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A Comprehensive Review Of "Pharmacovigilance Study of COVID-19 Disease Prevention"

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➢ ABSTRACT:

A pandemic is an outbreak of an infectious illness that has spread across a broad area, such as multiple continents or the entire world, and has affected a huge number of people. According to the World Health Organization, pandemic is the worldwide spread of a new illness. When a novel influenza virus arises and spreads over the world, and most individuals are not immune, an influenza pandemic ensues. Viruses that have produced pandemics in the past have usually come from animal influenza viruses. At Ashoka present whole world is suffering from COVID-19 pandemic disease. Clinical research to find an effective medication against a new corona virus has moved at a breakneck pace. To meet an unmet medical need, the regulations have been made more flexible and convenient, but medication safety reporting has not been relaxed. Because patient safety is the first priority, pharmacovigilance efforts, particularly adverse event reporting, should continue as usual, regardless of clinical trials or clinical practise. The increased exposure to investigational medications with inadequate risk-benefit data necessitates more stringent safety monitoring, accurate adverse event reporting, and early assessment. Causation evaluation will be more difficult due to the current restrictions on physical contact, travel, and free movements, isolation, quarantine, and a large clinical workload during a pandemic. It's probable that not all adverse incidents will be documented in detail, compromising the completeness and quality of safety reports.

➢ Key words:

COVID-19, Pharmacovigilance, Supportive therapy, Naturopathy, Vaccine, Covishield, Covaxine.

➢ INTRODUCTION

A pandemic is an epidemic of an infectious disease that has spread across a large region, for instance multiple continents or worldwide, affecting a substantial number of people. A widespread endemic disease with a stable number of infected people is not a pandemic. Widespread endemic diseases with a stable number of infected people such as recurrences of seasonal influenza are generally excluded as they occur simultaneously in large regions of the globe rather than being spread worldwide. According to WHO a pandemic is the worldwide spread of a new disease. An influenza pandemic occurs when a new influenza virus emerges and spreads around the world, and most people do not have immunity. Viruses that have caused past pandemics typically originated from animal influenza viruses.

History of pandemic diseases in the world**:**

Plague of Athens (430 to 426 BC): During the Peloponnesian War, typhoid fever killed a quarter of the Athenian troops and a quarter of the population. This disease fatally weakened the dominance of Athens, but the sheer virulence of the disease prevented its wider spread; i.e., it killed off its hosts at a rate faster than they could spread it. The exact cause of the plague was unknown for many years. In January 2006, researchers from the University of Athens analysed teeth recovered from a mass grave underneath the city and confirmed the presence of bacteria responsible for typhoid.

World pandemics up to now -

- Antonin Plague (165 to 180 AD)
- Plague of Justinian (541 to 750 AD)
- Black Death (1331 to 1353)
- The 1918-1920 Spanish flu
- Cholera
- Dengue Fever
- Influenza
- Typhus
- Measles
- Yellow fever
- Smallpox [1]
- Covid-19

➢ COVID 19

COVID 19 is Corona virus disease which is defined as illness caused by a novel coronavirus now called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; formerly called 2019-nCoV), which was first identified amid an outbreak of respiratory illness cases in Wuhan City, Hubei Province, China. Coronaviruses are a family of viruses that can cause respiratory illness in humans. They get their name, “corona” from the

many crown-like spikes on the surface of the virus. Severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and the common cold are examples of coronaviruses that cause illness in humans.[2]

Origin of covid-19 -

The initial outbreak in Wuhan, China, the virus and disease were commonly referred to as "coronavirus" and "Wuhan coronavirus", with the disease sometimes called "Wuhan pneumonia". The first human cases of COVID-19, the disease caused by the novel coronavirus causing COVID-19, subsequently named SARS-CoV-2 were first reported by officials in Wuhan City, China, in December 2019. Environmental samples taken from this market in December 2019 tested positive for SARS-CoV-2, further suggesting that the market in Wuhan City was the source of this outbreak or played a role in the initial amplification of the outbreak. The market was closed on 1 January 2020. SARS-CoV-2 was identified in early January and its genetic sequence shared publicly on 11-12 January. The full genetic sequence of SARS-CoV-2 from the early human cases and the sequences of many other virus isolated from human cases from China and all over the world since then show that SARS-CoV-2 has an ecological origin in bat populations.

