general**. e.g., anaphylaxis
  - **Known association with a specific vaccine platform** - e.g. myocarditis post mRNA vaccine platform
  - **Theoretical possibility based on wild type disease** as a result of viral replication (this is primarily a concern for live attenuated vaccine platforms) or immune response to pathogen. e.g. Thrombocytopenia following measles vaccine
  - **Theoretical possibility based on animal model studies** or in-vitro studies - This category was how vaccine associated enhanced disease was added to the AESI list.

  SPEAC AESI list then generated for that pathogen.

- **BC Case Definitions** to classify and confirm cases in a harmonized way.
- **Case Definition "Companion Guides"** to facilitate use of BC Case definitions.

AESI identified for Lassa Fever

AESI Related to Vaccines in General

BODY SYSTEM	AESI TYPE
Neurologic	Generalized convulsion
	Guillain-Barré Syndrome (GBS)
	Acute disseminated encephalomyelitis (ADEM)
Hematologic	Thrombocytopenia
Immunologic	Anaphylaxis
	Vasculitides

AESI Specifically Related to Lassa

BODY SYSTEM	LASSA FEVER
Neurologic	Sensorineural hearing loss
	Encephalopathy/cerebellar ataxia
	Aseptic meningitis
Hematologic	Bleeding (mucosal, urine, fecal, internal)
	Vascular leakage (edema of face/neck)
Immunologic	Polyserositis (pleural, pericardial, abdominal effusions)
	Alopecia*
Other	Maternal death, spontaneous abortion, stillbirth, neonatal death

Platform Related AESI

BODY SYSTEM	VACCINE PLATFORM SPECIFIC AESIS	KNOWN/POSSIBLE ASSOCIATION WITH
Neurologic	Aseptic meningitis Encephalitis / Encephalomyelitis	Live viral vaccines including measles
Immunologic	Arthritis	r-VSV platform
Other	Myocarditis	MVA platform
Hematologic	VITT	Adenovirus platform

B.C. SNHL case definition available and validated in a study in Ghana

SPEAC Project funded by CEPI

Selected Examples of RCT Vaccine Safety Assessment in LMIC

- Typhoid Conjugate trial in Asia
- GSK Malaria Vaccine trial in Africa
- Pneumococcal Conjugate trial in South Africa
- Meningococcal A conjugate vaccine in West Africa (post introduction)

Safety Assessment in a phase III Typhoid conjugate Vaccine Trial

- Participants were observed in the clinic for at least 20 minutes after the vaccine was administered.
- All participants received a **patient diary** in which to record local and systemic adverse events . On day 7, the parents and guardians of the participants were **contacted by telephone**, and any vaccine-related adverse events and all serious adverse events were recorded.
- **Follow-up calls and visits** every 3 months to capture serious adverse events - essentially stimulated passive surveilance.

Shakya M, Colin-Jones R, Theiss-Nyland K, Voysey M, Pant D, Smith N, Liu X, Tonks S, Mazur O, Farooq YG, Clarke J.
Phase 3 efficacy analysis of a typhoid conjugate vaccine trial in Nepal. New England Journal of Medicine. 2019 Dec 5;381(23):2209-18.

Safety Assessment in the GSK phase III Mosquirix™ Malaria Vaccine Trial

- Collected information on all **unsolicited reports of adverse events** (AEs) that occurred within 30 days after vaccination and on local and systemic reactogenicity within 7 days after vaccination among the **first 200 participants** enrolled at each centre
- Serious AEs **(SAEs)** were identified during study follow-up by **surveillance at health facilities in the study area** and through **monthly home visits** throughout the study period.
- **AESIs:** Meningitis, seizures (within 30 days of vaccine), autoimmune disease received special attention.
- **Verbal autopsies** using standardised procedures were done on deaths that occurred outside hospital. All deaths were reviewed by a special panel

Rts, S. C. T. P. (2015). Efficacy and safety of RTS, S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. *The Lancet*, *386*(9988), 31-45.

