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Community antibiotic prescriptions during COVID-19 era: a population-based cohort study among adults

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A B S T R A C T

Objectives: This study investigated the association between the COVID-19 pandemic and antibiotic prescription ratios and the determinants of antibiotic prescription in the community.
Methods: The study was based on a retrospective population cohort of adults in a community setting. Antibiotic prescription ratios from March 1, 2020 to February 28, 2021 (COVID-19 period) were compared to similar months in previous years. Differences in visit type, infectious disease–related visit, and antibiotic prescription ratios during these visits were compared. A logistic regression model was used to identify independent determinants of antibiotic prescription during the study period.
Results: The cohort included almost 3 million individuals with more than 33 million community medical encounters per year. In the COVID-19 period, the antibiotic prescription ratio decreased 45% (from 34.2 prescriptions/100 patients to 19.1/100) compared to the previous year. Visits due to an infectious disease etiology decreased by 10% and prescriptions per visit decreased by 39% (from 1 034 425 prescriptions/3 764 235 infectious disease visits to 587 379/3 426 451 respectively). This decrease was observed in both sexes and all age groups. Telemedicine visits were characterized by a 10% lower prescription ratio compared to in-person visits. Thus, a threefold increase in telemedicine visits resulted in a further decrease in prescription ratios. The COVID-19 period was independently associated with a decrease in antibiotic prescription, with an OR of 0.852 (95% CI 0.848–0.857).
Discussion: We describe a significant decrease in antibiotic prescription ratios during the COVID-19 periods that was likely related to a decrease in the incidence of certain infectious diseases, the transfer to telemedicine, and a change in prescription practices among community-based physicians. **Bat-Sheva Gottesman, Clin Microbiol Infect 2022;28:1134**

Introduction

The COVID-19 pandemic changed the landscape of healthcare services worldwide. At the beginning of the pandemic, there were concerns regarding antibiotic overuse due to possible coinfection, superinfection, or misdiagnosis with other infections. Another uncertainty was related to the effect of SARS-CoV-2 on seasonal viral infections, such as influenza and respiratory syncytial virus.

The COVID-19 pandemic completely changed social norms and behaviours, with the addition of lockdowns and other social

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distancing methods, enhanced handwashing, and mask wearing. Universal masking and social distancing were implemented in Israel throughout the entire year (March 2020 through February 2021). These dramatic changes were expected to decrease other transmissible infectious diseases and antibiotic use. Moreover, many visits that were previously conducted in-person were transferred to telemedicine encounters because of infection control policies. The effect of this change in patient–physician interactions on antibiotic prescription was unknown.

Reports from hospitals around the world described increased antibiotic use, which was driven mainly by severe COVID-19 cases [1,2]. This effect could not be extrapolated to the community because patient characteristics and antibiotic use differ. Initial reports from the community described decreased prescription of antibiotics, but those reports encompassed only the first few months of the pandemic, thereby missing a possible effect of seasonal variations [3–5].

This study describes community antibiotic prescription ratios over a full year during the COVID-19 pandemic, compared to the previous 2 years, among the population of the largest health maintenance organization (HMO) in Israel, categorized by patient demographics, visit type, and infectious diagnoses.

Methods

Study design

This retrospective, population-based, cohort study was conducted from March 1, 2018 to February 28, 2021. Three periods were defined: 2018, 2019, and 2020, each starting on March 1 and ending February 28 the following year.

Setting and population

The study was based on community electronic medical record (EMR) data from Clalit Health Services (CHS), the largest of four nationally mandated HMOs in Israel, which serves 4.5 million persons (54% of the Israeli population). All adults >18 years of age who were insured through CHS for the duration of the study were included. Data were collected based on medical encounters; thus, a patient could be included more than once.

