Technical paper

VACCINE BREAKTHROUGH SARS-CoV-2 INFECTIONS

Department of Health & Family Welfare

Government of Kerala

VACCINE BREAKTHROUGH SARS-CoV-2 INFECTIONS

COVID-19 vaccines are effective and are a critical tool to bring the pandemic under control. However, no vaccines are 100% effective at preventing illness in vaccinated people. There will be a small percentage of fully vaccinated people who might get moderate-severe COVID 19 despite full vaccination. Majority of the vaccine breakthrough infections are mild or asymptomatic and hence from May 1,2021 ,CDC USA transitioned from monitoring all reported vaccine breakthrough cases to focus on identifying and investigating only hospitalized or fatal cases due to any cause .

Surveillance definition of Vaccine breakthrough infections

For the purpose of surveillance, a vaccine breakthrough infection is defined as the detection of SARS-CoV-2 RNA or antigen in a respiratory specimen collected from a person ≥14 days after they have completed all recommended doses of a approved COVID 19 vaccine.

VACCINE EFFECTIVENESS

Data from UK Public Health on vaccine effectiveness against different outcomes when alpha variant was dominant

Outcome	Vaccine effectiveness			
	Pfizer-BioNTech		Oxford-AstraZeneca	
	1 dose	2 doses	1 dose	2 doses
Symptomatic disease	55 to 70%	85 to 95%	55 to 70%	70 to 85%
Hospitalisation	75 to 85%	90 to 99%	75 to 85%	80 to 99%
Mortality	70 to 85%	95 to 99%	75 to 85%	75 to 99%
Infection	55 to 70%	70 to 90%	55 to 70%	65 to 90%
Transmission (secondary cases)*	45 to 50%	No data	35 to 50%	No data

Vaccine effectiveness against symptomatic disease for Alpha and Delta variants

Vaccine Status	Vaccine Effectiveness	
	Alpha	Delta
Dose 1	49 (46 to 52)	35 (32 to 38)
Dose 2	89 (87 to 90)	79 (78 to 80)

Vaccine effectiveness against hospitalisation for Alpha and Delta variants

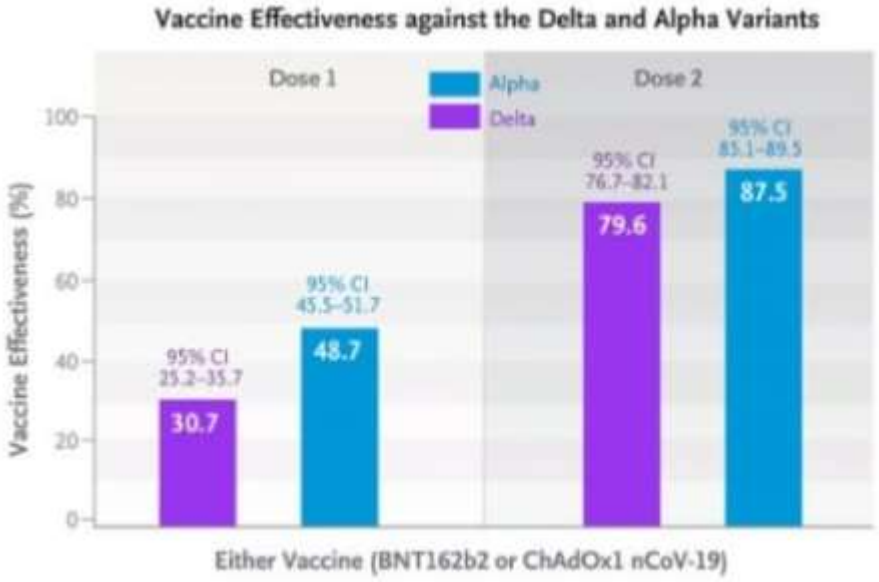
Vaccine Status	Vaccine Effectiveness	
	Alpha	Delta
Dose 1	78 (64 to 87)	80 (69 to 88)
Dose 2	93 (80 to 97)	96 (91 to 98)

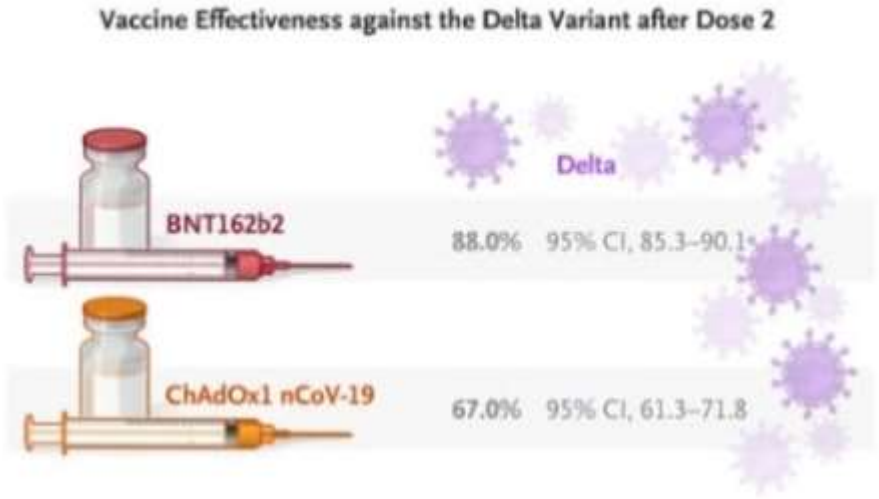
Impact of Variants of concern on Vaccine breakthrough Infections