Safety Assessment in South Africa in a Special Population – HIV infected

- Trial in HIV infected and non-infected children with the clinical endpoint of pneumonia
- Safety surveillance included assessment of **local and systemic reactions at office visits** as well as review of all **hospitalization and emergency visits**:
  - **Twenty-four–hour surveillance was conducted at the admission ward** of Chris Hani Baragwanath Hospital, a secondary and tertiary hospital that serves more than 90 percent of the children in Soweto. Data for all children born after December 1997 were compared at the time of admission with the data base of all children enrolled in the trial.
  - **Hospitalized children were examined by one of four study doctors within 24 hours after admission to determine the clinical diagnosis**, but the study doctors were not involved in the children's care.

Klugman, K. P., Madhi, S. A., Huebner, R. E., Kohberger, R., Mbelle, N., & Pierce, N. (2003).
A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *New England Journal of Medicine*, *349*(14), 1341-1348.

MenA Conjugate Vaccine introduction: lessons from Burkino Faso - phase IV

- Men A vaccine was introduced into the Sub-Saharan African meningitis belt in December 2010 and almost 12 million people vaccinated in one campaign in Burkino Faso

- Two safety surveillance systems established post introduction:
  - Nation wide passive surveillance
  - Active Surveillance in one district

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

Men A: Passive Surveillance

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

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

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

Men A: Active Surveillance

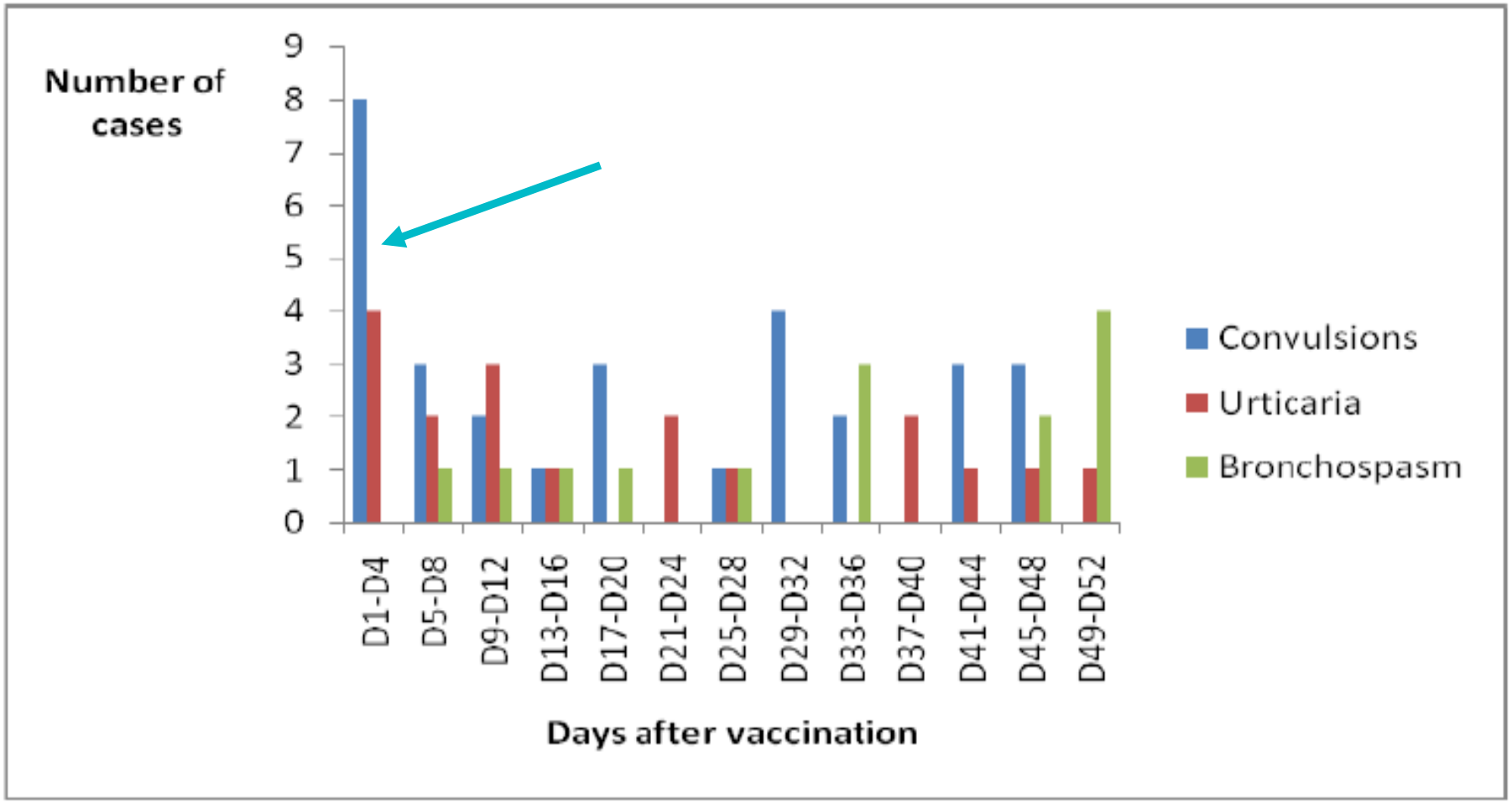
Table 3: Reported AEFI cases through active search in the district of Ziniaré

