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Lessons Learnt during the Second Wave of COVID-19: A Prospective Observational Study of the Effect of Single-Dose COVID-19 Vaccination on the Clinical Profile and Patient Outcome in a Suburban Area of Pune, India

By Arundhati Galande, Paulami Deshmukh, Suhrud Panchawagh, Vinod Bharti, Ashish Tapadiya, Riti Chandra, Fatema Safri, Pawan Salunke, Rekha Galande & Vaishali Deshmukh

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Methods: A prospective observational study was carried out at three community hospitals in a suburban area of Pune, during the second wave, after prior informed consent of patients through a digital questionnaire to record clinical, demographic and laboratory data.

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Lessons Learnt during the Second Wave of COVID-19: A Prospective Observational Study of the Effect of Single-Dose COVID-19 Vaccination on the Clinical Profile and Patient Outcome in a Suburban Area of Pune, India

Effect of COVID-19 Vaccination on Patient Outcome

Arundhati Galande [α], Paulami Deshmukh [σ], Suhrud Panchawagh [ρ], Vinod Bharti [Ω], Ashish Tapadiya [¥], Riti Chandra [§], Fatema Safri [χ], Pawan Salunke [ν], Rekha Galande [Θ] & Vaishali Deshmukh [ζ]

Abstract- ***Background:*** The COVID-19 pandemic, in the first wave in India, had a high case fatality rate. Vaccination and other preventive measures were implemented soon after. Our study was conducted with an aim to assess the effect of a single dose of COVID-19 vaccine on patient outcome and clinical profile of patients admitted with the disease in the second wave.

Methods: A prospective observational study was carried out at three community hospitals in a suburban area of Pune, during the second wave, after prior informed consent of patients through a digital questionnaire to record clinical, demographic and laboratory data.

Results: Out 643 patients were admitted to these hospitals during the aforementioned duration and were enrolled for the study. Out of these, 12.753% patients were vaccinated with a single dose while 87.247% were unvaccinated. Vaccinated patients required lower oxygen therapy ($p = 0.007$), heparin ($p = 0.002$), steroids ($p=0.017$). 100% of vaccinated patients survived while 95.365% survived and 4.635% of died among non-vaccinated persons ($p = 0.047$).

Conclusion: We established through this study that vaccination to have reduced disease severity and improved outcomes among patients affected with COVID-19.

Keywords: vaccination, severity, outcome, COVID-19, oxygen, survived.

Author α: MBBS Student, Bharti Vidyapeeth Deemed University Medical College and Hospital, Sangli.
Author σ: MBBS Student, Smt Kashibai Navale Medical College and General Hospital, Pune. e-mail: paulami.deshmukh@gmail.com
Author ρ: MBBS Student, Smt Kashibai Navale Medical College and General Hospital, Consultant statistician, Sancheti Hospital, Pune.
Author Ω: Director Rising Medicare Hospital, Kharadi, Pune.
Author ¥: Director Ganga Maternity hospital, Mundhava, Pune.
Author§ χ: Statistician SPHERE, Pune.
Author ν: Director Mobicloud Technologies, Pune.
Author Θ: Zonal Medical Officer Pune Municipal Corporation.
Author ζ: Consultant Endocrinologist, Secretary, SPHERE, Pune.

I. Introduction

The Centers for Disease Control and Prevention (CDC) refers to a pandemic as "an epidemic that has spread over several countries or continents, usually affecting a large number of people." [1]

The first wave of COVID-19 in India began in March 2020, with the peak affliction occurring in the month of September 2020 [2]. Patients affected with the SARS COV-2 virus during the first wave in India had an increased infliction of the respiratory system, with a heightened disease severity especially among an elderly and co-morbid demographic [3]. Common symptoms encountered in the first wave included fever, chills, cough, breathlessness, nasal congestion, loss of taste or smell, nausea or vomiting, diarrhoea, joint or muscle pain, and headache [4].

Important lessons learnt from the first wave of COVID-19 were manyfold. Training of staff for the effective management of COVID-19 patients, adopting protective measures like masks and social distancing and testing symptomatic patients early to reduce disease transmission, testing costs, therapeutic expenditure and overburdening of healthcare facilities. Adequate and timely enforcement of legislative measures to contain the disease along with vaccine development and administration.

