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Machine Learning Approaches for Signaling Adverse Drug Reaction with Covid-19 RNA Vaccines

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Abstract: Coronavirus disease 2019 (COVID-19) is currently resulted as a worldwide pandemic. It is caused by SARS-CoV-2. A COVID-19 vaccine is intended to provide acquired immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The objective of this paper is to define the severity and the intensity of adverse reaction for Covid-19 mRNA vaccines. Based on the dataset collected, how many of them got mild reactions, moderate and severe for each mRNA vaccine. 92.30% of them face severe symptoms after using Pfizer-BioNTech vaccine. 100% chance of people experience severe symptoms after using Moderna vaccine. There are slight changes in number of them face severe symptoms from these two mRNA vaccines. By using multi-class classification, found that comparatively Moderna give more adverse reactions than Pfizer-BioNTech.

Keywords: Machine Learning, Covid-19, Adverse Drug Reaction, Pfizer-BioNTech vaccine, Moderna Vaccine, Multi-class Classification.

I. INTRODUCTION

Adverse Drug Reaction (ADR) is the effect seen after the intake of medicine or a drug. **Adverse drug events** are any injury occurs at the time of medication which may or may not relate to the drug. Researchers define **Adverse Drug Reactions (ADR)** as the harmful reactions of the drugs caused to humans due to overdose or chemical reactions between two or more chemicals in the medicines, etc [1]. According to WHO, an adverse drug reaction (ADR) or drug facet result could be a response to a medicine that is pestilent and unmotivated, and that happens at doses normally used in humans [2]. It is within the terrible nature of medication that they will cause adverse reactions. However, the incidence rates of specific adverse drug reactions vary considerably from drug to drug. In the same way, certain high-risk groups of ADRs with specific drugs will always exist [3]. COVID-19 could be contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4].

II. BACKGROUND

A covid-19 vaccine is an immunizing agent against SARS-cov-2, the virus which is causing Covid-19. The pharmaceutical industry announced a major commitment to address Covid-19. Phase I is the preliminary stage in clinical trial to test the vaccine and phase II clinical trial will be done on large group of patients and then evaluate whether it has any adverse events or how the drug will work. In phase III the effectiveness of the drug will be assessed. It is also called " Pre-marketing phase". As on March 12th, totally 12 vaccines were authorised by National Regulatory authority for public use. In that two vaccines were Pfizer- BioNTech vaccine and Moderna vaccine. There is no specific, effective treatment or cure for COVID-19. Thus, the cornerstone of management of COVID-19 treatment is to relieve symptoms, fluid therapy, oxygen support and prone positioning as required, and medications to support other affected vital organs [4]. As the cases are increasing, we need to find the solution or to prevent from this deadly virus, medical organizations have come up with vaccinations to treat people.

The **Pfizer-BioNTech Covid-19 vaccine** is an mRNA based Covid-19 vaccine. The initial developer of the vaccine is German company BioNTech and partnered with American company Pfizer for support with clinical trials, logistics and manufacturing of vaccine. The vaccination requires two doses, and it must be given three weeks apart [5].

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The other RNA vaccine is the **Moderna Covid-19 vaccine**, which is developed by United States National Institute of Allergy and Infection Disease (NIAID), the Biomedical Advanced Research and Development Authority (BARDA), and Moderna. It is administered by two doses of 0.5mL. It must be given four weeks apart. Requiring storage at the temperature of a standard medical refrigerator of 2-8 ℃ (36-46 °F) for up to 30 days, whereas the Pfizer-BioNTech candidate requires ultracold freezer storage before between -80 and -60 °C, until five days before vaccination [6].

