Supplementary Appendix

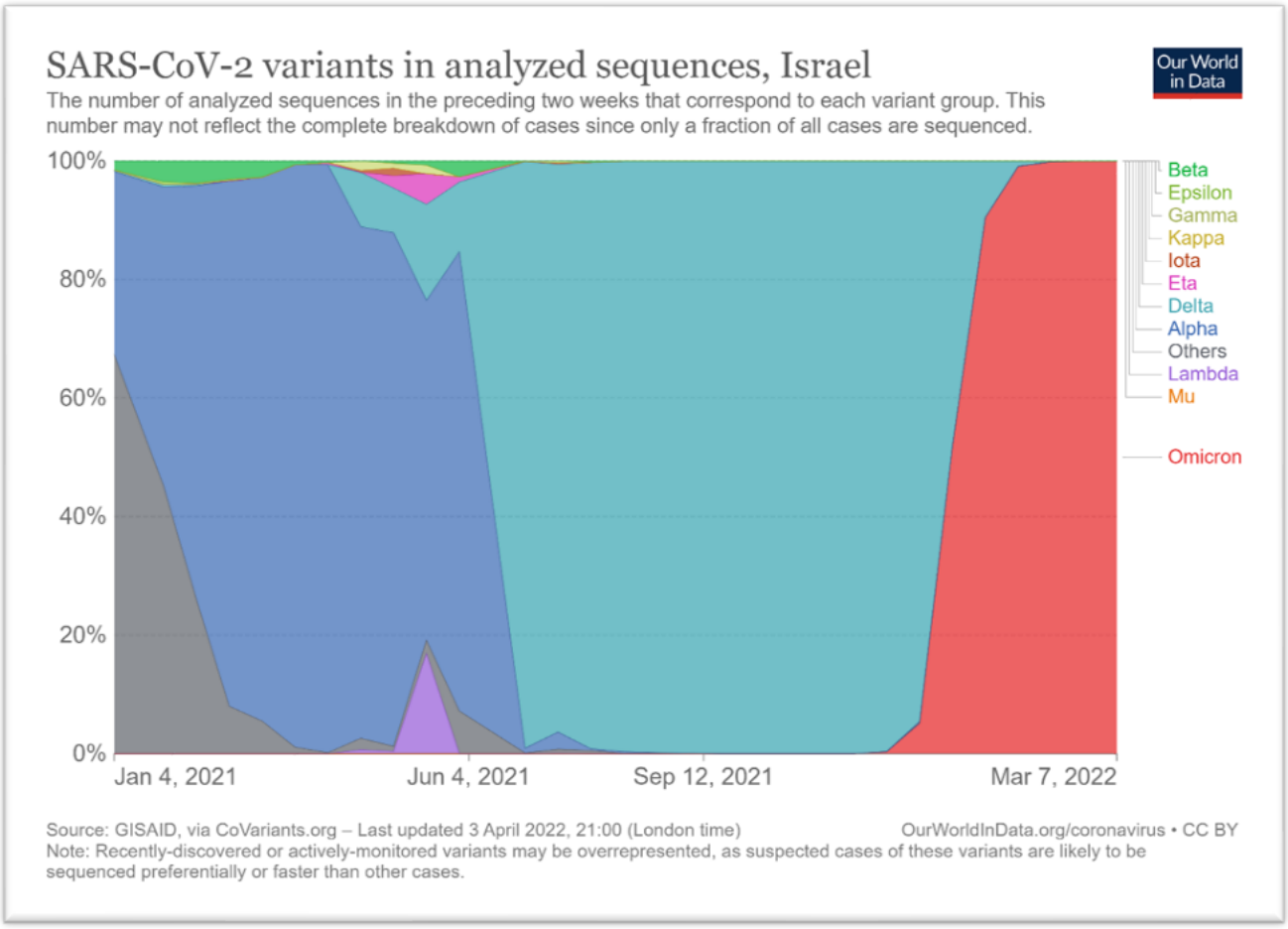
Supplement to: Arbel R, Wolff Sagy Y, Hoshen M, et al. Nirmatrelvir use and severe Covid-19 outcomes during the omicron surge. N Engl J Med. DOI: 10.1056/NEJMoa2204919

This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Material

Contents

Figure S1: SARS-cov2 Variants in Israel during the Study Period



Explanation on the Risk Score

Clalit Health Services (CHS) has used 'risk scores' based on predictive models throughout the pandemic and in a varying contexts as an integral part of its policy on how to prioritize patients for interventions in a resource-limited setting.

A manuscript describing the development and performance of a points-based model in CHS early in the pandemic and how it was implemented is available (1). The model was shown to perform extremely well in identifying the at risk population in a temporal test set, demonstrating high validity.

