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SAFETY SURVILLANCE & IMPLIMENTATION OF STRATEGIES FOR SAFE & QUALITY USE OF VACCINES

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Abstract:

Despite the appreciable efforts by government, immunization programs of India are not able to achieve its target, but also lagging behind to achieve immunization coverage as par with the global immunization coverage of 85%. It is important to understand the knowledge attitude and practice of parents towards immunization of their children and develop and implement suitable strategies to improve the immunization coverage. The strategies can vary based on the culture and education of the population. In this study, we observed that personalized education to the parents is very useful in complete immunization schedule. To promote safe and quality use of vaccines, starting from cold chain management of vaccine to AEFI reporting, appropriate educational interventions are necessary. HCPs communication can help any parents to gain confidence on vaccination, which leads to a successful immunization program of a country. Inadequate knowledge about reporting process, lack of time and interest were the identified challenges contribute to low reporting rate by spontaneous reporting method. Awareness and sensitization on identification and reporting of AEFIs is essential depending on the role played by each HCP on the immunization process.

Keywords: *Immunization programs, Safety Survillance, Quality use of Vaccines.*

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INTRODUCTION [1-3]:

VACCINES

Vaccines are biological substances, which produce and enhance immunity to a particular VPD. A vaccine contains an antigen, which may be a disease-causing microorganism / virus, or a subunit of it. Vaccines are made from either live attenuated or inactivated forms of the microbe / virus, or from its toxin or one of its surface proteins. Vaccines may be monovalent or polyvalent. Monovalent vaccine has a single strain of a single antigen /immunogen whereas a polyvalent vaccine contains two or more strains/serotypes of the same antigen/ immunogen. Two or more different antigens are present in combined vaccines. Combined vaccines significantly decrease the health care expenditures and increase the rate of completion of vaccination schedule.

Classification of Vaccines:

There are different types of vaccines available, such as: live attenuated, inactivated subunit and toxoid vaccines. The different characteristics of these vaccines determine mechanism by which the vaccines work.

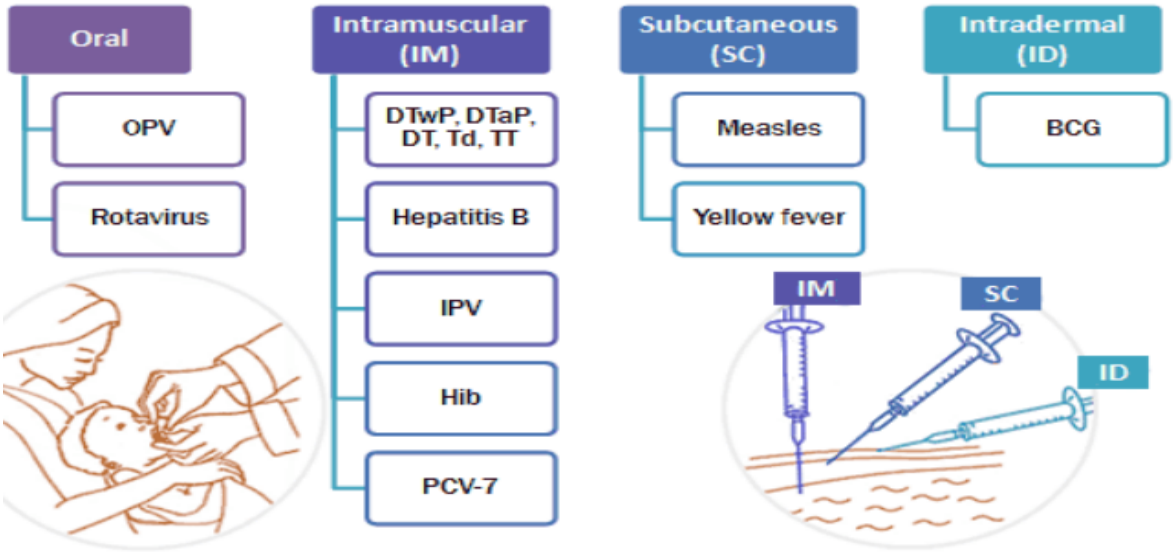

Figure 1: Route of administration of various vaccines

IMMUNIZATION PROGRAMS [4-7]:

History of global immunization programs:

Dr. Edward Jenner introduced modern concept of vaccination in 1796. He used matter from cowpox pustules to inoculate patients against smallpox, which is caused due to related virus. Most of the vaccines were developed during 20th century and currently vaccines against 27 VPDs are available and many are in pipeline.