A. Problem Overview

A COVID-19 vaccine is a vaccine intended to provide acquired immunity against SARS-CoV-2, the virus causing COVID-19. The vaccine had come to the market without limited clinical trial due to emergency requirement. Because the limited clinical trial and data can have unidentified adverse reactions. We have identified the intensity and the severity of the adverse reaction of two mRNA vaccines. Since Covid-19 medications did not go through clinical trials, the safety data for those products are not available. The solution what we are trying to identify adverse reactions which can happen with this product and much bigger severity and intensity and if we are able to identify and we should be able to better manage it. And this will help us to expand the clinical data which is currently lacking due to emergency use of medication.

B. Objectives

- To define the severity and the intensity of adverse reaction for Covid-19 mRNA vaccines.
- Use of suitable methods of machine learning and comparing the performance.
- Comparing the number of reactions and cases after intake of dose 1 and 2 of a particular vaccine.

III. LITERATURE REVIEW

Pharmacovigilance is a detection, evaluation, monitoring and prevention of adverse events of pharmaceutical products. Pharmacovigilance systems have a life cycle approach. This approach is a process of drug development from initial research and development Activities to final usage of consumer [8]. There are various ADR data sources, using those data in machine learning we can apply various methodologies to predict and analyse the results. These results give potential ADRs and offer various mechanism for further clinical trial to reinforce ADR Studies. Three main ADR Studies are Drug-ADR Benchmark data creation, Drug-ADR Prediction and ADR Mechanism Analysis. The Poisson Model, which is mostly used for personalized Drug-ADR prediction. The aim of the model is to predict the number of occurrences of ADRs during drug treatments. Also, the other method that was used is a feature-based similarity methodology to find out weights for the medical case vectors. The various methods that applied in medical case vectors are K-Nearest Neighbours (KNN) method, Kernel Method and Mining Networks to find ADR [15]. The real-world data taken from FDA Adverse Event Reporting System (FEARS), Food and Drug Administration (FDA) to identify the various adverse events associated with potential drug of Hydroxychloroquine and chloroquine for treating COVID-19 patients on 15th June 2020.These drugs may cause an adverse event on human organs or systems, Skin and Subcutaneous tissue, immune system, musculoskeletal and connective tissue. They have also observed the disparity bias of Adverse events based on gender and age. The age is the key factor for COVID-19 patients, so the authors further investigated the significant risk highly reported in different age groups likely <65 years and >=65 years.[7]. The main aim is to identify interaction between drug and target. There are 2 principles for predicting drug-target interaction (DTI) that is docking simulation and machine learning methods. The main assumption was made if drug d interacts with protein p then (i) drug is likely to interact with protein, (ii) protein are likely to interact with drug. Using Kernel, the similarities between drug compounds and protein sequences are measured [9]. Drug repositioning is the investigation of existing drug for new medical use. Its highly efficient and low cost. It is also known as Drug repurpose. It has been highly appealing and powerful technique to identify potential DTIs and drug-disease interactions. Based on computational models, consisting of network propagation, deep learning, classical machine learning and matrix factorization and completion approaches were used for drug repurposing [10].

ADRs are a serious clinical problem as new drugs coming into market. As we know we always focus on each drug individually for predicting ADRs by neglecting the informative knowledge that could be gained from unknown relation

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relationships among different drugs. The Classifier used as a baseline is Majority Rule Method which can generate novel hypothesis regarding ADR. Then second classifier is Augmented Random Walk with Restart (ARWAR). Comparing ARWAR with MRM indicates significantly different with each other. ARWAR method outperforming the Majority Rule Method (MRM) by 20% with respect to average F-measure and predicting novel and biologically meaningful side-effects [11]. Predictions of ADRS are done by exploring knowledge graph methods and casting ADR predictions. To reduce the cost of drug development and provide safer therapy for patients by computational predictions of ADRs during the development cycle of a drug before the drug get authorized for use. Use of FS-MLKNN model determines critical feature dimensions and build multi- label prediction models.[12].

IV. PROPOSED ARCHITECTURE

Here, we have used multi class classification to find whether the vaccine can be suggested based on the severity of Pfizer-BioNTech, Moderna vaccines. The complete architecture of proposed work is shown in Fig 1.