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

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

MenA Introduction in Burkino Faso: Active Surveillance Data

Figure 3: Onset of main selected conditions reported through active search in the district of Ziniaré



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

Men A Safety in Pregnancy: A Ghana HDSS Study

- Rates of events in 1730 immunized pregnant women and their infants were compared to the rates of the same events in pregnant women who did not receive the vaccine during the campaign and also to women who were pregnant in the prior year in a pre-existing HDSS in Navrongo, Ghana.

Table 4. Comparison of Birth Outcome and Delivery Mode Between Vaccinated Pregnant Women and Controls

Outcome	Group A Cohort (n = 1730)	Group A Rate/100	Concurrent Controls (n = 919)	Control Rate/100	IRR	95% CI	*P* Value
Live birth	1692	97.8	899	97.8			
Stillbirth	22	1.3	14	1.5	0.95	.62–1.46	.80
Miscarriage	16	0.9	6	0.7	1.06	.65–1.74	.82
Maternal Mortality	0	0	3	0.3	…	…	…
Normal delivery	1642	94.9	871	94.8			
Cesarean delivery	37	2.1	23	2.5	0.95	.69–1.32	.77

Wak, George, John Williams, Abraham Oduro, Christine Maure, Patrick LF Zuber, and Steven Black. ”
The safety of PsA-TT in pregnancy: an assessment performed within the Navrongo health and demographic surveillance site in Ghana.”
Clinical Infectious Diseases 61, no. suppl_5 (2015): S489-S492.

But is active surveillance feasible in LIC ???

The GAVI funded study In the ALIVE network.

