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Understanding COVID-19 vaccines and adverse events

Executive Summary

Given the main policy question, "How safe is COVID-19 Vaccine?", this paper aims to provide some answers regarding the COVID-19 vaccine specifically on its adverse effects. A scoping review was done to know the different adverse effects reported for the COVID-19 vaccines, the relationship of experiencing adverse effects and having co-morbidities (chronic illnesses and other health issues). This paper also briefly tackles vaccine surveillance and monitoring.

Recommendations

Vaccines save lives and money.

Active surveillance and monitoring of COVID-19 vaccines undergoing Phase III trials must be carried out **until they are fully licensed.**

Use careful assessment and investigation (using the different WHO guidelines) in establishing causality between adverse events of immunization and the vaccine.

Current trials have not presented evidence that there is causality between adverse events after immunization of COVID-19 Vaccine and co-morbidities.

Introduction

On December 2, 2020, an executive order was issued by President Rodrigo Duterte allowing the Food and Drug Administration to grant Emergency Use Authorization (EUA) for vaccines[1].

An Emergency Use Authorization facilitates the use of certain drugs during public health emergencies (such as the current COVID-19 pandemic) without completing and compiling all necessary evidence and clinical data that would usually be required from a drug before being allowed in the market. Drugs given EUA however still pass through the minimum but rigorous standards for drug safety and effectiveness.

Vaccination is one of the greatest of achievements of public health. This has enabled the global eradication of smallpox and reduction in the incidence of Vaccine-Preventable Diseases (VPD).

Through modern science, vaccines are made to be safe for the general public, however, no vaccine is entirely without risk and adverse reactions can occasionally happen. Some people may experience adverse events after immunization (AEFI), or any untoward medical occurrence

[1] Duterte allows FDA to issue emergency use authorization for COVID-19 vaccines, drugs. CNN Philippines Staff. https://cnnphilippines.com/news/2020/12/2/Duterte-FDA-emergency-use-authorization-COVID-19.html?fbclid=IwAR2AZk0iFBlI9IYauohX-sltKEx0WYvBBz7oiyX_PLkhtLra6xDIFOqe5Xo. Accessed December 4, 2020.

following immunization. These range from non-serious reactions to rare serious reactions and do not necessarily have a causal relationship with vaccination.

Methodology

A scoping review was done to provide answers for the different policy questions surrounding safety of COVID-19 vaccines. This paper aimed to answer questions on vaccine safety, monitoring and surveillance by looking through the official references given by the World Health Organization and the Department of Health. An exhaustive literature search was also done to find answers regarding the link between adverse effects and having co-morbid conditions.

This paper is limited to official and published results from the different vaccine manufacturers at the time of publication. COVID-19 vaccines are all in trial and development stages, therefore changes may be expected.

Results & Discussion

A. How do we differentiate between AEFI due to the vaccine and to other factors?

a. In determining if AEFI's are causally linked to vaccination or a mere coincidence, detailed investigations are led by recognized bodies.

b. In the Philippines, the National Epidemiology Center of the Department of Health is in charge of AEFI surveillance system with support from the Food and Drug administration. This has been in place at the national and local levels since 2007[2].

c. Causality assessment is a methodology employed by the WHO for vaccine pharmacovigilance. This is a systematic review of data about reported AEFIs and aims to determine the likelihood of causal association between the adverse event and the vaccine in question[3].

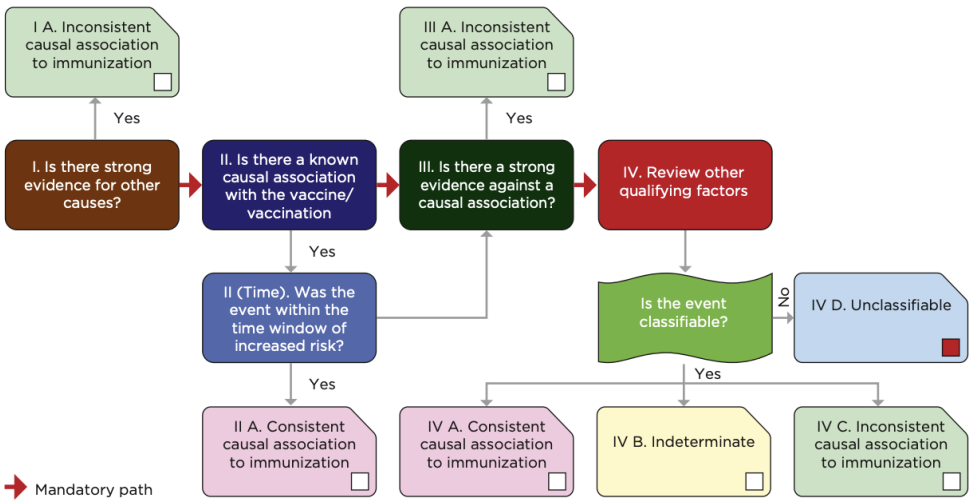

Figure 1. Causality Assessment Algorithm (WHO)

d. Adverse events after immunization are then further divided into 5 categories. Each reported case is carefully assessed and further investigated by the Epidemiology Surveillance Unit (ESU) led by each Local Government Unit within 48 hours of reporting.