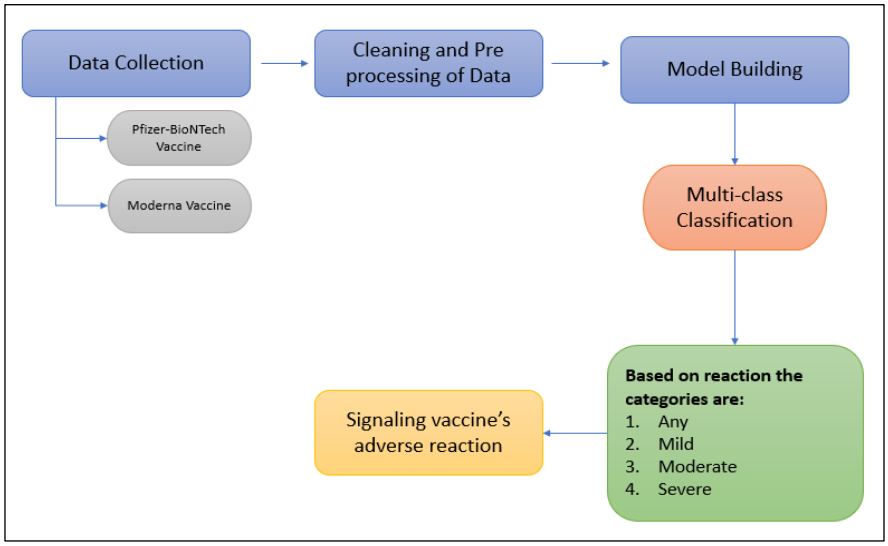

Fig 1: Architecture of Proposed Work

A. Data Collection Process

Gathered data of Local and Systematic reactions of Adverse Events, and Serious Adverse Events of Moderna, Pfizer-BioNTech COVID-19 Vaccine from the Centers for Disease Control and Prevention (**CDC**), which provided us the data based on the age group, how many cases after vaccinations. The severity of the adverse reaction is categorized into three, that is: Mild, Moderate and Severe.

In the dataset which we have taken, it contains the symptoms observed after every dose so there are 2 doses i.e., dose 1 and dose 2, along with this age group, and the local or systematic reaction. Each symptom is then categorised into mild, moderate, and severe. For example, Redness [a], swelling [a], Pain in the injection site [b] have these mild, moderate and severe. [a] Mild: >2.0 to 5.0 cm; Moderate: >5.0 to 10.0 cm; Severe: >10.0 cm. [b] mild pain which need not worry about, moderate is which need some physician consultation and severe – needs to hospitalise for severe pain.

Local reactions are like Redness, Swelling, Pain in the injection site, Axillary swelling/Tenderness. Systematic reactions include Fever, Headache, Myalgia, Fatigue, Arthralgia, Nausea or vomiting, Chills, Diarrhea, new or worsening muscle pain and new or worsening joint pain [13][14].

B. Cleaning and Preprocessing of Data

Pfizer-BioNTech vaccines dataset contains symptoms, severity, dose 1, dose 2, age group (2 groups: 18-55 and above 55), type of reaction (local or systematic). Moderna vaccines dataset contains symptoms, severity, dose 1, dose 2, age group, type of reaction (local or systematic). Here in Moderna, the age group differs that is 18-64 and >= 65, as

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shown Fig 2. Multi-class Classification on categories column. To find whether the vaccine can be suggested based on the severity to decide whether it can be suggested to use further.

