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BRIEF REPORT

Implementation of AZD7442 (Tixagevimab/Cilgavimab) COVID-19 Pre-exposure Prophylaxis (PrEP) in the Largest Health Maintenance Organization in Israel: Real-world Uptake and Sociodemographic and Clinical Characteristics Across Immunocompromised Patient Groups

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ABSTRACT

Introduction: AZD7442 is a combination of two neutralizing antibodies (tixagevimab/cilgavimab) with demonstrated efficacy in reducing the risk of symptomatic coronavirus disease 2019 (COVID-19) among individuals at high risk of severe COVID-19 ≤ 6 months after administration. On February 15, 2022, the Israeli Ministry of Health (IMoH) authorized the administration of 300 mg AZD7442 as pre-exposure prophylaxis (PrEP) against severe acute respiratory syndrome coronavirus 2 infection

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among immunocompromised individuals aged ≥ 12 years. This study describes the real-world uptake of AZD7442 in Israel.

Methods: This descriptive, observational study analyzed data from Israel's largest health maintenance organization, Clalit Health Services (CHS). Individuals were assessed for AZD7442 eligibility between February 13 and December 11, 2022, and were included if they were aged ≥ 12 years, had ≥ 1 year of continuous CHS membership, had ≥ 1 moderate or severe immunocompromising condition, and were eligible for AZD7442 per IMoH recommendations during this time frame.

Results: Overall, 19,161 AZD7442-eligible individuals with immunocompromising conditions were identified during the study period; 2829 (14.8%) received AZD7442. A higher proportion of individuals receiving AZD7442 were older (aged ≥ 65 years), male, not current smokers and residents in large cities; required more physician visits (> 50 visits); and had ≥ 1 COVID-19 hospitalization over 12 months, while uptake was lowest among ultra-orthodox Jewish individuals. AZD7442 uptake was also higher among individuals with multiple comorbidities (Charlson Comorbidity Index ≥ 5), including hypertension, diabetes and chronic kidney disease. In specific immunocompromised types, AZD7442 uptake was highest among individuals with lung transplantation (41%), primary immunodeficiency (32%), bone marrow transplantation (29%) and multiple myeloma (25%) or those receiving anti-CD20 therapy (26%) and was lowest in individuals with lymphoma (8%).

Conclusion: These results show AZD7442 uptake among the eligible population of Israel in 2022 was relatively low, at 14.8%. Uptake was generally higher among immunocompromised individuals who may be perceived to be frail or at highest risk of COVID-19 infection and complications, although at 25–41%, further improvements in uptake would be more impactful. These results also indicate there is opportunity to expand AZD7442 uptake across immunocompromised groups and ensure more equitable uptake among some other sociodemographic groups. Overall, this study will help inform and reassess future implementation strategies for vulnerable populations.

Keywords: AZD7442; COVID-19; Immunocompromised; Israel; Pre-exposure prophylaxis; Real-world evidence; SARS-CoV-2; Tixagevimab/cilgavimab

Key Summary Points

There is little real-world information about the use of non-vaccine prophylaxis for COVID-19.

AZD7442 had been administered to patients with immunocompromising conditions in Israel and worldwide prior to the withdrawal of its emergency use authorization.

This study sought to identify patterns of AZD7442 uptake in Israel to help optimize the distribution of future pre-exposure prophylaxis to those who remain vulnerable to severe COVID-19 outcomes.

Uptake was generally higher among immunocompromised individuals who may be at highest risk of COVID-19 infection and complications.

There is opportunity to expand AZD7442 uptake across immunocompromised groups and ensure more equitable uptake among other sociodemographic groups.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in > 700 million confirmed infections and almost 7 million deaths worldwide since December 2019 [1–3]. The SARS-CoV-2 vaccination campaigns successfully led to a high level of coronavirus

disease 2019 (COVID-19) vaccination and have more than halved the potential death toll of COVID-19 globally (before the emergence of the omicron [B.1.1.529] variant), with an estimated 19.8 million COVID-19 deaths averted [4].

