

Publication status: Preprint has been published in a journal as an article
DOI of the published article: <https://doi.org/10.21149/13456>

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<https://doi.org/10.1590/SciELOPreprints.3134>

Submitted on: 2021-11-01

Posted on: 2021-11-12 (version 1)
(YYYY-MM-DD)

Superspreading event of COVID-19 in adolescents: is there a difference between the vaccinated and the unvaccinated?

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Abstract

Objective:

The aim of this study is to estimate the incidence of COVID-19 in a vaccinated and an unvaccinated group of adolescents and describe their symptoms.

Methods: In May 2021 a private indoor event for high school adolescents took place resulting in a superspreading event. As part of the study, an anonymous questionnaire was sent to all adolescents invited to the event and details about symptoms, previous COVID-19 infection, vaccination status and behavior during the event was assessed. Two groups were formed, one of vaccinated individuals and the other of unvaccinated individuals. A sample from a fully vaccinated symptomatic individual was sequenced. General characteristics for the studied groups are described using categorical and continuous data. The incidence of COVID-19 in each group was estimated by taking the total number of COVID-19 positive cases (numerator) divided by the total number of individuals (denominator) multiplied by 100.

Results: A total of 41 out of the 164 adolescents (incidence 25%, 95%CI 18.6- 32.4) that attended the private indoor event developed COVID-19. A sample was sequenced from one of the symptomatic and fully vaccinated individuals with BNT162b2 (Pfizer-BioNTech vaccine) finding SARS-CoV-2 Delta (B.1.617.2) variant of concern. The incidence of COVID-19 in the unvaccinated was 35.1% (95%CI 25.5-45.6), and in the vaccinated 11.4% (95%CI 5.1-21.3). There were more unvaccinated than vaccinated teenagers that developed COVID-19 $\chi^2= 12.6$, ($p=0.00$). The crude Odds Ratio when comparing the unvaccinated vs the vaccinated was of 4.19, 95%CI 1.79-9.8. Almost all (40 out of the 41) developed more than one COVID-19 symptom. The mean number of symptoms reported was 6 in both vaccinated and unvaccinated individuals. Both unvaccinated and vaccinated positive adolescents developed fatigue, runny nose, anosmia,

fever, cough, and ageusia. None of the adolescents that reported a prior COVID-19 infection got reinfected during the event (N=47). At least two known positive individuals attended the event; all other attendees tested negative in a rapid antigen test performed 24 hours before the event. Attendees were there for 2 or more hours in the non-ventilated environment, without social distancing, without a face mask (87.8%) and socializing with high music volume. None of the COVID-19 positive adolescents, nor any of their close contacts who developed secondary infections required hospitalization nor died from COVID-19.

Conclusion: The results of this study shows that unvaccinated susceptible adolescents have a higher incidence of COVID-19 than vaccinated adolescents. But once infected, both unvaccinated and vaccinated adolescents had similar symptoms including fatigue, runny nose, anosmia, fever, cough, and ageusia. Adolescents recovered from previous COVID-19 infections were not reinfected. The lack of infection-mitigating strategies resulted in a superspreading event.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19 has infected over 200 million and killed over 4 million people worldwide by August 2021 (Harvey *et al.*, 2021). Since the start of the ongoing pandemic, multiple candidate vaccines have been developed, several of them highly effective and therefore, authorized under emergency use within a year of the first report of coronavirus disease 2019 (Polack *et al.*, 2020). The World Health Organization reports that vaccination is the second best public health strategy to mitigate and control infectious diseases after access to clean water (World Health Organization, no date). In December 2020, countries started an intense vaccination program to first protect the most vulnerable population, mainly the elderly, and persons with increased exposure to the SARS-CoV-2 virus due to high-risk occupations, health care workers and front-line workers (Russell and Greenwood, 2021).

