COVID-19 Disease Severity in Children Infected with the Omicron Variant

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Running title: Omicron severity in children

Short Summary:

SARS-CoV-2 infection due to the Omicron variant in children/adolescents is less severe than infection due to the Delta variant. Those 6-<18 years also have less severe disease than those <6 years old.

Abstract

Background

There are limited data assessing COVID-19 disease severity in children/adolescents infected with the Omicron variant.

Methods

We identified children and adolescents <18 years with SARS-CoV-2 infection with Delta and propensity-score matched controls with Omicron variant infection from the National COVID-19 Database in Qatar. Primary outcome was disease severity, determined by hospital admission, admission to ICU, or mechanical ventilation within 14 days of diagnosis, or death within 28 days.

Results

Among 1,735 cases with Delta variant infection between June 1 and November 6, 2021 and 32,635 cases with Omicron variant infection between January 1 and January 15, 2022 who did not have prior infection and were not vaccinated, we identified 985 propensity-score matched pairs. Among Delta infected, 84.2% had mild, 15.7% had moderate, and 0.1% had severe/critical disease. Among Omicron infected, 97.8% had mild, 2.2% had moderate, and none had severe/critical disease (P<0.001). Omicron variant infection (vs. Delta) was associated with significantly lower odds of moderate or severe/critical disease (adjusted odds ratio, 0.12; 95% CI 0.07-0.18). Those aged 6-11, and 12-<18 years had lower odds of developing moderate or severe/critical disease compared with those younger than six years (aOR, 95% CI 0.47; 0.33-0.66 for 6-11 year old; aOR 0.45, 95% CI 0.21-0.94 for 12-<18 years old).

Conclusion

Omicron variant infection in children/adolescents is associated with less severe disease than Delta variant infection as measured by hospitalization rates and need for ICU care or mechanical ventilation. Those 6-<18 years also have less severe disease than those <6 years old.

Key words: SARS-CoV-2; Omicron variant; Delta variant; children; outcomes; Qatar;

The epidemiology of SARS-CoV-2 pandemic is constantly evolving, with regular emergence of new variants of concern (VOCs), with each VOC associated with unique transmission, infectiousness, tissue tropism, and virulence characteristics.[1-5] A recent VOC is the Omicron variant, which, at least in adults, appears to be more infectious, perhaps because of more immune evasion, than the previous variants but less likely to be associated with more severe or critical disease.[6-8] For reasons that are incompletely understood, children appear less likely to be infected with SARS-CoV-2 and have a lower case fatality rate compared with older age groups.[9,10] However, serious complications may occur in children, especially those with chronic and underlying conditions. Rarely, a hyperinflammatory syndrome with multisystem involvement has been reported, associated with high hospitalization rates and the need for organ system support.[11,12] Multiple vaccines for SARS-CoV-2 have now been authorized for use in children 5 years and older, and are highly effective in preventing infection, hospitalization, admission to an intensive care unit (ICU), mechanical ventilation, or death.[13,14] The natural history and clinical outcomes of COVID-19 in children and adolescents remain insufficiently understood, and there is limited information available regarding the severity of disease caused by the Omicron variant compared with the previous variants. A recent study from the US reported a higher rate of hospitalization in children and adolescents with the Omicron variant compared with the Delta variant, but a lower proportion of the hospitalized children and adolescents required ICU admission or mechanical ventilation.[15] We conducted this study to compare the clinical outcomes of patients younger than 18 years who were infected with the Omicron variant.

Methods

Study Setting

The study was conducted in Qatar, which has high rates of testing and vaccination of the eligible population for SARS-CoV-2.[16] Since the identification of the first patient with SARS-CoV-2 on February 27, 2020, Qatar has experienced four distinct waves, now attributed to the wild-type, Alpha, Beta, and Omicron variants.[17-22] It also experienced a prolonged low-incidence phase with the Delta variant.[17-22] The first case of Omicron variant infection in Qatar was identified in a traveler on November 24, 2021, and within 4 weeks, it became the predominant circulating variant.[22] Starting very early in the pandemic, Qatar also instituted an aggressive testing policy, which included testing of all persons with compatible symptoms, contacts of confirmed cases, returning travelers, and persons in frontline high-risk professions (e.g. healthcare workers and school staff) and screening of certain high-risk groups. Real-time reverse-transcription PCR (RT-qPCR) was used to test for SARS-CoV-2 on nasopharyngeal swabs at two national laboratories at Hamad Medical Corporation and Sidra Medicine.