Data source and variables

The CHS electronic database contains nearly two decades of detailed, person-level inpatient and outpatient clinical data (diagnoses, medication prescription, and laboratory tests) [6]. The following information for each patient was retrieved from the database: date of birth, sex, and population sector. Of note, SARS-CoV-2 tests performed in any of national laboratories were captured in the EMR. In our study, a SARS-CoV-2 test was linked to a specific visit if performed up to 72 hours after the visit. The following information was retrieved for each encounter: date of visit, visit type (in-person vs. telemedicine), and diagnosis (based on International Classification of Diseases, Ninth Revision and International Classification of Primary Care). Any antibiotic dispensed to the patient in the week following the infectious disease (ID) visit was retrieved from the HMO community pharmacy database. In Israel, antibiotics are dispensed only with a physician's prescription. Definitions of infectious diagnoses subgroups appear in Table S1.

COVID-19 visits included only medical encounters with a definite diagnosis of COVID-19 or a visit due to patient exposure to COVID-19, necessitating referral for a SARS-CoV-2 test. The CHS Research Ethics Committee approved this retrospective study and waived the requirement for informed consent.

Statistical analysis

The antibiotic prescription event ratio per 100 registered patients was calculated for each year. Because there was some variability in the number of registered patients over the months, the denominator included the number of registered patients mid-year as a proxy for the number of patients registered in each year. In addition to the annual ratios, monthly antibiotic prescription ratios were calculated to check for seasonal variations and to identify main time points of change. Overall and subgroup-specific ratios were calculated for certain age groups (18–65, 66–75, and 76+), sex, and population sector.

The proportions of ID-related visits among all visits and the proportions of visits with antibiotic prescription among ID-related visits were calculated for each period and stratified according to demographic characteristics; χ^2 tests were used to compare categorical variables.

The overall change in antibiotic prescription ratios before and after the pandemic began in Israel (March 2020), controlling for seasonality and age, was assessed using an interrupted time series Poisson regression model. The data included the number of prescriptions summarized by age group and month across the investigated periods. Interrupted time series analysis was used as described by Bernal et al. [7] to evaluate the effect of the COVID-19 period on the prescription rate [8]. A quasi-Poisson model, which controls for overdispersion by allowing the variable to be proportional to the mean, was fit, with the prescription count as the dependent variable and the natural log of the insured population count as offset. The independent variables included the time since the start of the study, an indicator for the COVID-19 period, and the age group. In addition, a harmonic term, representing a sine-cosine trend across the two periods, was added to adjust for seasonality.

To assess the association between periods (COVID-19 vs. pre-COVID 2018–2019) and antibiotic prescription adjusted for potential intermediate determinants for antibiotic prescription, a generalized estimating equation multivariate logistic regression model was designed. The generalized estimating equation procedure allows for dependence within clusters of visits of the same patient. The model included a random sample of 50% of all visits with ID diagnosis during the study period of 2018–2020. The covariates included in the model were demographics (age, sex, and population sector), visit type (in-person vs. telemedicine), and the specific infectious diagnosis. Adjusted ORs for antibiotic prescription by period and for each covariate in the model were calculated. The 95% CIs of the adjusted ORs and the p values are presented.

Data were analyzed using SPSS, version 23 (IBM Corp., Armonk, NY). Results were considered significant when the p value was <0.05 in a two-sided test.

Results

The study cohort included 2 978 515 insured adults in 2018, which increased by less than 2% annually to 3 055 180 in 2020. The median age was 53 years (interquartile range 35–69), and 48% were male. Population sectors included 72.2% general Jewish population, 24% Arabs, and 4.1% ultra-orthodox Jews.

Antibiotic prescription

A 45.4% and 45.9% decrease in the antibiotic prescription ratio was observed in 2020 compared to 2018 and 2019 respectively (Table 1). This marked decrease was observed in both sexes, across age groups, and in the different population sectors. The decrease in antibiotic prescription over time according to age group is shown in Fig. 1. The monthly ratios show that the major decrease in antibiotic prescriptions occurred in April 2020, 1 month after the first COVID-19 cases appeared in Israel. The usual seasonal winter peaks did not appear in 2020. The interrupted time series analysis revealed adjusted age and season risk ratio of 0.6 (95% CI 0.545–0.665).

