



## Correlation between quadrivalent vaccine (H1N1+H3N2+flu strains) and COVID -19?

Rajadurai Meenakshi sundaram<sup>1\*</sup>, Joshua Vijay Joseph<sup>2</sup>, VJ Babu Baskar<sup>3</sup>, Salman Saeed<sup>4</sup>

<sup>1</sup> MBBS, MD Anaes, FEM RCGP-UK, FCCC, FLM, Sr Consultant and Head, Department of Emergency Medicine and Critical Care, Apollo KH Hospital, Melvisharam, Tamil Nadu, India

<sup>2</sup> M.B.B.S, MEM, PG D. Diab, Registrar in Emergency Medicine, Department of Emergency Medicine and Critical Care, Apollo KH Hospital, Melvisharam, Tamil Nadu, India

<sup>3</sup> M.B.B.S, Senior Resident, Department of Emergency Medicine and Critical Care, Apollo KH Hospital, Melvisharam, Tamil Nadu, India

<sup>4</sup> M.B.B.S, PG Registrar, Department of Emergency Medicine and Critical Care, Apollo KH Hospital, Melvisharam, Tamil Nadu, India

### Abstract

**Background:** There is worldwide urgency, efforts, and uncertainties for the discovery of a vaccine against SARS CoV2. Till the specific vaccine is available, there is need for repurposing existing other vaccines.

**Methods:** We conducted a prospective observational study based on historical data of quadrivalent vaccination in patients presenting to the Emergency Department (ED) with influenza like illness (ILI) over a period of 5 months (April 2020 to August 2020). The purpose of this study was to determine whether there is any correlation for Covid-19 among vaccinated patients compared to unvaccinated patients.

**Results:** During the study period, a total of 1237 patients with a mean age of 51.6 years presented to the ED with Influenza like illness. Majority of the patients were not vaccinated with any flu vaccine (93.2%). Among the study population 144(11.6%) patients were tested to be COVID 19 positive. Only 3(3.6%) patients who were vaccinated turned positive compared to non-vaccinated group [3.6% vs 12.2%; OR: 0.266: 95% CI- 0.008- 0.852; p=0.026].

**Conclusion:** This vaccination strategy will help fight against COVID-19 and other flu virus until we come up with a time tested specific vaccine for COVID-19. We recommend that administering quadrivalent vaccine to vulnerable population, frontline health care workers and pregnant women will decrease the incidence of COVID-19 during this pandemic.

**Keywords:** quadrivalent vaccine, emergency department, COVID-19, ILI

### Introduction

COVID-19, caused by the novel corona virus (SARS-CoV-2), is an emerging, rapidly evolving disease that needs rapid intervention as it shows high spread mortality and morbidity rates within very short time. Interestingly, the reported cases show different severity of symptoms, ranging from mild to severe with no symptoms in some cases. Indeed, different susceptibilities to COVID-19 disease were observed between different age groups where children showed lower rate of infection than adults and elderly <sup>[1]</sup>. Although the mechanism behind these differences in infection severity and susceptibility is not clear, one possible explanation could be the difference in the quality and quantity of the immune performance that is shaped by the history of recent infections and/or vaccinations.

Based on the recommended composition of influenza virus vaccines for use in the 2020 – 2021 by WHO(2) the quadrivalent vaccine contains four influenza virus strains two A subtypes and two B subtypes — H1N1 and H3N2, and Victoria and Yamagata respectively <sup>[1]</sup>. Indian Council of Medical Research (ICMR) recommend the vaccine to 4 major groups: elderly individuals ( $\geq 65$  years), children between the ages of 6 months and 8 years, pregnant women regardless of the duration of pregnancy, adults and children with medical conditions, and healthcare workers <sup>[3]</sup>. Hence we decided to study whether there is any role for quadrivalent vaccine in protecting against the COVID-19

pandemic. Though various studies have been done on many vaccines we decided to do in our population presenting with acute emergencies.

**Objective:** To determine the association between quadrivalent (H1N1+H3N2+Flu strains) vaccinated/unvaccinated and incidence of Covid-19 infection.

### Materials and Methodology

**Design:** This was a prospective observational cross sectional study with historical data of vaccination status.

**Setting:** The study was conducted in the Emergency Department (ED) of 150 bedded multi-specialty hospital in South India over a period of 5 months (April 2020 to August 2020). Our ED is a 18-bedded treating about 1000 emergencies per month which includes medical, surgical and trauma.

