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A REVIEW ON VACCINE SAFETY SURVEILLANCE IN PHARMACOVIGILANCE

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ABSTRACT

COVID-19 vaccines are the most important tool to stem the pandemic. They are being developed with unprecedented global collaboration and accelerated timelines to achieve regulatory pathways through national regulatory authorities, alongside preparations to ensure equitable access to the vaccines among people globally, preparations must be made within countries for COVID-19 vaccines safety surveillance on an urgent basis. Safety surveillance must be capable of investigating adverse events of special interest (AESI) and adverse events following immunization to determine a change in the benefit-risk profile of the vaccine, and to be able to anticipate coincidental events that might be attributed to the vaccine.

INTRODUCTION

There are currently no population-based systems in the united states to rapidly detect adverse events after newly introduced vaccines. To evaluate the feasibility of developing such systems, we used 5 years of data from 4 health maintenance organizations within the Centers for Disease Control and Prevention (CDC) vaccine safety Data link

Vaccine Safety Surveillance

Definition:- According to the Council for International organizations of medical sciences(CIOM)/WHO working group on Vaccine pharmacovigilance. Vaccine Pharmacovigilance is defined as the science and activities relating to the Detection, Assessment, Understanding, communication of adverse events following immunization-related issues, and to the prevention of untoward effect of the vaccine or immunization

- It is defined as a passive surveillance on un solicilated reports of adverse events that are sent to a central database (or) health authority
- In the united states these are received and entered in to the vaccine adverse events reporting system (AAERs) co-managed by FDA and CDC

Safety Surveillance

The science and activites relating to the Detection Assessment Understanding and prevention of adverse effect or any other drug-relating problems.

Importance of Vaccine Safety

- Decreases in disease risk and increased defensive on vaccine risks.
- Public confidence in vaccine safety is critical.
- Low tolerance for vaccine risks

Higher standard of safety is expected
Vaccines are generally healthy

Lower risk tolerance need to search for rare reaction

Vaccine Pharmacovigilance

Vaccine pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding, prevention and communication of adverse events following immunization (or) of any other vaccine (or) immunization related issues.

Steps of vaccine pharmacovigilance

i) Detect signal suggesting AEF(Adverse events following immunization) is related to vaccine.
ii) Develop hypothesis about causal association between an AEFI and vaccination Test hypothesis through appropriate epidemiological method.

Pharmacovigilance

- An active surveillance system to proactively identify risks for adverse events.
- It is now an integral part of the regulation of drug and vaccine safety.
- Pharmacovigilance requires that incidents of adverse events are followed up in the correct way.

Vaccine provide by government of India

Government of India is providing vaccination to prevent vaccine preventable disease (VPDs) namely,

A. DIPHTHERIA
B. PERTUSSIS
C. TETANUS
D. POLIO
E. MEASLES
F. HEPATITIS B
G. BCG
H. JE VACCINATION
I. HIB (given as penta valent containing Hib+DPT+HEP)

Other Vaccines……..
a) Pneumococcal vaccine
b) Rotavirus vaccine
c) Hepatitis A
d) MMR
e) Influenza
f) Meningococcal
g) Cholera
h) HPV
i) Varicella
j) Typhoid

Source of Vaccine Safety

- ❖ Local health workers
- ❖ Health education campaigns
- ❖ Visiting experts
- ❖ Online resources and communication network
- ❖ Religious and or community leader
- ❖ Parents, guardians and vaccine
- ❖ Radio and television
- ❖ Printed material
- ❖ Video or DVD

Classification of AEFIs

The adverse event may be any unfavorable or unintended sign, abnormal laboratory findings, symptoms or disease.

1) Vaccine product –Related reaction

An AEFI that is caused or precipitated by vaccine that is due to one or more quality defects of the vaccine product inducing its administration device as provide by the manufacturer.

Example:- failure by the manufacturer to completely inactivate a lot of inactivated polio vaccine leads to cause of paralytic polio.

2) Immunization error – Related reaction

An AEFI from anxiety about the immunization

Example:-Vasovagal syncope in an adolescent following vaccination.

3) Coincident event

An AEFI that is caused by something other than the vaccine product immunization error or immunization anxiety.