ID visits

ID visits represented 10.9% and 11% of total community medical visits in 2018 and 2019 respectively, which decreased to 9.8% in 2020. ($p < 0.001$; Table 2). Prior to 2020, the most common reasons for ID visits were upper respiratory tract infection (URTI), pharyngitis, and urinary tract infection (UTI). Although in 2020 COVID-19 diagnosis was added to the ID diagnoses and became the leading cause among them (859 842 visits [25%]), the total number of visits for an ID-related disease decreased by 10%. The change was mainly due to decreases in other respiratory diseases: URTI decreased from 3.38% of all visits in 2019 to 1.39% of all visits in 2020, pharyngitis from 1.4% to 0.8%, sinusitis from 0.47% to 0.23%, lower respiratory tract infection (LRTI) from 0.34% to 0.15%. A decrease in acute gastroenteritis was noted as well (from 0.45% in 2019 to 0.26% in 2020). The only aetiology that increased in frequency was fever (from 0.24% to 0.28%) ($p < 0.001$ for all comparisons).

Visit type

In the periods of 2018 and 2019, 87.0% and 86.3% of ID-related visits, respectively, were in person. In 2020, due to national health regulations, a shift to telemedicine visits occurred, resulting in marked increase in the proportion of telemedicine ID visits from 13.7% (516 027/3 764 235) in 2019 to 41.7% (1 430 886/3 426 451) in 2020 (Table 2). Throughout the study, telemedicine visits were characterized by 10% lower antibiotic prescription ratio compared to in-person visits. In 2019 the ratio for in-person visits was 28% (937 693/3 248 208) versus 18.7% (96 732/516 027) for telemedicine visits, and in 2020 it was 21% (419 176/1 995 565) for in-person visits versus 11.8% (168 203/1 430 886) for telemedicine visits (Table 3).

Antibiotic prescription per ID visit

As seen in Table 3, visits due to an ID aetiology decreased, as did antibiotic prescription per ID visit, from 28.7% in 2019 to 17.0% in 2020. The largest decrease in antibiotic prescription per visit was observed in respiratory diseases: URTI from 23.1% to 16.4%, pharyngitis from 54.3% to 40.2%, LRTI from 41.2% to 28.2%, and fever from 14.7% to 9.5% ($p < 0.001$ for all). Although COVID-19 was the leading ID diagnosis, only 1% of those visits led to an antibiotic prescription. The decrease appeared among all population sectors.

Independent predictors of antibiotic prescriptions

Antibiotic prescription for infectious diseases decreased significantly from the 2018 and 2019 baseline periods to the 2020 COVID-19 period (OR 0.852, 95% CI 0.848–0.857; Table 4). The independent associations of the different explanatory variables influencing antibiotic prescription are presented in Table 4. Advanced age (OR 1.009; 95% CI 1.009–1.009) and female sex (OR 1.062; 95% CI 1.056–1.068) were related to increased antibiotic prescription. Telemedicine (OR 0.540; 95% CI 0.536–0.544) and

Table 1
Antibiotic prescription ratio per 100 registered patients by period and demographic characteristics

Variable	Baseline 2018			Baseline 2019			COVID-19 period (2020)		
	Registered patients	Prescriptions	Prescription ratio/100 patients	Registered Patients	Prescriptions	Prescription ratio/100 patients	Registered Patients	Prescriptions	Prescription ratio/100 patients
Total	2 978 515	1 026 965	34.5	3 015 567	1 032 181	34.2	3 055 180	584 070	19.1
Age group (y)									
18–65	2 390 980	770 692	32.2	2 413 033	778 896	32.3	2 438 362	430 138	17.6
66–75	329 102	138 058	41.9	344 732	139 375	40.4	356 202	82 800	23.2
≥76	258 433	118 215	45.7	257 802	113 910	44.2	260 616	71 132	27.3
Sex									
Male	1 428 510	363 086	25.4	1 448 454	366 932	25.3	1 468 229	195 700	13.3
Female	1 550 005	663 879	42.8	1 567 113	665 249	42.5	1 586 951	388 370	24.5
Population sector									
General Jewish	2 151 869	716 810	33.3	2 164 714	726 593	33.6	2 173 780	404 489	18.6
Arab	703 871	266 824	37.9	724 416	261 379	36.1	749 401	152 749	20.4
Ultra-orthodox Jewish	122 775	43 331	35.3	126 437	44 209	35.0	131 999	26 832	20.3