Development of effective vaccines to prevent the infection and to reduce the severity of the disease was probably the most important lesson learnt during the first wave. The first vaccine to receive emergency validation from the WHO on 31st December 2020 was Pfizer/BioNTechs'sBNT162b2 mRNA Covid-19 Vaccine [5,6] Subsequently, India also developed its own vaccine – Bharat Biotech's BBV152, and also started vaccinating people with the ChAdOx1 nCoV-19 vaccine [7]

The second surge of COVID-19 started in April 2021 and peaked in May 2021. However, healthcare

professionals as well as healthcare systems were better equipped during the second wave due to an increased number of hospital beds, trained staff, better pharmacotherapeutic guidelines, and an increase in the vaccinated population. The vaccination drive implemented in India proved to be highly effective in reducing disease severity during the second wave of COVID-19 [8]. Thus, along with healthcare vigilance, even a single dose of vaccination seemed to prove effective to reduce healthcare burden in terms of hospital inpatient admissions and oxygen and ventilator requirements.

Our study aims to help clearly delineate the effect that a single dose of COVID-19 vaccines has had in reducing clinical symptoms and signs, and its effect on laboratory parameters and treatment strategies during the second wave of COVID-19 in Pune, India.

II. Materials & Methods

This was a prospective observational study conducted in coherence with the STROBE guidelines, in three general community hospitals in a suburban area of Pune, India with the assistance of a local non-government organisation SPHERE (Society for Prevention Healthcare Education and Research). Data was obtained from a period of 1st March, 2021 to 30th June, 2021(duration of the second wave in India).Digital informed consent on a pre-designed informed consent sheet in native as well as national languages was obtained from the patient/legally accepted representative of the patient (in cases of seriously ill patients). All patients admitted for COVID-19 infection in these hospitals and if patients or relatives (if patient was critically ill) willing to consent to sharing their data were included.

The study was conducted using a clinical assessment questionnaire designed using the available literature was incorporated in a software designed by Mobicloud Technologies and installed in all the participating centres. Demographic data, vital parameters, details about their clinical symptoms, clinical signs, laboratory parameters, and treatment given were entered into the questionnaire along with vaccination details which was then subjected to further statistical analysis.

The data on categorical variables was represented by n (% of cases) and the data on continuous variables was presented by Mean and Standard Deviation (SD) or Median and Interquartile Range (IQR). The inter-group statistical comparison of continuous variables is done using the independent samples t-test. The underlying normality assumption and homogeneity of variances were tested before subjecting the study variables to the independent samples t-test. The inter-group statistical comparison of categorical variables was done using the Chi-Squared test. Logistic regression was used to evaluate the association between variables. In the entire study, p-values less than 0.05 were considered to be statistically significant. All the hypotheses were formulated using two tailed alternatives against each null hypothesis (hypothesis of no difference). The entire data is statistically analysed using JASP 0.16.3 for MS Windows.

III. Results

A total of 643 patients were admitted to these hospitals during the aforementioned duration and were enrolled for the study. Out of these, 82 (12.753%) patients were vaccinated with a single dose of either ChAdOx1 nCoV-19 (AZD1222) vaccine (COVISHIELD™) or BBV152 (COVAXIN®) while 561 (87.247%) patients were unvaccinated. Only 2 (2.439%) vaccinated patients were given BBV152 (COVAXIN®), while the remaining received ChAdOx1 nCoV-19 (AZD1222) vaccine (COVISHIELD™). The male to female ratio in vaccinated patients was 2.037:1 while the male to female ratio in unvaccinated patients was 1.318. Symptoms were comparable among the 2 groups. The vital parameters were better among vaccinated patients as compared to non-vaccinated patients (Table 1).

Table 1: Comparison between clinical signs between vaccinated and unvaccinated patients

Symptom	Vaccinated (n=82), mean±SD	Unvaccinated (n=561), mean±SD	p-value
Pulse rate (bpm)	93.293±13.331	98.831±15.493	<0.001***
Respiratory rate (cpm)	18.671±1.988	19.444±2.950	<0.001***
Body temperature (F)	98.123±1.442	99.062±3.682	<0.001***
Oxygen saturation (%)	96.598±1.246	95.528±3.140	0.002**

Evaluated using the Mann-Whitney test.
**p <.05, **p <.01, ***p<.001*

Significantly lower CT severity score, higher haemoglobin levels, lower D-dimer levels, and lower lymphocyte levels were seen in the vaccinated group (Table 2).