The B.1.617.2 [delta] variant of SARS-CoV-2 became the dominant variant circulating in India by mid-April 2021.In Kerala also results from genome sequencing indicate that delta is the predominant variant circulating in the state. Effectiveness of available vaccines in preventing infection and disease with delta variant is less compared to their effectiveness in preventing infection/disease with alpha variant. This is evidenced from real world data from countries like Israel, Malta, Iceland etc where vaccination coverage is more than 70%. Reports of how the vaccines fared against delta in Canada, Qatar, Israel and England plus Scotland shows that vaccine effectiveness at preventing infection with delta variant ranged from about 40 percent up to nearly 80 percent. Effectiveness against severe illness was consistently higher, in the ballpark of 90 percent for vaccine recipients overall.

The study on the effectiveness of COVID 19 vaccines against the delta variant by Lopez Bernal J et al in NEJM clearly demonstrates that the effectiveness of vaccines in preventing infection with delta variant is less than that due to alpha variant. Effectiveness after one dose of vaccine (BNT162b2 or ChAdOx1 nCoV-19) was notably lower among persons with the delta variant (30.7%; 95% confidence interval [CI], 25.2 to 35.7) than among those with the alpha variant (48.7%; 95% CI, 45.5 to 51.7); the results were similar for both vaccines. With the BNT162b2 vaccine, the effectiveness of two doses was 93.7% (95% CI, 91.6 to 95.3) among persons with the alpha variant and 88.0% (95% CI, 85.3 to 90.1) among those with the delta variant. With the ChAdOx1 nCoV-19 vaccine, the effectiveness of two doses was 74.5% (95% CI, 68.4 to 79.4) among persons with

the alpha variant and 67.0% (95% CI, 61.3 to 71.8) among those with the delta variant.





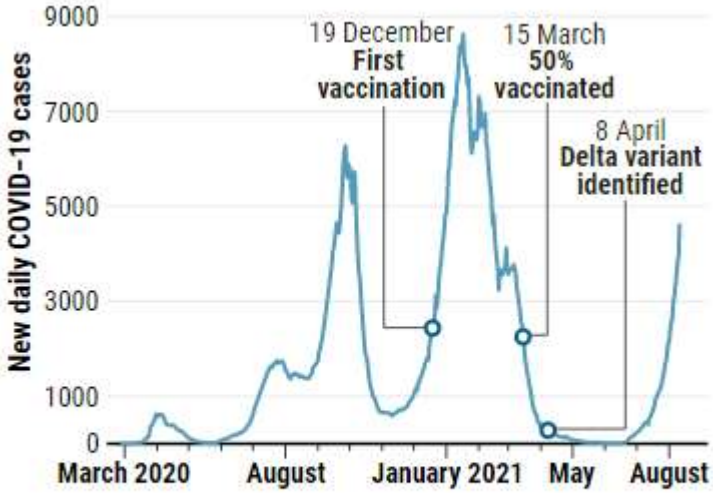
SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness

EAVE II is a Scotland-wide COVID-19 surveillance platform that has been used to track and forecast the epidemiology of COVID-19, inform risk stratification, and investigate vaccine effectiveness and safety. Considering the whole population cohort (rather than just hospital cases), the test-negative analysis to estimate vaccine effectiveness in preventing RT-PCR-confirmed SARS-CoV-2 infection showed that, compared to those unvaccinated, at least 14 days after the second dose, BNT162b2 (Pfizer–BioNTech vaccine) offered very good protection: 92% (95% CI 90–93) against alpha variant and 79% (75–82) against

delta variant. Protection associated with ChAdOx1 nCoV-19 (Oxford–AstraZeneca vaccine) was, however, substantial but reduced: 73% (95% CI 66–78) for alpha cases versus 60% (53–66) for delta cases. Both the Oxford–AstraZeneca and Pfizer–BioNTech COVID-19 vaccines were effective in reducing the risk of SARS-CoV-2 infection and COVID-19 hospitalisation in people with the Delta VOC, but these effects on infection appeared to be diminished when compared to those with the Alpha VOC.

VACCINE BREAKTHROUGH INFECTIONS IN ISRAEL

It is clear from Israel data that "**Vaccinations blunts, but does not beat delta".** Israel has among the world's highest levels of vaccination for COVID-19, with 78% of those 12 and older fully vaccinated, the vast majority with the Pfizer vaccine. Yet the country is now logging one of the world's highest infection rates, with nearly 650 new cases daily per million people. More than half are in fully vaccinated people, underscoring the extraordinary transmissibility of the Delta variant and stoking concerns that the benefits of vaccination ebb over time.