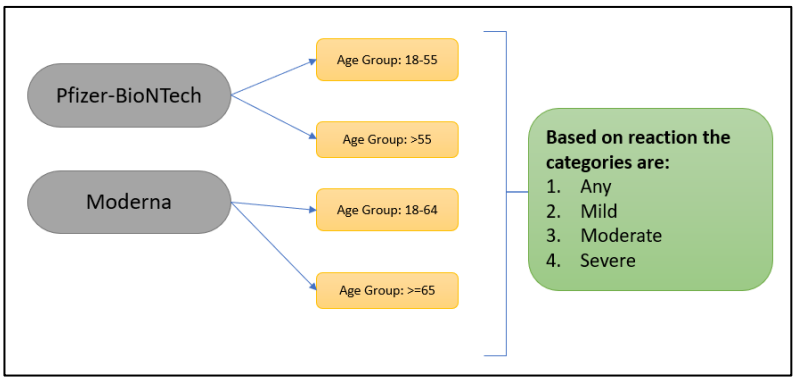

Fig 2: Data Preprocessing

C. Classification models

Classification models to see which algorithm performs well and give us the good accuracy. Detailed analysis of each vaccine is explained in section V.

V. METHODS AND MATERIALS

A. One-vs-Rest for Multi-Class Classification

The **one-vs-rest** strategy, additionally called as one-vs-all, is enforced in onevsrestclassifier. The strategy consists in fitting one classifier per class. We are splitting the multi-class dataset into multiple binary classification problems. A binary classifier is then trained on every binary classification problem and predictions are made using the model that is the most confident.

- Binary Classification Classifier 1: Any vs [Mild, Moderate, Severe]
- Binary Classification Classifier 2: Mild vs [Any, Moderate, Severe]
- Binary Classification Classifier 3: Moderate vs [Mild, Any, Severe]
- Binary Classification Classifier 4: Severe vs [Mild, Moderate, Any]

After binary classification for each vaccine, Support Vector Machine is used to find the adverse reaction based on severity.

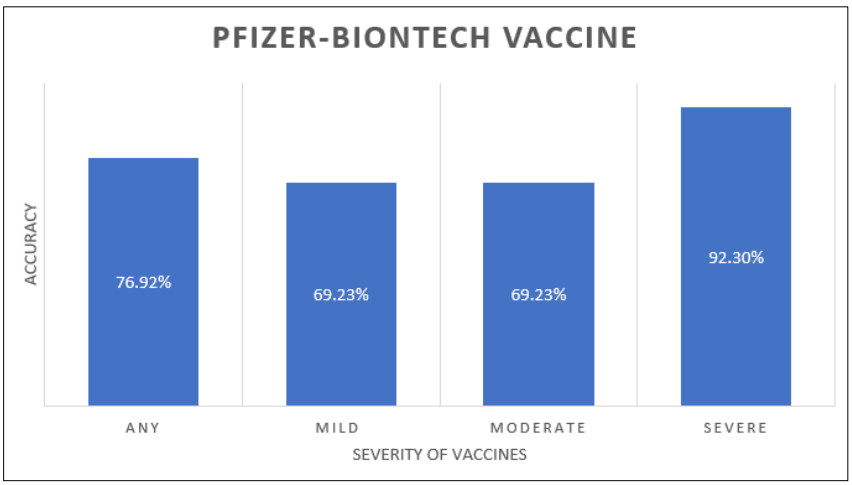

Fig 3: Severity of Pfizer-BioNTech Vaccine

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Here Fig 3 tells us about the Adverse drug reaction from Pfizer-BioNTech vaccine which is having a Local reaction (like Redness, Swelling, and Pain in the injection site) and systemic reaction (Fever, Headache, Chills, Diarrhea, worsening of joint pain, muscle pain, and so on). Based on the dataset, how many of them got mild reactions, moderate and severe. 76.92% of them come under "any" because patient is neither come under mild, moderate, or severe case. 69.23% of them face moderate symptoms so they can consult doctors for a cure. Similarly, for mild cases. 92.30% of them face severe symptoms after using Pfizer-BioNTech vaccine.