For example, at a threshold that identifies only 18% of the CHS population as having an elevated risk for severe Covid-19 the model manages to capture 92% of the individuals that ended up with severe Covid-19 or Covid-19-related death after infection

The landscape of the pandemic was dynamic and therefore such models had to be updated at a number of time points over the previous two years. The model specifically used in the prioritization of nirmatrelvir was very similar to that described in the manuscript above, with slight changes to the points criteria including:

- The addition of risk points for unvaccinated or partially vaccinated individuals
- Changes to the way points were designated based on an individual's age with individuals less than 60 receiving a 'penalty' and individuals over 70 receiving additional points
- The addition points for immunosuppressed individuals.

Table S1: Components of the Risk Score Model

Risk Criteria	**Risk Score**
Age >= 70	Adds 2 points
Age 50-59 inclusive	Removes 1 point
Age 40-49 inclusive	Removes 3 points
Unvaccinated or a single dose of vaccine	Adds 5 points
Immunosuppression* (including indviduals between ages 12 and 40, who otherwise are not included in the intervention list)	Adds 7 points
Hospitalization in the past 3 years	Adds 1 point (Each hospitalization event)
COPD or >10 pack years	Adds 1 point
BMI > 30	Adds 1 point
Heart disease, vascular disease or cerbrovascular disease	Adds 1 point
Renal Disease	Adds 1 point
Hepatic Disease	Adds 1 point
Neurological Disease	Adds 1 point
Active Malignancy	Adds 1 point
Diabetes	Adds 1 point
Organ Transplant	Adds 1 point
Bone Marrow Transplant or previous splenectomy or AIDS patient or HIV carrier	Adds 1 point
Treatment at least twice with immunosuppressants in the last year or steroid treatment at least twice in the last year	Adds 1 point
Immunosuppression*	
Bone marrow transplant	
Combined Anti-Retroviral Therapy (CAR-T)	
Chronic Lymphocytic Leukemia	
Acute Lymphocytic Leukemia	
Multiple Myeloma	
Non-Hodgkin Lymphoma	
Aplastic Anemia	
Hodgkin Lymphoma / Myelodysplastic Syndrome / Acute Myeloid Leukemia + hematological treatment	
Myeloproliferative Disease + ruxolitinib treatment	
Rutixumab treatment	

Data Sources

Data in this study comes from the electronic medical records of Clalit Health Services (CHS). CHS is the largest of four integrated payer-provider health care organizations that provide mandatory health care coverage in Israel. CHS covers approximately 52% of the population of Israel (4.7 million persons). The dropout rate from CHS is 1- 2% yearly (2).

CHS pools the data from its many operational systems into a unified central data warehouse used for policy and research. This data repository includes detailed primary and secondary care information on hospitalizations, medications, laboratory results, and imaging tests. Due to the early adoption of electronic medical records and the low yearly dropout rate, CHS has good long-term follow-up of patients, ranging from the year 2000 (3).

Since the COVID-19 pandemic, the Israeli Ministry of Health (MOH) has centrally collected all COVID-19 related data. These include complete data on PCR testing, vaccination status, hospitalizations, and COVID-19 associated deaths, as reported daily to the MOH by all Israeli hospitals. The MOH transfers this data daily to the Israeli health funds (4). This allows integration of background medical information with vaccination status and COVID-19 related outcomes for the entire CHS patient population. The integrated data was used to generate the dataset for this study.

Data on Nirmatrelvir utilization was ascertained by CHS medical staff: A nurse in each CHS district was responsible for delivering nirmatrelvir therapy to the patients' homes and verifying adherence to the treatment regimen.

Explanation on the Socio-Economic Status (SES) Measure

SES was based on the small statistical areas (SSA) used in the 2008 Israeli census. The SSAs contain 3000–4000 people and are created to maintain homogeneity in terms of the sociodemographic composition of the population (5). The Israeli Central Bureau of Statistics (CBS) utilized demography, education, employment, housing conditions, and income to define the SSAs, and these were grouped into 20 categories. This data was updated by the POINTS Location Intelligence Company (6) to improve the accuracy of the SES measure, using up-to-date sociodemographic, commercial, and housing data (7). The entire CHS population was grouped into ten categories, ranging from 1 (lowest) to 10 (highest).