All available evidence to date suggests that the virus has a natural animal origin and is not a manipulated or constructed virus. Many researchers have been able to look at the genomic features of SARS-CoV-2 and have found that evidence does not support that SARS-CoV-2 is a laboratory construct. If it were a constructed virus, its genomic sequence would show a mix of known elements. All available evidence for COVID-19 suggests that SARS-CoV-2 has a zoonotic source.[3]

- TREATMENT**:**

Supportive therapy to treat Covid 19:

Herbal medicine has played an important role in controlling infectious diseases. Clinical evidence from a range of studies of herbal medicine in the treatment of SARS coronavirus (SARS-CoV) has shown significant results, and supported the idea that herbal medicine has a beneficial effect in the treatment and prevention of epidemic diseases.

In China, the National Health Commission has declared the use of herbal medicine combined with Western medicine as a treatment for COVID-19, and has issued many guidelines on herbal medicine-related therapy. To date, there is much clinical evidence that reports favourable effects of the usage of herbal medicine in the treatment of COVID-19.[4]

Currently, there is no specific treatment for COVID-19. Furthermore, people in the community and researchers are trying to find the best way to cure or prevent the disease, including using herbal medicine. A recent trend in the community is the consumption of herbal medicines containing certain active compounds, which have antimicrobial or antiviral, anti-inflammatory, and immune stimulatory activities, such as Echinacea, quinine, and curcumin. Herbal compounds are assumed to have the capacity to modulate the immune response and, therefore, they are believed to have beneficial effects on preventing or treating COVID-19. Curcuma longa, for

example, has been used traditionally by many countries in Asia as a drug or supplement because of its antioxidant, anti-inflammatory, ant mutagenic, anticancer, and antimicrobial effects. Many branded products contain an active compound that can act as an antiviral and immunostimulatory. During the spread of COVID-19, several pharmaceutical companies offered their main stay herbal products commercially.[5]

Vaccine Therapy:

A COVID-19 vaccine is a vaccine intended to provide acquired immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing coronavirus disease 2019 (COVID-19). Prior to the COVID-19 pandemic, there was an established body of knowledge about the structure and function of coronaviruses causing diseases like severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which enabled accelerated development of various vaccine technologies during early 2020.[6]

In Phase III trials, several COVID-19 vaccines have demonstrated efficacy as high as 95% in preventing symptomatic COVID-19 infections. As of April 2021 14 vaccines are authorized by at least one national regulatory authority for public use two RNA Vaccine (Pfizer–BioNTech and Moderna),five conventional inactivated vaccines (BBIBP-CorV, CoronaVac, Covaxin, WIBP-CorV and CoviVac), five viral vector vaccines (Sputnik Light, Sputnik V, Oxford–AstraZeneca, Convidecia, and Johnson & Johnson), and two protein subunit vaccines (EpiVacCorona and RBD-Dimer). In total, as of March 2021, 308 vaccine candidates are in various stages of development, with 73 in clinical research, including 24 in Phase I trials, 33 in Phase I–II trials, and 16 in Phase III development.[7]

AstraZeneca anticipates producing 3 billion doses in 2021, Pfizer–BioNTech 1.3 billion doses, and Sputnik V, Sinopharm, Sinovac, and Johnson &Johnson 1 billion doses each. Moderna targets producing 600 million doses and Convidicea 500 million doses in 2021.[8]

- PHARMACOVIGILANCE STUDY OF COVID-19 MANAGEMENT:

WHO defines pharmacovigilance as the "science and activities related to the detection, assessment, Understanding and prevention of adverse effects or any other possible drug-related problem".[9]

It focuses on investigating and monitoring adverse drug reactions after medicinal products are licensed. Adverse drug reactions are a response that is noxious and unintended and that occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease or for modifying physiological function. [10]

They may vary in presentation and occurrence and are commonly divided into type A (augmented pharmaceutical response) and type B (bizarre or hypersensitivity) adverse drug reactions.[11]

An example of a type A reaction in relation to antiretroviral (ARV) drugs for treating HIV is the negative effect of Tenofovir on bone mineral density, which may increase fracture risk. An example of a type B reaction is Efavirenz-related hypersensitivity in the form of a skin rash with systemic symptoms.[12]

The global system of pharmacovigilance was first developed following the thalidomide tragedy in the 1960s, where thalidomide was used to treat nausea in pregnancy, resulting in serious teratogenic events among infants exposed in utero. [13]