Study Participants

Using the national COVID-19 database in Qatar, which includes every PCR test performed in Qatar since the beginning of the pandemic,[23-25] we identified children (0-<18 years) with Delta variant infection diagnosed between June 1 and November 6, 2021, and those with Omicron variant infection diagnosed between January 1 and January 15, 2022. We excluded those with prior documented infection and those who had received any SARS-CoV-2 vaccination. Among these, we propensity-score matched each Delta infection case with an Omicron infection case based on age, gender, nationality, and presence of comorbidities. We performed 1:1 matching, using the nearest neighbor matching with a caliper of 0.2SD.

Definitions

The primary outcome of interest was severity of COVID-19 disease in children and adolescents infected with the Delta variant compared with those infected with the Omicron variant. Disease severity was categorized into mild (RT-PCR confirmed infection not requiring hospitalization), moderate (requiring acute care hospitalization but no intensive care unit admission or mechanical ventilation or death), and severe/critical (admission to an intensive care unit, mechanical ventilation, or death). All outcomes within 14 days of the index positive test were included, except death for which a 28-day period was included. All children with COVID-19 in Qatar requiring hospitalization are admitted to designated public hospitals, thereby ensuring complete capture of all hospital admissions and subsequent inpatient care. Comorbidities were identified based on associated diagnostic codes in the electronic medical records, as used in our previous publications.[26-28] SARS-CoV-2 infection was confirmed from the national COVID-19 database.[23-25] Vaccination status was also confirmed from the national COVID-19 database, which contains a record of every SARS-CoV-2 vaccinated person in Qatar.[23,24]

Laboratory Methods and Classification by Variant Type

Nasopharyngeal and/or oropharyngeal swabs were collected for PCR testing and placed in Universal Transport Medium (UTM). Aliquots of UTM were: 1) extracted on a KingFisher Flex (Thermo Fisher Scientific, USA), MGISP-960 (MGI, China), or ExiPrep 96 Lite (Bioneer, South Korea) followed by testing with real-time reverse-transcription PCR (RT-qPCR) using TaqPath COVID-19 Combo Kits (Thermo Fisher Scientific, USA) on an ABI 7500 FAST (Thermo Fisher Scientific, USA); 2) tested directly on the Cepheid GeneXpert system using the Xpert Xpress SARS-CoV-2 (Cepheid, USA); or 3) loaded directly into a Roche Cobas 6800 system and assayed with the Cobas SARS-CoV-2 Test (Roche, Switzerland). The first assay targets the viral S, N, and ORF1ab gene regions. The second targets the viral N and E-gene regions, and

the third targets the ORF1ab and E-gene regions. All PCR testing was conducted at the Hamad Medical Corporation Central Laboratory or Sidra Medicine Laboratory, following standardized protocols.