### Inclusion Criteria

All patients with features suggestive of ILI and SARI were included

### Exclusion criteria

Patients who denied consent and other surgical and trauma emergencies were excluded.

**Variables**

Data were recorded on a standard data abstraction sheet by interviewing patient or their close relatives after getting a written informed consent. Details of presenting illness, physical examination, demographic factors associated with presentation, triage priority at presentation, quadrivalent immunization status and clinical diagnosis were analyzed. Triage priority level was defined by the standard Canadian Triage Association Society (CTAS) guidelines.

**Outcome Variable:** The symptoms, severity and COVID-19 positivity were compared between the patients who received quadrivalent vaccine and who haven't received the vaccine.

**Primary Outcome**

- To determine the incidence of COVID 19 among quadrivalent vaccine (H1N1+H3N2+Flu strains) vaccinated and unvaccinated patients

**Secondary Outcome**

- To determine the coverage of quadrivalent vaccine
- To determine the factors causing low coverage of quadrivalent vaccine
- To determine the trend of Covid-19 and ILI

**Diagnostic criteria**

Influenza like illness (ILI) is defined as an acute respiratory

infection with: measured fever of  $\geq 38\text{ }^{\circ}\text{C}$  and cough with onset within the last 10 days. Sudden acute respiratory illness (SARI) is defined an acute respiratory infection with history of fever or measured fever of  $\geq 38\text{ }^{\circ}\text{C}$  and cough with onset within the last 10 days and requires hospitalization [4].

**Bias:** The data was collected by the primary investigator or co-investigators and not by the treating physician; also consecutive patients were enrolled in the study.

**Statistical analysis:** The data was entered in excel sheet and analysed using Statistical Package for Social Science (SPSS Inc. Released 2018, version 25.0.0.0 Armonk, NY, USA) software. Descriptive statistics were reported using Mean (SD) for continuous variables and Frequency and percentage for categorical variables. Predictors of poor outcome positivity for COVID were determined by bivariate analysis and their 95% confidence intervals were calculated. For all tests a 2-sided p value less than 0.05 was considered statistically significant.

**Results**

During the study period 4347 patients presented to the ED were screened using our ED screening tool. 1237 (28.5%) patients were found to have ILI and SARI symptoms were included in the study after applying exclusion criteria [Figure 1].