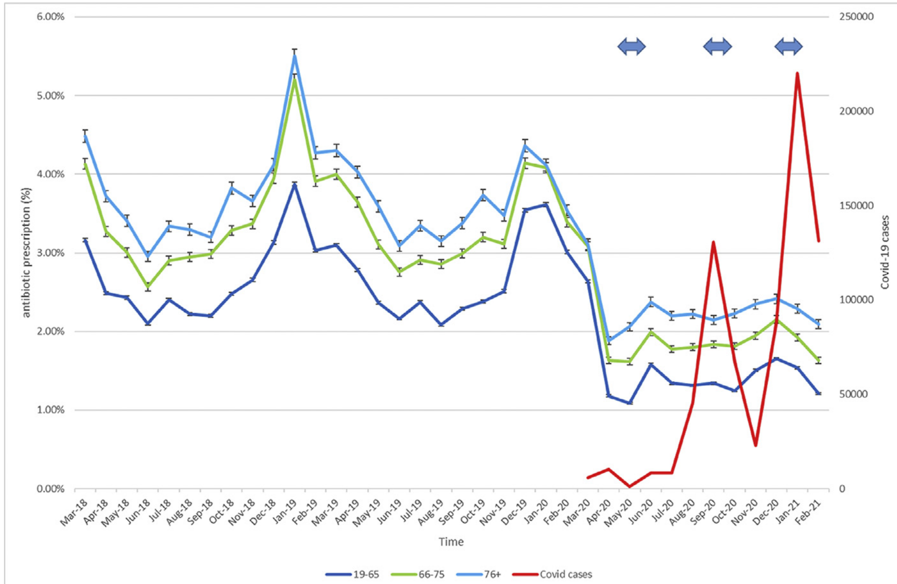

Fig. 1. Monthly antibiotic prescription ratio by age groups and month in parallel to COVID-19 cases (red). The blue arrows represent lockdown periods. Risk ratio of 0.6 (95% CI 0.545–0.665) for COVID-19 period by interrupted time series analysis.

belonging to the general Jewish sector (OR 0.812; 95% CI 0.807–0.818) were related to increases in antibiotic prescriptions. All clinical diagnoses independently influenced antibiotic prescription. Compared to acute gastroenteritis, most diagnoses were related to increased antibiotic prescription. COVID-19 diagnosis was associated with a marked decrease in antibiotic prescription, with an OR 0.219 (95% CI 0.211–0.227) compared to acute gastroenteritis (Table 4).

Discussion

In this population-based study, a 45% decrease in community antibiotic prescription was observed in 2020 during the COVID-19 pandemic. This decrease was observed across age groups, sexes, and population sectors. We investigated possible explanatory factors that could have influenced antibiotic prescription. Several changes occurred in parallel and were found as drivers of this decline: (a) a new viral disease that did not require antibiotic treatment; (b) a decrease in visits due to ID aetiology, in particular transmissible diseases; and (c) a shift toward telemedicine, in which lower antibiotic prescription was traditionally the common practice in Israel.

A clear decline was observed in respiratory diseases, a known driver of antibiotic consumption [9–11]. This decline was witnessed worldwide, both in the southern and northern hemispheres [8,12]. One possible explanation for the decrease was social distancing, compulsory mask usage, and enhanced hand hygiene [13]. The concurrent decrease in other transmissible diseases, such as acute gastroenteritis, supports this explanation. Another explanation is that the biological niche occupied by SARS-CoV-19 displaced traditional viral diseases such as influenza and respiratory syncytial virus. This explanation is supported by the near disappearance of these diseases, even in countries in which social distancing was not enforced, such as Brazil [14].