[2] National Epidemiology Center Department of Health Adverse Events Following Immunization (AEFI) A Manual of Procedure for Surveillance and Response to AEFI. DOH. https://doh.gov.ph/sites/default/files/publications/AEFI_MOP%202014%20Final.pdf Accessed December 4, 2020.

[3] Causality assessment of an adverse event following immunization (AEFI) 2nd Edition. 2019. https://www.who.int/vaccine_safety/publications/CausalityAssessmentAEFI_EN.pdf?ua=1 Accessed January 7, 2020.

Vaccine product	Vaccine quality defect	Immunization error	Immunization anxiety	Coincidental event
caused or precipitated by **inherent properties** of the vaccine product e.g. extensive limb swelling after DTP vaccination	caused or precipitated by **quality defects** of the vaccine product, including administration device provided by the manufacturer e.g failure to completely inactivate a viral strain causing viral infection	caused by **inappropriate vaccine handling, prescribing or administration** e.g. infection outbreak from CONTAMINATED multidose vial	arising from **anxiety about the immunization** e.g. fainting after vaccination from anxiety	caused by something **other than vaccine products or immunization related reactions** e.g. fever after vaccination (but after investigation, with bacterial infection)

Figure 2. Categories of adverse events after immunization

e. Like all other pharmaceutical products found in the market, vaccines are required to undergo rigorous testing and review for safety, efficacy and effectiveness before it can be granted a license for distribution. Pharmacovigilance, is defined by the World Health Organization, as the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem."

B. What should be the length of observation for AEFI following COVID-19 vaccination?

a. These new COVID -19 Vaccines given the EUA are recognized to be in PHASE III Trials, technically, they should be actively monitored according to their protocols until they have completed their trials and have applied for license to distribute. However, it should be emphasized that monitoring for a vaccine's safety or AEFI's never end.

b. Vaccines and other drugs are regulated and constantly monitored by the Food and Drug administration to protect public health in ensuring the safety and efficacy of these products.

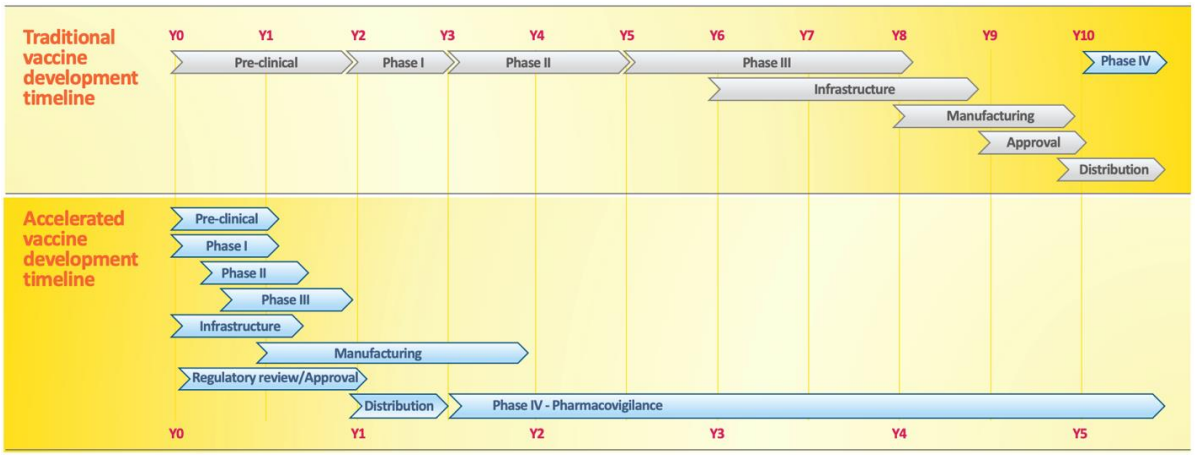

Figure 3: COVID -19 Vaccine Accelerated Development (WHO)