Example:- A fever after vaccination (temporal association) and, malarial parasite isolated from blood.

AEFI frequency terminology

Very common	>1/10	>10%
Common(frequent)	>1/100 and <1/10	>1%and <10%
Uncommon(infrequent)	>1/1000and <1/100	>0.1 %and <1%
Rare	>1/10000 and <1/1000	>0.001% and<0.1%
Very rare	<1/10000	<0.01%

Which AEFIs should be reported?

- Serious AEFI.
- Signal and events associated with newly introduced vaccine.
- AEFI that may have been caused by an immunization error.
- Significant events of unexplained cause occurring within 30 days after a vaccination.
- Event causing significant parental or community concern.
- Swelling, redness, soreness at the injection site if it lasts for more than 3 days or swelling extended beyond nearest joint.

Adverse event following immunization (AEFI)

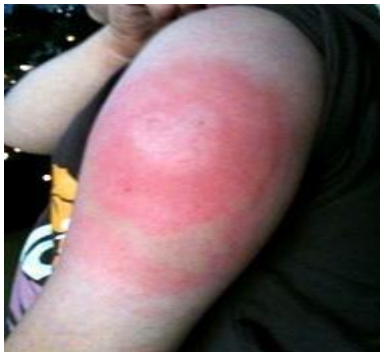
Definition: An AEFI is any untoward medical occurrence which follows immunization and which does not necessarily have a caused relationship with the usage of the vaccine.

Two types of vaccine reaction

i) Minor reaction
ii) Severe reaction

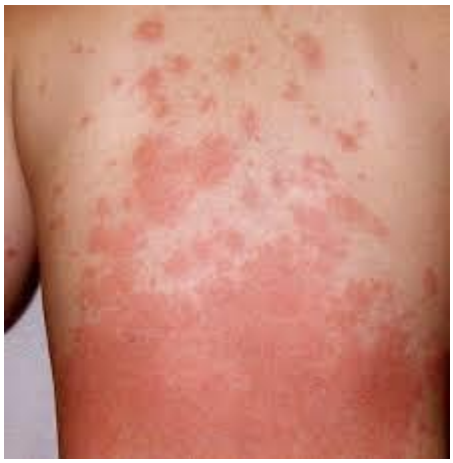
MINOR REACTION

- ➢ Usually occur within a few hours of injection.
- ➢ Resolve after short period of time and pose little danger.
- ➢ Local (includes pain swelling or redness at the site of injection).
- ➢ Systemic (includes fever, malaise, muscle pain, headache or loss of appetite)



Severe reaction

- ❖ Usually do not result in long-term problems.
- ❖ Can be disabling.
- ❖ Are rarely lives threatening.
- ❖ Include seizures and allergic reaction caused by the body's reaction to a particular component in a vaccine.



Vaccine Evaluation

I) Pre-licensing

Randomized, blinded, controlled clinical trails

II) Vaccine efficacy

Protective effect under ideal conditions

RTC: controlled experiment, simple interpretation

III) Post-licensing

Observational studies

IV) Vaccine effectiveness

Protective effect under ordinary conditions of a public health programme prone to bias more complex interpretation.

Basic calculation of vaccine evaluation

Vaccinated

o o o o o o o o o o → lu=2/10=0.2

o o o o o → o o o o o

Unvaccinated

o o o o o o o o o o → lu=9/10=0.9

o o o o o → o o o o o

VE =0.9 – 0.2 =78%

0.9

VE(%)=AEU-ARV/ARU).100

Precautions

- ➢ A condition in a recipient which may increase the chance or severity of an adverse event,(or)
- ➢ May compromise the ability of the vaccine to produce immunity

Safety surveillance of COVID-19 mRNA vaccines through the vaccine safety data link Vaccines represent one of the greatest public health achievement of modern medicine. They must pass rigorous and predetermined efficacy and safety metrics prior to licensure. Additionally, post marketing safety surveillance is essential to detect rare or severe vaccine-associated adverse events, particularly because of the large number of individuals exposed.

