COVID-19 VACCINE SAFETY

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VACCINE SAFETY

- Defined as the process that maintains the highest efficacy of, and lowest adverse reaction to, a vaccine by addressing its production, storage and handling. Vaccine safety is a part of immunization safety
- As with all medicines, every vaccine needs to go through extensive and rigorous testing before it can be introduced in a country
- Once they are in use, they must be continuously monitored to make sure they are safe for the people who receive them
- Classified
  - Pre-licensure
  - Post-licensure

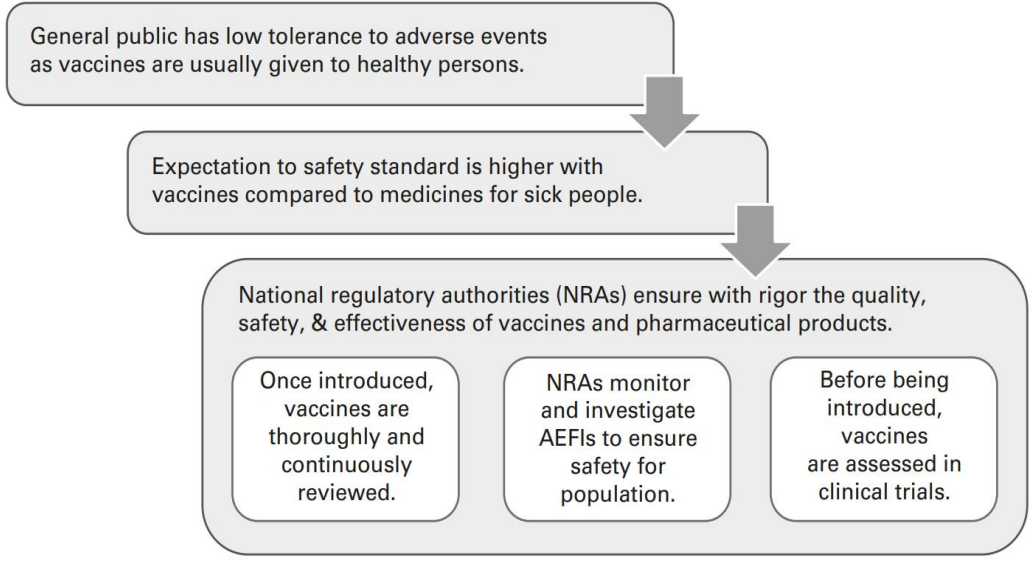
EXPECTATIONS TOWARDS SAFETY OF VACCINES

- Vaccines are not completely risk-free
- Adverse events will occasionally result from vaccination
- Most adverse events are minor
  - Redness at injection site
  - Fever
- More serious reactions can occur albeit at a very low frequency
  - Seizures
  - Anaphylaxis

EXPECTATIONS TOWARDS SAFETY OF VACCINES

- The general public has low tolerance to any adverse events following vaccination
- Vaccines are given to healthy persons to prevent disease
- Higher standard of safety is expected of immunizations compared with medications that are used to treat people who are sick (e.g. antibiotics, insulin)
- Greater need to detect and investigate any adverse event following immunization (AEFI) than is generally expected for other pharmaceutical products

Low public tolerance requires safe vaccination



ADVERSE EVENTS

- An adverse event following immunization (AEFI) is any untoward medical occurrence which follows immunization
- It does not necessarily have a causal relationship with the usage of the vaccine
  - Related
  - Unrelated
- AEFIs are divided in 5 categories

Consistent with causal association to immunisation

Vaccine product-related reaction

Caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product

Implications for COVID-19

- Identification of rare and very rare adverse events is not sufficient at the time of COVID-19 vaccine registration
- More information will be needed for which AEFI surveillance has to be strengthened

Vaccine quality defect-related reaction

Caused/precipitated by a vaccine, due to one/ more quality defects of the product

Implications for COVID-19

- Knowledge of potential vaccine quality defects might not be sufficient for new vaccine platforms at time of registration
- Rapid scaling up of vaccine production poses additional potential risks
- Identification of exact substance causing event is needed

Immunisation error-related reaction

Caused by inappropriate vaccine handling, prescribing or administration

Implications for COVID-19

- Vaccines will be administered on massive scale within short time interval; larger number of immunization error-related reactions are anticipated if preparation is insufficient
- Staff who are not familiar with immunisation might assist
- Multiple vaccines with different specifications for administration, dose and storage, may in be in use

Immunisation anxiety-related reaction

Arising from anxiety about the immunisation and fear of injection

Implications for COVID-19

- Larger number of immunisation anxiety-related reactions are anticipated due to numerous factors including
  - older age groups
  - different vaccinating environments
  - novelty of the vaccines and their administration modalities
- Example: Vasovagal syncope following vaccination

Inconsistent with causal association to immunisation

Coincidental event

An event that happens after vaccination but is not caused by the vaccine or vaccination process

Implications for COVID-19

- Coincidental events will be of utmost importance for COVID-19 vaccination and one of the reasons for active surveillance of AESI
- Because of potential comorbidities in vaccine recipients, it will be challenging to differentiate true coincidental events from COVID-19 vaccine product-related reactions or drug reactions or interactions
- Coincidental events can occur in healthy individuals without comorbidities
- Knowing population-based incidence (background rates) of pre-specified AESI helps to anticipate and respond to such events

CAUSES OF ADVERSE EVENTS

- Vaccines contain different components to make them effective
- Each component in a vaccine adds a potential risk of an adverse reaction
- Regulatory authorities must ensure that all vaccine components, singly and in combination, do not compromise vaccine safety
- Vaccines are prepared with different types of antigens, using different scientific methods such as attenuation, inactivation, and recombination DNA technology

CAUSES OF ADVERSE EVENTS

- Some vaccines include components to enhance immune response, such as adjuvants and conjugated proteins
- Vaccines can also include antibiotics, stabilizers, and preservatives to reduce contamination during the manufacturing process and to maintain their effectiveness during transport and storage
- Manufacturers usually recommend the route of administration that limits best adverse reactions of the respective vaccine