Ideally, Pharmacovigilance systems take a life-cycle Approach, focusing not only on the properties of the prescribed medicine but also on how it is Formulated, dispensed and administered. This Approach is a continuum throughout the process of drug development, from initial research and Development activities to final consumer use and is Commonly divided into two stages:

Pre-marketing surveillance: Adverse drug reactions from preclinical screening and Phase I, II and III clinical trials;

Post-marketing surveillance: Adverse drug reactions from the post-approval stage and throughout a drug's market life.[14]

Pharmacovigilance in clinical trials:

Clinical trials were utilized all through the planet to see the security and adequacy of a chemical or natural compound with significance its activities on indications or a known illness prepare. Trials are closely observed by agent conjointly the medicate company included inside the inquiry about and advancement of a restorative item. There are four particular stages of a drug's clinical test cycle after creature considers are completed.[15]

This stage I trials include a very little bunch (<100) of volunteers with the focused-on illness. The ponders are unblinded, uncontrolled and habitually final but one month. Stage II trials watch the adequacy, dosage reaction and resilience, and unfavourable impacts of the sedate. These trials incorporate a greater bunch of subjects (ordinarily 200-300) with the focused-on illness handle and have fine characterized and controlled inclusion/exclusion criteria. Clinical test trials are more often than not placebo-controlled or active-controlled comparison thinks about and final a few months. Stage III trials are the extreme step, sometime recently the sedate designer can apply for promoting authorization. Stage III clinical trials centre totally on the drug's security and adequacy in assorted sub-groups with broader inclusion/exclusion criteria counting concomitant drugs and concurrent maladies than clinical test trials. The risk-benefit proportion is created, checked and overhauled in like manner. After fruitful completion of clinical trial clinical trials and authorization for showcasing, the sedate company may conduct clinical trial stage IV so as to still screen the medicate on a distant bigger scale and in an awfully less controlled globe environment.[16]

Need of pharmacovigilance:

It is widely accepted that clinical development of medicines is a complex process which require huge amount of time for its completion. Once a drug is marketed, it leaves the secure and protected scientific environment of clinical trials and is free for consumption by the general public. At this point, most medicines will only have been tested for short-term safety and efficacy on a limited number of carefully selected individuals. Hence, need of pharmacovigilance arises which include, securing the early detection of new adverse reactions or patients' subgroups of exceptional sensitivity; and introducing certain measures in order to manage such risks. Moreover,

it is essential that new and medically still evolving treatments are monitored for their effectiveness and safety under real-life conditions after being marketed. Furthermore, more information is generally needed about use in specific population groups like children, pregnant women and the elderly, about the efficacy and safety of chronic use in combination with other drugs. [17,18]

Objectives of Pharmacovigilance:

The main objectives of pharmacovigilance involve exhibiting the efficacy of drugs by monitoring their adverse effect profile for many years from the lab to the pharmacy; tracking any drastic effects of drugs improving public health and safety in relation to the use of medicines; encouraging the safe, rational and cost-effective use of drugs; promoting understanding, education and clinical training in pharmacovigilance; and effective communication to the generic public. [19]

How contagious is the corona virus –

The transmission rate is relatively high. Early research has estimated that one person who has it can spread it to between 2 and 3.5 others. One study found that the rate was higher, with one case spreading to between 4.7 and 6.6 other people. By comparison, one person who has the seasonal flu will pass it to between 1.1 and 2.3 others.

The CDC reports, there is evidence that, it can be transmitted if you get within 6 feet of someone who is infectious for a total of 15 minutes throughout a day. It had previously been believed the exposure had to be 15 minutes at a time. For prevention, wash your hands for at least 20 seconds before and after bringing things into your home. The coronavirus can linger on hard surfaces, so clean and disinfect countertops and anything else.

Symptoms of corona virus-

People with COVID-19 have had a wide range of symptoms reported – ranging from mild symptoms to severe illness. Symptoms may appear 2-14 days after exposure to the virus. Anyone can have mild to severe symptoms. People with these symptoms may have COVID-19:

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting [20]

Co-morbidities and COVID 19 - The medical definition of Co-morbidities is when a person has more than one underlying health-related conditions present in them at once. Each condition is considered as comorbidity, and sometimes comorbidities could be present in the form of physical or mental conditions. Older adults are more likely to get severely ill from COVID-19. More than 80% of COVID-19 deaths occur in people over age 65, and more than 95% of COVID-19 deaths occur in people older than 45.[21]

How do comorbidities impact Coronavirus infection - People who have a weak immune system are more susceptible to contract coronavirus? Studies have shown that people with pre-existing conditions face a higher mortality rate when compared to people affected with no comorbidities.