A primary method for post marketing vaccine safety surveillance is voluntary reporting through the vaccine adverse event reporting through the vaccine adverse event reporting system (VAERS), co-sponsored by the centers for disease control and prevention (CDC) and the food and drug administration (FDA). However, voluntary reporting has limitations, such as case under reporting. The sensitivity of VAERS for capturing anaphylaxis ranged from 13% to 76% and guillain-barre syndrome from 12% to 64% for different vaccines. Additional concerns with VAERS data include challenges with determination of causality between the vaccine and the reported event and the lack of a comparison group to assess excess vs. baseline risk in a given population. A 2011 report from the institute of medicine found in-adequate evidence to accept or reject a causal relationship for 85% of vaccine-adverse event pairings studied.

People in the US have received more than 342million doses of covid-19 vaccines, with the vast majority being mRNA vaccines from Pfizer-Biotech or Moderna. In the study by Klein et al, mRNA COVID-19 vaccines were safe for the population overall (i.e., there was no difference for any of the serious outcomes assessed), but an excess risk of Myocarditis/pericardities was identified for vaccines aged 12 to 39 years.

Anaphylaxis after mRNA vaccination was rare additional monitoring by VSD will continue to assess for clinically relevant adverse events associated with mRNA vaccination, including following booster doses. Support for collaborations like VSD, which include detailed data on large and diverse populations, is essential for on large and diverse population, is essential for robust vaccine safety assessments to inform the public and help overcome vaccine hesitancy, particularly in pandemic situations when large-scale vaccination is critical and

very large number of individuals are ex-posed to new vaccine.

Planning for covid-19 vaccines safety surveillance

COVID-19 vaccines are the most important tool to stem the pandemic. They are being developed with unprecedented global collaboration and accelerated timelines to achieve WHO emergency use listing, while using regulatory pathways through national regulatory authorities, alongside preparations to ensure equitable access to the vaccines among people globally, preparations must be made within countries for COVID-19 vaccines safety surveillance on an urgent basis. Safety surveillance must be capable of investigating adverse events following immunization to determine a change in the benefit-risk profile of the vaccine, and to be able to anticipate coincidental events that might be attributed to the vaccine.

The corona virus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome corona virus 2(SARS-COV-2), has led to over 13million cases. COVID-19 vaccines development is occurring with unprecedented speed. This is partially due to the coalition for epidemic preparedness innovations (CEPI)

CEPI, formed in 2017, is a novel partnership between private, public, philanthropic and civil society organizations. It aims to develop vaccines for future epidemics. CEPI is mandated to accelerate the development and manufacture of vaccines against previously unknown pathogens with 16 weeks from identification of antigen to vaccine candidate release for clinical trials.

- CEPI has announced the initiation of nine COVID-19 vaccine programs
- Rapid response platforms for vaccine development supported by CEPI are being utilized.
- Platform technology use systems with the same basic components as a backbone and insert new protein or genetic sequences to adapt for use against different pathogens.
- The vaccine candidates include a DNA vaccine candidates (administered with eletroporation), a molecular-clamp vaccine (synthesis of viral surface proteins, which attach to host.
- During infection and clamps them into shape, so that the immune system can recognize them as the correct antigen); recombinant protein nanoparticle technology to generate antigens derived from the coronaviruse spike(S) protein (proprietary saponon - based adjuvant); a recombinant protein vaccine with the S trimmer, a replication-deficient simian adenoviral vaccine (chAdox 1-5); a live-attenuated influenza vaccine and two mRNA vaccine. A pandemic vaccine adjuvant will be available to enhance development

There are currently 21 COVID-19 vaccines candidates in clinical trials, including four funded by CEPI (including the mRNA (the first to enter clinical trials, co-developed with the national institute of allergy and infectious diseases (NIAID), USA) DNA, chAdox1-s and protein submit vaccine) as shows the candidates in preclinical development COVID-19 vaccine candidates in preclinical development COVID-19 vaccine candidates in clinical development (21 as of june 29,2020)

COVID-19 vaccine candidates in pre-clinical development (estimated to be 182 as of June 29, 2020)