Previous studies have shown that adolescents are less prone to severe COVID-19, hospitalization and death due to COVID-19 compared to adults (CDC, 2021; Stein, 2021). Also, some studies report that COVID-19 positive adolescents have mild respiratory symptoms, namely fever, dry cough, and fatigue or are asymptomatic (Castagnoli *et al.*, 2020). Less than 1% can develop multi systemic inflammatory syndrome (MIS-C) (Hoste, Van Paemel and Haerynck, 2021) and 5.1% can develop Long COVID (Mellis, 2021).

The BNT62b2 (Pfizer/BioNTech) COVID-19 vaccine was the first to be authorized under emergency use for individuals over 16 years old on December 11 2020 (Office of the Commissioner, 2021). On March 31 2021, it was the first vaccine with published results of its phase 3 on adolescents 12-15 years of age, finding that it was well tolerated, safe, immunogenic and had 100% efficacy in preventing symptomatic COVID-19 (Frenck *et al.*, 2021). However, there is not much information on the dynamic of COVID-19 in adolescents, both vaccinated and unvaccinated, under conditions that differ from those in an experimental trial.

In April 2021, the Delta (B.1.617.2) variant was identified in India and classified on May 11 as variant of concern (VOC) due to its fast spread and potential immune escape (Singh *et al.*, 2021).

The more infectious Delta variant of concern increased the incidence of breakthrough infections in different countries and populations (Baral *et al.*, 2021; Lopez Bernal *et al.*, 2021). In fully vaccinated health workers, most breakthrough infections were reported as mild or asymptomatic (Linsenmeyer *et al.*, 2021). Nevertheless, to date, information is scarce on the dynamics of COVID-19 in vaccinated and unvaccinated adolescents.

The aim of this study is to estimate the incidence of COVID-19 in a vaccinated and an unvaccinated group of adolescents, and describe their symptoms.

Methods

Study population

In May 2021, a private event for high school adolescents with ages between 15 and 19 years, took place in Mexico City. The event was held in a closed room with no ventilation. A rapid antigen test with confirmed negative results of COVID-19 was mandatory to attend the event and was performed 24 hours prior to the event. All of the vaccinated adolescents had been vaccinated in the United States, as vaccines were not available for adolescents in Mexico at that time. After the event, several cases of COVID-19 were reported. All attendees were requested to take a COVID-19 test within a week of attending the event. One of the samples, from a symptomatic fully vaccinated person, was sequenced to determine the SARS-CoV-2 genetic variant.

Questionnaire

We sent a questionnaire to all the high school adolescents invited to the private event (N=199). Only those that attended the event were included in the study (N=164). Informed consent was requested at the start of the questionnaire. For those under 18 informed consent was asked from one of the parents based on guidelines from the WHO (World Health Organization, 2021). We emphasized that participation in the study was anonymous and voluntary, and we held an open virtual meeting with adolescents and their parents to share the objectives and methods of this study. The questionnaire included close-choice items and one open-ended question. We collected data on age, sex, prior COVID-19 infection, status of the COVID-19 rapid antigen test before the event, result of the COVID-19 test after the event, the use of face masks, the amount of time spent at the event, vaccination status, symptoms after the event, and people from their close contacts that developed COVID-19 after the event.

Statistical Analyses

General characteristics for the whole studied population are described using categorical and continuous data by frequency and percentage, and mean and standard deviation (SD), respectively. Two different cohorts were created: vaccinated and unvaccinated. Vaccinated were defined as individuals who had received 1 or more doses of a COVID-19 vaccine at the time of the event. Unvaccinated were defined as individuals without any vaccine dose. We further describe how many adolescents were fully vaccinated with all recommended doses administered more than 14 days prior to the event, and how many were partially vaccinated.

The incidence of COVID-19 in vaccinated individuals was computed by taking the total number of COVID-19 positive cases in the vaccinated group (numerator) divided by the total number of vaccinated individuals (denominator) multiplied by 100. The incidence of COVID-19 in the unvaccinated group was computed by taking the total number of COVID-19 positive cases in the unvaccinated group (numerator) divided by the total number of unvaccinated individuals (denominator) multiplied by 100. Confidence intervals were constructed using the exact Clopper-Pearson method (Desu and Raghavarao, 2003).