FREQUENCY AND SEVERITY

- Under recommended conditions, vaccines should cause no adverse events and completely prevent the infection that they target
- Unfortunately, current technology does not allow for such perfection
- The key therefore is to minimize as much as possible adverse events and ensure a safe use of vaccines

Frequency and severity of adverse vaccine reactions

Frequency	Occurrence among persons vaccinated in percent	Severity of reactions
Very common	≥ 10%	**Common and usually minor reactions:** • Are part of the immune response to vaccine, • Reactions settle on their own, • Examples include: – Fever, – Malaise.
Common (frequent)	≥ 1% and < 10%	
Uncommon (infrequent)	≥ 0.1% and < 1%	**Rare, usually more severe reactions:** 1. Usually require clinical management, 2. Examples include: – Severe allergic reaction (e.g., anaphylaxis) including an exaggerated response to the vaccine antigen or component, – Vaccine specific reactions, such as BCG osteitis.
Rare	≥ 0.01% and < 0.1%	
Very rare	< 0.01%	

Common Side Effects

On the arm where you got the shot:

- Pain
- Redness
- Swelling

Throughout the rest of your body:

- Tiredness
- Headache
- Muscle pain
- Chills
- Fever
- Nausea

ADVERSE EVENTS OF SPECIAL INTEREST

A preidentified and predefined medically-significant event that has the potential to be causally associated with a vaccine product that needs to be carefully monitored and confirmed by further specific studies

AESIs

AESI	Brighton Collaboration case definition status
Vaccine-associated enhanced disease (VAED)	https://doi.org/10.1016/j.vaccine.2021.01.055
Multisystem inflammatory syndrome in children or adults (MIS-C/A)	https://doi.org/10.1016/j.vaccine.2021.01.054
Acute respiratory distress syndrome (ARDS)	10.1016/j.vaccine.2021.01.053
Acute cardiovascular injury	See below for myocarditis and pericarditis case definitions. Others not yet started
Coagulation disorders	• Thrombosis and thromboembolism (draft case definition) • Thrombosis with thrombocytopenia syndrome (TTS) (interim case definition) • Thrombocytopenia—as per Appendix B, based on existing Brighton Collaboration case definition
Acute kidney injury	Published lab-based criteria as suggested by the Brighton Collaboration*
Acute liver injury	Published lab-based criteria as suggested by the Brighton Collaboration**
Anosmia, ageusia	Working group to be formed
Chilblain – like lesions	Working group to be formed
Single Organ Cutaneous Vasculitis	10.1016/j.vaccine.2016.09.032
Erythema multiforme	Not yet started
Acute pancreatitis (NEW)	Not yet started
Rhabdomyolysis (NEW)	Not yet started
Subacute thyroiditis (NEW)	Not yet started
Thrombosis with thrombocytopenia syndrome (TTS)	Interim case definition available: https://brightoncollaboration.us/thrombosis-with-thrombocytopenia-syndrome-interim-case-definition/
Myocarditis	Case definition available at: https://brightoncollaboration.us/myocarditis-case-definition-update/
Pericarditis	Case definition available at: https://brightoncollaboration.us/myocarditis-case-definition-update/

BALANCING EFFICACY AND SAFETY

- Vaccine efficacy refers to the ability of a vaccine to bring about the intended beneficial effects on vaccinated individuals in a defined population under ideal conditions of use
- The potential benefits of an effective vaccine must be weighed against the potential risk of an adverse event following immunization (AEFI) with that vaccine
- Vaccine-associated risk is the probability of an adverse or unwanted outcome occurring, and the severity of the resulting harm to the health of vaccinated individuals in a defined population, following immunization with a vaccine under ideal conditions of use

BALANCING EFFICACY AND SAFETY

- An important criterion of vaccine safety that regulatory authorities must establish is the risk/benefit assessment of immunization with a particular vaccine in a defined population
- Public confidence in vaccine safety is increased by clear communication of risk/benefit assessments, comparing the very low vaccine-associated risk with the very significant benefits of vaccination
- Risk/benefit assessments should be applied to most situations relating to the efficacy or safety of vaccines to ensure public safety and public health

VACCINE SAFETY IN IMMUNIZATION PROGRAMMES

In the pre-vaccine era

High morbidity and mortality caused by infectious disease

No vaccines → no adverse events

The pre-vaccine stage in the graph (STAGE 1) is the phase before the vaccine gets introduced

VACCINE SAFETY IN IMMUNIZATION PROGRAMMES

- In STAGE 2
- Effective vaccine is introduced to prevent a particular disease
- An increase in immunization uptake → decrease in disease incidence
- ↑ adverse events (AEFI), real or perceived
- Paradoxically, it is just when vaccine benefits are most apparent and vaccine coverage is highest that vaccine safety concerns are most likely to increase in the general public
- This increased focus on AEFIs, often intensified by media coverage of one or a few case reports, may lead to
  - A loss of confidence in the vaccine by the public
  - A reduction in vaccine coverage

VACCINE SAFETY IN IMMUNIZATION PROGRAMMES

- The more successful a vaccination campaign is, the less visible the prevented disease may become to the public
- As the threat of the original disease vanishes in the perception of the public, the attention of the population may focus to the adverse events of the vaccine
- A distorted perception of the risk of vaccines and negligence of the much greater health threat by the original disease may lead to decreased acceptance of the vaccine

VACCINE SAFETY IN IMMUNIZATION PROGRAMMES

Stage 3

A resurgence of the disease to higher or even epidemic levels

The resurgence of disease or the availability of an alternative vaccine results in renewed public acceptance of vaccination against the disease

Vaccination levels increase and the disease is reduced to earlier low levels (STAGE 4)

VACCINE SAFETY IN IMMUNIZATION PROGRAMMES

- For vaccine-preventable diseases such as smallpox that can be eradicated, vaccine use can be stopped, thereby removing the risk of any adverse event resulting from its use (STAGE 5)
- To ensure that the cycle displayed does not repeat, any vaccine safety issue requires timely:
  - Detection
  - Evaluation
  - Response efforts to gain and maintain high public confidence