Although the World Health Organization has now declared that COVID-19 is no longer a public health emergency of international concern [5], SARS-CoV-2 infections are still occurring. In the 7 days before December 24, 2023, 259,104 new cases were reported globally [6]. Furthermore, this figure may underestimate the true extent of isolation and infection because of a reduction in the availability of COVID-19 tests. Immunocompromised (IC) individuals and other high-risk groups are still vulnerable to severe COVID-19 outcomes [7]. These groups are not only more likely to have severe COVID-19 outcomes [8] but are also more likely to have suboptimal responses to vaccination, leading to protracted infections, delays in primary condition treatment and possible escape variant evolution [9, 10]. Therefore, these populations will benefit from additional protection.

AZD7442, which comprises two neutralizing monoclonal antibodies (tixagevimab/cilgavimab), was granted emergency use authorization (EUA) as a pre-exposure prophylaxis (PrEP) for COVID-19 by the US Food and Drug Administration (FDA) in December 2021 based on the results of the PROVENT trial [11, 12]. AZD7442 was approved at a dose of 300 mg (150 mg tixagevimab/150 mg cilgavimab; later changed to 600 mg [300 mg tixagevimab/300 mg cilgavimab]) for individuals aged ≥ 12 years and weighing ≥ 40 kg with moderate to severe immunocompromising conditions, on immunosuppressive medications or treatments, or unable to receive a COVID-19 vaccination [13–15]. The rollout of AZD7442 was initiated midway through the B.1.1529 (Omicron variant) dominant period (January 10–March 2, 2022) [16].

Although AZD7442 has proven efficacy against COVID-19 hospitalization and death [12], the EUA was subsequently withdrawn in January 2023 by the FDA when the circulating SARS-CoV-2 variants non-susceptible to AZD7442 in in vitro neutralization assays (BQ.1, BQ.1.1, BF.7, BF.11, BA.5.2.6, BA.4.6, BA.2.75.2, XBB and XBB.1.5) reached ≥ 90% [17]. Based on the FDA ruling, AZD7442 was also withdrawn by the Israeli Ministry of Health (IMoH) and across other countries.

Despite the wide-scale rollout of non-vaccine prophylaxis in recent years, there are few studies reporting their real-world use, particularly in high-risk populations, which could inform and improve future interventions. Understanding patterns of uptake may help to develop public health PrEP utilization policy and help optimize the distribution of future therapies to those who remain vulnerable to severe COVID-19 outcomes. Here, we report results of an observational study utilizing data from Israel's largest health maintenance organization (HMO), Clalit Health Services (CHS), which aimed to determine AZD7442 real-world uptake in Israel among IC individuals and characterize those who received AZD7442, and compare baseline factors among those eligible for AZD7442 who did or did not receive AZD7442.

METHODS

Study Design and Data Source

This descriptive analysis is based on the eVusheld Assessment reaL wORld effectiveness (VALOR-C19) observational study, which assessed the effectiveness of AZD7442 PrEP in reducing COVID-19 hospitalizations among AZD7442-eligible IC populations in Israel (NCT05712096). This paper characterizes AZD7442 uptake in IC individuals eligible for AZD7442 administration as PrEP as per IMoH recommendations.

Israel is a country with national health insurance, and AZD7442 was distributed to eligible individuals through integrated payer-provider HMOs. CHS is the largest HMO in Israel, with > 4.7 million members (~ 53% of the population). Data were obtained from the CHS electronic health record (EHR) database containing inpatient, outpatient and COVID-19 repositories, which was described previously [18, 19].

In total, the IMoH received 20,104 doses of AZD7442 between February 13 and November 24, 2022. CHS received 8000 of these doses, which were proactively offered to eligible members.

Study Population

Individuals were eligible for inclusion if they were aged ≥ 12 years and fulfilled the IMoH criteria for AZD7442 PreP during the study period (February 13 to December 31, 2022), defined as having at least one comorbidity or condition causing severe immunosuppression (i.e., chimeric antigen receptor T-cell therapy [CAR-T], solid organ transplant [SOT], autologous or allogenic bone marrow transplant [within the previous year if allogenic], hypogammaglobulinemia, active lymphoma, active multiple myeloma, diagnosis of chronic lymphocytic leukemia [CLL] or receiving treatment for CLL, and B-cell-depleting therapies). The full list of disease definitions is included in Supplemental Table S1. Exclusion criteria included documented history of a positive SARS-CoV-2 polymerase chain reaction or antigen test prior to AZD7442 administration. Lack of SARS-CoV-2 test history was not exclusionary.