Some of the major comorbidities are

- Cancer
- Chronic kidney disease
- Chronic lung diseases, Asthma, cystic fibrosis
- Hypertension
- Diabetes (type 1 or type 2)
- Cardiovascular diseases
- HIV infection
- Liver disease
- Immunocompromised state (weakened immune system)
- Heart conditions (Heart failure) [21]

- **Some of the pandemics and related data** [22,23,24]

Disease	Occurrence year	Countries affected	Treatment available	People affected /Deaths
1.Typhus	1489-1922	Europe, Germany and worldwide	Antibiotic Doxycycline and follow up for fever	Nearly 15 million deaths
2.Small pox	1789	Australian continent	Tecovirimat (TPOXX), Supportive care and vaccination	40 thousand to 1.5 lack deaths
3.Spanish Flu	1918-1920	Pacific Island, Arctic	Open-air treatment was used, Aspirin, And suppository medicines	20-100 million Deaths
4.Cholera	1817- 1975	Indian subcontinent ,China,Russia,North America	Rehydration therapy,Doxycycline azithromycin and ciprofloxacin	Billions of deaths
5.Tuberculosis	19 Century	Europe, Asia	Isoniazid, rifampicin, pyrazinamide, and ethambutol for two months	
6.HIV / AIDS	1966-1972	Africa, USA,can be seen worldwide	Antiretroviral therapy (ART). ART can't cure HIV, but HIV medicines help people with HIV live longer, healthier lives.	32.7 million Deaths
7.Swine Flu	2009-10	China,Mexico, India	Tamiflu, zanamivir and cold and flu follow up	1.5 to 5 lack deaths
8.Covid 19	2019	China, USA, INDIA and major part of the world	Monoclonal Antibody Tamiflu, Respiratory support, Increasing Immune Response, Treatment followed by symptoms. Since there is not any particular treatment **Vaccination** is the most important key and taking care is much necessary.	39 Lacks till date

Supportive therapy in COVID 19 disease:

Herbal Medicine Candidates

In this situation, in which the preventive and therapeutic agents have not been established and recommended for administration to patients, herbal medicines are frequently used by many people in the community. According to the characteristics of the SARS-CoV-2 virus, a molecular mechanism of the host is involved in the immune response. As discussed above, we did a critical review of several papers from different journals. We highlighted at least four herbal medicines that could prevent or supplement the treatment of COVID-19 patients. Eg.Echinaceapurpurea, Curcumin, Cinchona, Xanthorrhizol. [25]

Immunity in Ayurveda

In Ayurveda, immunity is referred to as vyadhikshamatva. Ayurveda has a comprehensive approach of immunity encompassing two-fold management, respectively of health and disease. Vyadhikshamatva is the resistance of the body to fight a disease by either of the following two ways: a. Vyadhi-Bala-Virodhitvam – The resisting power of the body to restrain or withstand the strength or severity orprogression of a disease, orb. Vyadhi-Utpada-Pratibandhakatvam – The resisting power of the body to prevent the manifestation of a disease. Significantly, various modifiable factors have been enlisted in Ayurveda that influence the host defence responses (Bala/Vyadhikshamatva). These factors include a healthy diet (Pathyaahara), condition of biological humors (Dosha) and the state of physical and mental health (Sareera). The previous Covid 19 related advisories issued by the Ministry of AYUSH are based on this host defence mechanism or autogenesis and also on various empirical evidences available from peer reviewed and indexed publications.[26]