Potential stages in the evolution of an immunization programme

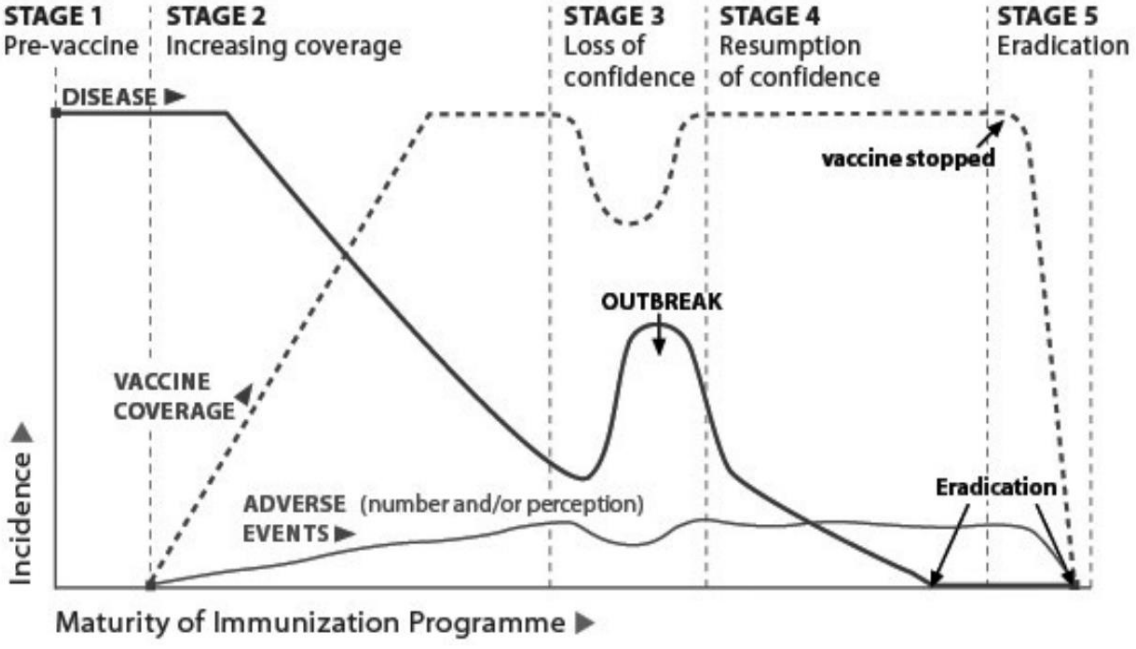


Diagram adapted from Chen RT et al. The Vaccine Adverse Event Reporting SystemVaccine Adverse Event Reporting System (VAERS). Vaccine, 1994: 12(6):542–550.

PRE-LICENSURE VACCINE SAFETY

- Vaccines, like other pharmaceutical products, undergo extensive testing and review for:
  - Safety
  - Immunogenicity
  - Efficacy
- In the laboratory, in animals, and in three phases of clinical trials in human subjects before licensure
- Monitoring adverse vaccine reactions is a major safety component of pre-licensure clinical trials

PRE-LICENSURE VACCINE SAFETY

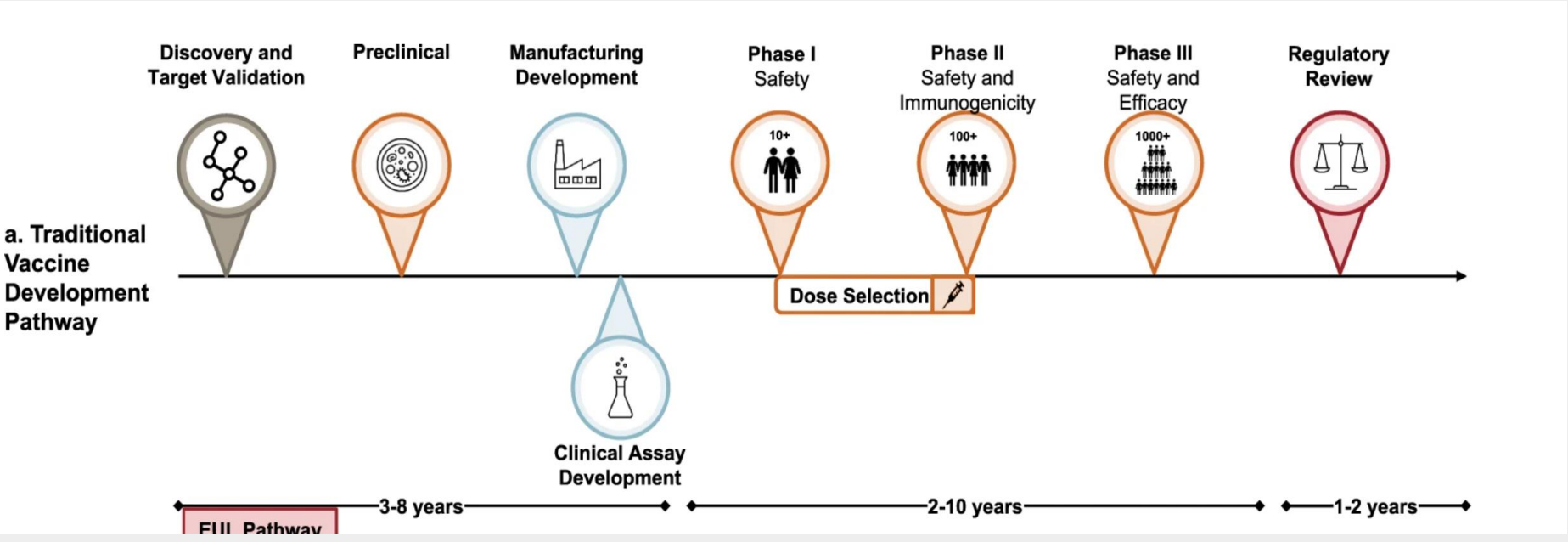
- Pre-licensure studies often identify common and acute negative reactions that occur with a frequency greater than 1 in 10,000 vaccinations, depending on total sample size of the study
- The sensitivity of detection of uncommon or rare adverse events, or those with delayed onset is, however, low in these trials
- As a result, continuous post-licensure monitoring of vaccine safety is needed to identify and evaluate such adverse events