SARS-CoV-2 test

After the event, positive and negative results from each participant were determined with different commercial COVID-19 test kits at private laboratories (PCR or rapid antigen). Given that there were some individuals that only took a rapid antigen test and its sensitivity is lower than the PCR “gold standard” tests, they were included in the COVID-19 positive cohort if they reported more than 3 symptoms including anosmia, even if the rapid antigen test was falsely negative and no PCR test was performed (Pilarowski *et al.*, 2021). The symptoms of each group were described using categorical data by frequency and percentage, and compared with χ^2 among the vaccinated and unvaccinated groups.

SARS-CoV-2 genome sequencing and Bioinformatics analysis

Extracted RNA isolated with the TRIZOL protocol (*TRIZOL™ Reagent*, no date; Rio *et al.*, 2010) from a sample of a SARS-CoV-2 fully vaccinated symptomatic positive patient, with a Ct value of 22.53 using the RIDAGENE SARS-COV-2 RT-PCR MULTIPLEX kit (R-BIOPHARM AG), was used to prepare an Illumina library using the ARTIC v3 protocol as described in (Pipelines R&D *et al.*, 2020). The SARS-CoV-2 amplicons library was prepared and sequenced at the “Unidad Universitaria de Secuenciación Masiva y Bioinformatica - UNAM” using the Illumina NextSeq500 platform with a 300 cycle kit with a pair end configuration to obtain reads with a 150 base pair length.

About 3 million paired end reads were obtained and processed using the ncov2019-artic-nf pipeline (GitHub, 2021) with default parameters. The reconstructed genome in fasta format, was analyzed at the Pangolin COVID-19 Lineage Assigner site (Å. O’toole, V. Hill JT. McCrone, E. Scher, A. Rambaut, 2021) to obtain the lineage of the sequenced virus.

Results

Overall population

All of the individuals that were invited to the event answered the questionnaire (N=199). A total of 35 were excluded, six because their parents did not give authorization to participate in the study, and 29 because they did not attend the event.

As shown in Figure 1, the studied population included N=164 adolescents. The mean age was 16.8 (SD 1.07) and the age ranged from 15 to 19. 53.7% were male and 46.3% female. In the past year 28.7% (N=47) had COVID-19 and were fully recuperated before the event; none of

these adolescents developed COVID-19 during the event. Of the attendees, 43% were vaccinated (n=70) and 57% (n=94) were unvaccinated. 98.8% performed an antigen test 24 hours prior to the event. The 2 people that did not take the test before the event, took a test after the party and resulted negative. The total incidence of COVID-19 in the total studied population was 25% (95%CI 18.6 to 32.4) (N=41). There were 2 people that were positive in the antigen rapid test taken 24 hours before the event. One was vaccinated and reported using a face mask during most of the event, the other one was not vaccinated and took off its face mask during most of the event. The rest (98.4%) had a negative antigen test result prior to the event. Most (87.8%) only used a face mask to enter the event and removed it once inside or did not use it at all. Most of the participants remained for 2 or more hours in the event (86.4%) and were indoors most of the time (82.9%). High volume music was played at all times in the non-ventilated indoor area, increasing the risk of SARS-CoV-2 transmission through elevated vocal effort contributing to higher aerosol emissions (Kopechek, 2020).

After the event 90.3% (148) took a COVID-19 test, 33.6% took a PCR test, and 56.7% a rapid antigen test. 41 people were COVID-19 positive, of which 35 had a positive test result and 6 had a negative test result or did not have a test but reported 6 symptoms including anosmia.