WHO Launched EPI in 1974, after the success of smallpox eradication program. Initially the goal of EPI was to ensure that every child globally should receive protection against six diseases such as tuberculosis, polio, diphtheria, pertussis, tetanus and measles by the time they were two years of age and give tetanus toxoid injection to all pregnant woman to protect them and their newborn against tetanus. By 1990, EPI protected 80% of the children globally against six main diseases and newly introduced vaccines were added to the EPI in many countries. Global Alliance for Vaccines and Immunization (GAVI) was created in 1999, to extend the reach of EPI and help the poorest countries to introduce new vaccines to their national immunization programs. The number of vaccines in the immunization programs vary from country to country; however few vaccines are common in most of the countries in the world; diphtheria, pertussis, tetanus, poliomyelitis, Hepatitis B and measles.

Immunization program in India:

India introduced EPI program in the year 1978 with only four vaccines (BCG, DTP, OPV, typhoid), but the access was limited to urban areas. The program was re-introduced in 1985 under the banner of UIP and expanded the reach to the entire country and added one more vaccine measles. In spite of all positive changes, there are some ongoing challenges and short- coming in the programme. NIP of India has only nine vaccines [BCG, Hepatitis B (HepB), OPV, Pentavac(DPT+HepB+ Hemophilus Influenza), Inactived Polio Vaccine (IPV),DPT, Tetanus Toxoid (TT), Measles-

Rubella (MR), Japanese Encephalitis (JE) & Rotavirus vaccine (in selected regions)]. The National Immunization Schedule (NIS).

Implementation of routine immunization programs:
Routine Immunization (RI) in India targets 26 million newborn, 100 million children of 1-5 years of age and 30 million pregnant women each year. To vaccinate this cohort of 150 million, 9 million immunization sessions are conducted majorly at village level. Large networks of 27,000 cold chain points are created to ensure the delivery of potent and
safe vaccination to the beneficiaries.

Implementation of mass immunization programs:
Mass immunization programs involve delivering immunizations to a large population at one or more locations in a short interval of time. Pulse Polio immunization program is an example of the mass campaigns at India and provided two doses of vaccines to the entire children less than five years of age irrespective of their vaccination status. The
program was so successful and WHO declared India as polio free country in the year 2014 with the last reported case of wild polio in the year 2008 from West Bengal.

Table 1. NIS for pregnant woman, infants and children:

Vaccine	When to give	Dose	Route	Site
For Pregnant Woman				
TT-1	Early in pregnancy	0.5 ml	IM	Upper Arm
TT-2	4 weeks after TT-1*	0.5 ml	IM	Upper Arm
TT- Booster	If received 2 TT doses within the last 3 years*	0.5 ml	IM	Upper Arm
For Infants				
BCG	At birth or as early as possible till one year of age	0.1ml	ID	Left Upper Arm
Hepatitis B - Birth dose	At birth or as early as possible within 24 hours	0.5 ml	IM	Antero-lateral side of mid-thigh
OPV-0	At birth or as early as possible within the first 15 days	2 drops	Oral	Oral
OPV 1, 2 & 3	At 6 weeks, 10 weeks & 14 weeks (OPV can be given till 5 years of age	2 drops	Oral	Oral
Pentavalent 1,2&3	At 6 weeks, 10 weeks & 14 weeks	0.5 ml	IM	Antero-lateral side of mid-thigh
Rotavirus#	At 6 weeks, 10 weeks & 14 weeks (can be given till one year of age)	5 drops	Oral	Oral
IPV	Two fractional dose at 6 and 14 weeks of age	0.1 ml	ID	ID Right upper arm
Measles/ MR 1st Dose$	9 completed months-12 months.	0.5 ml	SC	Right Upper arm
JE-1**	9 completed months-12 months	0.5 ml	SC	left Upper arm
Vitamin A (1st Dose)	At 9 completed months with measles and Rubella	1 ml (1 lakh unit)	Oral	oral
For Children				
DTP Booster - 1	16-24 months	0.5ml	IM	Antero-lateral side of mid-thigh
Measles/ MR	16-24 months	0.5 ml	SC	Right Upper arm