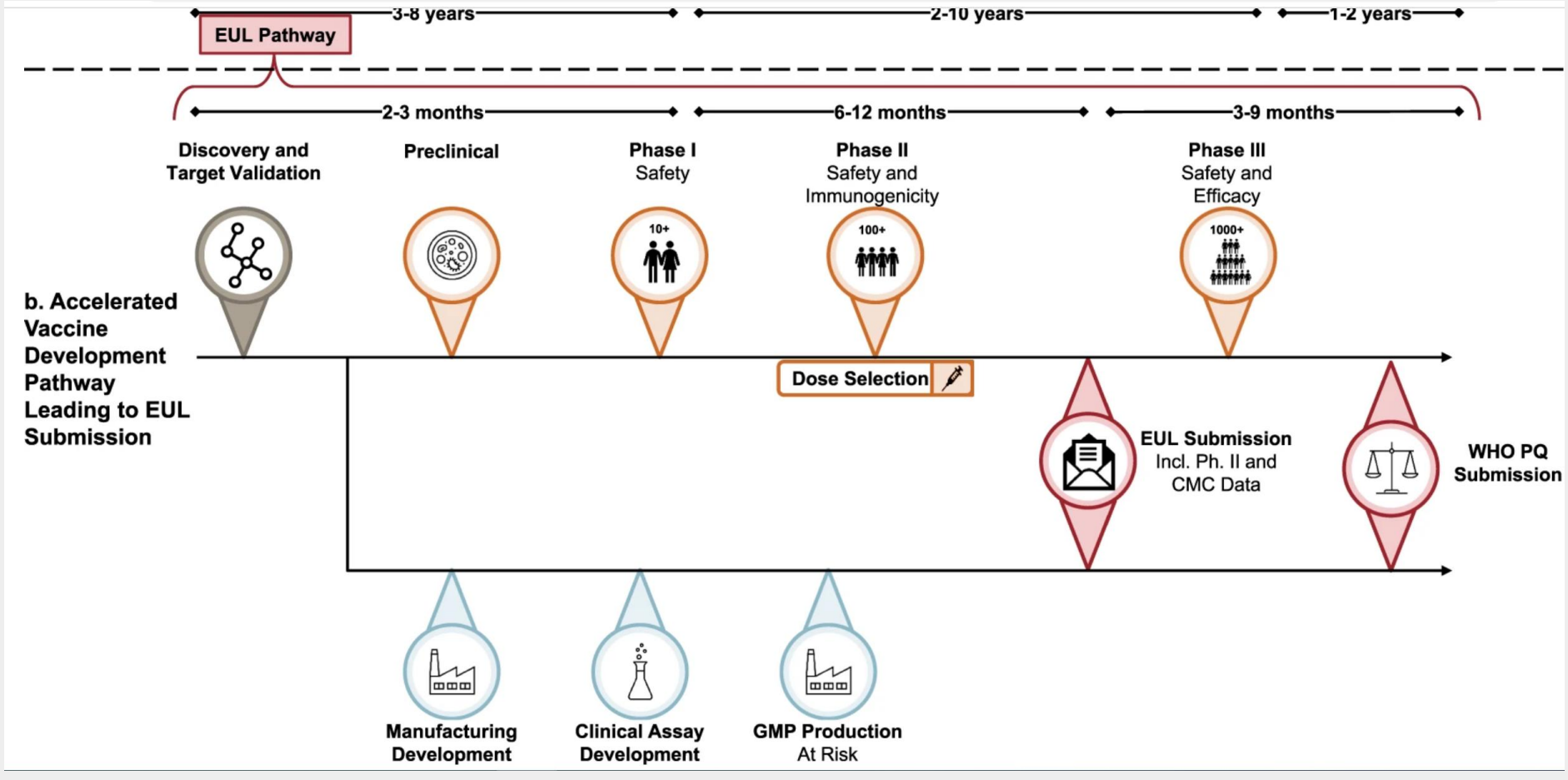
Clinical trials and assessment of vaccine safety