Surveillance for SARS-CoV-2 variants in Qatar is mainly based on viral genome sequencing and multiplex RT-qPCR variant screening[29] of random positive clinical samples,[19-21,23,24,30] complemented by deep sequencing of wastewater samples.[30,31] Between March 23, 2021 and November 18, 2021 (prior to suspected introduction of the Omicron variant), RT-qPCR genotyping of 19,234 randomly collected SARS-CoV-2-positive specimens on a weekly basis identified 3,494 (18.2%) Alpha (B.1.1.7)-like cases, 5,768 (30.0%) Beta (B.1.351)-like cases, 9,914 (51.5%) "other" variant cases, and 58 (0.3%) B.1.375-like or B.1.258-like cases.[20,22,30] The accuracy of the RT-qPCR genotyping was verified against either Sanger sequencing of the receptor-binding domain (RBD) of SARS-CoV-2 surface glycoprotein (S) gene, or by viral whole-genome sequencing on a Nanopore GridION or MGI-G50 sequencing devices. From 236 random samples (27 Alpha-like, 186 Beta-like, and 23 "other" variants), PCR genotyping results for Alpha-like, Beta-like, and 'other' variants were in 88.8% (23 out of 27), 99.5% (185 out of 186), and 100% (23 out of 23) agreement with the SARS-CoV-2 lineages assigned by sequencing. Within the "other" variant category, Sanger sequencing and/or Illumina sequencing of the RBD of SARS-CoV-2 spike gene on 728 random samples confirmed that 701 (96.3%) were Delta cases and 17 (2.3%) were other variant cases, with 10 (1.4%) samples failing lineage assignment. Accordingly, a Delta case was proxied as any "other" case identified through the RT-qPCR based variant screening. All the variant RT-qPCR screening was conducted at the Sidra Medicine Laboratory following standardized protocols.

A total of 315 random SARS-CoV-2-positive specimens collected between December 19, 2021 and January 22, 2022 were viral whole-genome sequenced on a MGI-G50 sequencing device.

Of these, 300 (95.2%) were confirmed as Omicron infections and 15 (4.8%) as Delta (B.1.617.2) infections.[22,30,32,33] No Delta case was detected in the viral genome sequencing after January 8, 2022. The large Omicron-wave exponential-growth phase in Qatar started on December 19, 2021 and peaked in mid-January, 2022.[22,30,33] The study duration for Omicron coincided with the intense Omicron wave where Delta incidence was very limited. Accordingly, any PCR-positive test between January 1 and 15, 2022 was used as a proxy for Omicron infection.

Statistical Analyses

In our recent analysis of the adult population in Qatar, we found that 15.2% of those infected with the Delta variant and 1.5% of propensity score matched persons infected with the Omicron variant had moderate disease requiring hospitalization within 14 days of the index positive SARS-CoV-s test. (Adeel Butt, unpublished data) Since children generally experience less severe disease, we assumed that the rate of hospitalization among those infected with the Delta variant would be half of what is experienced in adults. Based on a very conservative *a priori* assumption that a 50% reduction in rate of hospitalization in those infected with the Omicron variant constitutes a clinically significant difference, we calculated that a minimum sample size of 1,182 persons (591 in the Delta group and 591 in the Omicron group) would detect this difference at an alfa level of .05 with a power of 80%.

We calculated and compared the proportions of persons with mild, moderate, or severe/critical disease among those infected with the Delta and the Omicron variants. 95% confidence intervals (CIs) were calculated to express the spread. Multivariable logistic regression was used to calculate the adjusted odds ratios (aORs) and 95% CIs for factors associated with these outcomes. Where p-values were used for comparison, a p-value<0.05 was considered

statistically significant. All analyses were done using IBM-SPSS version 27.0 (Armonk, NY, USA).

Ethical Review:

Hamad Medical Corporation, Weill Cornell Medicine-Qatar, and Qatar University Institutional Review Boards approved this study. A waiver of informed consent was granted due to the retrospective nature of data retrieval.

Results

Among 1,359 children and adolescents with Delta variant infection and 32,635 with Omicron variant infection during the study period, we identified 985 propensity score matched pairs which were included in the final analysis. **(Figure 1)** Among those with Delta variant infection, the median age was 7 years (IQR 3-9), 54.6% were females, 39.5% were Qataris and 85.7% had no comorbidities. Among those with Omicron variant infection, the median age was 6 years (IQR 3-10), 52.2% were females, 36.8% were Qataris and 85.6% had no comorbidities. **(Table 1)** Individual comorbidities and the baseline characteristics of the entire study population before propensity score matching (1,359 with Delta and 32,635 with Omicron variant infection) are also provided in **table 1**.