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2nd Dose$				
OPV Booster	16-24 months	2 drops	Oral	Oral
JE -2	16-24 months	0.5 ml	SC	left Upper arm
Vitamin A* (2nd to 9th Dose)**	16-18 months. Then one dose every 6 months up to the age of 5 years	2 ml (2 lakh unit)	Oral	oral
DTP Booster - 2	5-6 Years	0.5ml	IM	Upper arm
TT	10 years and 16 years	0.5ml	IM	Upper arm

Implementation of routine immunization programs:
Routine Immunization (RI) in India targets 26 million newborn, 100 million children of 1-5 years of age and 30 million pregnant women each year. To vaccinate this cohort of 150 million, 9 million immunization sessions are conducted majorly at village level. Large networks of 27,000 cold chain points are created to ensure the delivery of potent and safe vaccination to the beneficiaries.

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Immunization coverage of the country:
In India, 62% of the children receive all basic vaccinations until the age of 2 years and the coverage was high for BCG vaccine (92%) and lowest was 3rd dose of polio vaccine, (73%). Total 6% children are left out unimmunized. Vaccination coverage in India was increased with increase in the education level of mothers, improvement in socio economic status of the family.

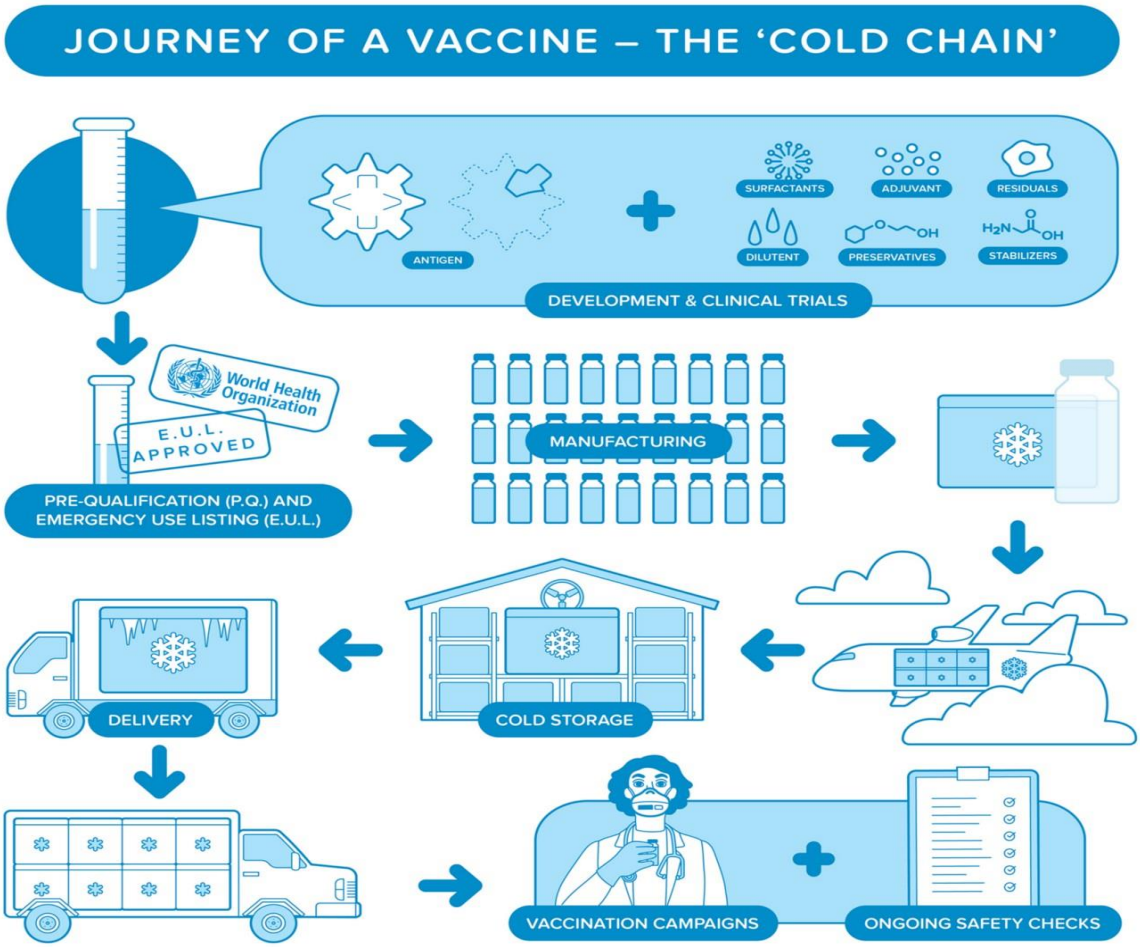
Strategies to improve the safe and quality use of vaccines:
Development of Educational Module:
The educational module was prepared addressing the problems identified in the immunization process (the data from objective III). Extensive literature search was done for preparing the educational module. Key words used for the literature search were quality and safe use of vaccine, vaccine transport, vaccine storage, vaccine administration, adverse events following immunization (AEFIs), monitoring of AEFIs, reporting of AEFIs, problems associated with immunization process, causality assessment of AEFIs, errors made during vaccination using search engines such as Google scholar, Science Direct, PubMed/Medline and Clinical Key. Observations made by the researcher during the visit to the different immunization centers in the city and the knowledge gained by interacting with the experts in the related field was also utilized to prepare the educational module. The module had information on immunization process, which is practically applicable to HCPs in their routine practice. The educational module was subjected to face validity by three subject experts in the related field. The educational material was finalized after discussions and deliberations among the researchers by taking the feedback received from the experts into consideration.