Table S2: Characteristics of the population affected by SARS-CoV-2 during the study period

Characteristic	Population at baseline (N= 1,164,902)
Age, years	
Mean ± SD	29.4 ± 21.2
Distribution- no. (%)	
40-64 yr	1,075,756 (92)
≥65 yr	89, 146 (8)
Female sex - no. (%)	642,920 (55)
Population sector- no. (%)	
General Jewish	865,052 (74)
Ultra-Orthodox Jewish	54,074 (5)
Arab	245,776 (21)
Socioeconomic status	
Mean ± SD	5.6 ± 1.9
Median (IQR)	6 (2)
Clinical risk factors - no. (%)	
Obesity	144,058 (12)
Hypertension	92,775 (8)
Diabetes	65,056 (6)
Current or former smoking	101,388 (9)
Immunosuppression	43,415 (4)
Neurologic disease	41,071 (3)
Current cancer disease	19,884 (2)
Asthma	58,813 (5)
History of stroke	15,099 (1)
Chronic hepatic disease	13,612 (1)
Chronic obstructive pulmonary disease	9,574 (1)
Chronic heart failure	11,021 (1)
Chronic kidney failure	12,662 (1)
Recent hospitalization	155,102 (13)

Covid-19 immune status - no. (%)	
No prior immunity	365,605 (31)
With prior immunity (overall)	799,297 (69)

Table S3: Association between participant characteristics and nirmatrelvir uptake*

Variable	Adjusted Hazard Ratio (95% CI)
Age group	
40-64	Reference
≥65	1.94 (1.8-2.08)
Male Sex	0.97 (0.9-1.03)
Population sector	
General Jewish	Reference
Ultra-orthodox Jewish	1.00 (0.85-1.18)
Arab	0.63 (0.55-0.71)
Socio-Economic Status**	1.16 (1.13-1.18)
Clinical risk factors	
Obesity	1.34 (1.25-1.43)
Diabetes	1.49 (1.39-1.60)
Asthma	1.21 (1.08-1.35)
Hypertension	1.08 (1.00-1.16)
Current or former smoking	1.12 (1.04-1.21)
Immunosupression	2.09 (1.93-2.26)
Neurologic disease	1.22 (1.10-1.34)
Current cancer disease	1.97 (1.81-2.15)
Chronic hepatic disease	1.02 (0.89-1.17)
Chronic obstructive pulmonary disease	1.53 (1.35-1.74)
Chronic heart failure	1.13 (0.98-1.31)
Chronic kidney failure	1.00 (0.81-1.25)

History of stroke	1.16 (1.04-1.31)
Recent hospitalization	1.46 (1.36-1.56)
History of organ transplant	0.86 (0.12-6.14)
Chronic imunologocal disease	1.94 (1.45-2.60)
History of TIA	1.02 (0.87-1.20)
Covid-19 immune status	
With prior immunity	Reference
No prior immunity	0.76 (0.68-0.84)
Clalit Health Services District	
Haifa	reference
Jerusalem	1.37 (1.19-1.57)
Tel-Aviv	1.57 (1.38-1.79)
Dan- Petach-Tikva	1.37 (1.21-1.55)
Center	1.01 (0.89-1.14)
South	1.53 (1.35-1.74)
Sharon- Shomron	0.88 (0.78-1.01)
North	1.90 (1.69-2.14)
Eilat	0.34 (0.17-0.69)

***** The association between all covariates and nirmatrelvir uptake was estimated using a multivariate Cox proportional-hazards regression model. The higher the hazard ratio, the greater the association between the listed characteristic and nirmatrelvir uptake**.**

****** A hazard ratio of more than 1.00 indicates an association between a higher score for socioeconomic status and nirmatrelvir uptake.

Table S4: HR of Hospitalization in patients aged 65 years or older, from day 3 of follow-up onwards

Variable	HR for Hospitalization Due to Covid-19 (95% CI) **≥65 Years of Age**
Nirmatrelvir therapy	0.28 (0.15-0.55)
Male Sex	1.73 (1.44-2.09)
Age (years)	1.09 (1.07-1.10)
Score for socioeconomic status	0.90 (0.85-0.94)
No prior immunity	6.60 (5.42-8.03)
Clinical risk factors	
Recent hospitalization	2.11 (1.73-2.56)
Obesity	1.09 (0.89-1.33)
Diabetes	1.34 (1.11-1.62)
Chronic hepatic disease	1.01 (0.67-1.51)
Neurologic disease	1.70 (1.37-2.11)
Chronic heart failure	1.37 (1.04-1.81)
COPD	1.67 (1.26-2.21)
History of stroke	1.13 (0.88-1.44)
Chronic kidney failure	2.59 (1.86-3.60)

Table S5: HR of Hospitalization in patients with **No** Prior Immunity, by age group