Table 2: Comparison between laboratory parameters between vaccinated and unvaccinated patients

Laboratory parameter	Vaccinated (n=82), mean±SD	Unvaccinated (n=561), mean±SD	p-value
CT severity score (0 to 25)	6.429±3.275	10.955±5.280	0.002**
Hemoglobin (gm %)	13.235±1.998	12.392±2.012	<0.001***
CRP (mcg/mL)	36.056±17.342	39.745±32.032	0.782
LDH (U/L)	794.720±77.955	756.013±277.499	0.132
Ferritin (mcg/L)	272.952±80.430	291.944±139.477	0.411
D-dimer (ng/mL)	56.308±160.789	59.965±170.048	0.046*
Blood urea (mg/dL)	53.524±56.947	46.778±41.876	0.324
WBC (/mm^3)	8592.22±1792.506	8246.219±3782.777	0.137
Neutrophils (%)	65.829±12.119	68.110±10.564	0.156
Lymphocytes (%)	25.476±10.548	39.299±299.213	0.030*
Eosinophils (%)	2.683±1.699	2.881±4.551	0.735
Monocytes (%)	3.866±1.891	3.679±2.731	0.209
Basophils (%)	1.585±1.663	1.268±0.900	0.108
Platelets (/mm^3)	236426.829±79397.582	239502.317±91703.532	0.802

Evaluated using the Mann-Whitney test.
**p <.05, **p <.01, ***p<.001*

A significantly lower proportion of vaccinated patients required oxygen therapy (p = 0.007), heparin (p = 0.002), steroids (p = .017) (Table 3).

Table 3: Comparison between requirement of various treatments in vaccinated and unvaccinated patients

Management	Vaccinated (n=82), n (%)	Unvaccinated (n=561), n (%)	p-value
Oxygen therapy	2 (2.439%)	70 (12.478%)	0.007**
Heparin	4 (4.878%)	106 (18.895%)	0.002**
Steroids	9 (10.976%)	126 (22.460%)	0.017*
Steroid duration (mean±SD in days)	4.111±2.028 days	6.405±3.091 days	0.014* (Mann-Whitney test)
NIV	10 (12.195%)	111 (19.786%)	0.100
Ventilator	0 (0%)	7 (1.248%)	0.309
Antiviral therapy	79 (96.341%)	509 (90.731%)	0.090
Tocilizumab	8 (9.756%)	74 (13.191%)	0.384
Oral antipyretics	32 (39.024%)	266 (47.415%)	0.155

Evaluated using the chi-squared test of independence (unless stated otherwise)
**p <.05, **p <.01, ***p<.001*

Age, history and duration of hypertension, a high mean arterial pressure, non-vaccinated status, a low oxygen saturation, high CRP level and ventilatory requirement were significant predictors of poor outcomes (Table 4).

Table 4: Univariate & forward stepwise multivariate logistic regression for various variables predicting the outcome in patients

	Univariate			Multivariate		
	OR	95% CI	*p-value*	OR	95% CI	*p-value*
Age (years)	0.965	0.941-0.990	.007**	-	-	-
Hypertension	0.216	0.090-0.519	<.001***	0.306	0.0771.208	.091
Duration of HTN (years)	0.881	0.810-0.959	.003**	-	-	-
Vaccination (1 dose)	1.897	1.479-2.252	.007**	1.974	1.7652.378	<.001***
Mean arterial pressure	0.909	0.858-0.964	.001**	0.937	0.859-1.022	.143
SpO2	1.091	1.006-1.183	.036*	-	-	-
CRP	0.988	0.980-0.995	.001**	0.986	0.9789.994	<.001***
Need for oxygen therapy	0.260	0.109-0.623	.002**	-	-	-
Need for ventilator	0.027	0.006-0.127	<.001***	0.016	0.0039.086	<.001***

Out of 643 total patients, 518 (80.56%) patients were vaccinated against tuberculosis with the BCG vaccine. Patients who were vaccinated with BCG were less likely to develop generalized weakness ($p < 0.001$), and nausea ($p < 0.001$). Furthermore, patients who were vaccinated with BCG had a lower pulse rate (mean = 96.527 beats per minute, $p < 0.001$), had a lower respiratory rate (mean = 19.236 cycles per minute, $p = 0.025$), and had lower body temperature (mean = 98.746 F, $p < 0.001$) possibly indicating a less intense cytokine induced response.

Out of 82 patients who were vaccinated, 82 (100%) were discharged (survived). Out of 561 patients who weren't vaccinated, 535 (95.365%) were discharges (survived) while 26 (4.635%) died ($p = 0.047$).

IV. Discussion

SARS-CoV-2 is a single-stranded RNA virus [9] with the established capacity to transmit from human to human [10] by virtue of an envelope-anchored spike protein which mediates viral entry into the host and fusion of viral and host cell membranes[11].

Various components of the virus including the spike protein, plasmid DNA and or mRNA were utilised to make different vaccines. At present the vaccines available in India are , plasmid DNA vaccine- ZyCoV-D, Gam-COVID-Vac combined vector vaccine, Biological E's novel Covid-19 vaccine containing Receptor Binding Domain of SARS-CoV-2, Intranasal Adenoviral vector COVID-19 vaccine (BBV154), mRNA based vaccine (HGCO19) and are certified safe to use for above the age of 18years; Covishield (SII-ChAdOx1 nCoV-19), Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152)- COVAXIN™ permitted for use among adults and children above 12 years of age, CORBEVAX-a protein subunit COVID-19 permitted for use among everyone including children above 5 years of age and COVOVAX (SARS-CoV-2 recombinant spike protein nanoparticle vaccine with Matrix-M1™ adjuvant) for everyone including children above 2 years of age[12].