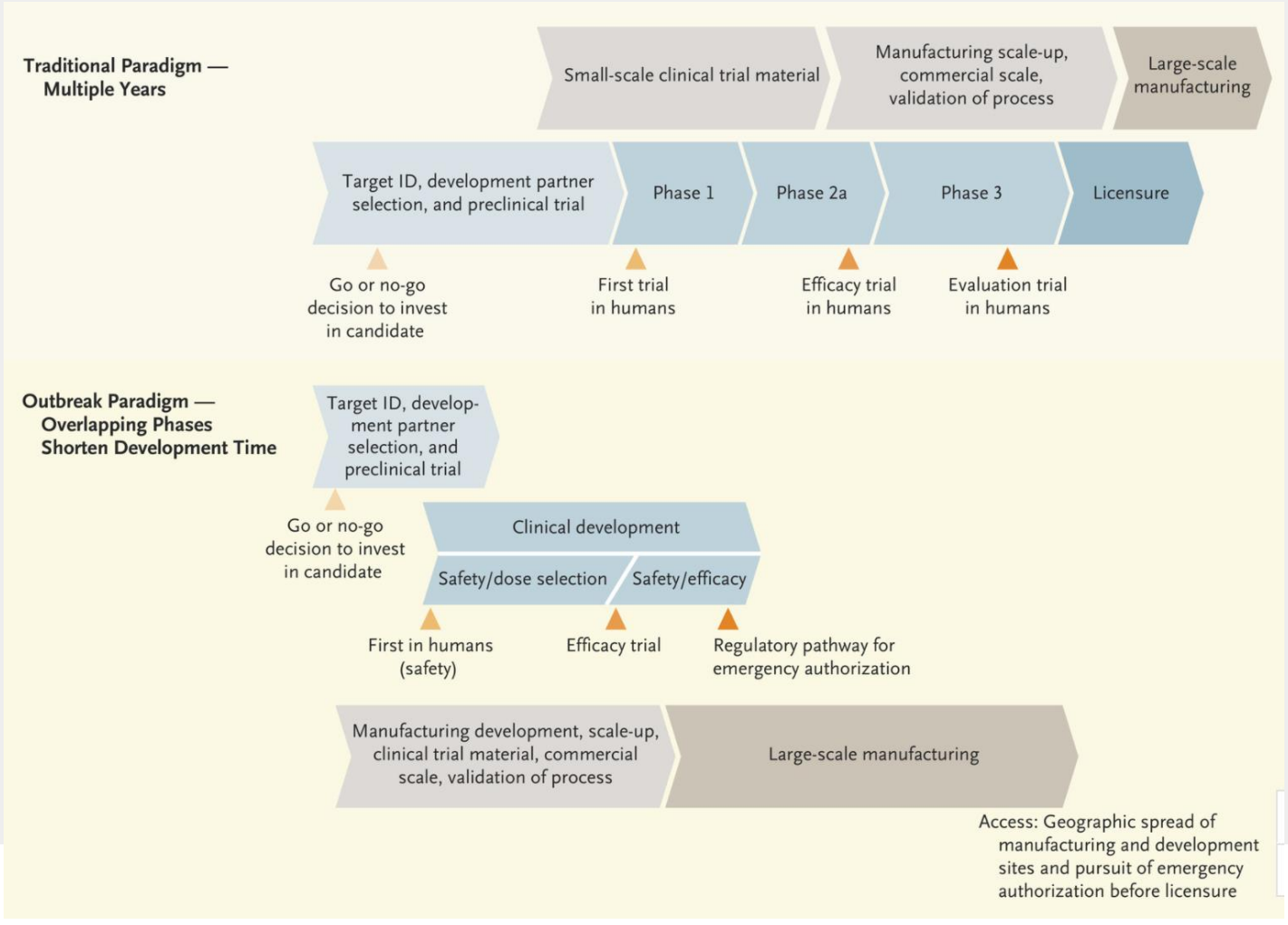
	Activity	Sample size (estimates)	Detection of Adverse events	
			Common	Rare
Clinical Trial Phase I	Test the safety and immunogenicity of a vaccine candidate in a few low-risk individuals (usually healthy adults) to determine tolerability.	10–100	+/–	–
Clinical Trial Phase II	Monitor safety, potential side effects, immune response, and determine optimum dosage and schedule.	100–1,000	+	–
Clinical Trial Phase III	Address clinical efficacy in disease prevention and provide further safety information from more heterogeneous populations and longer times of observation.	1,000–10,000	+	–
Submission	The vaccine application is submitted to regulatory authorities for approval to market.			
Introduction	Involves making the vaccine available for use.			

EMERGENCY USE LISTING

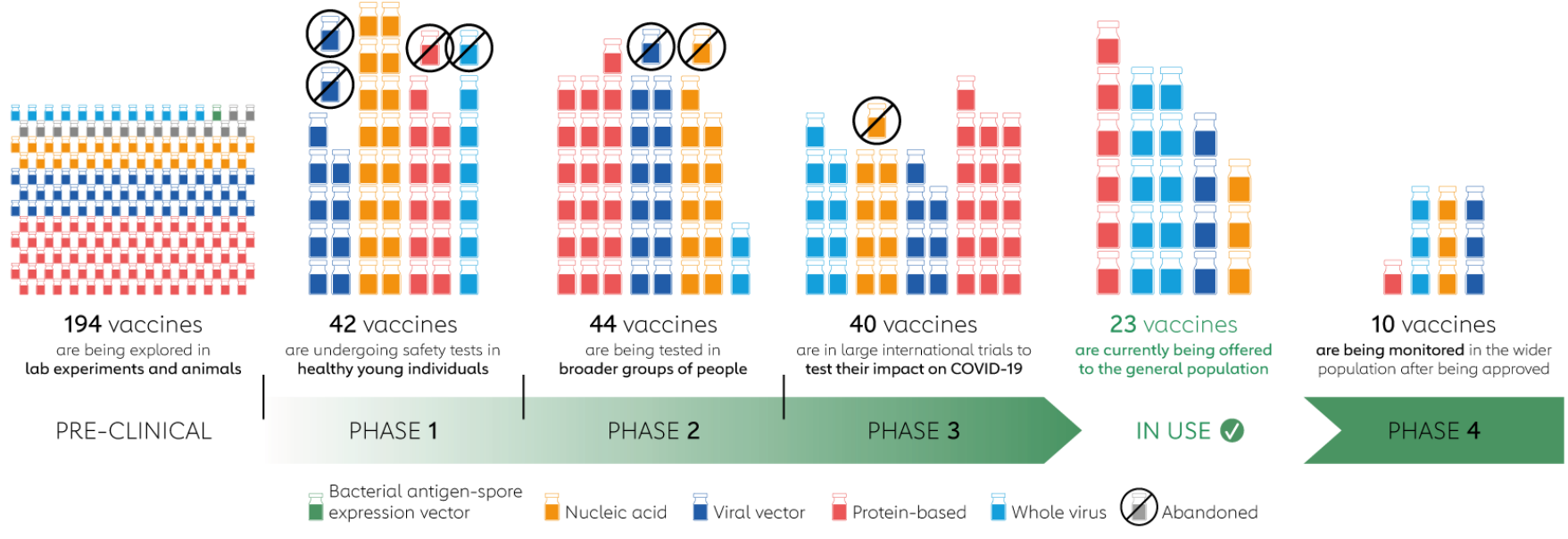
- Unique WHO-facilitated regulatory pathway that can only be used in a declared public health emergency of international concern (PHEIC) or other public health emergency designated by the WHO Director-General
- This emergency scenario allows for a product to be listed based on an earlier package of safety and efficacy data than is the norm
- Novel oral polio vaccine type 2 (nOPV2) vaccine in 2019-2020
  - Developed to better address the evolving risk of type 2-circulating, vaccine-derived poliovirus, a risk that elicited a declaration of a PHEIC by the WHO in 2014
- The novel vaccine became the first vaccine to be submitted for WHO EUL under the revised procedure
- The EUL will likely play a critical role in accelerating equitable access to COVID-19 vaccines, enabling manufacturing countries to use an emergency pathway to authorize products


a. Traditional Vaccine Development Pathway
Discovery and Target Validation
Preclinical
Manufacturing Development
Phase I Safety
10+
Phase II Safety and Immunogenicity
100+
Phase III Safety and Efficacy
1000+
Regulatory Review
Dose Selection
Clinical Assay Development
3-8 years
2-10 years
1-2 years