How it's made:
Typically, companies will work independently to complete clinical development plans for a vaccine. Once a vaccine is authorized, manufacturing begins to scale up. The antigen (part of the germ that our immune system reacts to) is weakened or deactivated. To form the full vaccine, all ingredients are combined. The whole process, from preclinical trial to manufacture, can sometimes take over a decade to complete. In the search for a COVID-19 vaccine, researchers and developers are working on several different phases in parallel, to speed up results. It is the scale of the financial and political commitments to the development of a vaccine that has allowed this accelerated development to take place. Also, nations and international health organizations are working together through COVAX to invest in development capacity upfront to streamline the process, as well as to ensure equitable distribution of vaccines.

Safe and quality use of vaccines:
Vaccines used in NIPs are considered safe and effective when used appropriately. Immunization quality and safety surveillance has become as important as the efficacy of the national VPD programs. To achieve the quality and safe use of vaccines, we need to consider the following factors such a transportation and storage of vaccines, safe administration of vaccines, safe disposal of immunization waste, monitoring and reporting of AEFIs.

How it's packaged:
Once the vaccine has been made in bulk quantities', it is bottled in glass vials and then carefully packaged for safe cold storage and transport.

Vaccine packaging must be able to withstand extreme temperatures, as well as the risks involved in being transported globally. Therefore, vaccine vials are most commonly made from glass, as it is durable and able to maintain its integrity in extreme temperatures.



How it's stored:
When a vaccine is too hot or too cold, it becomes less effective or even inactive. If stored at the incorrect temperature, vaccines can be ruined or unsafe for use. Most vaccines require refrigerated storage at between 2 and 8 °C. Some vaccines require temperatures as cold as -20°C. Some of the newer vaccines need to be kept ultra cold at -70°C. For frozen vaccines some of them can be safely stored for a limited time between 2 and 8°C. Regular refrigerators cannot maintain an even temperature consistently, so specialized medical refrigerators are required for these precious products.