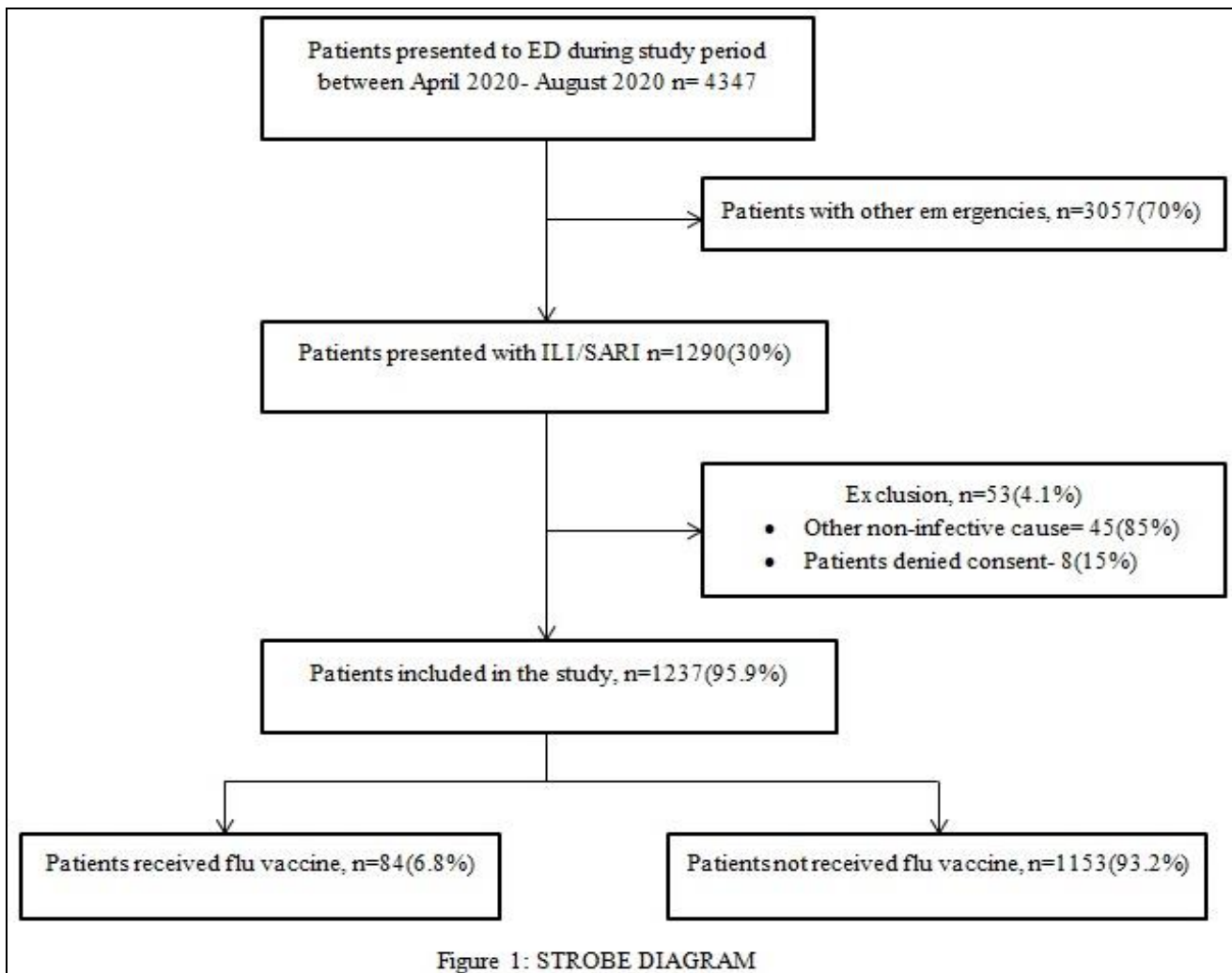


Figure 1: STROBE DIAGRAM

Fig 1: Storbe Diagram

**Demographic profile**

Our study cohort had a mean age of 51.56 (SD 15.5) years with a male predominance (62.9%). Most common comorbidities were diabetes mellitus 534(43.2%) and systemic hypertension 398(32.2%). Among the ILI patients 546(44.1%) were triaged to Priority 2. The baseline characteristics are shown in Table 1.

**Table 1:** Baseline characteristics of ILI patients

Characteristics		n=1237(%)
Mean Age ( SD)		51.56(15.5)
Male		778(62.9)
Female		459(37.1)
Triage priority	Priority 1	348(28.1)
	Priority 2	546(44.1)
	Priority 3	343(27.8)
Comorbidities	Diabetes	534(43.2)
	Hypertension	398(32.2)
	Chronic Liver disease	129(10.4)
	Bronchial asthma/COPD	108(8.7)
	Chronic kidney disease	94(7.6)

\*ILI- Influenza like illness, SD- Standard deviation, COPD- chronic obstructive pulmonary disease.

**Presenting complains and clinical parameters**

The most common symptoms reported were fever (55.6%), cough (37.8%), breathlessness (25.1%) and sore throat (24%). Among the study cohort 923(74.6%) were febrile at presentation. The need for oxygen at presentation was observed in 548(44.3%) patients who had oxygen saturation <90%.

**Quadrivalent vaccination**

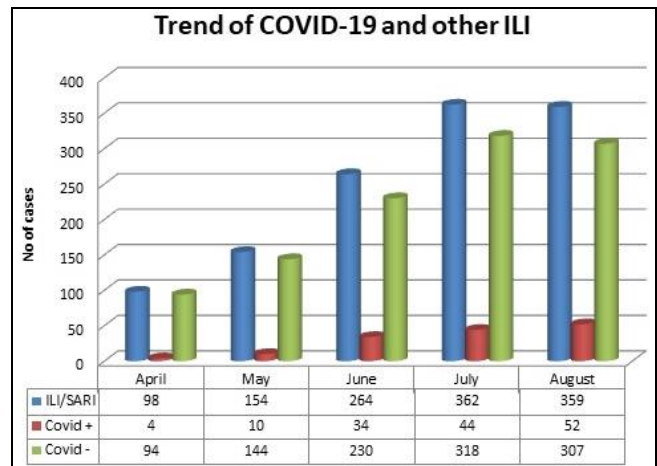
Only 84 patients (6.8%) had received vaccine within one year compared to majority being not vaccinated. Two third of the people who had received prior vaccine were above 60 years. The most common reason for non-vaccination was lack of awareness (52.3%) followed by cost of vaccine (24.4%) and doubtful about efficacy (18.4%). Among healthcare workers only 4 out of 54(7.4%) had received vaccine (Table 2).