Out of the 41 adolescents with COVID-19, 75.6% said no one got sick around them (secondary infections), 19.6% said they infected 1 or 2 more persons. 73.2% said they did not have any contact with other persons, 7.3% had contact with 3 to 4 persons, and 7.3% had contact with 5 to 6 persons. None of the adolescents or their close contacts were hospitalized or died.

Vaccinated group

In total, there were 70 (42.7%) people that were vaccinated with at least one dose, 50 persons were fully vaccinated and 20 were partially vaccinated. 19 (27.1%) had COVID-19 in the year before the event and fully recovered before attending the event; none had a reinfection due to the event. 92.9% reported not using a face mask during the event. After the party, 8 (11.4%) out of the 70 vaccinated adolescents resulted COVID-19 positive; 7 (14%) were fully vaccinated and 1 (5%) was partially vaccinated. Only one fully vaccinated person was asymptomatic. The most common symptoms were runny nose, anosmia, fatigue, general discomfort, cough, ageusia and low fever.

Unvaccinated group

In total there were 94 (57.3%) people that were unvaccinated. 28 (29.8%) had COVID-19 in the year before the event and fully recovered before attending the event; none had a reinfection due to the event. 83.7% reported not using a face mask during the event. After the party, 33 (35.1%) of the unvaccinated adolescents were COVID-19 positive; there were no asymptomatic persons in this cohort. The most common symptoms were fatigue, anosmia, general discomfort, runny nose, cough, low fever and ageusia.

SARS-CoV-2 in Vaccinated and Unvaccinated groups

In Table 1 we present that the incidence of COVID-19 in unvaccinated individuals was 35.1% (95%CI 25.5 to 45.6), and in vaccinated individuals was 11.4% (95%CI 5.1 to 21.3). There was a

statistically significant difference of COVID infected individuals in the unvaccinated group compared to the vaccinated group ($\chi^2= 12.6$, $p=0.00$). The Odds Ratio when comparing unvaccinated vs. vaccinated was of 4.19 (95%CI 1.79-9.8).

In Figure 2 we present the symptoms reported both by the vaccinated and unvaccinated adolescents. The mean number of symptoms was 6 in both the vaccinated and unvaccinated cohorts. Vaccinated adolescents reported a runny nose more frequently (87.5% vs 48.5% $p=0.046$). Unvaccinated adolescents reported fatigue more frequently (90.9% vs 62.5% $p=0.04$). The rest of the reported symptoms, including anosmia, were present in both vaccinated and unvaccinated individuals (75.0% and 72.7% respectively).

Genome sequencing

A sample of one of the symptomatic fully vaccinated individuals was sequenced using the extracted RNA material from the positive qPCR test as described in our Methods. The result was a genome with a 99.48% coverage assigned as the Delta variant of concern (B.1.617.2) lineage according to the Pangolin COVID-19 Lineage Assigner website. Sequence was submitted to GISAID, Submission Number: EPI_ISL_3982391