In addition to the decline in the number of ID visits, fewer visits resulted in antibiotic prescription. This phenomenon was more pronounced in viral-related aetiologies, such as URTIs, as reported by Mamun et al. [15]. A possible explanation is greater awareness of

Table 2
Number and proportion of visits with an infectious diagnosis by specific diagnosis and visit type

Total visits	Baseline 2018, $N = 33\,654\,236$	Baseline 2019 $N = 34\,074\,404$	COVID-19 period (2020) $N = 34\,692\,483$
All infectious disease visits	3 665 897 (10.9%)	3 764 235 (11.0%)	3 426 451 (9.8%)
Infection diagnosed			
Upper respiratory tract	1 110 893 (3.30%)	1 151 995 (3.38%)	482 850 (1.39%)
Pharyngitis	453 134 (1.35%)	478 092 (1.40%)	277 636 (0.80%)
Sinusitis	159 239 (0.47%)	158 619 (0.47%)	79 800 (0.23%)
Otitis	77 715 (0.23%)	79 079 (0.23%)	54 547 (0.16%)
Lower respiratory tract	101 761 (0.30%)	115 563 (0.34%)	51 648 (0.15%)
Acute gastroenteritis	149 954 (0.45%)	154 102 (0.45%)	91 083 (0.26%)
Urinary tract	317 691 (0.94%)	315 465 (0.93%)	302 948 (0.87%)
Skin and soft tissue	700 263 (2.08%)	709 511 (2.08%)	661 297 (1.91%)
Fever	80 682 (0.24%)	82 106 (0.24%)	96 853 (0.28%)
Other	514 565 (1.53%)	519 703 (1.53%)	467 947 (1.35%)
COVID-19	Not applicable	Not applicable	859 842 (2.48%)
Visit type			
In-person	3 188 464 (9.47%)	3 248 208 (9.53%)	1 995 565 (5.75%)
Telemedicine	477 433 (1.42%)	516 027 (1.51%)	1 430 886 (4.12%)

Table 3
Antibiotic prescription at visits with an infectious disease diagnosis, by diagnosis, visit type, demographic characteristics, and period

Variable	Baseline 2018, received antibiotics	Baseline 2019, received antibiotics	COVID-19 period (2020), received antibiotics
Infectious disease visits	1 026 965/3664897 (28%)	1 034 425/3 764 235 (27.5%)	587 379/3 426 451 (17.1%)
Sex			
Male	363 086/1 397 947 (26.0%)	366 932/1 441 923 (25.4%)	195 700/1 366 187 (14.3%)
Female	663 879/2 267 950 (29.3%)	665 249/2 314 499 (28.7%)	388 370/2 045 167 (19.0%)
Age group (y)			
18–65	770 692/2 783 389 (27.7%)	778 896/2 864 292 (27.2%)	430 138/2 652 702 (16.2%)
66–75	138 058/482 025 (28.6%)	139 375/497 577 (28.0%)	82 800/463 373 (19.0%)
>76	118 215/400 483 (29.5%)	113 910/394 553 (28.9%)	71 132/322 279 (22.1%)
Population sector			
General Jewish	716 810/2 654 647 (27.0%)	726 593/2 719 245 (26.7%)	404 489/2 420 725 (16.7%)
Arab	266 824/862 031 (30.9%)	261 379/881 502 (29.7%)	152 749/792 888 (19.3%)
Ultra-orthodox Jewish	43 331/149 219 (29.0%)	44 209/155 675 (28.4%)	26 832/197 741 (13.6%)
Diagnosis			
Upper respiratory tract infection	275 145/1 110 893 (24.8%)	266 645/1 151 995 (23.1%)	79 023/482 850 (16.4%)
Pharyngitis	248 657/453 134 (54.9%)	259 815/478 092 (54.3%)	116 716/277 636 (42.0%)
Sinusitis	96 550/159 239 (60.6%)	95 696/158 619 (60.3%)	42 474/79 800 (53.2%)
Otitis	29 934/77 715 (38.5%)	30 353/79 079 (38.4%)	19 976/54 547 (38.6%)
Lower respiratory tract infection	42 436/101 761 (41.7%)	47 664/115 563 (41.2%)	14 555/51 648 (28.2%)
Acute gastroenteritis	10 467/149 954 (7.0%)	10 458/154 102 (6.8%)	5934/91 083 (6.5%)
Urinary tract	178 770/317 691 (56.3%)	175 401/315 465 (55.6%)	164 910/30 2948 (54.4%)
Skin and soft tissue	98 921/700 263 (14.1%)	102 517/709 511 (14.4%)	94 529/661 297 (14.3%)
Fever	12 098/80 682 (15.0%)	12 073/82 106 (14.7%)	9202/96 853 (9.5%)
Other	33 987/514 565 (6.6%)	33 803/519 703 (6.5%)	31 645/467 947 (6.8%)
COVID-19–related visit			8415/859 842 (1.0%)
Visit type			
In person	937 916/3 188 464(29.4%)	937 693/3 248 208 (28.9%)	419 176/1 995 565 (21.0%)
Telemedicine	89 049/477 433 (18.7%)	96 732/516 027 (18.7%)	168 203/1 430 886 (11.8%)