Study Variables

Key demographic and clinical characteristics, including immunocompromising condition, select comorbidities (e.g., heart disease, type 2 diabetes, hypertension, etc.) up to 5 years prior to the date of AZD7442 administration, medication use and number of physicians visits a year prior to the index date, were extracted from EHRs.

Statistical Analysis

The demographic and clinical characteristics of the total study population and by AZD7224 recipient or non-recipient status were described using summary statistics: number and percentage for categorical variables and median and interquartile range for count variables. Statistical analyses were performed using R software, version 4.2.1.

Ethical Approval

This study used de-identified patient data and was approved by the Clalit Health Services institutional review board.

RESULTS

In total, 19,161 IC individuals eligible for AZD7442 PrEP between February 13 and November 24, 2022, were identified from the CHS database. Among these, AZD7442 uptake was 14.8% ($n = 2829$ received AZD7442). The distribution of AZD7442 uptake by month is presented in supplemental Fig. 1.

Baseline characteristics for the overall eligible population and by AZD7442 recipient status are shown in Table 1 and Supplemental Tables S2–4. Among the total eligible population, individuals were older (54% were aged ≥ 65 years) and had multiple comorbidities (66% had a Charlson Comorbidity Index score ≥ 5), and the most common IC type was lymphoma (43%). When categorized by AZD7442 status and compared with AZD7442 non-recipients, a higher proportion of AZD7442 recipients were aged ≥ 65 years, not current smokers, had comorbidities (e.g., hypertension, diabetes, chronic kidney disease) and were organ transplant recipients (Table 1 and Fig. 1). Overall, AZD7442 uptake increased with an increased number of comorbidities (Table 1).

When comparing across IC types, AZD7442 uptake was highest in lung transplant recipients (41%), followed by individuals with primary immunodeficiency (32%) and bone marrow transplant recipients (29%) (Fig. 1). AZD7442 uptake was lowest in individuals with lymphoma (8%) and < 20% in individuals with SOT, CAR-T/graft versus host disease and CLL. The full characteristics for AZD7442 recipients and non-recipients by immunocompromising

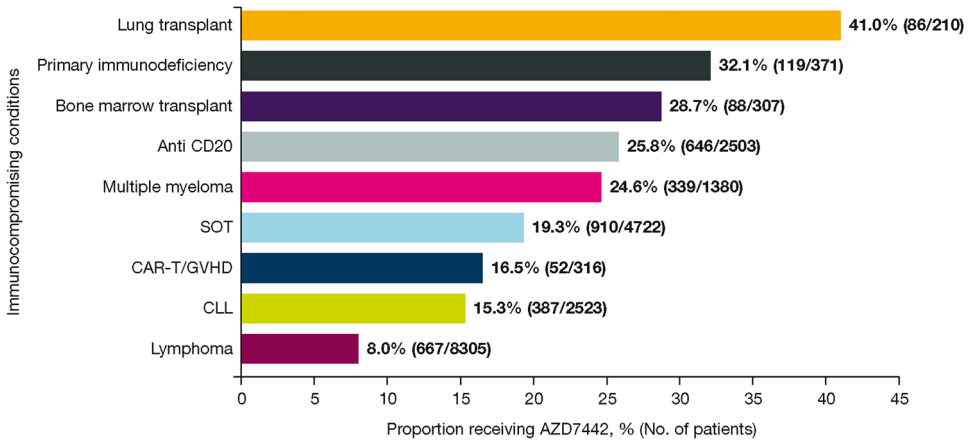

Fig. 1 Uptake of AZD7442 by **a** immunocompromising condition and **b** number of immunocompromising conditions. *CLL* chronic lymphocytic leukemia, *CAR-T* chimeric antigen receptor T-cell, *GVHD* graft versus host disease, *SOT* solid organ transplant

condition are shown in Supplemental Tables S2–S4.

According to sociodemographic factors, AZD7442 uptake was lowest among ultra-Orthodox Jewish individuals versus the general population and Arab population (7% vs 16% vs 15%, respectively) and highest in residents of large cities versus small cities (16% vs 13%, respectively) (Fig. 2). When analyzed by vaccination status, uptake was highest in individuals with ≥ 3 previous COVID-19 vaccinations (Table 1).