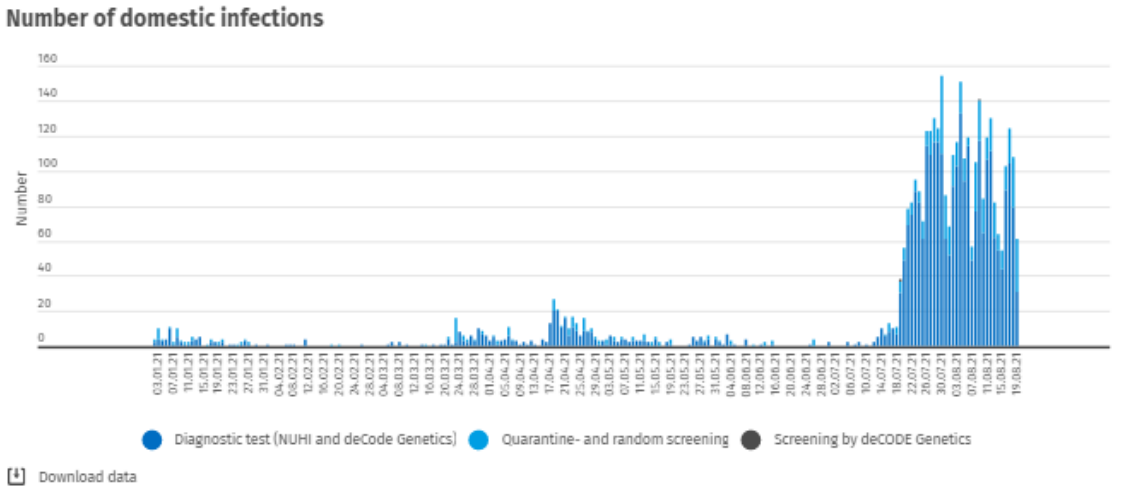


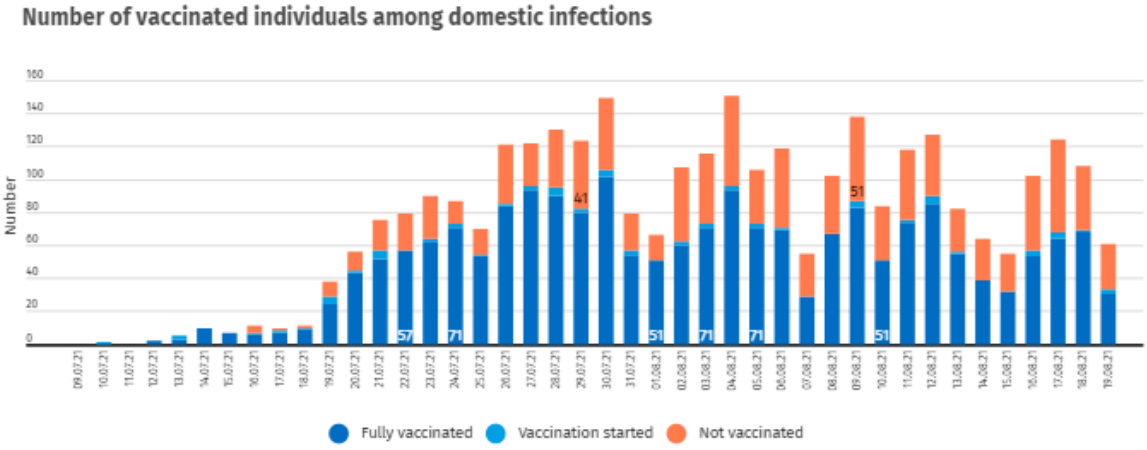
(GRAPHIC) K. FRANKLIN/*SCIENCE*; (DATA) H. RITCHIE *ET AL.*, OURWORLDINDATA.ORG, 2020

Among 1497 fully vaccinated health care workers for whom RT-PCR data were available at the largest medical center in Israel [Sheba Medical Center], 39 SARS-CoV-2 breakthrough infections were documented. In that study it was found that although the BNT162b2 vaccine is extremely effective, rare breakthrough infections carry an infectious potential and create a special challenge, since such infections are often asymptomatic and may pose a risk to vulnerable populations. Most of the vaccine breakthrough infections were mild or asymptomatic. [**COVID 19 breakthrough infections in vaccinated health care workers:** Moriah Bergwerk et al:**nejm;july 28:2021]**