Table 1. Clinical Trials and Assessment of Vaccine Safety (WHO: Vaccine Safety Basics) [4]

Phase	Activity	Recommended sample size
Phase I	Tests for SAFETY and IMMUNOGENICITY	10 -100
Phase II	Monitors SAFETY, IMMUNE RESPONSE, determine DOSAGE and schedule	100 – 1,000
Phase III	Addresses EFFICACY, continued monitoring for SAFETY	1,000 – 10,000
	Submission for Licensure	
Phase IV	Post-licensure SURVEILLANCE for SAFETY	

As of this writing, there are 56 COVID-19 candidate vaccines in clinical evaluation of which 13 are in Phase III trials.

- Pfizer/ BioNTech/ Fosun Pharma
- Novavax
- Moderna/ NIAID
- Bharat Biotech
- Sinovac
- Gamaleya Research Institute
- Sinopharm/Wuhan Institute of Biological Products
- Anhui Zhifei Longcom Biopharma/Institute of Microbiology, Chinese Academy of Sciences
- Sinopharm/Beijing Institute of Biological Products CanSino Biological Inc./ Beijing Institute of Biotechnology
- AstraZeneca/ University of Oxford
- Janssen Pharmaceutical Companies
- Medicago Inc

An exhaustive literature review was done and the trial results for each vaccines is presented below.

[4] Module 1: Introduction to Vaccine Safety. World Health Organization Vaccine Safety Basics e-learning course. https://vaccine-safety-training.org/pre-licensure-vaccine-safety.html. Accessed December 4, 2020.

Table 2. COVID-19 vaccines fact sheet

Vaccine	Efficacy	Dose	Storage	Trial Phase	Population Studies	Comorbidities included in the studies	AEFI's Reported	EUA Granted
Pfizer/ BioNTech	**95%** Sample size for interim results: 43, 661	Two doses, given 28 days apart	-70 ºC	II/III	16 – 85 year old 150 clinical trial sites including the US, Brazil, Argentina, Germany, Turkey and South Africa Around 40% of participants from the study sites were of 56 – 85 years	included individuals with **stable pre-existing health conditions**	• short-term, mild-to-moderate pain at the injection site, fatigue, and headache • adverse serious event at 0.6% incidence	Canada UK European Medicines Agency Switzerland USA ** being reviewed in India
AstraZeneca/ University of Oxford [5]	**70.4%** **(different studies show 62-90%)** Sample size for interim results: 11 636	Two doses, given 28 days apart	2 to 8 ºC *** viable in routine refrigerated cold chain*	II/III	18 years and older 4 randomized controlled trials in UK, South Africa and Brazil adults ** 87.8% : 18–55 years , 12.2% participants were above 55 and of the 12.2%, there were only less than 4% were 70 years or older	Three of the trials included individuals with **stable pre-existing health conditions**	• Transverse myelitis • high fever of 40deg Two transverse myelitis cases considered **unlikely to be related** to the intervention occurred: 1 was attributed to **pre-existing multiple sclerosis** No deaths that were treatment associated occurred.	** being reviewed in India

[5] Oxford-AstraZeneca COVID-19 Vaccine Efficacy. Knoll, Maria et al. The Lancet. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32623-4/fulltext. Accessed December 10, 2020.

Moderna[6]	**94.5%** Sample size for interim results: 30,000	Two doses, given 1 month apart	-25º to -15ºC	II/III	18 years and older At least 10 experimental arms in the US ** 25%: >/= 65 years old	Individuals with **stable pre-existing health conditions** were included in this study. CoMorbidities identified in the study: Diabetes, Severe Obesity, Significant Cardiac Disease, Chronic Lung Disease and Liver Disease[7]	• local site reactions (axillary swelling/tenderness) • fever, chills, fatigue, headache, myalgia, arthralgia, nausea and vomiting	USA ** being reviewed in the European Medicines Agency
Gamaleya Research Institute (Sputnik V)[8]	91.4%	Two doses, given 28 days apart	2 to 8 ºC *** viable in routine refrigerated cold chain*	III	Sample size for interim results: 22, 714 Ongoing clinical trials in UAE, India, Venezuela and Belarus	unpublished	• short-term, mild-to-moderate pain at the injection site, malaise, headache and fever	Russia
Sinovac [9]	** Brazilian researches claim >50% , however research details/results are unpublished *** from Phase I/II trial seroconversion*	Two doses, given 28 days apart	Unpublished	II/III	18 – 59 year old from Suining County of Jiangsu province, China Sample size for interim results: 743	Unpublished	• local site reactions (injection-site swelling/tenderness)	-

[6] Vaccines and Related Biological Products Advisory Committee Meeting December 17, 2020 FDA Briefing Document Moderna COVID-19 Vaccine. ModernaTx Inc. https://www.modernatx.com/covid19vaccine-eua/eua-fact-sheet-providers.pdf. Accessed December 20, 2020.