EUL Pathway
3-8 years
2-10 years
1-2 years
2-3 months
6-12 months
3-9 months
Discovery and Target Validation
Preclinical
Phase I Safety
Phase II Safety and Immunogenicity
Phase III Safety and Efficacy
10+
100+
1000+
b. Accelerated Vaccine Development Pathway Leading to EUL Submission
Dose Selection
EUL Submission Incl. Ph. II and CMC Data
WHO PQ Submission
Manufacturing Development
Clinical Assay Development
GMP Production At Risk


Traditional Paradigm — Multiple Years
Small-scale clinical trial material
Manufacturing scale-up, commercial scale, validation of process
Large-scale manufacturing
Target ID, development partner selection, and preclinical trial
Phase 1
Phase 2a
Phase 3
Licensure
Go or no-go decision to invest in candidate
First trial in humans
Efficacy trial in humans
Evaluation trial in humans
Outbreak Paradigm — Overlapping Phases Shorten Development Time
Target ID, development partner selection, and preclinical trial
Go or no-go decision to invest in candidate
Clinical development
Safety/dose selection
Safety/efficacy
First in humans (safety)
Efficacy trial
Regulatory pathway for emergency authorization
Manufacturing development, scale-up, clinical trial material, commercial scale, validation of process
Large-scale manufacturing
Access: Geographic spread of manufacturing and development sites and pursuit of emergency authorization before licensure

COVID-19 VACCINES IN DEVELOPMENT



POST-LICENSURE VACCINE SAFETY

- Post-licensure surveillance of vaccine safety is critical
- The conditions and reasons for safety monitoring change, following licensure and introduction of a new vaccine
- Vaccines are now in use in the general population and recipients are no longer monitored in clinical trials with narrow inclusion/exclusion criteria
- Subpopulations commonly excluded in clinical trials (e.g. those with underlying medical conditions) get vaccinated

POST-LICENSURE VACCINE SAFETY

- Large numbers of people are being vaccinated
- Other factors that can lead to AEFIs, such as incorrect administration practices, need to be monitored for safety
- Uncommon and rare vaccine reactions, and reactions with delayed onset may not be detected before vaccines are licensed
- Health providers should understand that vaccines can demonstrate rare and potentially serious adverse events
- In these instances, policy-making bodies have judged that the individual and community benefits of vaccination outweigh the risks.

POST LICENSURE SURVEILLANCE OPTIONS

Definition of surveillance

The continual, systematic collection of data that are analyzed and disseminated to enable decision-making and action to protect the health of populations

AEFI surveillance systems are specific to monitoring adverse events associated with vaccine use

Passive surveillance systems

Active surveillance systems


AEFI Detection
Notification
Reporting
Investigation
Analysis
Causality assessment
Feedback

PASSIVE SURVEILLANCE SYSTEMS

- Passive surveillance systems
- Spontaneous reporting systems
- The cornerstone of most post-licensure safety monitoring systems because:
  - Relative ease of implementation
  - Their cost and ability to capture unexpected events
  - Monitor events reported by health care providers and consumers
  - Do not actively seek out and collect data or measure outcomes using study protocols

ACTIVE SURVEILLANCE SYSTEMS: POST-LICENSURE CLINICAL TRIALS AND PHASE IV SURVEILLANCE STUDIES

- Vaccines may undergo clinical trials after licensure to assess the effects of changes in:
  - Vaccine formulation
  - Vaccine strain
  - Age at vaccination
  - Number and timing of vaccine doses
  - Simultaneous administration and interchangeability of vaccines from different manufacturers on vaccine safety and immunogenicity
- To improve the ability to detect adverse events that are not detected during pre-licensure trials

ACTIVE SURVEILLANCE SYSTEMS: LARGE LINKED DATABASES (LLDBS)

LLDBs are large administrative databases from defined populations (such as a single health care provider or HMO) that were created separately from each other and linked to enable the sharing of data across platforms

Such linked databases have become useful to vaccine safety surveillance

Because LLDBs cover enrolled populations numbering from thousands to millions, they can detect very rare adverse events

ACTIVE SURVEILLANCE SYSTEMS: CLINICAL CENTERS, INCLUDING THE CLINICAL IMMUNIZATION SAFETY ASSESSMENT (CISA) CENTERS

- More recently, tertiary clinical centers have been used to conduct research on immunization-associated health risks
- The USA's Clinical Immunization Safety Assessment (CISA) Network is a national network of six medical research centers with expertise in immunization safety conducting clinical research on immunization-associated health risks

IMMUNIZATION SAFETY SURVEILLANCE

- Immunization safety is the process of ensuring and monitoring the safety of all aspects of immunization, including
  - Vaccine quality
  - Adverse events
  - Vaccine storage and handling
  - Vaccine administration
  - Disposal of sharps
  - Management of waste
- The skills and infrastructure to deal with genuine vaccine adverse reactions are essential to public safety, as well as to prevent or manage fear caused by false or unproven signals from patients and health workers

VACCINE PHARMACOVIGILANCE

- Definition According to the CIOMS/WHO Working Group on Vaccine Pharmacovigilance, Vaccine pharmacovigilance is defined as “the science and activities relating to the
- Detection
- Assessment
- Understanding and
- Communication of adverse events following immunization and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization”

SPECIAL CONSIDERATIONS FOR AEFI SURVEILLANCE

- Training of healthcare workers
  - Health workers administering vaccinations are on the frontlines and are usually the first responders to an AEFI and AESI
  - They need to be trained how to detect, report, and respond to adverse events, including stabilizing the patient (for example, in a case of anaphylaxis) and communicating with end-users, the community and the media
- Determining causality

SPECIAL CONSIDERATIONS FOR AEFI SURVEILLANCE

- Independent review is needed
- There is a need for independent review of adverse events, separate from the immunization programme
- Causality assessment requires a team of investigators, including an immunologist or other experts, depending on the nature of the adverse event
- The team usually does not directly include officials from the NIP
- They may be perceived to have a conflict of interest as they are responsible for investigating adverse events related to administration of a vaccine