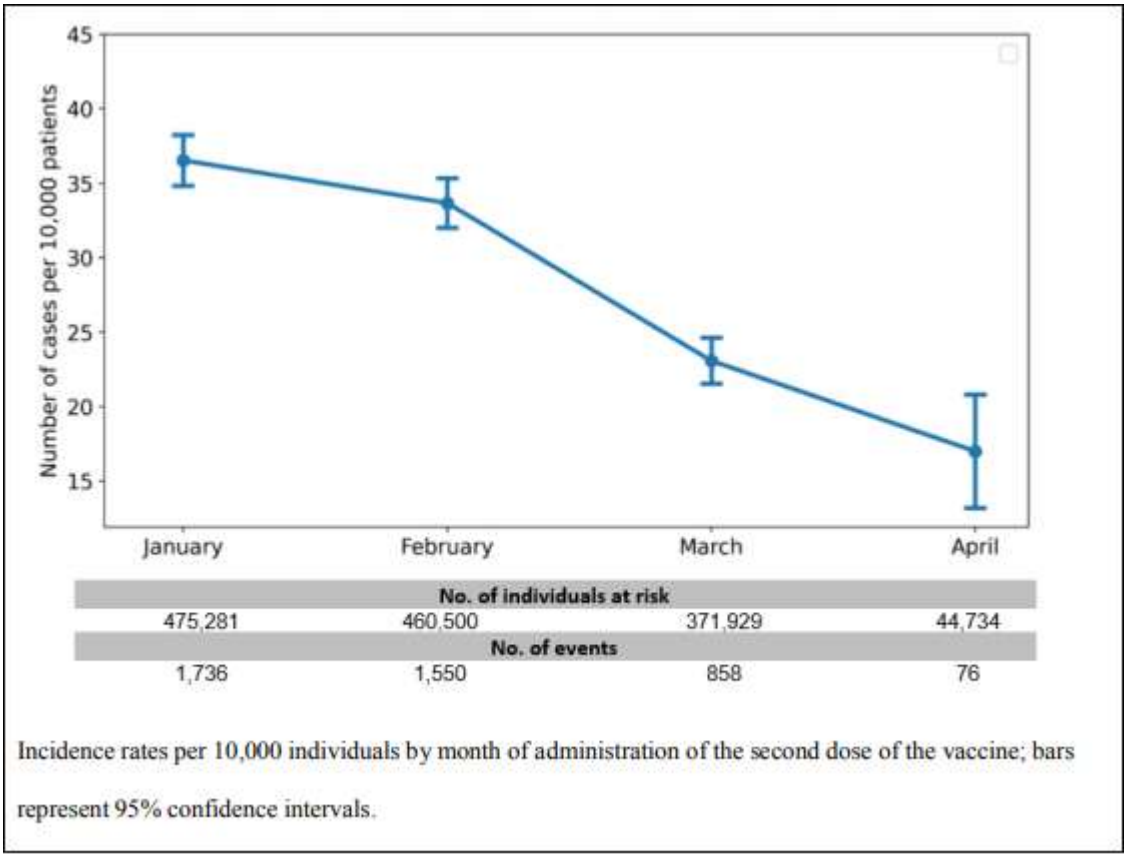
VACCINE BREAKTHROUGH INFECTIONS :DATA FROM ICELAND

Despite having 71.5% of its population fully vaccinated, Iceland is seeing a surge in cases due to vaccine breakthrough infections due to delta variant.





INCIDENCE RATE OF VACCINE BREAKTHROUGH INFECTIONS BY MONTH OF COMPLETION OF SECOND DOSE OF VACCINE [DATA FROM ISRAEL]



Incidence rates per 10,000 individuals by month of administration of the second dose of the vaccine; bars represent 95% confidence intervals.

Using data from the computerized database of Maccabi Healthcare Services (MHS), the correlation between time-from-vaccine and incidence of breakthrough infection was assessed . The study demonstrated higher risks for breakthrough infections in persons who were vaccinated early compared to late probably due to antibody decay kinetics. Individuals who were vaccinated in January 2021 had a 2.26-fold increased risk (CI 1.80- 3.01) for breakthrough infection compared to individuals who were vaccinated in April 2021 (Figure 1). In this cohort of MHS members, all of whom are vaccinated with the BioNTech/Pfizer mRNA BNT162b2 vaccine in a two-dose regimen, a significant correlation was identified. The risk for breakthrough infection was significantly higher for early vaccinees compared to those were vaccinated earlier.[**Correlation of SARS-CoV-2 Breakthrough Infections to Time-from-vaccine; Preliminary Study: Barak Mizrahi et al**]

DATA FROM COUNTRIES WHICH HAVE FULLY VACCINATED MORE THAN 50% OF THEIR POPULATION

Even in countries with very high vaccination coverage, vaccine breakthrough infections are reported however the hospitalization, severe infections and death are far less compared to pre-vaccine era.