Among children and adolescents with Delta variant infection, 84.2% had mild disease, 15.7% had moderate disease, and 0.1% had severe/critical disease. Among children with Omicron variant infection, 97.8% had mild disease, 2.2% had moderate disease, and none had severe/critical disease. **(Table 2)** In multivariable logistic regression analysis, infection with the Omicron variant was associated with significantly lower odds of moderate or severe/critical disease as compared with Delta variant infection (adjusted odds ratio, aOR 0.12; 95% CI 0.07-0.18). Compared with children younger than 6 years old, those 6-11 years old and those 12-<18 years old had lower odds of developing moderate or severe/critical disease (aOR, 95% CI 0.47;

0.33-0.66 for 6-11 year old; aOR 0.45, 95% CI 0.21-0.94 for 12-<18 years old). Sex, nationality, and comorbidity count were not associated with the odds of developing moderate or severe/critical disease. **(Table 3)**

We also conducted logistic regression analysis by disease severity stratified by the infecting variant. **(Table 4)** For both Delta and Omicron variant infection, those aged 6-11 years had lower odds of developing moderate or severe/critical disease compared with those younger than 6 years old (aOR 0.50, 95% CI 0.34-0.73 for Delta; aOR 0.25, 95% CI 0.09-0.71 for Omicron). For those with Omicron variant infection, the presence of one or more comorbidity was associated with higher odds of developing moderate or severe/critical disease (aOR 3.16, 95% CI 1.11-9.00). This association was not significant among those with Delta variant infection. **(Table 4)**

Discussion

In this large national study, we describe the severity of COVID-19 disease in children infected with the Omicron variant compared with children infected with the Delta variant. We found the COVID-19 disease due to the Omicron variant to be significantly less severe than disease due to the Delta variant.

We recently demonstrated that adults infected with the Omicron variant are 10-fold less likely to develop moderate or severe/critical disease compared with those infected with the Delta variant. (Adeel Butt, unpublished data) Our current results mirror those results with a nearly 8-fold lower rate of moderate or severe/critical disease in children infected with the Omicron variant. While a direct comparison cannot be made, the proportion of adults with moderate and severe disease due to the Omicron and Delta variants was remarkably similar to what we found in children with disease due to the same variant. The reasons for this are not known. Increasing age and presence of comorbidities are associated with more severe disease in the adult population, and

it is intuitive to assume that children and adolescents with inherently lesser comorbidities would experience significantly less severe disease outcomes. It is possible that the threshold for admission was lower in children and adolescents, which is the definition of moderate disease. However, criteria for mechanical ventilation are not likely to be much different, with such interventions executed only in those with severe or critical disease.

Within children and adolescents, those who were 6-11 years old were less likely to have moderate or severe/critical disease compared with those younger than 6 years old. Whether this is due to a poorer immune response or other reasons such as the anatomy of the upper respiratory tract in small children is not clear. As mentioned earlier, another possibility is the lower threshold for admitting younger patients compared with older individuals with the same severity of symptoms. If the safety and efficacy of the current vaccines are confirmed in children younger than 6 years old, these data provide supporting evidence to extend the vaccination to this age group.

We noted that the presence of comorbidities was associated with moderate or severe outcomes among those with the Omicron variant infection but not with the Delta variant infection. The reason(s) for this are unclear. A potential explanation of this finding is that Omicron may affect the respiratory tract differentially and selectively compared with the Delta variant in children and adolescents. Approximately 14% of the individuals in each group had at least one comorbidity, and only a single individual in either group had more than one comorbidity. Among the 14% with at least one comorbidity, all but one had only 1 comorbidity, and 98% of those were chronic lung disease (including chronic asthma). While we excluded all those with previous SARS-CoV-2 infection, some may have had undiagnosed infection, which may have induced immunity in one group. Vaccine induced immunity is lower against the Omicron variant compared with the Delta variant. Whether this is true for natural immunity after infection is unknown.