Immunity against COVID-19: Potential Role of Ayush Kwath

SARS-CoV-2 infection associated respiratory disease- COVID-19 has evolved into a pandemic but, being a new form of virus, pathogenesis of disease causation is not fully understood and drugs and vaccines against this virus are still being tested so that no effective drugs or vaccines have been advised by regulatory authority. In this context, the Ministry of AYUSH, Government of India has recommended 'Ayush Kwath' to improve the immunity and combat the infection. Our objective of this literature review is to review the role of immunity in pathogenesis of COVID-19 and role of Ayush Kwath against the virus and regulation of immunity. Current review was conducted using a search of available literature on COVID-19 and immunity, Vyadhikshamatwa , Ayurveda and COVID-19, Rasayana , Coronavirus, SARS-CoV-2, immunomodulatory effects of medicinal plants; Tulsi /Holy Basil/Ocimum sanctum, Dalchini /Cinnamon/Cinnamomum zeylanicum, Sunthi /Ginger/Zingiber officinale and Marich /Black Pepper/Piper nigrum. Ayurveda, being an ancient science have both medicinal and cultural values and had stimulated our kitchen and influenced what we ate in different seasons and the remedies we used for common ailments. Herbs such as Tulsi, Marich, Sunthi, Dalchini are the most commonly used and easily available drugs in home. Thus, Ayush Kwath due to its immune-modulatory, antiviral, anti-oxidant, anti-inflammatory, anti-platelet, anti-atherosclerotic, hepato-protective, Reno-protective properties; seems to be effective in immune-regulation for controlling viral infections like COVID-19. Further

pre-clinical and clinical trials need to be done for the evaluation of safety and efficacy of this polyherbal formulation.[27]

Government of India Ministry of Ayush recommended as per guidelines

Ayurveda for management of Covid-19 General and Physical measures

1) Follow physical distancing, respiratory and hand hygiene, wear mask
2) Gargle with warm water added with a pinch of turmeric and salt. Water boiled With Triphala also can be used for gargling.
3) Steam inhalation with Ajwain or Pudina or Eucalyptus oil once a day
4) Adequate sleep of 6 to 8 hrs.
5) Moderate physical exercises

Dietary measures

1) Use warm water or boiled with herbs like ginger or coriander or basil or cumin seeds etc.
2) Fresh, warm, balanced diet
3) Drink Golden Milk (Half tea spoon Haldi powder in 150 ml hot milk) once at night
4) Drink AyushKadha or Kwath once day.[28]

Guidelines For Naturopathy Practitioners for COVID 19

Role of Naturopathy in prophylaxis during Covid-19 pandemic this guideline document is for Naturopathy practitioners to impart yoga therapy, naturopathy treatment modalities, nutrition, diet and lifestyle approaches to improve immunity in our population. Research has shown that there is heterogeneity in susceptibility to infections during a flu epidemic. Psychological stress, Fitness and physical activity, Nutrition, Sleep, comorbid conditions and lifestyle play a vital role in shaping this immune response. Naturopathy is a system of lifestyle medicine that works in modulating these factors that improve body's innate healing properties i.e. immunity. This may be useful in this current scenario where we are facing a Covid 19 pandemic.

Exercise: Regular exercise of moderate-intensity is associated with a reduced incidence of upper respiratory tract infection. The recommended means of aerobic exercise is walking, with an optimal frequency of three to five days a week and an optimal duration of 20 to 30 minutes of continuous activity.

Sleep: Sleep and the circadian system exert a regulatory influence on immune functions. Sleep deprivation can affect immune function in several ways that lead to enhanced susceptibility to the common cold and pneumonia with poor sleep efficiency.[29]

List of authorized and approved vaccines: -

National regulatory authorities have granted emergency use authorizations for fifteen vaccines. Six of those have been approved for emergency or full use by at least one WHO-recognized stringent regulatory authority

Vaccine Developers	Country of origin	Type	Doses, interval	Current phase (participants)
Oxford–AstraZeneca COVID-19 vaccine .	United Kingdom, Sweden	Adenovirus Vector (chAdOX1)	2doses 4–12 weeks	Phase III (30,000) Interventional; randomized, placebo-controlled study for efficacy, safety, and immunogenicity. Overall efficacy of 76% after the first dose and 81% after a second dose taken 12 weeks or more after the first. May 2020 – Aug 2021, Brazil (5,000), United Kingdom, India
Pfizer–BioNTech COVID-19 vaccine	United States, Germany	RNA modRNAin lipid nanoparticles	2 doses 3–4 weeks	PhaseIII (43,448) Randomized,placebo-controlled. Positive results from an interim analysis were announced on 18 November 2020] and published on 10 December 2020 reporting an overall efficacy of 95%. Jul–Nov 2020, Germany, United States
Moderna COVID-19 vaccine	United States	RNA modRNA in lipid nanoparticles	2 doses 4 weeks	PhaseIII (30,000) Interventional; randomized, placebo-controlled study for efficacy, safety, and immunogenicity. Positive results from an interim analysis were announced on 15 November 2020and published on 30 December 2020 reporting an overall efficacy of 94%.
BBIBP-CorV Sinopharm: Beijing institute of biological products	China	Inactivated SARS Cov-2	2 doses 3–4 weeks	**PhaseIII** (48,000)Randomized, double-blind, parallel placebo-controlled, to evaluate safety and protectiveefficacy. Sinopharm's internal analysis indicated