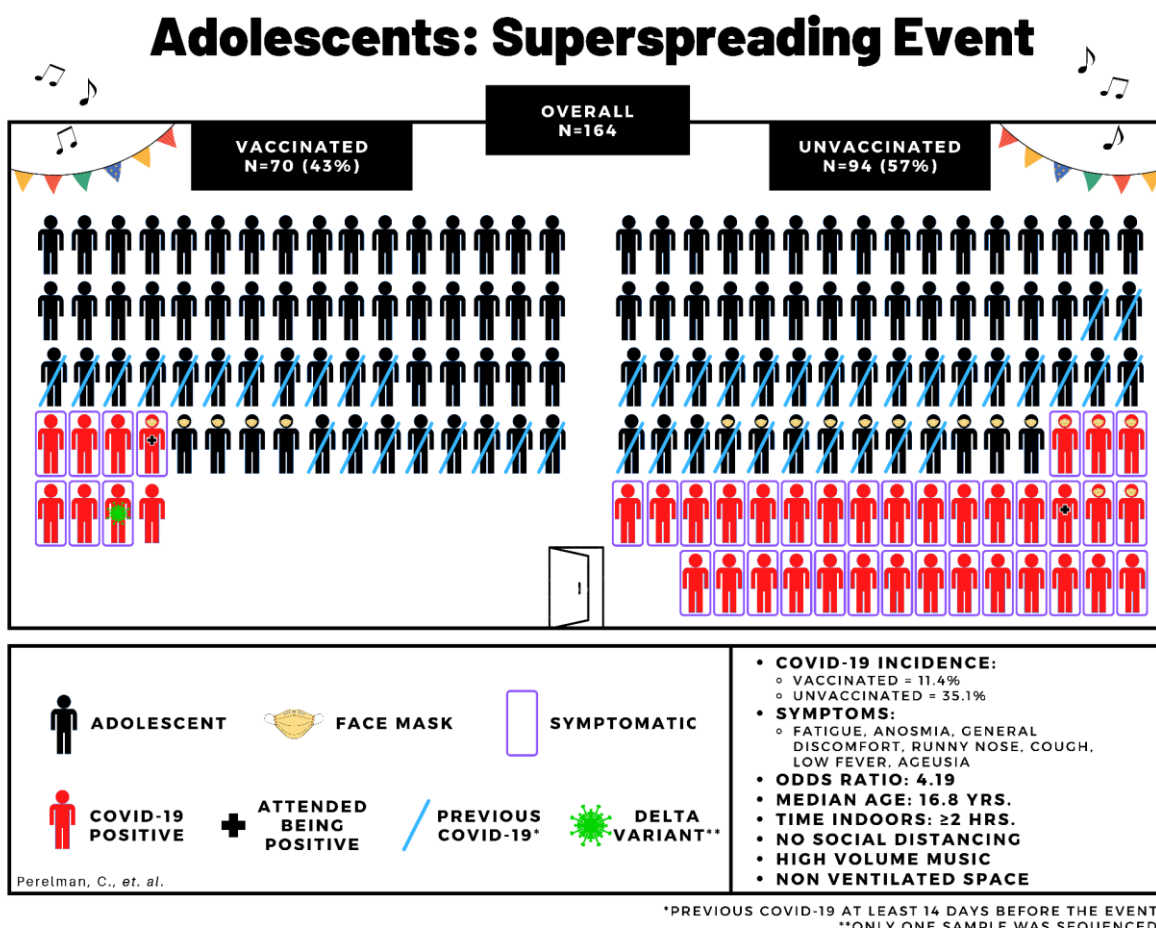


Figure 1. Adolescents Superspreading Event. 164 adolescents with a median age of 16.8 attended a private, non-ventilated event with high volume music, no social distancing measures and a low use of face masks for 2 or more hours. All performed an antigen rapid test 24 hours prior to the event. Two known COVID-19 positive individuals attended the event resulting in 41 (25%) positive cases of which 40 were symptomatic. No reinfection resulted from the event; the 47 individuals (28.7%) that reported having COVID-19 in the previous year were negative and reported no symptoms after the event. 70 (42.7%) of the attendees were vaccinated with at least one dose having lower incidence of COVID-19 (11.4%, 95%CI 5.1-21.3) than the unvaccinated cohort (35.1%, 95%CI 25.5-45.6). The crude OR was 4.19 (95%CI 1.79-9.8). None of the adolescents, or their close contacts, needed hospitalization, or died from COVID-19. One sample of a fully vaccinated symptomatic individual was sequenced, and the Delta variant of concern was found.

	Total attendees N=164	COVID-19 N=41	COVID-19 Incidence 95%CI
Vaccinated (Fully or partially)	70	8	11.4% (5.1-21.3)
Unvaccinated	94	33	35.1% (25.5-45.6)

Table 1: Incidence of Covid-19 cases A total of 164 individuals attended the event. 70 with at least one vaccine dose. The incidence of COVID-19 was 11.4% (8) in the vaccinated cohort and 35.1% (33) in the unvaccinated cohort. There were more unvaccinated than vaccinated teenagers that developed COVID-19 $\chi^2= 12.6$, ($p=0.00$). The crude Odds Ratio when comparing the unvaccinated vs the vaccinated was of 4.19, 95%CI 1.79-9.8 We found no reinfection, 47 (28.6%) adolescents reported having had COVID-19 in the past year and none was infected during the event.