Strengths of our study include a large national population, extensive testing, and uniform data collection methods. All children and adolescents requiring inpatient care were admitted to designated facilities, providing a high degree of uniformity in admission criteria and subsequent care, including decisions to transfer to an intensive care setting and initiation of mechanical ventilation. Certain limitations also need to be noted. This was a retrospective study, and despite propensity-score matching, the possibility of residual confounding cannot be excluded. While the study excluded persons with a documented prior infection, some of the prior infections may have not been documented. With Omicron cases being diagnosed several weeks after Delta cases, it is possible that some of the observed lower severity of Omicron infections could be due to a higher level of accrued natural immunity. However, this may only explain a small part of the lower severity of Omicron infections as the infection diagnosis rate is high in the pediatric population in Qatar as a consequence of the high testing rates.

In conclusion, infection with the Omicron variant in children and adolescents is associated with significantly lower severity of infection as measured by hospitalization rates and need for intensive care unit care or mechanical ventilation. This is reassuring considering the large number of children and adolescents infected during the Omicron wave across the globe.

NOTES

Author Contributions

Concept and study design: AAB, LJA

Drafting of the manuscript: AAB

Data acquisition: AHK, ANL, SL, RMS, HC

Data analysis: SRD, AAB, LJA

Data interpretation: AAB, SRD, LJA

Laboratory testing: PVC, PT, MRH, HMY, HAA, MKS

Critical appraisal and review: AAB, LJA, SRD, HC, AAK, PVC, PT, MRH, HMY, HAA, MKS, MAA, AZ, AHK, ANL, RB, AA

Final approval: AAB, LJA, SRD, HC, AAK, PVC, PT, MRH, HMY, HAA, MKS, SL, RMS, MAA, AZ, AHK, ANL, RB, AA

Drs. Butt and Abu-Raddad had complete access to the data at all times and accept responsibility for the integrity of this article.

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Disclaimer

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Figure 1. Study flow sheet.

* Propensity-score matching done on age, sex, nationality, and comorbidities; nearest neighbor matching with caliper of 0.2SD

Table 1. Baseline characteristics of propensity score matched persons infected with the Delta and Beta variants.

	Before matching			After propensity score matching		
	Delta variant infection N=1,359	**Omicron variant infection N=32,635**	**SMD[a]**	**Delta variant infection N=985**	**Omicron variant infection N=985**	**SMD[a]**
	N (%)	**N (%)**		**N (%)**	**N (%)**	
Age; median (IQR)	8 (5-11)	6 (3-10)	0.269	7 (3-9)	6 (3-10)	0.104
Age						
0-5 yrs	424 (31.2)	14,068 (43.1)	0.253	424 (43)	460 (46.7)	0.082
6-11 yrs	708 (52.1)	14,529 (44.5)		485 (49.2)	445 (45.2)	
12-17 yrs	227 (16.7)	4,038 (12.4)		76 (7.7)	80 (8.1)	
Sex						
Female	620 (45.6)	15,728 (48.2)	0.052	538 (54.6)	514 (52.2)	0.049
Male	739 (54.4)	16,907 (51.8)		447 (45.4)	471 (47.8)	
Nationality						
Qatari	761 (56.0)	13,703 (42.0)	0.320	389 (39.5)	362 (36.8)	0.151
Southeast Asian	115 (8.5)	5,328 (16.3)		115 (11.7)	167 (17)	
Other	483 (35.5)	13,604 (41.7)		481 (48.8)	456 (46.3)	
Comorbidities[b]						
Hypertension	1 (0.1)	22 (0.1)	0.002	1 (0.1)	0 (0)	0.045
Diabetes	3 (0.2)	43 (0.1)	0.021	0 (0)	0 (0)	N/A
Chronic lung disease[c]	236 (17.4)	4,821 (14.8)	0.071	138 (14.0)	140 (14.2)	0.006
Cardiovascular disease	3 (0.2)	111 (0.3)	0.023	3 (0.3)	2 (0.2)	0.020
Chronic kidney disease	0 (0.0)	3 (0.0)	0.014	0 (0)	1 (0.1)	0.045
Chronic liver disease	0 (0.0)	2 (0.0)	0.011	0 (0)	0 (0)	N/A
Cancer	0 (0.0)	2 (0.0)	0.011	0 (0)	0 (0)	N/A
Comorbidities count						
0 comorbidity	1,118 (82.3)	27,696 (84.9)	0.072	844 (85.7)	843 (85.6)	0.003
1 comorbidity	239 (17.6)	4,879 (15.0)		140 (14.2)	141 (14.3)	
2+ comorbidity	2 (0.1)	60 (0.2)		1 (0.1)	1 (0.1)	

[a] Standardized mean difference; a value of <0.1 suggest good matching.
[b] There were no cases of autoimmune disease, chronic kidney disease, cancer, or cerebrovascular disease in any group.
[c] Including asthma.