VACCINE REGULATIONS

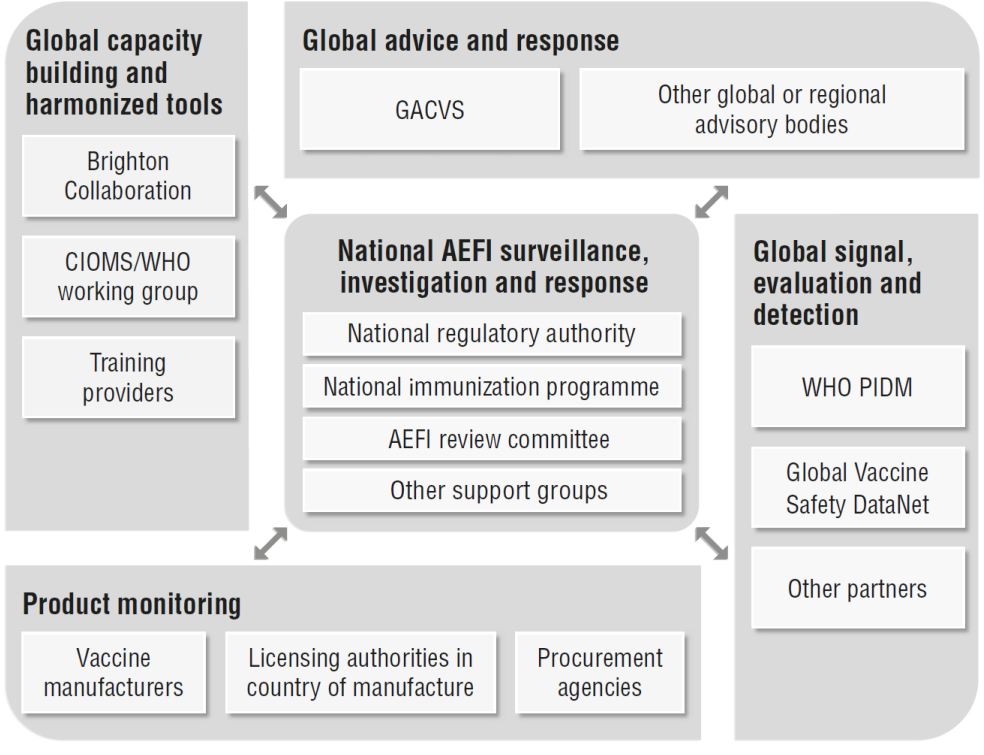
Today vaccine regulation includes a range of functions that cover the entire continuum of vaccine development, licensure, and use

Regulatory bodies

National level

International level

Components of a 21st Century global vaccine safety monitoring, investigation, and response system.



SOUTH AFRICA

- The South African Health Products Regulatory Authority (SAHPRA) is the National Regulatory Authority
  - Oversees the safety, efficacy and quality of all medicines registered in South Africa, including vaccines
- The National Department of Health Expanded Programme on Immunisation (EPI)
  - Responsible for the COVID-19 vaccination programme, and therefore collaborates with SAHPRA to oversee vaccine safety monitoring and reporting of adverse events following immunisation (AEFIs) throughout the country.
- Passive surveillance
  - The public and health professionals are encouraged to report AEFIs to the health facility delivering the vaccine, on the Med Safety App (which can be downloaded from App Stores for Android and iOS phones), or by calling the COVID-19 hotline on 0800 029 999
- National Immunization Safety Expert Committee (NISEC)
  - Conduct causality assessment