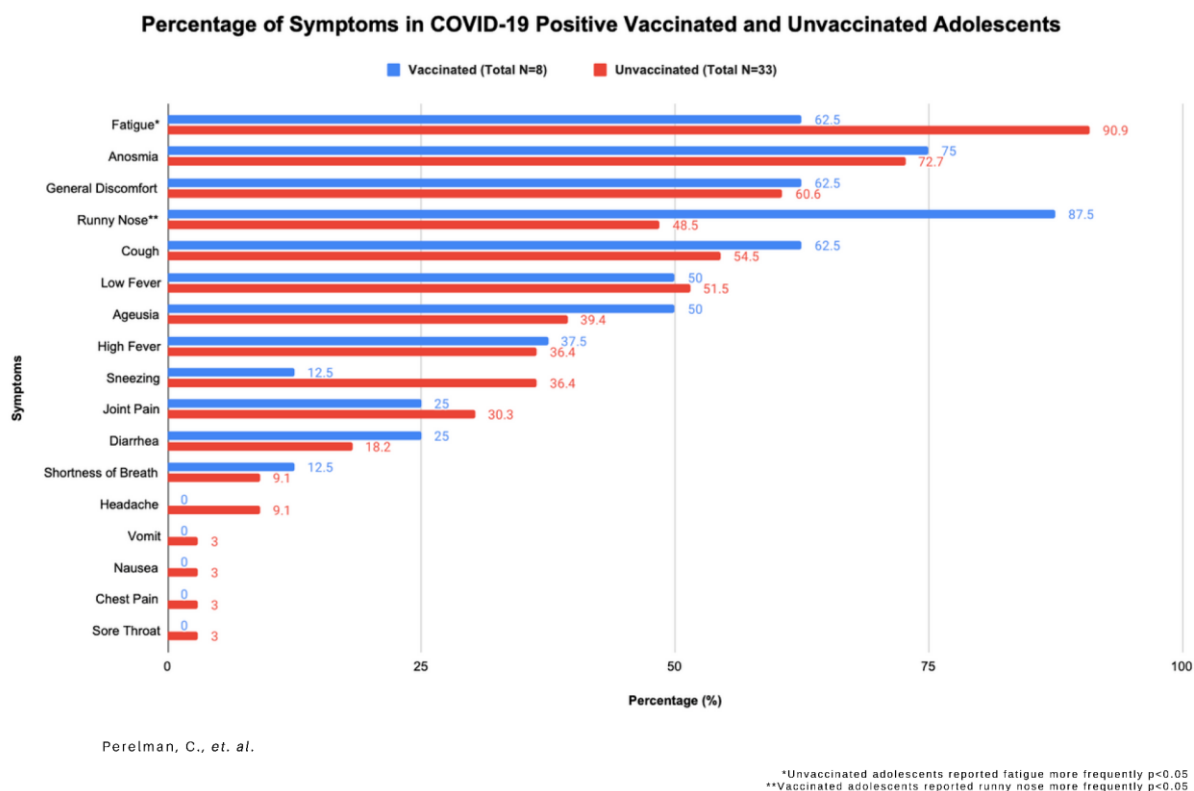


Figure 2. Percentage of Symptoms in COVID-19 Positive Vaccinated and Unvaccinated Adolescents. Both cohorts had similar symptoms. Only one fully vaccinated individual was asymptomatic. Fatigue was reported mainly in the unvaccinated and runny nose was mainly reported in the vaccinated *p<0.05