How it's shipped:
To maintain this cold chain, vaccines are shipped using specialized equipment that does not compromise the integrity of the product. Once shipments land in the destination country, refrigerated lorries transport the vaccines from the airport to the warehouse cold room. From there, portable iceboxes are used to transport vaccines from the cold room to regional centres where they're stored in refrigerators. If vaccination takes place outside of the regional facility, the final step often requires portable iceboxes to transport the goods to local areas for vaccination campaigns. New technologies have invented some portable devices that can keep vaccines at ther cold temperature for several days without needing electricity.

Quality control:
Once vaccines start being administered, national authorities and WHO constantly monitor for — and establish the severity of — any possible adverse side effects and responses from people who have received the vaccine. The safety of the vaccine is paramount, with regular assessments post-approval clinical studies to report on its safety and effectiveness. Studies are often conducted to determine how long a given vaccine remains protective.

ROLE OF IEC IN CLINICAL TRIALS FOR VACCINES [8-12]:

A vaccine is a biological preparation that provides active acquired immunity to a particular infectious disease. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins, or one of its surface proteins.

As per the WHO definition, a clinical trial is any research study that prospectively assigns human participants to one or more health related interventions to evaluate the effects on health outcome.

Ethics are concerned with the distinction between Right and Wrong, with moral choices, duties and obligations.
The four main principles of Biomedical Ethics are:
1. AUTONOMY.
2. NON-MALEFICENCE.
3. BENEFICENCE.
4. JUSTICE.

Institutional Ethics Committee (IEC) is the committee formed of a group of people who go through the research protocol / proposal and state whether or not it is ethically acceptable. 1947– Nuremberg Code of Medical Ethics.
1948– Universal Human Rights – United Nations.
1956– Code of Medical ethics-Medical Council of India
1964– Declaration of Helsinki. Last revision in 2008 at Seoul, Korea by WMA.
1974– Belmont Report by National Commission by US, PHS.
1980– Policy Statement on Ethical Consideration involved in Research on HumanSubjects ICMR.
1982– Proposed International guidelines for Biomedical Research involving Human Subjects-WHO & CIOMS
1991– International Guidelines for Ethical Review in Epidemiological Studies by CIOMS.
1996– ICH – GCP Guidelines.
2001– Directorate of Health Services, Government of India published GCP.
2001– European Union Directive, 2004- revised.
2006– Ethical Guidelines for Biomedical Research on Human Participants published by ICMR.

Composition and responsibilities of IEC:
Institutional Head constitutes an IEC and it is independent, competent and multidisciplinary unit. The number of persons are fairly small [8 – 12].

The IEC appoints from among its members a chairperson who should be from outside the Institution and not head of the same Institution, and the Member Secretary from the same Institution who conducts the business of the committee. Members of IEC are**:**
1. Chairperson.
2. One to two persons from basic medical science**.**
3. One to two clinicians from various Institutes.
4. One legal expert or retired judge.
5. One social scientist/ representative of non-governmental voluntary agency.
6. One philosopher/ ethicist/ theologian.
7. One lay person from the community.
8. Member Secretary.

The Quorum (i.e. the minimum number of people required to conduct a meeting) has 5 persons minimum. As per revised Schedule Y of Drugs & Cosmetics Act, 1940 which is amended in 2005, they should be as :
1. One basic medical scientist (pharmacologist).
2. One clinician3. One legal expert or retired judge.
4. One social scientist/ representative of non-governmental organization/Philosopher/ ethicist/ theologian or a similar person.
5. One lay person from the community

Responsibilities of IEC are to protect the dignity, rights and well-being of the potential research participants, to ensure that universal ethical values and international scientific standards are expressed and to assist in the development and the education of a research community responsive to local health care requirements

Functions of IEC:
IEC's member-secretary screens the research proposals for their completeness and depending on the risk involved categorize them into 3 types 1) Exemption from review for proposals that involve less than minimal risk.
2) Expedited review for more than minimal risk proposals, minor protocol amendments, research on disaster management, and research on material collected during routine patient care like CT scans.
3) Full review for more than minimal risk and that involve vulnerable subjects

The ethical review should be done in formal meetings by all primary reviewers and decision is made only when quorum complete:

- Protection of privacy and confidentiality.
- Plans for data anaiysis and report.
- Patient information sheet and informed consent form in local language.
- Justification for placebo and availability of products after the study.
- Record keeping and archiving

INFORMED CONSENT FORM FROM VOLUNTEERS FOR CLINICAL TRIALS ON VACCINES [12-16]:

What is Informed Consent?