ALIVE Project Participants

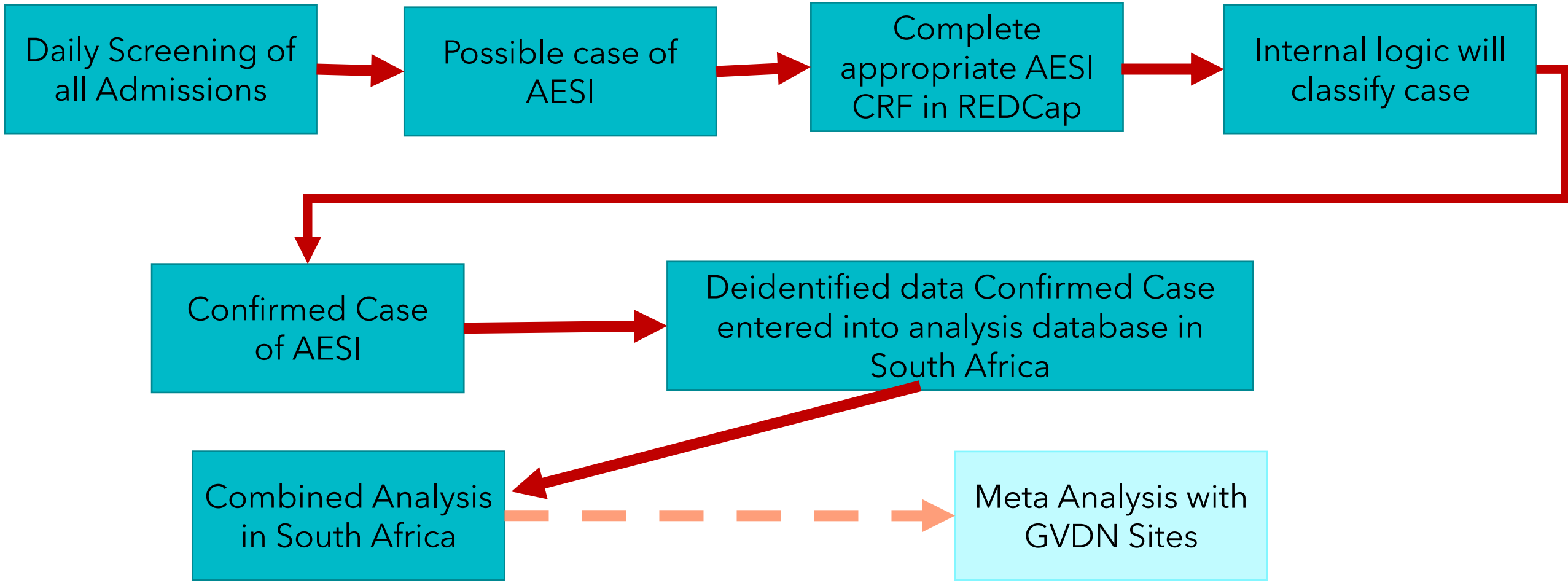
Country	Site	Site lead/ contact
Mali	Bamako	Samba Sow
Ghana	Navrongo Health Research Centre	Nana Akosua Ansah
Nigeria	National	Ehimario Igumbor Stephen Obaro
Ethiopia	Gondar	Biniyam Tilahun
Kenya	Kilifi	Wangeci Kagucia
Malawi	National	Kondwani Jambo
Mozambique	Maputo city	Ilesh Jani Celso Khosa
Eswatini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

Alive Project

GAVI funded establishment of COVID-19 vaccine safety active surveillance in eight AMC-92 countries in Africa.

- *Coordinating site is WITS University in Johannesburg.*
- *The Global Vaccine Data Network (GVDN) a technical partner – supporting database development for a pilot in South Africa.*
- *Data on target AESIs is being successfully collected and classified on more than 20,000 screened individuals*
- *Data is collected from in person hospital surveillance and data on possible AESI cases in entered into a REDCap app which classifies the case based upon key data as a case or not and also assigns a level of certainty to each case.*
- *IMPORTANTLY, this type of infrastructure can be applied to identify hospitalized SAEs in clinical trials.*

ALIVE Project Data Collection Model



Summary:
The GVDN "LMIC Model"

- The data collection model was initially developed for real time hospital data collection in South Africa.
- It has now been adapted for use in the ALIVE network of LIC countries as well as sites in India with active data collection ongoing
- This model is exportable to other countries and sites for use in clinical trials as well as post introduction studies.

Conclusions

- Background rates of events requires establishment of infrastructure and data collection in advance of a clinical trial or phase IV study. These are very useful for rapid assessment of observed events.
- Prior clinical trials have incorporated
  - Collection of local and systemic reactions on a subset of the total trial population.
  - Surveillance for SAEs and AESI using dedicated hospital and emergency department surveillance that was established for the trial. This requires advance planning
- Post introduction surveillance
  - Requires either use of existing infrastructure such as demographic surveillance sites or custom-built infrastructure
  - Passive surveillance reporting rates been very low in LIC and are subject to reporting bias
  - Active surveillance is possible in LMIC and LIC.
  - In the past (including COVID) post introduction studies have relied on data from HIC- this will not work for Lassa !
- Special populations such as pregnant women require special attention