Discussion

This study shows that in the described superspreading event the unvaccinated adolescent cohort had a statistically higher incidence of COVID-19 than the vaccinated adolescent cohort. The incidence of COVID-19 in the unvaccinated cohort was 35.1% (95%CI 26.1 to 46.5), and in the vaccinated cohort was 11.4% (95%CI 5.1 to 21.3), (crude OR= 4.19 (95%CI 1.79-9.8)). Almost all COVID-19 positive adolescents (40 out of the 41) developed more than one symptom. Only one fully vaccinated positive individual was asymptomatic. We found that although vaccines decreased the risk of getting COVID-19, once an adolescent was infected with COVID-19, the symptoms were similar for both vaccinated and unvaccinated persons including fatigue, runny nose, anosmia, general discomfort, ageusia, fever and cough. Fatigue was more common in unvaccinated adolescents, and runny nose in vaccinated adolescents.

In the anonymous questionnaire, 47 (28.6%) attendees reported having COVID-19 during the previous year and were fully recovered before the event, 28 were not vaccinated and 19 were vaccinated with at least one dose. No reinfection resulted from this event. All 47 previously infected adolescents were negative and did not have symptoms after the event. This is consistent with the lower risk of reinfection found by other authors in people younger than 65 years of age (Hansen et al., 2021) and the preliminary data that shows that natural immunity confers higher protection against infection with Delta VOC than vaccine-induced immunity (Gazit et al., 2021). In this study we cannot assume that the superspreading event was caused by Delta since we only sequenced one sample from a symptomatic fully vaccinated individual, however we did observe a higher risk of infection in naive or vaccinated adolescents than in recovered individuals with natural immunity.

A breakthrough infection is defined as the detection of SARS-CoV-2 RNA in a PCR test or positive rapid antigen test in a respiratory specimen collected from a person ≥ 14 days after receipt of all recommended doses of a COVID-19 vaccine (Bergwerk et al., 2021). In our vaccinated cohort (70) we had 20 individuals partially vaccinated of whom 1 (5%) had COVID-19 and 50 fully vaccinated individuals of whom 7 (14%) had breakthrough infections. In most countries, breakthrough infections are only monitored if a fully vaccinated patient is hospitalized or dies. A study in Israel found that health care workers with breakthrough infections accounted for 2.6% of fully vaccinated individuals and persistent symptoms were present in 19% of COVID-19 cases (*COVID-19 vaccine breakthrough cases: Data from the states, 2021*). To date, there is no information on mild breakthrough infections in adolescents.

24.4% reported secondary infections of close contacts. None of the adolescents in this study nor their positive close contacts resulted in severe cases, needed hospitalization or died of COVID-19. The results of this study are in line with other studies that show that COVID-19 vaccines are highly effective for preventing hospitalization and death (Mlcochova et al., 2021; Sheikh et al., 2021). Vaccinated adolescents can develop mild or moderate symptoms when infected with SARS-CoV-2 and overall, they have less risk of severe disease or death due to COVID-19 than older individuals.

Understanding the setting of the event might explain why one of every four attendees was found positive. Of the total 164 attendees, 86.4% reported being present for 2 or more hours, where 82.9% were mostly in the enclosed non-ventilated environment and 87.8% did not use face masks nor kept social distancing measures. High volume music was played at all times in the indoor non-ventilated area, increasing the risk of SARS-CoV-2 transmission through elevated vocal effort contributing to higher aerosol emissions (Kopechek, 2020; Bergwerk et al., 2021). Of the 41 COVID-19 resulting positive individuals, 37 (90.3%) were at the event for over 2 hours, reported being in the enclosed environment at all times and none (100%) used a face mask at any time. The only mitigating measure that the adolescents took to ensure a safe event was to perform a rapid antigen test 24 hours prior to the event, in which two adolescents were positive and still attended the event. Of these two positive individuals, one was vaccinated and reported wearing a face mask at all times while the other positive individual was not vaccinated and did not wear a face mask at all. This superspreading event shows the lack of knowledge, low risk assessment