				a 79% efficacy. Jul 2020.
Johnson &Johnson COVID-19 vaccine	United States, Netherlands	Adenovirus Vector (Ad26)	1 dose	**PhaseIII** (40,000)Randomized, double-blinded, placebo-controlled Positive results from an interim analysis were announced on 29 January 2021. J&J reports an efficacy of 66% against mild and moderate symptoms, and 85% against severe symptoms. Further, the mild and moderate efficacy ranged from 64% in South Africa to 72% in the United States. Jul 2020 – 2023, United States, Argentina, Brazil,
BBV152 (COVAXin) Bharat Biotech, Indian Council of Medical Research	India	Inactivated SARS-CoV-2	2 doses 4 weeks	Phase III (25,800) Randomised, observer-blinded, placebo-controlled the interim efficacy rate is 81% as per third phase trial. All data from the animal, first, second phase trials have been made public through peer-reviewed journals. Phase III trials had shown 81% efficacy. Nov 2020 – Mar 2021, India.

1.Oxford–AstraZeneca COVID-19 vaccine :

Efficacy: - AstraZeneca vaccine the overall efficacy was 70.4%

Medical Use:- The Oxford–AstraZeneca COVID-19 vaccine is used to provide protection against infection by the SARS-CoV-2 virus in order to prevent COVID-19 in adults aged 18 years and older.[30]

The medicine is administered by two 0.5 ml doses injected intramuscularly into the deltoid muscle (upper arm) four to twelve weeks apart, with the world health organisation (WHO)recommending the second is given 8 to 12 weeks after the first for optimum efficacy.[31]

List of excipients: - L-histidine, L-histidine hydrochloride monohydrate, Magnesium chloride hexahydrate, Polysorbate80(E433), Ethanol, Sucrose, Sodium chloride, disodium edetate, water for injection.

Side Effect: -Headache (52.6%) Fatigue (53.1%) Muscle or Joint pain (44% or 26.4%) Fever (33.6) Chills (31.9) Nausea (21.9%).[32]

2.Pfizer–BioNTech COVID-19 vaccine:

Efficacy: - 88% Effectiveness rate against delta variants.

Medical Use: The Pfizer–BioNTech COVID-19 vaccine is used to provide protection against infection by the SARS-CoV-2 virus in order to prevent COVID-19.[33]

The vaccine is supplied in a multidose vial as "a white to off-white, sterile, preservative-free, frozen suspension for intramuscular injection". It must be thawed to room temperature and diluted with normal saline before administration.[34]

List of Excipients: ALC-0315, ((4-hydroxybutyl) azanediyl) bis(hexane-6,1-diyl)bis(2-hexyldecanoate) ALC-0159,2- [(polyethylene glycol)-2000]-N, N-ditetradecylacetamide 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) Cholesterol Dibasic sodium phosphate dihydrate Monobasic potassium phosphate Potassium chloride Sodium chloride Sucrose Water for injections.[35]

Side Effect: Pain Redness Swelling Tiredness Headache Muscle Pain Chills Fever Nausea [36]

3.Moderna COVID-19 vaccine:

Efficacy: 80%

List of excipients: Polyethylene glycol [PEG] 2000-dimyristoyl glycerol [DMG], Cholesterol, And 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]; Tromethamine; Tromethamine hydrochloride; Acetic acid; Sodium acetate; And sucrose.[37]

Side Effect: Pain at the injection site Tiredness Headache Muscle Pain Chills Joint Pain Swollen lymph node Fever [38]

4.BBIBP-CorVSinopharm :-

Efficacy: A large multi-country Phase 3 trial has shown that 2 doses, administered at an interval of 21 days, have an efficacy of 79% against symptomatic SARS-CoV-2 infection 14 or more days after the second dose. Vaccine efficacy against hospitalization was 79%.

Dose: Sinopharm vaccine given in two dose of 0.5 ML intramuscularly

Side effect: Headache, Fatigue, Injection site reaction [39]

5.Sputnik V COVID-19 vaccine:

Efficacy: As per a February 2021 peer-reviewed article published in The Lance; the Sputnik V phase 3 trial showed 91.6 per cent efficacy against Covid-19.