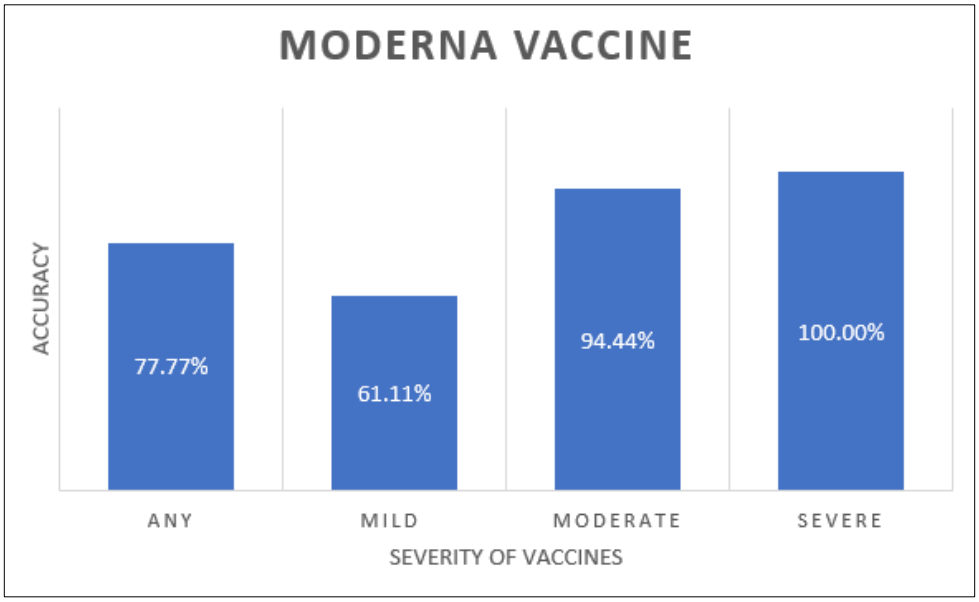

Fig 4: Severity of Moderna Vaccine

Here Fig 4 tells us about the Adverse drug reaction from Moderna vaccine which is having a Local reaction (like Redness, Swelling, and Pain in the injection site) and systemic reaction (Fever, Headache, Chills, Diarrhea, worsening of joint pain, muscle pain, and so on). Based on the dataset, how many of them got mild, moderate, and severe reactions. 77.77% of them come under "any" because patient is neither come under mild, moderate, or severe case.
61.11% of them face mild symptoms. 94.44% of them face moderate symptoms so they can consult doctors for a cure. 100% chance of people experience severe symptoms after using Moderna vaccine.

VI. Performance Analysis

The experimental results are of number of cases based on severity for each vaccine are given below:

A. Graphs

As shown in Fig 5, Taking first dose of Pfizer-BioNTech vaccine, from the sample population of 1802, 1 person have severe fever (>40 degree Celsius). As we mentioned in section 2, mild pain which need not worry about, moderate is which need some physician consultation and severe – needs to hospitalise for severe pain or illness.

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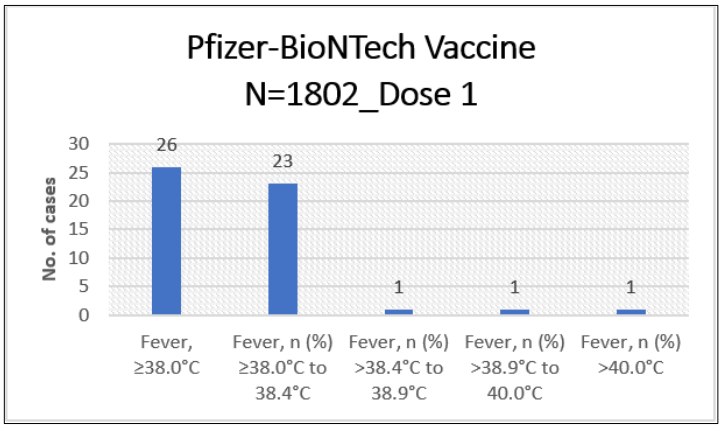

Fig 5: Fever Symptom of Dose 1 for Pfizer-BioNTech Vaccine

Taking first dose of Pfizer-BioNTech vaccine, from the sample population of 1802, 2 cases have severe Fatigue, 240 moderate cases, as shown in Fig 6.