**Table 2:** Quadrivalent vaccination among ILI patients

Characteristics		Vaccinated n=84(%)	Not vaccinated n=1153(%)
COVID positive		3(3.6)	141(12.2)
Pregnant mothers		0(0)	38(3.3)
Health care workers		4(4.8)	54(4.7)
Age	<18 years	3(3.6)	126(10.9)
	18-40 years	12(14.3)	230(20)
	40-60 years	14(16.7)	551(47.8)
	>60 years	55(65.5)	246(21.3)

**Covid-19 infection vs quadrivalent vaccine**

Among the ILI identified through clinical assessment, 144 (11.6%) tested positive for COVID-19. Of the patients who received prior quadrivalent vaccine 3(3.6%) were positive for COVID 19 compared to 142(12.2%) patients who were not vaccinated (OR: 0.266: 95% CI- 0.008- 0.852; p=0.026). The COVID infection is on the rise along with other influenza illness leading to alarming twin pandemic. The rise in infection rate is expressed in figure 2.



**Fig 2:** Trend of Covid-19 and other ILI

**Discussion**

Our study showed there is significant relation between the quadrivalent vaccine and the incidence of COVID infection. We observed there is less coverage of quadrivalent vaccine in our region and its importance is lacking even among the healthcare workers. Though all pregnant patients had dose of tetanus toxoid vaccination none of them had received quadrivalent flu vaccine and were not aware of such vaccination.

The cross reactivity of immunity between flu and coronavirus has been reported in earlier studies [5, 6]. The anti-Flu immune responses can induce bystander immunity that is expected to non-specifically augment immunity against other viral infection such as SARS-CoV-2 [7].

The incidence of ILI in our study is high compared to previous studies mainly due to increase in COVID 19 pandemic [8]. The case load is on the rise mainly due to other seasonal flu which is commonly prevalent during this season.

The flu vaccine coverage is low in our study compared to coverage in developed nations [9] but it is similar to the coverage rate done in Indian population [3, 10]. The need and awareness has to be given to increase the vaccination rate and protect from various respiratory infections.

Our study had a contrasting result that it has reduced the incidence of COVID 19 infection among vaccinated individuals compared to Cleveland Clinic study done by Joe Zein *et al* stating that no significant difference due to flu vaccination [11].

A study done in Brazil on inactivated trivalent influenza vaccine as shown to be associated with lower mortality among Covid-19 patients which is significant and similar to our study in decreasing the incidence of COVID 19 infection [12].

**Strength**

- This was a prospective observational study, minimizing the bias and missing data observed in many retrospective studies.
- Our study design with consecutive sampling ensured that almost all ILI were screened and included in the study.
- All patients with ILI were swabbed for COVID 19 RT-PCR

### Limitation

- This was a single centre hospital based study. A community level multicentre study will help to know more about the effects of flu vaccine and its efficacy.
- Asymptomatic and atypical presentations of COVID could have been missed as we took only ILI symptoms.
- Our study represents only patients presenting to Emergency and will not represent the whole population

### Conclusion

We hereby conclude that administering quadrivalent vaccine to vulnerable population, frontline health care workers and pregnant women during this pandemic will decrease the prevalence of ILI without any added risks. Based on our data, quadrivalent vaccine will decrease the pandemic COVID-19 severity; hence vaccination strategy should increase to stop COVID-19 pandemic. All patients getting discharged following COVID infection should be given quadrivalent vaccine to protect them from reinfection. Adequate awareness and improved vaccination strategy will help fight against COVID and other flu virus until we come up with a separate time tested vaccine for COVID 19.

### Research Quality and Ethics Statement

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting and reproducibility guidelines set forth by the EQUATOR Network. The authors also attest that this clinical investigation was determined to require Institutional Review Board / Ethics Committee review, and the corresponding protocol / approval no is KH/EC/2020/001 dated 11/3/2020. We also certify that we have not plagiarized the contents in this submission and have done a Plagiarism Check.

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