Composition: Tris(hydroxymethyl)aminomethane Sodium chloride (salt) Sucrose (sugar).

Magnesium chloride hexahydrate Disodium EDTA dihydrate (buffer)n Polysorbate 80 Ethanol 95% Water [40]

Side effect: Fatigue (70%) Joint Pain (46.4%) Headache (64.7%) Chills (45.4%) Fever (15.5%) Nausea and vomiting (23%) [41]

Pharmacovigilance and assessment of drug safety reports during COVID 19:

The speed and volume of clinical research to discover effective drug against novel corona virus has been remarkable. To address the unmet medical need, the regulations are made flexible and convenient without any relaxation in drug safety reporting. The pharmacovigilance activities, especially adverse event reporting regardless of clinical trials or clinical practice should continue as usual because patient safety is the priority.

Not a single event over the last century has had such an impact on human life, such as the COVID-19 pandemic. It is a devastating serious public health risk, hard and at times scary. Unfortunately, there is not a single drug treatment with proven efficacy, and almost all drugs being tested are repurposed and used on compassionate ground. The world is desperate to find ways to slow the spread of the novel coronavirus and discover game changer. Interestingly, a web search term COVID 19 clinical trials revealed the ever-increasing number of clinical trials registered across the globe. [42,43]

Drug safety reporting:

In view of the enthusiasm, urgency and rush to find out effective drug treatment and vaccine for COVID 19, the question is, how do we ensure the safety? Several new and old drugs ranging from anti-malaria to anti-viral and immune-modulators with the potential effect on novel coronavirus are being deployed, tested for clinical care and research. The use of drugs on compassionate grounds, exposing the participants to the investigational product with limited evidence of risk-benefit makes it more vital to adapt robust safety monitoring, adverse event reporting, and assessment. However, majority of the trials during pandemic are primarily designed to define clinical benefits and outcomes with less attention to adverse events and safety aspects. On the other hand, there is no acceptable gold standard study design to determine a true drug safety issue.[44]

Causality assessment of drug safety reporting:

The basic essence of the pharmacovigilance and suspected adverse event reports is to detect the risk profile of the drug at the earliest and identify the population at risk. The assessment of safety reports comprises evaluation of probability (causal association or link) of the relationship between exposure to medicine and the occurrence of adverse events. The essential primary step is to suspect an adverse drug event (a causal link) and then "prove or disprove it."

The assessment criteria are based upon some specific features of the event of interest including time relationship between drug administration and appearance of the event, pharmacological characteristics of the suspected drug (pharmacokinetic and pharmacodynamic actions), medical plausibility (clinical presentation and supporting investigations), likelihood or exclusion of other causes, de-challenge information and re-challenge, if done.

Challenges of causality assessment:

causality assessment in pharmacovigilance is a challenging and time-consuming task. The complex nature of adverse events, wide variations in clinical manifestations, background frequency of the adverse event,

characteristic of the disease process, and use of multiple drugs with the same temporal sequence, etc., are some of the factors that may not facilitate the analysis.[45]

The adverse reactions due to the drug may vary from mild symptoms to serious life-threatening or significant medical event and can be rare or common. An adverse event immediately after the drug therapy establishes a strong causal association while an AE after a long latent period can be missed, requires long-term follow-up, adequate resources, and expertise for safety evaluation. Adverse events with high background frequency, especially fever, cough, pneumonia at times of crisis also poses a challenge. In addition, there can be multiple contributing factors for drug-induced adverse events. The use of concomitant drugs with overlapping toxicities, pre-existing medical conditions/co-morbidities, elderly patients, alcoholics, are possibly either contributory or confounding factors.