DISCUSSION

Our study indicates the uptake of AZD7442 among eligible individuals in Israel was relatively low at ~ 15%. This is consistent with previous reports from the two largest Israeli HMOs, CHS and Maccabi HealthCare Services (MHS; second largest HMO in Israel), where AZD7442 uptake ranged from 9 to 16% over a similar time frame [20, 21]. The distribution of AZD7442 to all CHS districts was based on demand, and low uptake was not due to a shortage of supply. It is possible that the structure and organization of HMOs within Israel may have influenced the uptake of AZD7442. Within CHS, AZD7442 administration was managed by the community division, with eligible individuals offered AZD7442 PreP via their primary care clinics. Although eligible individuals were closely managed in the outpatient clinics of general hospitals, the IMoH had not delineated the role of hospitals in the administration of AZD7442. Additionally, only a few hospitals participated in a patient outreach effort by the CHS community division. These factors may explain the relatively low rates of AZD7442 administration to eligible individuals.

Uptake varied widely across different populations, consistent with previous studies using the CHS and MHS databases [10, 21]. High uptake in individuals with comorbidities, increased physician visits at baseline and high numbers of dispensed prescriptions suggest that AZD7442 was administered to more frail individuals. Uptake was also high in individuals who were vaccinated with ≥ 3 doses of the COVID-19 vaccine and previously hospitalized with COVID-19, which may indicate that those perceived to be at higher risk of severe COVID-19 were more likely to receive PrEP.

Sociodemographics revealed AZD7442 uptake was higher in males versus females, and lower in ultra-orthodox Jewish than Arab individuals, with uptake highest in the rest of the population. This is contrary to previous reports where AZD7442 uptake was higher in ultra-Orthodox Jewish individuals [10, 11]. Reports on non-COVID-19 vaccine uptake

Table 1 Baseline demographics and AZD7442 uptake

	AZD7442 recipient (*N* = 2829)	**Non-AZD7442 recipient (*N* = 16,331)**	**Total number with each characteristic (total population *N* = 19,160), *n***	
Characteristic, *n* (%)[a]				AZD7442 uptake per characteristic (%)
Age, years, median (IQR)	68 (58–74)	66 (51–75)	–	–
Sex				
Female	1196 (42)	7880 (48)	9076	13
Male	1633 (58)	8451 (52)	10,084	16
Obese (BMI ≥ 30 kg/m^2)	627 (22)	4108 (25)	4735	13
Currently smokes	219 (88)	2082 (13)	2301	10
Comorbidities[b]				
Hypertension	1553 (55)	7605 (47)	9158	17
CHF	368 (13)	2117 (13)	2485	15
Other cardiovascular diseases	1333 (47)	6743 (41)	8076	17
Diabetes	885 (31)	4293 (26)	5178	17
Asthma	253 (9)	1408 (9)	1661	15
COPD	187 (7)	703 (4)	890	21
Chronic liver disease	705 (25)	3689 (23)	4394	16
Chronic kidney disease	1243 (44)	5711 (35)	6954	18
Chronic neurological disease	230 (8)	1340 (8)	1570	15
Anxiety/depression	67 (2)	397 (2)	464	14
Number of prior physician visits, median (IQR)	65 (46–90)	45 (28–66)	–	–
0–50	851 (30)	9506 (58)	10,357	8
> 50	1978 (70)	6825 (42)	8803	22
Number of prior COVID-19 hospitalizations, median (IQR)	1 (0–2)	0 (0–1)	–	–
0–10	2802 (99)	16,199 (99)	19,001	15
≥ 11	27 (< 1)	132 (< 1)	159	17

Table 1 continued

	AZD7442 recipient ($N = 2829$)	Non-AZD7442 recipient ($N = 16,331$)	Total number with each characteristic (total population $N = 19,160$), *n*	
Number of dispensed prescriptions				
0–10	1606 (57)	12,341 (77)	13,947	12
≥ 11	1223 (43)	3990 (24)	5213	24
Number of prior COVID-19 vaccinations				
0	40 (1)	1562 (10)	1602	2
1	47 (2)	555 (3)	602	8
2	203 (7)	1848 (11)	2051	10
≥ 3	2539 (90)	12,366 (76)	14,905	17
Charlson Comorbidity Index score				
0	53 (2)	500 (3)	553	10
1	78 (3)	393 (2)	471	17
2	187 (77)	1539 (9)	1726	12
3	240 (88)	1473 (9)	1713	14
4	285 (10)	1728 (11)	2013	14
≥ 5	1979 (70)	10,640 (65)	12,619	16

Further baseline characteristics are in the supplementary materials

BMI body mass index, *CAR* chimeric antigen receptor, *CHF* congestive heart failure, *COPD* chronic obstructive pulmonary disease, *GVHD* graft versus host disease, *IQR* interquartile range

[a]Unless stated otherwise

[b]Not mutually exclusive

among children show Arab individuals are more likely to be vaccinated than ultra-orthodox Jewish individuals, although at a lower rate in both than the rest of the population, a trend also observed with COVID-19 vaccine uptake [22–24].