		Current		First wave	
Country	Vaccination	Cases	Death	Cases	Death
Singapore	69.6	58	1	55	0
Chile	67.87	833	9	797	52
Qatar	64.95	211	2	200	0
Denmark	64.73	999	4	992	1
Portugal	64.67	2338	14	2321	16
Spain	63.15	15058	66	17442	120
Israel	62.53	5554	18	5599	30
UK	59.47	28296	90	27249	462
Italy	57.01	6322	30	6172	45
France	51.79	23697	65	23828	114
USA	50.26	130808	662	130449	1045

VACCINE EFFECTIVENESS STUDIES FROM INDIA

ChAdOx1 nCoV-19 effectiveness during an unprecedented surge in SARS COV-2 infections was studied in Gangaram hospital , New Delhi during second wave of COVID 19.Vaccine effectiveness for two doses of ChAdOx1 nCoV-19 given at a median interval of 30 days (IQR: 28-36) was 28% (10-41%) for symptomatic infections, 67% (44-81%) for moderate to severe disease, 76% (37-89%) for supplemental-oxygen-therapy and nearly 97% (43-99.8%) for deaths.

This study reports lower protection by two doses from symptomatic infections than that reported by CMC Vellore, India (67%], or by Public Health England (65% against the delta variant). It appears closer to that reported by Public Health Scotland (25-60% against the delta variant). However, of note, is similar high protection offered by two doses, as in these studies against moderate to severe disease, supplemental-oxygen-therapy and deaths. Secondly, a single dose offered no protection in this study against symptomatic infections (18% (-10 to 38) or any outcome of interest. This appears to be in line with the Public Health Scotland data on single-dose protection against the delta variant (7%; -7 to18% within 28 days and 18%; 9-27%; beyond 28 days). However, it is in contrast to a modestly reduced but significant protection offered by a single dose as seen in the study from CMC Vellore (50%) and from Public Health England (33%).

GB PANT DATA

Outcomes	2 doses versus no dose		1 dose versus no dose		2 doses vs no dose >=14 days		1 dose vs. no dose >=21 days		Previous infection versus no infection	
	Effectiveness	95%CI	Effectiveness	95%CI	Effectiveness	95%CI	Effectiveness	95%CI	Effectiveness	95%CI
Symptomatic infections	24%	6 to 38	4%	-26 to 27	28%	10 to 41	18%	-10 to 38	93%	87 to 96
Moderate to Severe Disease	65%	42 to 79	7%	-68 to 48	67%	44 to 81	37%	-24 to 68	89%	57 to 97
Need for oxygen therapy	75%	42 to 89	12%	-111 to 63	76%	37 to 89	53%	-44 to 85	85%	-9 to 98
Deaths	97%	43 to 99.8	70%	-157 to 97	97%	43 to 99.8	69%	-160 to 97	NA	NA

[**ref: ChAdOx1 nCoV-19 effectiveness during an unprecedented surge in SARS COV-2 infections;Ruma Satwik et al: European Journal of Internal Medicine**]

CMC VELLORE DATA

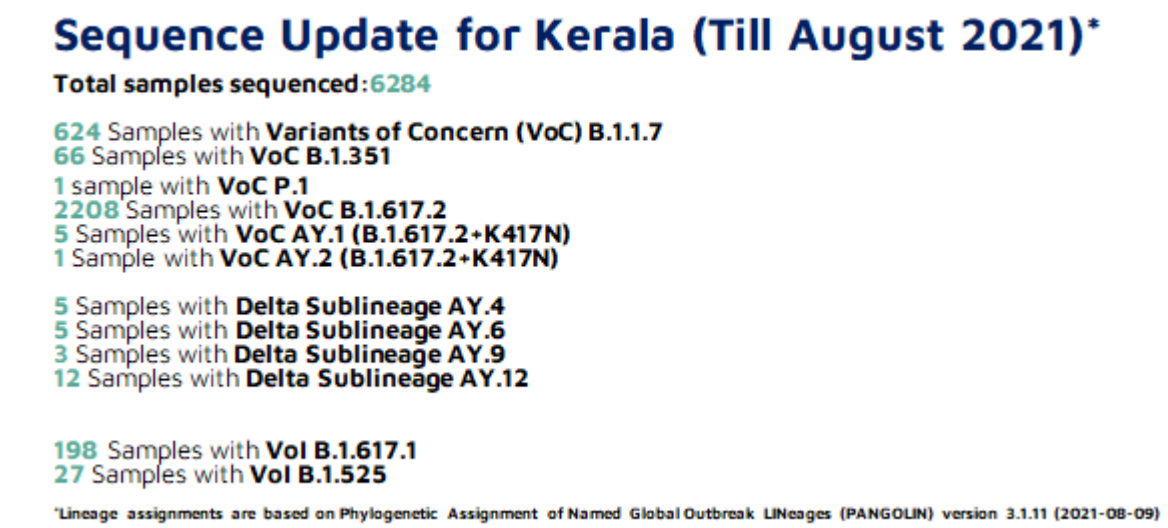
TABLE. Staff Who Contracted COVID-19 Infection[a,b]