Variable	HR for Hospitalization Due to Covid-19 (95% CI)	
	40-64 Years of Age	≥65 Years of Age
	N=20,555	N=3,318
Number of events (event rate, %)	183 (0.9%)	277 (8.3%)
Nirmatrelvir therapy	0.23 (0.03-1.67)	0.15 (0.04-0.60)
Male Sex	1.87 (1.39-2.52)	2.25 (1.76-2.88)
Age (years)	1.08 (1.06-1.11)	1.10 (1.08-1.11)
Score for socioeconomic status	0.99 (0.92-1.08)	0.87 (0.81-0.94)
Clinical risk factors		
Recent hospitalization	2.63 (1.9-3.64)	1.10 (0.85-1.42)
Obesity	1.68 (1.23-2.3)	1.52 (1.17-1.97)
Diabetes	1.57 (1.08-2.27)	1.33 (1.04-1.71)
Chronic hepatic disease	2.10 (1.27-3.45)	1.11 (0.67-1.84)
Neurologic disease	1.68 (1.01-2.79)	1.24 (0.93-1.66)
Chronic heart failure	2.45 (1.33-4.51)	1.30 (0.91-1.86)
Chronic obstructive pulmonary disease	1.66 (0.88-3.13)	1.75 (1.22-2.51)
History of stroke	2.11 (1.22-3.66)	1.45 (1.07-1.97)
Chronic kidney failure	1.03 (0.32-3.29)	1.55 (0.90-2.68)

Table S6: HR of Hospitalization, in patients **With** Prior Immunity, by age group

Variable	HR for Hospitalization Due to Covid-19 (95% CI)	
	40-64 Year of Age N= 45,878	≥65 Year of Age N=39,503
Number of events (event rate, %)	158 (0.3%)	505 (1.3%)
Nirmatrelvir therapy	1.13 (0.50-2.58)	0.32 (0.17-0.63)
Male Sex	1.04 (0.75-1.43)	1.39 (1.16-1.66)
Age (years)	1.03 (1.01-1.06)	1.08 (1.07-1.10)
Score for socioeconomic status	1.04 (0.96-1.14)	0.09 (0.85-0.94)
Clinical risk factors		
Recent hospitalization	4.35 (3.02-6.26)	3.01 (2.47-3.66)
Obesity	0.96 (0.69-1.34)	0.90 (0.73-1.09)
Diabetes	1.25 (0.87-1.79)	1.39 (1.16-1.67)
Chronic hepatic disease	1.54 (0.93-2.56)	1.11 (0.76-1.62)
Neurologic disease	1.90 (1.22-2.96)	1.76 (1.44-2.16)
Chronic heart failure	2.44 (1.42-4.19)	1.54 (1.19-1.99)
Chronic obstructive pulmonary disease	2.83 (1.70-4.70)	1.81 (1.39-2.35)
History of stroke	1.57 (0.93-2.62)	1.33 (1.06-1.67)
Chronic kidney failure	2.53 (1.17-5.47)	1.88 (1.33-2.65)

Table S7: HR of Death due to Covid-19, by age group

Variable	**HR for death Due to Covid-19 (95% CI)**	
	40-64 years of Age	≥65 years of Age
Nirmatrelvir therapy	1.32 (0.16-10.75)	0.21 (0.05-0.82)
Male Sex	1.63 (0.55-4.79)	1.95 (1.41-2.71)
Age (years)	1.19 (1.06-1.33)	1.12 (1.10-1.14)
Score for socioeconomic status	0.97 (0.74-1.28)	0.86 (0.78-0.94)
No prior immunity	5.65 (1.98-16.16)	9.54 (6.87-13.25)
Clinical risk factors		
Recent hospitalization	3.90 (1.17-13.01)	1.62 (1.16-2.27)
Smoking	1.49 (0.48-4.64)	1.48 (0.97-2.27)
Diabetes	0.88 (0.27-2.86)	1.42 (1.03-1.94)
Immunosuppression	2.09 (0.60-7.31)	2.23 (1.49-3.32)
Active cancer	2.51 (0.68-9.28)	2.17 (1.43-3.29)
Neurologic disease	4.89 (1.61-14.82)	2.01 (1.43-2.85)
Chronic obstructive pulmonary disease	1.84 (0.33-10.22)	1.97 (1.22-3.19)
History of stroke	1.58 (0.40-6.27)	1.79 (1.23-2.61)
Chronic kidney failure	9.93 (2.48-39.75)	2.88 (1.74-4.77)
History of TIA	8.41 (2.22-31.81)	0.86 (0.45-1.61)
Asthma	1.89 (0.39-9.15)	0.58 (0.30-1.11)
Area of residence		
Haifa	*reference*	*reference*
Tel-aviv district	1.97 (0.5-7.81)	1.89 (1.17-3.06)
Central district	NA	1.72 (1.13-2.64)
Sharon-Shomron district	1.03 (0.22-4.8)	1.91 (1.24-2.95)

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