Most vaccine candidates are targeting the SARS-COV spike(S) protein, displayed on the virus surface, which is composed of two submits, the S1 submit contains a receptor-binding domin (RBD) that binds with the host cell receptor angiotensin-converting enzyme 2(ACE2),S protein priming occurs through the serine protease TMPRSS2 (to cleave S protein at S1/S2) and fusing of the viral and host membranes occurs through the S2 submit.[18]

Different COVID-19 vaccines

Types of vaccines available updated Dec 14 2021 CDC (centers for disease control and prevention) has updated it's recommendations for COVID-19 vaccines with a preference for people to receive an mRNA COVID-19 vaccine (Pfizer-BioNTech and moderna)

Different types of COVID-19 vaccine are available

COVID-19 vaccines are now widely available for people ages 5 years and older. In most cases, you do not need an appointment. So you can get vaccinated as soon as possible.

All currently approved or authorized COVID-19 vaccines are safe and effective and of severe illness. CDC does not recommend one vaccine over another.

i. Vaccine brand name: Pfizer-bioNTech
ii. Ages recommended: 5+ years old
iii. Primary series : 2-doses given -3-weeks (21 days) a part
iv. Booster dose

Everyone ages 16 years and older is eligible at least 6 months after the dose in their primary series for people ages 18 years and older any of the three COVID-19 vaccines can be used for the booster dose. Teens 16-17 years old can only get a Pfizer-bioNTech covid-19 vaccine booster.

v. When fully vaccinated: 2-weeks after 2nd dose

A. Vaccine brand name: Moderna
B. Ages recommended:18+ years old
C. Primary series: 2 doses given 4 weeks (28 days) a part
D. Booster dose

Everyone ages 18 years and older is eligible at least 6 months after the last dose in their primary series. Any of the three COVID-19 vaccine can be used for the booster dose.

E. When fully vaccinated: 2 weeks after 2nd dose

i. Vaccine brand name: Johnson and Johnson's Janssen
ii. Ages recommended: 18+ years old
iii. Primary series:1 dose
iv. Booster dose
At least 2 months after first dose in all people ages 18 years and older. Any of the three COVID-19 vaccines can be used for the booster dose.
v. When fully vaccinated: 2 weeks after 1st dose
If you had a severe allergic reaction after a previous dose or if you have a known (diagnosed) allergy to a COVID-19 vaccine ingredient, you should not get that vaccine.
If you have been instructed not to get one type of COVID-19 vaccine, you may still be able to get another type.
You should get your second shot as close to the recommended 3-week or 4-week interval as possible.

COVID-19 Vaccine Reporting System
Vaccine reporting system updated November 15, 2021 Hundreds of millions of people in the United States have safely received COVID-19 vaccination. These vaccines have undergone the most intensive safety monitoring in US. History that includes both established and new safety monitoring system.

Safety of COVID-19 vaccines
The U.S food and drug administration (FDA) has fully approved the use of the Pfizer-BioNTech COVID-19 vaccine vaccine in people ages 16 years and older and has authorized its emergency use for children ages 5 years and older. The FDA has granted for the Moderna COVID-19 vaccine and the janssen (jhonson and Johnson) COVID-19 vaccine for people ages 18 years and older. The Pfizer-BioNTech moderna, and janssen (Johnson and Johnson) vaccines have been shown to be safe and effective in clinical trials. The trials showed that the known and potential risks and benefits of COVID-19 vaccines outweigh the known and potential risks of becoming infected with COVID-19.

COVID-19 vaccine effectiveness research
The U.S food and drug administration (FDA) has fully approved the use of the Pfizer-BioNTech COVID-19 vaccine in people ages 16 years and older and has authorized its emergency use for children ages 5years and older. The FDA has granted for the Moderna COVID-19 vaccine and the Janssen (Johnson and Johnson) COVID-19 vaccine for people ages 18 years and older. The Pfizer-BioNTech moderna, and Janseen (Johnson and Johnson) vaccines have been shown to be safe and effective in clinical trials.