Variable	Not vaccinated (n=1609)	Received 1 dose (n=1878)	RR[c] (95% CI)	Protective effect of 1 dose of vaccine[d]	Fully vaccinated (n=7080)[e]	RR[c] (95% CI)	Protective effect of 2 doses of vaccine[d]
Developed infection[f]	438 (27.2)	200 (10.6)	0.39 (0.34-0.46)	61% (54%-66%)	679 (9.6)	0.35 (0.32-0.39)	65% (61%-68%)
Hospitalized[g]	64 (4.0)	22 (1.2)	0.30 (0.18-0.48)	70% (52%-82%)	64 (0.9)	0.23 (0.16-0.32)	77% (68%-84%)
Needed oxygen therapy[g]	11 (0.7)	0 (0)	0.04 (0.0-0.63)	96% (37%-100%)	4 (0.06)	0.08 (0.03-0.26)	92% (74%-97%)
Needed ICU care[g]	8 (0.5)	0 (0)	0.05 (0.0-0.87)	95% (13%-100%)	2 (0.03)	0.06 (0.01-0.27)	94% (73%-99%)
Deaths	1	0	0.29 (0.01-7.0)	NC	0	0.08 (0.0-1.86)	NC

[**ref: Protective effect of COVID 19 vaccine among health care workers during second wave of pandemic in India:Peter John Victor et al: Mayo Clinical Proceedings**].

Kerala

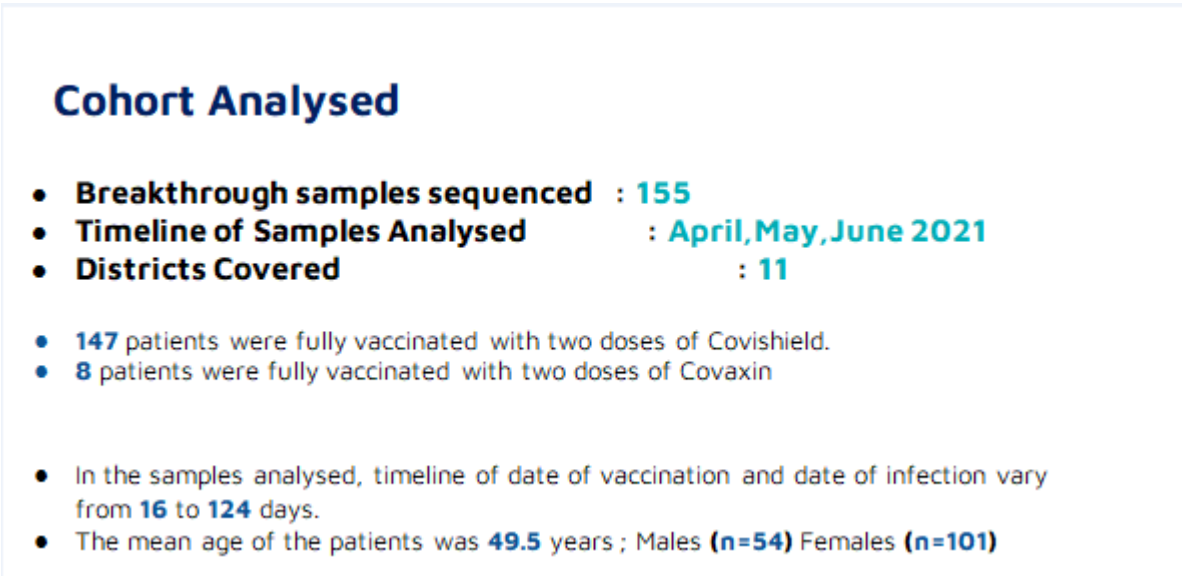
GENOMIC SURVEILLANCE DATA FROM KERALA



Genomic surveillance data from Kerala shows that the variant predominant in Kerala now is VoC B.1.617.2 [Delta] which is associated with comparatively reduced vaccine effectiveness against infection compared to Alpha variant.

Genomic Analysis of Vaccine breakthrough Infections in Kerala

Genomic analysis of 155 cases of vaccine breakthrough infections showed that Delta variant was responsible for 81.29% of them. All the sequenced cases were mild and none of them required hospitalization.