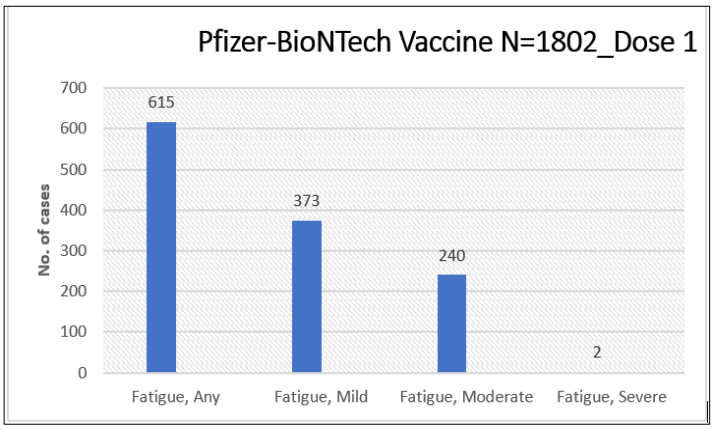

Fig 6: Fatigue Symptom of Dose 1 for Pfizer-BioNTech Vaccine

After three weeks of dose 1 vaccination, people appear for second dose have developed adverse reaction are more than compared to dose 1. 46 severe cases after dose 2 and 442 moderate cases, as shown in Fig 7.

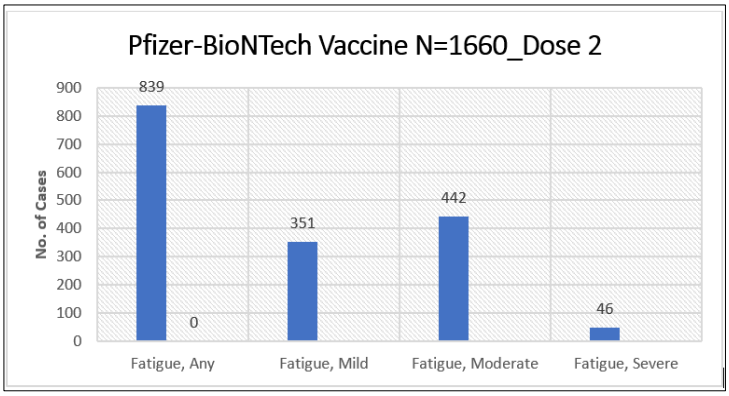

Fig 7: Fatigue symptom of Dose 2 for Pfizer-BioNTech Vaccine

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As shown in Fig 8, Antipyretic is used to prevent or reduce fever. The body then works to lower the temperature, which results in reduction in fever. 46% of people from the sample population (N = 1660) after the second dose of Pfizer – BioNTech vaccine have used antipyretic to reduce the fever or reduce the pain.

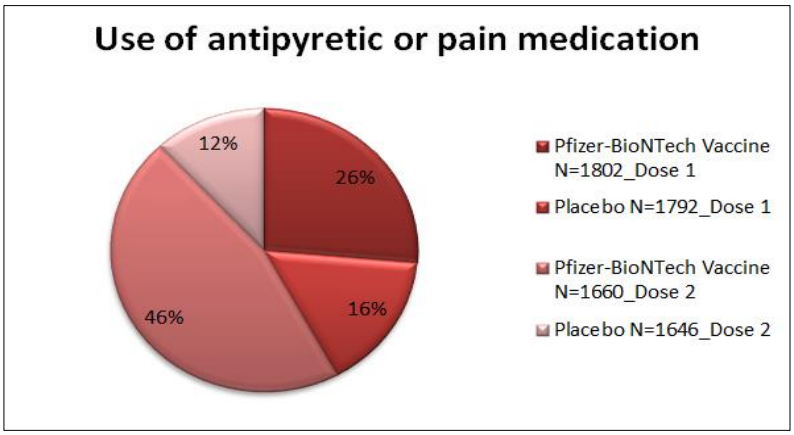

Fig 8: Use of Antipyretics

For the symptom Diarrhea of Pfizer-BioNTech Vaccine, as we compare, there are almost similar number of cases after dose 1 and the dose 2, as shown in Fig 9.