[7] COVE Study Enrollment. ModernaTx Inc. https://www.modernatx.com/sites/default/files/content_documents/2020-COVE-Study-Enrollment-Completion-10.22.20.pdf Accessed December 10, 2020

[8]Second Interim Analysis Of Clinical Trial Data Showed A 91.4% Efficacy For The Sputnik V Vaccine On Day 28 After The First Dose; Vaccine Efficacy Is Over 95% 42 Days After The First Dose. Gamaleya Research Institute. https://sputnikvaccine.com/newsroom/pressreleases/second-interim-analysis-of-clinical-trial-data-showed-a-91-4-efficacy-for-the-sputnik-v-vaccine-on-d/#:~:text=Gamaleya%20Center%20experts%20have%20once,platform%20of%20human%20adenoviral%20vectors. Accessed December 15, 2020

[9]Safety, Tolerability, And Immunogenicity Of An Inactivated SARS-Cov-2 Vaccine In Healthy Adults Aged 18–59 Years: A Randomised, Double-Blind, Placebo-Controlled, Phase 1/2 Clinical Trial. Zhang, Y. et al. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30843-4/fulltext. Accessed December 15, 2020.

	was seen in 20 (83%) of 24 in 3 µg/dose group and 19 (79%) of 24 in the 6 µg/dose group							
Sinopharm/ Beijing Institute of Biological Products[10]	79.3% (as claimed by manufacturer) 86% effective according to clinical trials in UAE	Two doses, given 21 days apart	2 to 8 °C *** viable in routine refrigerated cold chain*	II/IIII	18 to 60 year old From UAE with diverse population and over 200 nationalities included in the study Sample size for interim results: 15000	Unpublished	Unpublished	China, UAE, Bahrain, Egypt, Monaco
Janssen Pharmaceutical Companies[11]	No published results yet	Single dose	2 to 8 °C *** viable in routine refrigerated cold chain*	III	18 years and older 60,000 participants from Argentina, Brazile, Chile, Colombia, Mexico, Peru, South Africa and the US.	Individuals with **stable pre-existing health conditions** were included in this study.	Unpublished	-
Novavax[12]	No published results yet	2 doses given 21 days apart	2 to 8 °C *** viable in routine refrigerated cold chain*	III	Phase I/II trial: 131 healthy adults 18 – 59 year old Phase III: 30,000 from the UK and US	Individuals with **stable pre-existing health conditions** were included in this study.	Unpublished	-

[10] Effect of an Inactivated Vaccine Against SARS-CoV-2 on Safety and Immunogenicity Outcomes: Interim Analysis of 2 Randomized Clinical Trials . Shengli Xia et al. https://jamanetwork.com/journals/jama/fullarticle/2769612. Accessed December 20, 202

[11] Johnson & Johnson Initiates Pivotal Global Phase 3 Clinical Trial of Janssen's COVID-19 Vaccine Candidate. Janssen Global. https://www.janssen.com/johnson-johnson-initiates-pivotal-global-phase-3-clinical-trial-janssens-covid-19-vaccine-candidate Accessed December 5, 2020.

[12]Phase 1–2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine. Keech et al. https://www.nejm.org/doi/full/10.1056/NEJMoa2026920. Accessed December 15, 2020.

C. Are persons with co-morbidities more likely to develop AEFI?

a. Of the COVID Vaccine studies that included individuals with stable pre-existing health conditions, only Pfizer, Moderna and AstraZeneca published results regarding adverse events after immunization. Their results showed that there was no causality between having co-morbidities and presenting with adverse events after immunization.

b. As the world continues to deal with this Pandemic and the knowledge and evidence grow, further guidance on comorbidities and AEFI on COVID-19 vaccines, monitoring and surveillance must be continued and well-communicated.

Recommendations

1. Vaccines save lives and money.

2. Active surveillance and monitoring of COVID-19 vaccines undergoing Phase III trials must be carried out until they are fully licensed.

3. Use careful assessment and investigation (using the different WHO guidelines) in establishing causality between adverse events of immunization and the vaccine.

4. Current trials have not presented evidence that there is causality between adverse events after immunization of COVID-19 Vaccine and co-morbidities.

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