As new medical products are being developed, no one knows for sure how well they will work, or what risks they will find. Clinical trials are used to answer questions such as:

- Are new medical products safe enough to outweigh the risks related to the underlying condition?,
- How should the product be used? (for example, the best dose, frequency, or any special precautions necessary to avoid problems),
- How effective is the medical product at relieving symptoms, treating or curing a condition.

The main purpose of clinical trials is to "study" new medical products in people. It is important for people who are considering participation in a clinical trial to understand their role, as a "subject of research" and not as a patient.

While research subjects may get personal treatment benefit from participating in a clinical trial, they must understand that they:

- may not benefit from the clinical trial,
- may be exposed to unknown risks,
- are entering into a study that may be very different from the standard medical practices that they currently know

To make an informed decision about whether to participate or not in a clinical trial, people need to be informed about:

- what will be done to them,
- how the protocol (plan of research) works,
- what risks or discomforts they may experience,
- participation being a voluntary decision on their part. This information is provided to potential participants through the informed consent process. Informed consent means that the purpose of the research is explained to them, including what their role would be and how the trial will work.
- A central part of the informed consent process is the informed consent document. The Food and Drug Administration (FDA) does not dictate the specific language required for the informed consent document, but does require certain basic elements of consent be included.

Before enrolling in a clinical trial, the following information must be given to each potential research subject:

- A statement explaining that the study involves research.
- An explanation of the purposes of the research.
- The expected length of time for participation.
- A description of all the procedures that will be completed during enrollment on the clinical trial.
- Information about all experimental procedures the will be completed during the clinical trial.
- A description of any predictable risks.
- Any possible discomforts (e.g., injections, frequency of blood test etc.) that could occur as a result of the research.
- Any possible benefits that may be expected from the research.
- Information about any alternative procedures or treatment (if any) that might benefit the research subject.
- A statement describing:
- the confidentiality of information collected during the clinical trial,
- how records that identify the subject will be kept
- the possibility that the FDA may inspect the records.
- For research involving more than minimal risk information including
- an explanation as to whether any compensation or medical treatments are available if injury occurs,
- what they consist of, or
- where more information may be found.
- questions about the research,
- research subjects' rights,
- injury related to the clinical trial.
- Research subject participation is voluntary,
- Research subjects have the right to refuse treatment and will not losing any benefits for which they are entitled,
- Research subjects may choose to stop participation in the clinical trial at any time without losing benefits for which they are entitled.
- Contact information will be provided for answers to:
- A statement that:

When Appropriate, one or more of the following elements of information must also be provided in the informed consent document:

- A statement that the research treatment or procedure may involve unexpected risks (to the subject, unborn baby, if the subject is or may become pregnant).
- Any reasons why the research subject participation may be ended by the clinical trial investigator (e.g., failing to follow the requirements of the trial or changes in lab values that fall outside of the clinical trial limits).
- Added costs to the research subject that may result from participating in the trial.
- The consequence of leaving a trial before it is completed (e.g. if the research and procedures require a slow and organized end of participation).
- A statement that important findings discovered during the clinical trial will be provided to the research subject.
- The approximate number of research subjects that will be enrolled in the study.

A potential research subject must have an opportunity to

- read the consent document,
- ask questions about anything they do not understand.

Usually, if one is considering participating in a clinical trial, he or she may take the consent document home to discuss with family, friend or advocate.
An investigator should only get consent from a potential research subject if:

- enough time was given to the research subject to consider whether or not to participate
- the investigator has not persuaded or influenced the potential research subject.