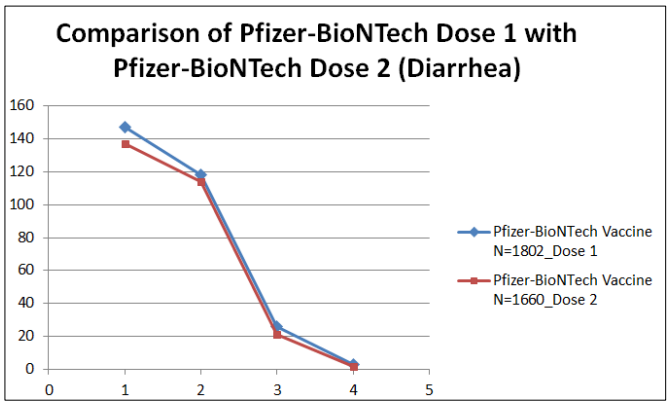

Fig 9: Comparison of Dose 1 and dose 2

As shown in Fig 10, The dose 1 & 2 of Moderna vaccine are highly correlated.

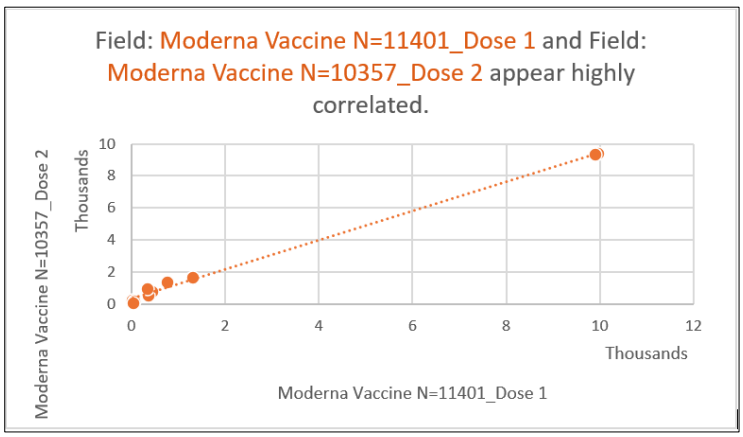

Fig 10: Correlation of Moderna Dose 1 and dose 2 vaccine

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VII. CONCLUSION

Our objective was to find which vaccine are like to have more ADRs. To understand where these drugs can be suggested for kids below 18 who are suffering from Covid-19. Based on the dataset, how many of them got mild reactions, moderate and severe. 77.77% of them come under "any" because patient is neither come under mild, moderate, or severe case. 61.11% of them face mild symptoms. 94.44% of them face moderate symptoms so they can consult doctors for a cure. 100% chance of people experience severe symptoms after using Moderna vaccine. Based on the dataset, 76.92% of them come under "any" because patient is neither come under mild, moderate, or severe case. 69.23% of them face moderate symptoms so they can consult doctors for a cure. Similarly, for mild cases. 92.30% of them face severe symptoms after using Pfizer-BioNTech vaccine. Based on the available data, there are slight changes in number of them face severe symptoms from these two mRNA vaccines. Also, one of the main reasons for more adverse reaction is not gone through the proper clinical trial before approval. Due to the emergency, they manufactured vaccines to cure the Coronavirus. By using multi-class classification, found that comparatively Moderna give more adverse reactions than Pfizer-BioNTech.

VIII. SCOPE AND FUTURE ENHANCEMENT

The sample population which CDC have taken to do the clinical trial for the normal people or who is already suffering from any illness, or under any medications. Also, one of the main reasons for more adverse reaction is not gone through the proper clinical trial before approval. Future Work to analyse on the people who have any illness before and under any medication like diagnosis, etc.

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