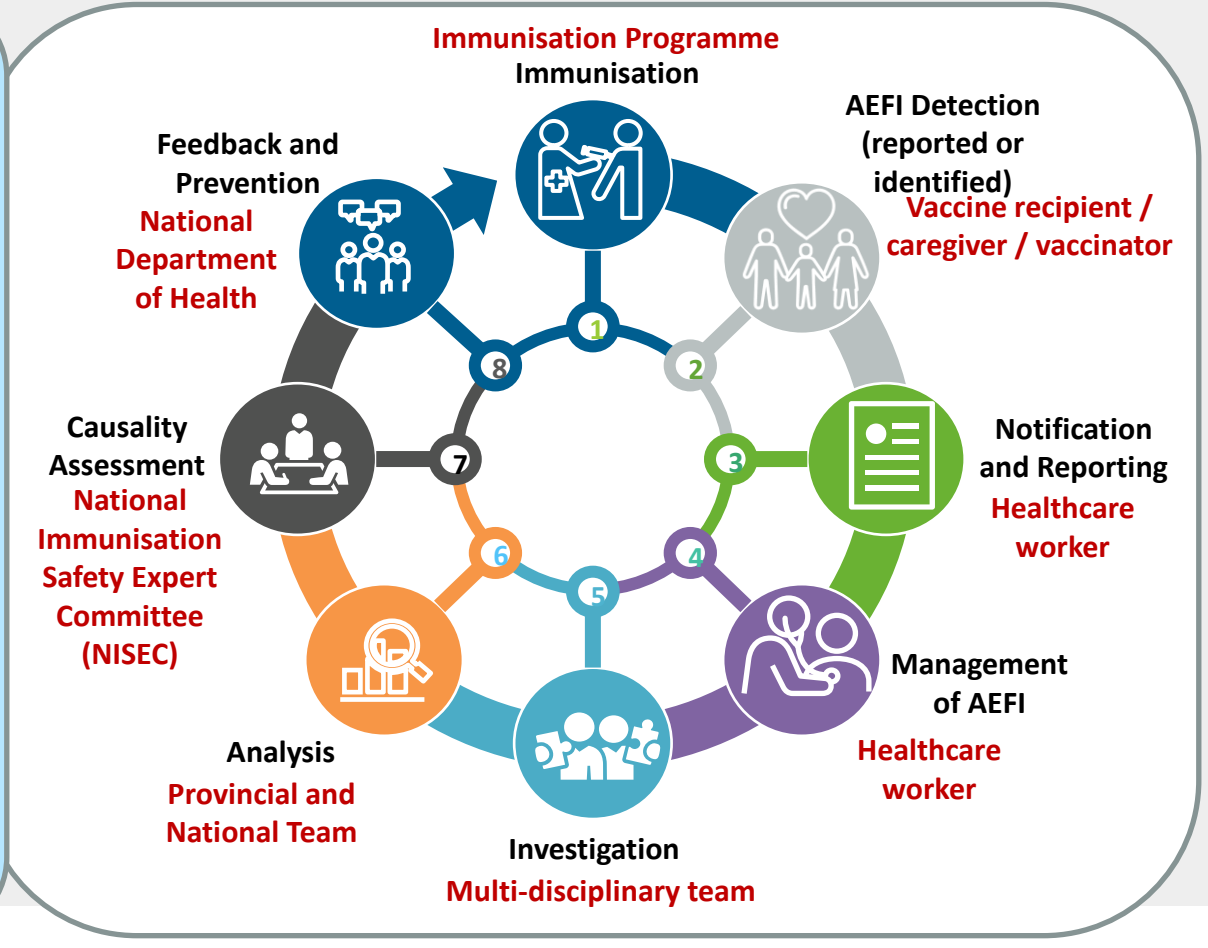
Vaccine Manufacturing Industry

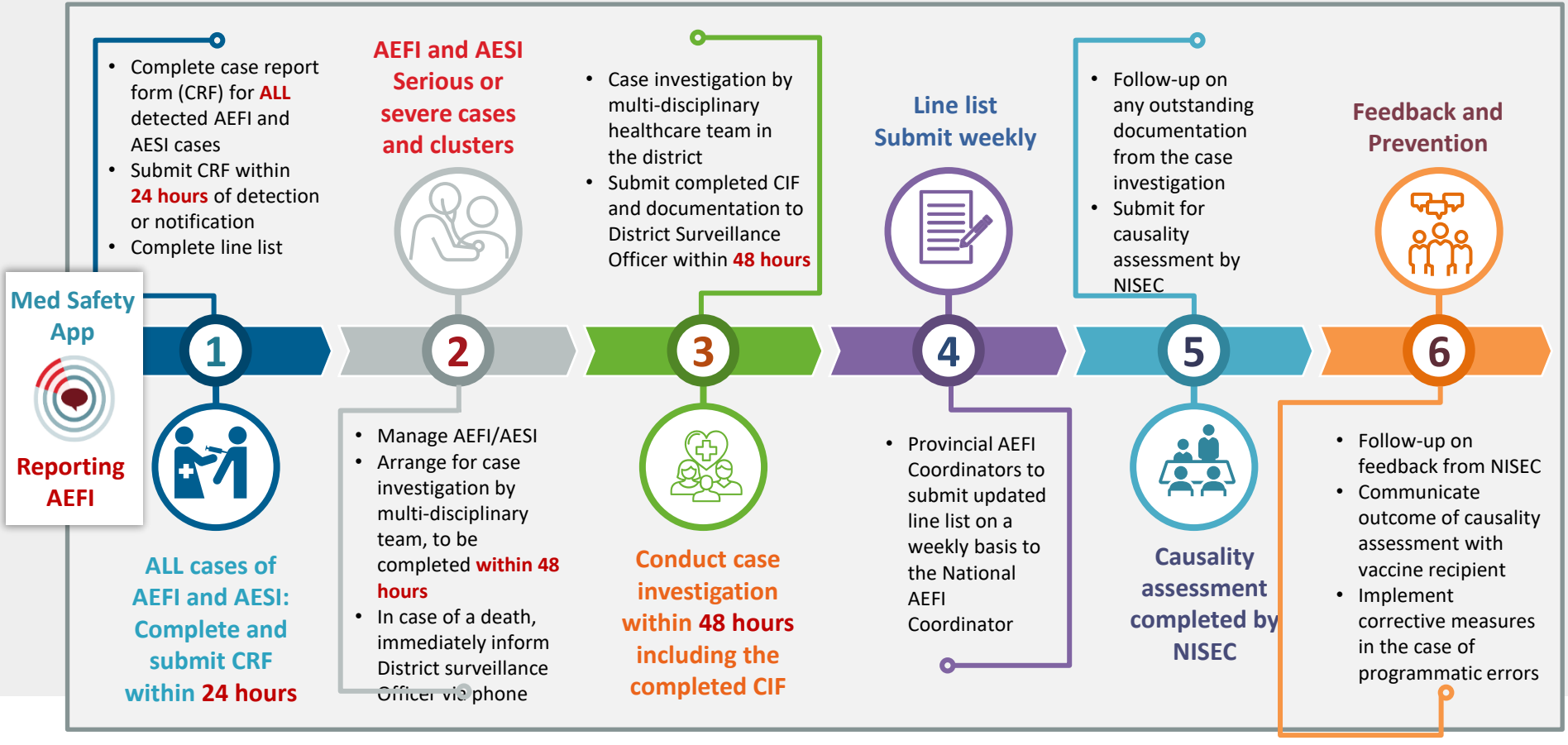
South African Health Products Regulatory Authority (SAHPRA)

National Department of Health (NDoH)

World Health Organization (WHO)

Ministerial Advisory Committees on Vaccines and Immunisation




Med Safety App
Reporting AEFI
1
ALL cases of AEFI and AESI: Complete and submit CRF within 24 hours
• Complete case report form (CRF) for ALL detected AEFI and AESI cases
• Submit CRF within 24 hours of detection or notification
• Complete line list
AEFI and AESI Serious or severe cases and clusters
2
• Manage AEFI/AESI
• Arrange for case investigation by multi-disciplinary team, to be completed within 48 hours
• In case of a death, immediately inform District surveillance Officer via phone
3
Conduct case investigation within 48 hours including the completed CIF
• Case investigation by multi-disciplinary healthcare team in the district
• Submit completed CIF and documentation to District Surveillance Officer within 48 hours
Line list Submit weekly
4
• Provincial AEFI Coordinators to submit updated line list on a weekly basis to the National AEFI Coordinator
5
Causality assessment completed by NISEC
• Follow-up on any outstanding documentation from the case investigation
• Submit for causality assessment by NISEC
Feedback and Prevention
6
• Follow-up on feedback from NISEC
• Communicate outcome of causality assessment with vaccine recipient
• Implement corrective measures in the case of programmatic errors

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