The information must be in language that is understandable to the research subject.

Informed consent may not include language that:

- the research subject is made to ignore or appear to ignore any of the research subject's legal rights,
- releases or appears to release the investigator, the sponsor, the institution, or its agents from their liability for negligence.

Participating in clinical trials is voluntary. You have the right not to participate, or to end your participation in the clinical trial at any time. Read the informed consent document carefully. Ask questions about any information you don't understand or find confusing.

Clinical Significance in Human Clinical Studies:
Informed consent is mandatory for all clinical trials involving human beings. The consent process must respect the patient's ability to make decisions and adhere the individual hospital rules for clinical studies. Adherence to ethical standards in study design and execution is usually monitored by an Institutional Review Board (IRB). The IRB was established in the United States in 1974 by the National Research Act which called for regulation in human research that was prompted by questionable research tactics used in the Tuskegee syphillis experiments and others. Ethical and safe research standards have been an area of federal and presidential interest since then, with the development of many organizations and task forces since 1974 dedicated to this topic alone. Valid informed consent for research must include three major elements:
(1) disclosure of information,
(2) competency of the patient (or surrogate) to make a decision, and (3) voluntary nature of the decision. US federal regulations require a full, detailed explanation of the study and its potential risks.

What are the benefits of getting vaccinated
Getting vaccinated could save your life. COVID-19 vaccines provide strong protection against serious illness, hospitalization and death. There is also some evidence that being vaccinated will make it less likely that you will pass the virus on to others, which means your decision to get the vaccine also protects those around you.

Even after getting vaccinated, keep taking precautions to protect yourself, family, friends and anyone else you may come into contact with. COVID-19 vaccines are highly effective, but some people will still get ill from COVID-19 after vaccination. There is also still a chance that you could also pass the virus on to others who are not vaccinated. Stay at least 1 metre away from other people, wear a properly fitted mask over your nose and mouth when you can't keep this distance, avoid poorly ventilated places and settings, clean your hands frequently, stay home if unwell and get tested, and stay informed about how much virus is circulating in the areas where you travel, live and work.

Is it safe for me to take the antibiotics after vaccine
There is no known influence or interaction between antibiotics and COVID-19 vaccines. If you are prescribed antibiotics by a health professional before or after your vaccination, you should go ahead and take the full course. However, if you have a

temperature over 38.5 ºC at the time of your vaccination appointment, you should reschedule for when you feel better.

Once I have been vaccinated,can I safely travel internationally:

- You should follow national advice and the advice of the countries you are travelling to and from. Some countries are allowing fully vaccinated people to avoid quarantine and testing on arrival. This is because these individuals are at a lower risk of COVID-19 and are less likely to get infected and pass the virus to others. But even once you are fully vaccinated, continue to practice the same prevention measures – no vaccine is 100% effective, and doing it all helps protect yourself and others. Stay at least 1 metre away from other people, wear a properly fitted mask over your nose and mouth when you can't keep this distance, avoid poorly ventilated places and settings, clean your hands frequently, stay home if unwell and get tested, and stay informed about how much virus is circulating in the areas where you travel, live and work.
- The vaccine stimulates your immune system to protect you from the virus. This process can sometimes cause side effects like fever, chills or headache, but not everyone will experiences any side effect. The presence or magnitude of the reaction you may have vaccination does not predict or reflect your immune response to the vaccine.
- You do not have to have side effects in order to be protected.

Even once you are fully vaccinated, stay at least 1 metre away from other people, wear a properly fitted mask over your nose and mouth when you can't keep this distance, avoid poorly ventilated places and settings, clean your hands frequently, stay home if unwell and get tested, stay informed about how much virus is circulating in the areas where you travel, live and work, and get vaccinated as soon as turn.

CONCLUSION:

All institutions which carry out any form of biomedical research involving human beings should establish an appropriate IEC that is consistent with international and local guidelines and regulations. They must follow ICMR guidelines in India to protect safety and well-being of all participants and should prevent unethical research.

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