and the hesitance to implement several layers of protection. The analysis of this superspreading event shows how taking only one measure, in this case the 24-hour prior antigen test, was not enough to minimize the risk of infection. As the Swiss Cheese Model by James Reason suggests, (Perneger, 2005; Azuma *et al.*, 2020) knowing that there isn't a mitigation measure with 100% protection it is imperative to employ several layers of protection to reduce the risk of transmission and infection. In this scenario, without multiple transmission mitigation measures like admitting only negative adolescents, having proper ventilation, universal use of face masks, lower volume music, and social distancing, the superspreading event occurred.

One of the nasopharyngeal samples from a symptomatic fully vaccinated individual was sequenced. It was determined that it was the Delta variant of concern (VOC) which at that time was present in only 2.12% of samples screened according to the National Genomic Program's report of June by the Consorcio de Vigilancia Genómica in Mexico (Programa de Vigilancia Genómica, no date). We cannot conclude that this superspreading event was caused by this VOC because at least two positive individuals attended the event, however it was relevant to detect Delta as the dynamic of the spread could help describe Delta's ability to infect adolescents, both vaccinated and unvaccinated, and a lack of mitigation measures are employed. Also, this study can give some sense of how Delta can cause breakthrough infections even when the BNT162b2 (Pfizer-BioNTech vaccine) reported being 100% effective in their phase 3 study involving adolescents while other variants were circulating (Frenck *et al.*, 2021). As reported previously, Delta variant infections dominate vaccine-breakthrough cases in other countries such as India and the United Kingdom, probably driven by a combination of evasion of neutralising antibodies and increased virus infectivity (Mlcochova *et al.*, 2021).

The strengths of this study are the high rate of participation, that almost all were tested for COVID-19 before and after the event, and that the conditions during which the private event was held were constant for most of the attendees. The limitations of this study are that it was not possible to sequence all COVID-19 positive adolescents to determine if they all had the Delta variant and not all of the vaccinated individuals were fully vaccinated. Future studies are needed to determine the incidence of COVID-19 in adolescents in fully vaccinated individuals in bigger samples to be able to determine if the incidence is similar to what is observed in this smaller population and if the symptoms of vaccinated and unvaccinated individuals are similar.

Spreading events have become more common since vaccinated individuals engage with other people in social events, with almost complete relaxation of safety measures. Interesting to note that two positive cases were from adolescents that decided not to miss the event regardless of their condition. This reckless behavior puts other people in a vulnerable position where infection with a VOC is more probable, especially in places with high community transmission. The results of this study show the permeability of implementing a unique mitigating strategy thus evidencing the urgency to communicate the importance of layering protective measures to reduce risk of transmission and infection during the COVID-19 pandemic.

Acknowledgments

We would like to thank Sandra López-León MD PhD for her guidance as an epidemiologist, physician and her support in the data analysis and interpretation. Bioethicist German Carreto Chavez reviewed and approved the questioner and the project. He determined that there was no risk for any of the participants. That anonymization of the participant was guaranteed, and the bioethical international guidelines were followed since all participants and/or their parents, when needed, were signed. A special thanks to Ariela Landsmanas Goldberg for providing crucial information and helping with the distribution of the questionnaire. We acknowledge Ricardo Grande and Karel Estrada for their support in sequencing and bioinformatics technical support, respectively and who are part of the "Unidad Universitaria de Secuenciación Masiva y Bioinformática - UNAM" and "Laboratorio Nacional de Apoyo Tecnológico a las Ciencias Genómicas - CONACyT"

Competing interests

The authors are solely responsible for all content. The authors have no competing interests to declare.

Authors' contribution

Conception and design: CP, TWO.; data acquisition: CP, AF data coordinator: CP.; data management: ASF; data analysis: CP, TWO, data interpretation: all authors, figures and tables: AF, financial and administrative support: ASF, TWO ; and writing, review, and editing: all authors

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