In light of the huge clinical workload and lack of systematic monitoring during the pandemic, only a team of proactive professionals strictly following the treatment protocols will capture the details. The hue and cry for the use of hydroxychloroquine for COVID 19 patients have been the best example. [46,47]

The effect of hydroxychloroquine on QTc interval is also shared by concomitant drugs (antimicrobials, antiviral, antifungal, diuretics, etc.,) and electrolyte disturbances. Nonavailability of specific diagnostic tests and critical details will make the causal assessment inconspicuous. A substantial number of COVID 19 patients treated for lifestyle diseases will be taking long-term medications along with an experimental drug. Possibly these patients may also receive multiple other medications for associated clinical manifestations. Currently, the data is not sufficient for evaluating the safety and risk profile of combining drugs in such a situation. Furthermore, the proposed COVID 19 drugs (antivirals) are metabolized through cytochrome 3A4 pathway; either substrate or inhibitor may result in significant drug – drug interactions.[48]

Clinical Endpoints for Evaluating Efficacy in COVID-19 Vaccine Trials:

Several vaccine candidates to protect against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or coronavirus disease 2019 (COVID-19) have entered or will soon enter large-scale, phase 3, placebo-controlled randomized clinical trials. To facilitate harmonized evaluation and comparison of the efficacy of these vaccines, a general set of clinical endpoints is proposed, along with considerations to guide the selection of the primary endpoints on the basis of clinical and statistical reasoning. Widespread use of safe and durably effective vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), especially in combination with multiple concomitant prevention strategies.[49]

We address 4 salient issues on study endpoints in COVID-19 vaccine efficacy trials.

First, we propose a general set of clinical endpoints to facilitate a harmonized evaluation and comparison of the efficacy of vaccine candidates, overall and across relevant subgroups. Second, we consider the pros and cons of various endpoints for use as primary endpoints. Third, we recommend adequate follow-up of all participants to enable enhanced sensitivity regarding effects on severe COVID-19 as well as assessment of the longer-term vaccine effect on the set of endpoints, including an assessment of durability of protection. Fourth, we recommend including asymptomatic infection as a study endpoint, given that vaccine protection against

COVID-19 could be accompanied by a shift toward more asymptomatic SARS-CoV-2 infections, a plausible outcome if the vaccine does not confer sterilizing immunity.

Set of clinical endpoints to facilitate harmonized vaccine efficacy evaluation and comparison:

Two of the endpoints—virologically confirmed symptomatic SARS-CoV-2 infection regardless of the severity of symptoms (COVID-19) and virologically confirmed SARS-CoV-2 infection with symptoms classified as severe (severe COVID-19)—will likely be universally used because they fit standard endpoints used in virtually all vaccine efficacy trials.[50]

For the COVID-19 endpoint, per FDA guidance, outcomes can include fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, and diarrhoea. Corresponding outcomes for severe COVID-19 include clinical signs at rest indicative of severe illness; respiratory failure; evidence of shock (on the basis of specific blood pressure thresholds); clinically significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; and death.[51]

Every infection endpoint is either a COVID-19 endpoint or an asymptomatic infection endpoint, and a harmonized analysis of these 3 endpoints can assess the overall vaccine effect on infection and the proportion of this effect on each component endpoint. [52]

The COVID-19 endpoint is scored as 0 for no disease and 1 for disease. The BOD endpoint score extends this by using 0 for no COVID-19, 1 for non-severe COVID-19, and 2 for severe COVID-19.[53]

➢ CONCLUSION:

The pandemics are transmissible and life-threatening diseases. Covid-19 is pandemic cause by SARS – COV2 which out breaked from food market of Hubei, Wuhan, CHINA. Seems to have transmitted from bat. The transmission rate is quite high and constantly changing its DNA strain causing challenge to health workers and scientist. The proper treatment takes time, since there is not any proper treatment yet for Covid the vaccination seems to be important key in prevention and selfcare is an important factor.

In the current pandemic scenario, precautions and boosting immunity are one of the best choices to get away from COVID-19 infection. The uses of spices and herbs may play a significant role against viral infections. It was analysed a vital role against SARS-CoV-2 (COVID-19) as well as other viral infections, which were also supported by some other recent studies. Therefore, detailed studies about the supportive treatment in common Ayurveda and naturopathy and their effectiveness and mode of action against lethal viruses need to be explored.

To prevent the occurrence of COVID 19 infection, vaccines are useful. Discussing of viral structure and life cycle of SARS-CoV-2 as owing a comprehensive visualization is the key factor of the pandemic condition.

To treat such pandemic disease the drugs are given which are useful harmful too. So, systematic monitoring of all adverse outcomes, adverse events must be recorded and reported for a meaningful causality and risk-benefit assessment balancing individual safety and scientific necessities. It is likely that the number of safety reports

may increase during the pandemic. To cope up, an efficient pharmacovigilance rapid response expert team to assess the drug safety reports on a weekly basis and respond to the concerns immediately will help in this regard.

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