Table 2. Summary of disease outcomes of the two SARS-CoV-2 variant groups

	Delta variant infection N=985	Omicron variant infection N=985	
Disease Severity[a]	**N (%)**	**N (%)**	**P-value**
Mild/Not hospitalized	829 (84.2)	963 (97.8)	<0.001
Moderate disease	155 (15.7)	22 (2.2)	
Critical disease	1 (0.1)	0 (0.0)	
Moderate or Severe outcome	156 (15.8)	22 (2.2)	<0.001

[a] Mild: infection confirmed but no hospitalization; Moderate: hospitalized but no ICU admission or mechanical ventilation or death; Severe/critical: Mechanical ventilation OR ICU admission OR death

Table 3. Multivariable logistic regression with outcome disease status as dependent variable.

	Moderate or Severe/critical outcome[a]		Moderate disease[a]	
	aOR (95% CI)	**P-value**	**aOR (95% CI)**	**P-value**
Omicron variant (comparator: Delta variant)	0.12 (0.07-0.18)	<0.001	0.12 (0.07-0.19)	<0.001
Age (comparator: 0-5 years)				
6-11 years	0.47 (0.33-0.66)	<0.001	0.47 (0.33-0.67)	<0.001
12-17 years	0.45 (0.21-0.94)	0.034	0.45 (0.22-0.94)	<0.034
Male sex (comparator: female)	1.03 (0.74-1.44)	0.850	1.02 (0.73-1.43)	0.909
Nationality (comparator: Qatari)				
Southeast Asian	0.88 (0.52-1.49)	0.632	0.89 (0.52-1.52)	0.669
Other nationalities	0.84 (0.58-1.21)	0.350	0.85 (0.59-1.23)	0.391
Comorbidities count (comparator: zero)				
1+	1.01 (0.63-1.61)	0.977	1.02 (0.64-1.62)	0.942

[a] Moderate: hospitalized but no ICU admission or mechanical ventilation; Severe/critical: Mechanical ventilation OR ICU admission OR death. There was only one cases of severe/critical disease.

Table 4. Multivariable logistic regression with outcome disease status as dependent variable, stratified by variant.

	Moderate or Severe outcome[a]			Moderate disease[a]		
	Delta	Omicron		Delta	Omicron	
	aOR (95% CI)	aOR (95% CI)	P-value[$]	aOR (95% CI)	aOR (95% CI)	P-value[$]
Age (comparator: 0-5 years)						
6-11 years	0.50 (0.34-0.73)	0.25 (0.09-0.71)	0.340	0.50 (0.34-0.73)	0.25 (0.09-0.71)	0.340
12-17 years	0.55 (0.25-1.18)	N/A	N/A	0.55 (0.26-1.18)	N/A	0.N/A
Male sex (comparator: female)	0.94 (0.65-1.35)	1.75 (0.69-4.42)	0.078	0.93 (0.64-1.33)	1.75 (0.69-4.42)	0.073
Nationality (comparator: Qatari)						
Southeast Asian	0.78 (0.42-1.41)	1.36 (0.42-4.45)	0.477	0.79 (0.43-1.44)	1.36 (0.42-4.45)	0.488
Other nationalities	0.80 (0.54-1.19)	1.05 (0.39-2.84)	0.881	0.81 (0.54-1.21)	1.05 (0.39-2.84)	0.901
Comorbidities count (comparator: zero)						
1 or more comorbidity	0.82 (0.48-1.38)	3.16 (1.11-9.00)	0.033	0.83 (0.49-1.39)	3.16 (1.11-9.00)	0.034