Across immunocompromising conditions, AZD7442 uptake was highest (41%) among individuals with lung transplants and lowest among individuals with lymphoma (8%), despite lymphoma being the most common IC type among the eligible population. Lower uptake of AZD7442 among individuals with lymphoma than in those with other immunocompromising conditions has been observed in another study in Israel; the reasons for this lower uptake are unclear and should be elucidated in future investigations [21]. In Israel, lung transplant recipients are almost exclusively managed in one CHS hospital, which may explain the high AZD7442 uptake among this population as these individuals were managed by the same healthcare team. Although previous studies did not report lung transplants specifically, the trend in uptake in overall SOT recipients presented here aligns with these studies [10, 21].

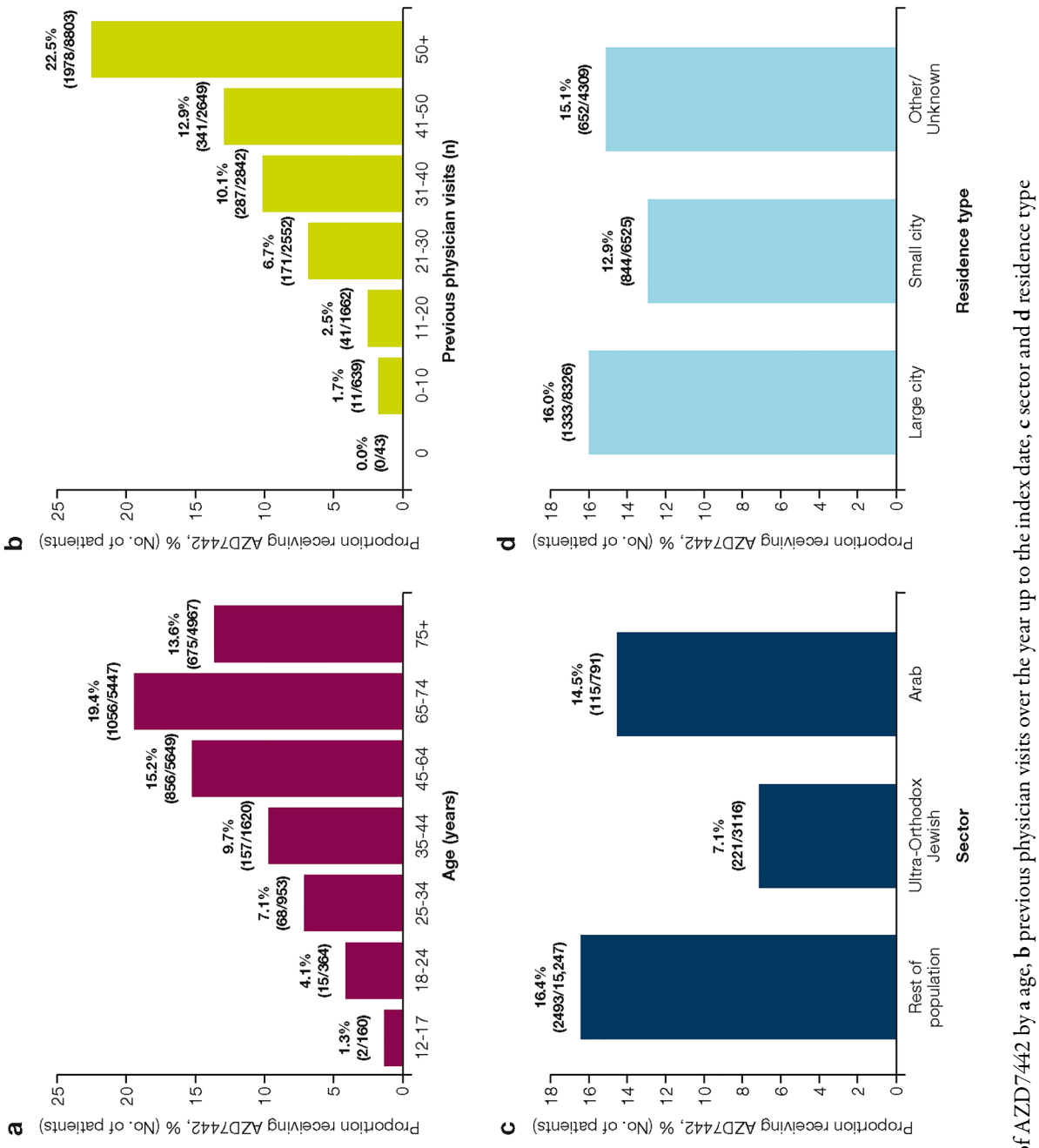

Fig. 2 Uptake of AZD7442 by **a** age, **b** previous physician visits over the year up to the index date, **c** sector and **d** residence type

The results presented here highlight the low uptake of AZD7742 in eligible IC individuals, especially in certain subgroups. Understanding the factors underlying these lower-than-expected uptake rates may help inform future non-vaccine PrEP rollout strategies. This study also suggests improving the alignment between the CHS community division and the hospital clinics in managing AZD7442 distribution to eligible individuals. This may allow greater uptake, which could have implications for HMOs other than CHS, as well as for those beyond Israel.

Strengths include that this study was undertaken using a database from the largest HMO in Israel, representing > 50% of the population. This database is complete and includes a large number of individuals with immunocompromising conditions, and the results reported here align with a previous study in the second largest HMO. We therefore believe these results are a close reflection of the overall population.

Limitations of the study include that accuracy of results is dependent on the availability and accuracy of information entered into EHRs. We report only descriptive analyses, limiting conclusions on whether specific baseline factors are independently associated with AZD7442 update; further statistical analysis would be needed to investigate this.

CONCLUSIONS