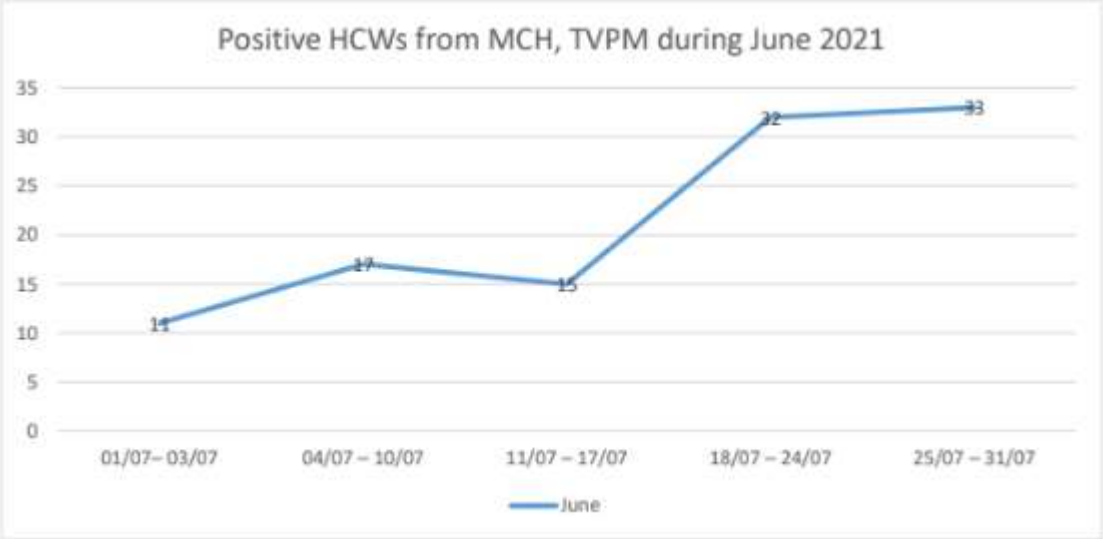


Breakthrough samples analysed -Kerala 2021

126 Samples with **VoC** **B.1.617.2**
9 Samples with **VoI** **B.1.617.1**
1 Sample with **VoI** **B.1.525**
1 samples with **VoC** **AY.1**
2 samples with **VoC** **AY.4**
2 samples with **VoC** **AY.9**
1 samples with **VoC** **AY.12**
13 samples were not assigned any lineage.

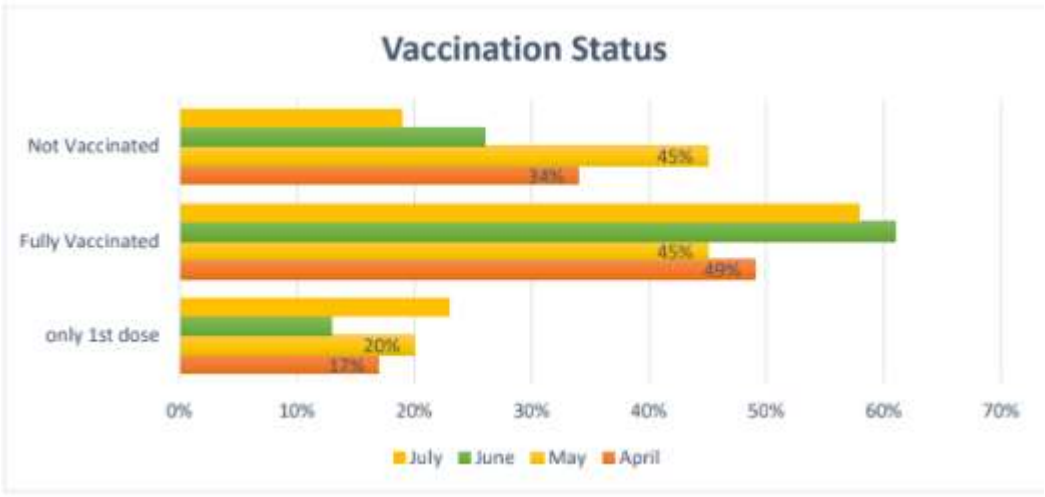
151 were symptomatic with mild symptoms
57 were Health Care Workers
None of the cases had severe disease which required hospitalisation