[a] Moderate: hospitalized but no ICU admission or mechanical ventilation; Severe/critical: Mechanical ventilation OR ICU admission OR death

[b] p-value comparing odds ratios between Delta and Omicron variants

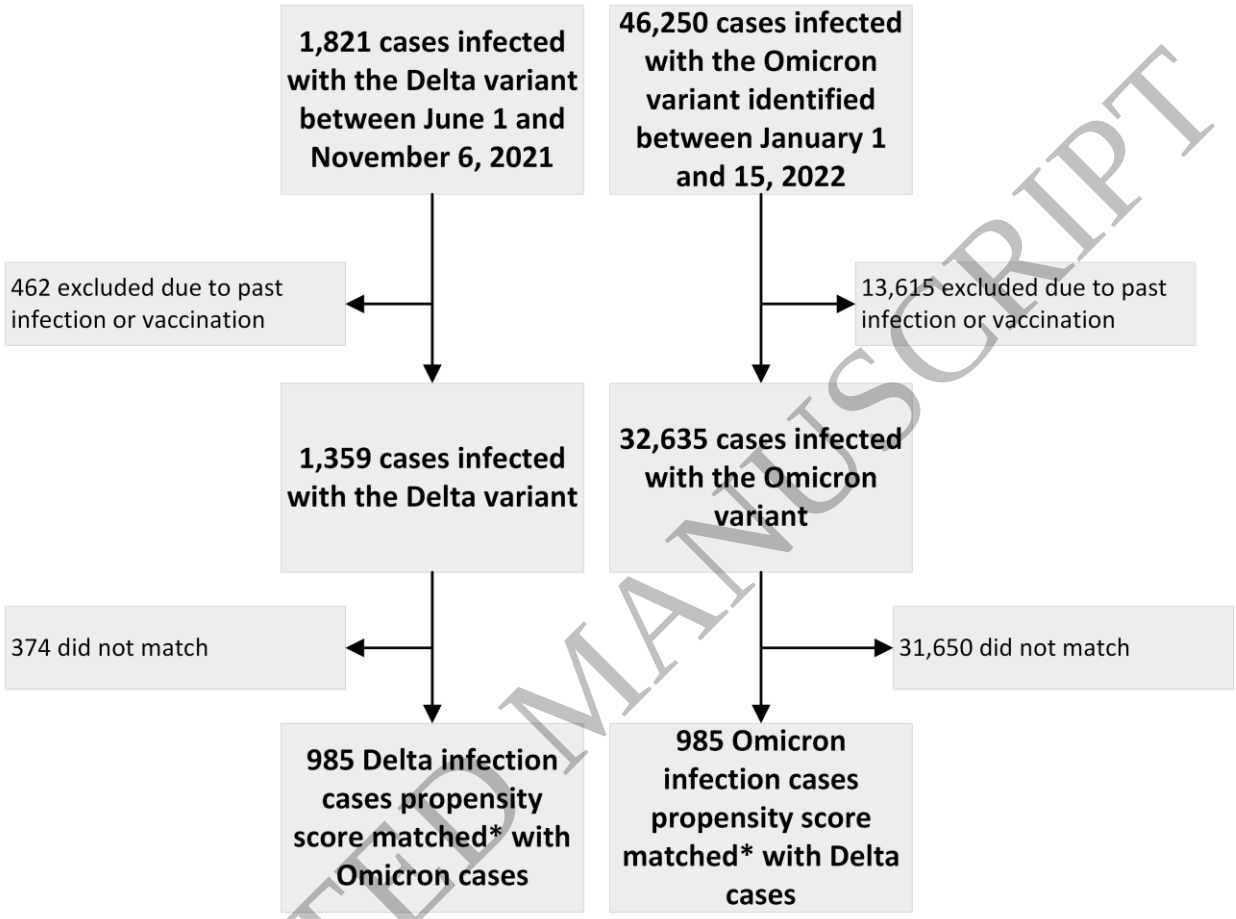

Figure 1
164x124 mm (5.8 x DPI)