These findings highlight low uptake of AZD7442 among a population vulnerable to COVID-19. As the IC populations remain at high risk of severe COVID-19 outcomes, the results presented here may provide valuable information for targeting future interventions, particularly next-generation COVID-19 PrEP, toward the most-at-risk populations. These results may also serve as a call to action to consider how rollout is managed for at-risk groups, regardless of the type of intervention.

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Author Contributions. Samah Hayek, Joseph Levy, Galit Shaham, Noa Dagan, Idit Livnat, Sabada Dube, Sylvia Taylor, Sudhir Venkatesan and Ran D. Balicer conceived and designed the study. Joseph Levy and Galit Shaham participated in data extraction and analysis. Danielle Serby, Hadar Duskin-Bitan, Doron Netzer and Alon Peretz contributed to data collection. Samah Hayek, Joseph Levy, Galit Shaham, Noa Dagan, Idit Livnat, Sabada Dube, Sylvia Taylor, Sudhir Venkatesan, Ran D. Balicer and Alon Peretz wrote the manuscript. Noa Dagan, Danielle Serby, Hadar Duskin-Bitan, Ran D. Balicer, Doron Netzer and Alon Peretz provided clinical guidance. All authors critically reviewed the manuscript and decided to proceed with publication.

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Data Availability. National and organizational data privacy policies prohibit the sharing of individual-level data, such as those used for this study, even if anonymized.

Declarations

Conflict of Interest. Samah Hayek, Galit Shaham, Noa Dagan, Danielle Serby, Hadar Duskin-Bitan, Ran D. Balicer, Doron Netzer and Alon Peretz are employees of Clalit Health Services. Joseph Levy was an employee of Clalit Health Services at the time of this study and manuscript development; Dr Levy's current affiliation is the Hebrew University of Jerusalem. Clalit Research Institute received funding from AstraZeneca to support execution of this study. Institutional grants to Clalit Research Institute from Pfizer outside the submitted work and unrelated to COVID-19, with no direct or indirect personal benefits. Adva Yarden, Cátia Ferreira, Idit Livnat, Sabada Dube, Sylvia Taylor

and Sudhir Venkatesan are employees of, and hold or may hold stock in, AstraZeneca.

Ethical Approval. This study used de-identified patient data and was approved by the Clalit Health Services institutional review board.

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