VACCINE BREAKTHROUGH INFECTION AMONG HEALTH CARE WORKERS [HCW]: DATA FROM GMC THIRUVANANTHAPURAM



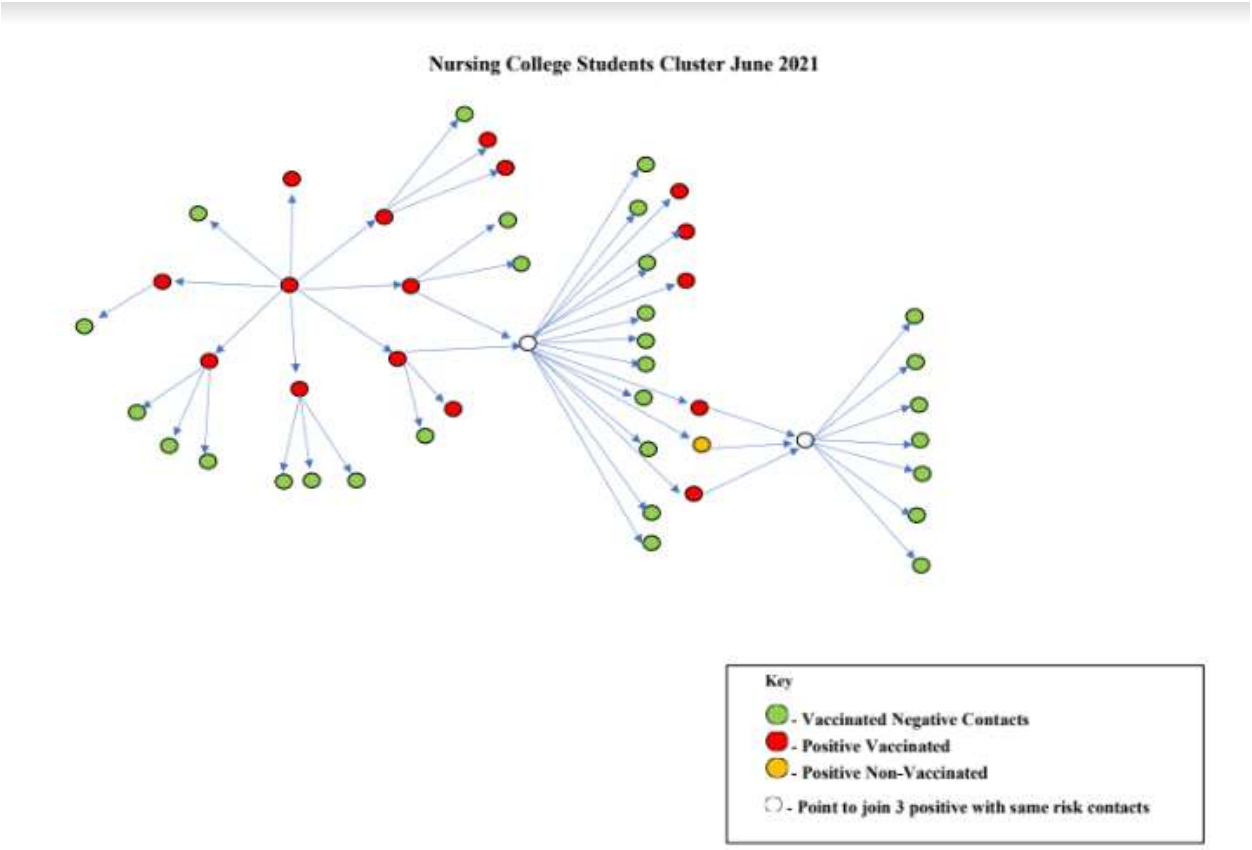
Vaccination Status of Positive HCWs of April, May, June & July 2021

Month	Only First dose	Fully Vaccinated	Not Vaccinated
April	17%	49%	34%
May	20%	45%	45%
June	13%	61%	26%
July	23%	19%	58%



All the vaccine breakthrough infections reported in GMCT, were mild infections. All the sequenced isolates of breakthrough infections turned out to be due to Delta variant.

NETWORK ANALYSIS OF A VACCINE BREAKTHROUGH INFECTION CLUSTER TO UNDERSTAND TRANSMISSION DYNAMICS



This network analysis clearly shows that persons with vaccine breakthrough infections can spread infection to others thereby highlighting the importance of masking, physical distancing and hand hygiene even for fully vaccinated persons.

CONCLUSIONS

1.Real world data from countries with very high vaccination rates like Israel,UK,Malta, Iceland etc clearly prove that vaccination is not 100% effective in preventing COVID 19 infection especially with delta variant. However vaccinations are very effective in preventing disease severity and death due to COVID 19.Majority of the vaccine breakthrough infections are mild or asymptomatic and hence from May 1,2021 ,CDC USA transitioned from monitoring all reported vaccine breakthrough cases to focus on identifying and investigating only hospitalized or fatal cases due to any cause.

2. Against delta variant effectiveness after the first dose of ChAdOx1 nCov-19 to prevent infection is only 30.7% and after both doses is 67%. This means that there is chance of breakthrough infections even in fully vaccinated as the variant prevalent in Kerala and India now is Delta. However, as vast majority of the vaccine breakthrough infections are asymptomatic or mild, only a State with very good surveillance and testing strategy will be able to identify them. Data from developed countries and centres like GB pant and CMC Vellore also support the view that vaccine breakthrough infections can be identified only with very good active surveillance and testing strategy.More over as per ICMR fourth round sero-survey, Kerala identifies one in every 5 cases while National average is catching one in 28 cases.This gap in detection rate is likely to widen further in case of vaccine breakthrough infections as they are more difficult detect due to mild symptom severity.

3. CMC Vellore data shows that 9.6% of fully vaccinated health care workers developed breakthrough infections, This clearly shows that as the population vaccination coverage goes up , in parallel number of vaccine breakthrough infections will also increase. But since majority of them are mild, its clinical impact will be low.

4.Of the vaccine breakthrough infections in kerala, 82% were due to Delta variant. Majority of the breakthrough infections were of mild severity clearly demonstrating the fact that vaccination can prevent severe disease and death.

Discussion-

Breakthrough infection is being discussed in all scientific communities and forums to assess efficacy of vaccination and future approaches to tackle Covid pandemic.
However, at this point of time vaccination is of a great value as it is clear from the data analysis from various parts of the world that the vaccination reduces severity of the disease. Therefore, it is very important to continue vaccination and also ensure covid appropriate behaviour not only at the individual level but at community and society level. This will need involvement of people and community to change behaviour and the way we do social interaction. Such behavioural change takes time but it is not impossible.