Before the USFDA approves a vaccine or authorizes a vaccine for emergency use, clinical trials are conducted to determine vaccine effectiveness

- After FDA approves vaccine or authorizes a vaccine for emergency use CDC and other federal parents continue to assess the vaccine to determine, now well it works under real world conditions
- Perform in specific subpopulations
- Reduce the risk of infection (including infection without symptoms)
- Prevent more serious outcomes, including hospitalization
- Protect against changes in the virus (new variants)

Vaccine safety monitoring
After a vaccine authorized or approved for use, vaccine safety surveillance system monitor adverse events and watch for potential safety problems.
- FDA's also includes important recommendation for ongoing to safety evaluation after any COVID-19 vaccine is made available under EUA
- CDC has explained safety surveillance through new system and additional information sources, as well as by scaling up existing safety monitoring system.

PHARMACOVIGILANCE METHODS

Objective
- To establish a functional reporting system to monitor the safety of all medicines
- To learn more about the safety profile of new medicine in the early post-marketing phase
- To learn more about the ADR profile of a specific medicine(S) in your population
- To estimate the incidence of a known ADR to a specific medicine in your population
- To make use of existing electronic health records and registries to support pharmacovigilance activities

Methods
i) Passive surveillance
ii) Spontaneous reports
iii) Case series
iv) Stimulating reporting
v) Active surveillance
vi) Sentinel sites
vii) Drug event monitoring
viii) Registries
ix) Targeted clinical investigations
x) Comparative observational studies
xi) Cross sectional study
xii) Case control study
xiii) Cohort study
Descriptive studies
Natural history of disease, drug utilization study

Spontaneous reports
A communication by consumers or healthcare professional to a company or regulatory authority, that describes one or more ADR in a patient, who has given the drug
It plays a major role in the, identification of safety signals once the drug is marketed.
Gives alerts on rare AEs that were not detected in earlier clinical trials or pre-marketing studies

Case series

➢ Series of case reports can provide evidence of an association of a drug and AEs

➢ Generally, More useful for generating hypothesis than for verifying an association between drug exposure and outcome

➢ Certain distinct adverse events occurs more frequently with drug therapy, such as anaphylaxis, a plastic anemia and Stevens-Johnson syndrome events such as these are spontaneously reported for detailed and rapid follow-up.

Stimulated Reporting

➢A method used to encourage and facilitate reporting by health professionals for new product, or for a limited period.

➢ Online reporting of AE, systematic stimulation of reporting of AEs.

➢Drawbacks- data are often incomplete.

Not useful to generate accurate incidence rates.

Active surveillance

➢ To ascertain completely the no. of AEs via a continuous pre-organized process.

E.g. follow up of patient treated with a particular drug.

➢ More feasible to get comprehensive data on individual AE reports.

Sentinel Sites:- Active surveillance carried out at Institutions, Nursing Homes and Hospitals etc. provides information such as data from specific patient subgroups, drug abuse etc.

Drug Event Monitoring

Patients are identified by electronic prescription data or automated health insurance claims. A follow up questionnaire can be sent to each physician or patient at specified intervals. Information on patient demographics, indication for treatment, Duration of therapy, dosage, clinical events, and reasons for discontinuation can be included in the questionnaire.

Communication Process

Principles of Good Pharmacovigilance Communication

✓ Relate the messages to the audience's perspective
✓ Avoid comparisons which trivialize the concern
✓ Ensure completeness of the message
✓ Be balanced, honest and sympathetic
✓ Focus on the specific issue that needs to be handled
✓ Pay attention to what the audience already knows
✓ Be respectful of people's right to be concerned
✓ Be honest about the limits to scientific knowledge
✓ Acknowledge uncertainty
✓ Evaluate the impact of your message

CONCLUSION

The availability of new and underutilized vaccines against Hib, rota-virus, pneumococcal meningococcal and human papilloma virus provide an opportunity to increase the impact of immunization activities in terms of prevented morbidity and mortality and represents substantial health benefits for populations of all ages.

- Getting vaccinated against COVID-19 can lower your risk of getting and spreading the virus that causes COVID-19 vaccines can also help prevent serious illness and death. All steps have been taken to ensure that vaccines are safe and effective for people ages 5 years and older.
- Real-time surveillance combining dynamic data files, aggregation of data, and sequential analysis methods offers a useful and highly adaptable approach to early detection of adverse events after the introduction of new vaccines.

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