In this study we found a better clinical and biochemical profile and improved survival statistics ($p<0.05$) among vaccinated patients with merely one dose. Prior vaccination is postulated to have improved humoral and cell mediated immune response to the virus and viral proteins. There have been many trials on vaccines for safety and efficacy since the very advent of the pandemic. Certain trials assessing efficacy of administering a different vaccine booster to a cohort previously administered a different vaccine against COVID-19 found a more robust immune response owing to greater reactogenicity of the mixed vaccine with minimal to no serious adverse effects.[13]. In the CombiVacS study [14], which was a phase two randomised controlled trial conducted to assess immunogenicity of heterologous vaccination of BNT162b2 booster in ChAdOx1-S-primed participants, showed a significantly high immune response in the test arm as opposed to the control arm (95% CI 7371·53-8161·96 at day 14, $p<0·0001$)

A nationwide cross-sectional study conducted by Singh et al (COVAT study) among healthcare workers in India showed a significantly high seropositivity among people vaccinated with initially one dose of ChAdOx1 nCoV-19 (AZD1222) vaccine (COVISHIELD™) (86.8 vs. 43.8% respectively, $p < 0.001$) after the first dose. as compared to BBV152 (COVAXIN®) [15]. Vaccine safety among pregnant women was also established by a systematic review and meta-analysis conducted by Prasad et al which proved vaccine safety, a 15% decrease in the odds of stillbirth was associated with vaccination (vs. no vaccination) in pregnancy ($p=0.035$) and decreased odds of birth asphyxia by 71% by virtue of vaccination (as opposed to no vaccination) with no higher risk of obstetric complications ($p>0.05$) among vaccinated women as compared to non-vaccinated women [16].

In our study we additionally documented the effect of prior BCG vaccination on patient outcomes. All patients vaccinated with the BCG Vaccine had less generalised weakness, nausea, a low respiratory rate, low pulse(in all $p<0.001$) compared to those who were not vaccinated with BCG. These effects are postulated to have occurred due to transcriptional, epigenetic and metabolic reprogramming of the myeloid cells in the BCG-vaccinated individuals. The epigenetic changes are manifested as chemical modifications of the histone, resulting in enhanced chromatin accessibility, easier transcription of genes important for antimicrobial responses and improved cell function [17]. In a global retrospective analysis by Madan et al, countries with a high burden of tuberculosis had a lower incidence of COVID-19, irrespective of the BCG vaccine status of the country. On the other hand, in countries with a lower burden of tuberculosis, BCG vaccine administration showed a significantly lower incidence of COVID-19 ($p<0.001$), suggesting some protective mechanisms in TB-endemic areas [18]. Ozdemir et al have shown proportionately less cases, milder illness and a lower death rate in BCG vaccinated population as compared to BCG non-vaccinated across countries and hemispheres [19].

Through this prospective study, demographic factors like increased age ($p=0.007$), no vaccination against COVID-19($p<0.001$), history and longer duration of hypertension ($p<0.001$; $p=0.003$ respectively), a high CRP level in blood ($p<0.001$), a lower oxygen saturation on room air ($p=0.036$) and the requirement of a ventilator for respiratory support ($p<0.001$) to be a strong predictor of poor patient recovery and outcome.

V. Limitations

This study, has a smaller sample size due to a reduction in the number of people willing to test themselves for the disease and limited access to other hospitals actively involved in management of COVID-19 affected patients on a larger scale. This study was conducted as a prospective analysis of patients in the second wave of COVID-19 infection in India; since then there have been many changes implemented to vaccination schedules, patient categorisation and screening coupled with the concept of herd immunity which could have changed patient outcomes which may or may not be coherent with the findings of our study.

VI. Conclusion

Our study along with many others conducted among different populations in many parts of the world proves vaccination to have reduced disease severity and improved outcomes among patients affected with COVID-19. Vaccines have also been argued upon to have resulted in several serious adverse effects, however, it must be well understood and impressed upon the public that vaccine development is a dynamic process which entails careful post-marketing surveillance of the product and persistent efforts to avert any such mishappenings.

Although primordial prevention in the form of self-protection, isolation and education of frontline workers, students in healthcare and the public is being conducted even today on a daily basis, given the rapid transmission and phylogenetic variations of the Sars-CoV2 virus, vaccination is imperative as a means of risk reduction in both the diseased and healthy population in the best interests of the healthcare facilities and the population alike.

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