viral pathogens, which increased physician and public acceptance of the inefficacy of antibiotics against viruses. This is supported by the extremely low antibiotic prescription for COVID-19–related visits (1%), whereas little change was noted in the antibiotic prescription ratio for UTI, a bacterial disease. Of note, this is in sharp contrast to a report from London, England, where 31% of patients diagnosed with COVID-19 received an antibiotic prescription within 14 days of diagnosis [16].

In Israel, a country with highly accessible primary care, telemedicine for ID aetiologies traditionally comprised less than 15% of visits, with a lower antibiotic prescription ratio compared to in-person visits (Table 2). This is in contrast to many reports from other health systems [17,18]. During 2020, telemedicine visits became more frequent than in-person visits, changing the composition of the range and severity of diseases managed through telemedicine encounters. The uncertainty of the diagnosis during virtual visits could potentially increase antibiotic prescription [19], but unexpectedly, the opposite was observed in our study.

Fever was the only ID diagnosis that increased in 2020. In our adult population, fever with no focal signs was an uncommon reason to seek formal medical advice (2.2%). At the beginning of the pandemic, a SARS-CoV-2 test required referral from a physician. We assumed that the increase in fever complaints was driven by the need to exclude the diagnosis of COVID-19. In support of this assumption is an observation that 26% of visits due to fever resulted in SARS-CoV-2 testing, with 23.6% positive results. Thus, the increase observed in visits due to fever in 2020 can be attributed to concern regarding COVID-19 (Table S2).

In multivariable analysis, all explanatory variables tested (age, sex, population sector, visit type, ID diagnosis, and the period) remained independently significant. After accounting for all variables studied, the COVID-19 period was responsible for a 14.8% decrease in antibiotic prescription. This is attributed to the change in physician prescribing habits and to unmeasured residual confounders.

A few papers on decreases in community antibiotic prescription have been published recently. Reports from the United States, Spain, South Korea, Italy, and the Netherlands describe a decrease in the first 3 to 4 months of the COVID-19 pandemic. These did not include the winter months and thus did not assess the full scale of the pandemic's effect on trends in antibiotic prescription

Table 4
Logistic regression analysis using generalized estimating equation procedure of period effect (COVID-19 vs. 2018–2019) on antibiotic prescription at infectious disease visits adjusted for potential intermediate determinants ($N = 7\,190\,686$)

Variable	OR	95% CI	p
Period	0.852	0.848–0.857	<0.001
Age (continuous)	1.009	1.009–1.009	<0.001
Sex			
Female	1.062	1.056–1.068	<0.001
Male	1	1	
Population sector			
Arab	1		
General Jewish	0.812	0.807–0818	<0.001
Ultra-orthodox Jewish	0.868	0.856–0880	<0.001
Type of visit			
In person	1		
Telemedicine	0.540	0.536–0544	<0.001
Infectious diagnosis			
Acute gastroenteritis	1		
Fever	2.311	2.254–2.370	<0.001
Lower respiratory tract infection	7.799	7.626–7.976	<0.001
Upper respiratory tract infection	3.705	3.636–3.776	<0.001
Otitis media	7.477	7.303–7.656	<0.001
Pharyngitis	15.003	14.719–15.294	<0.001
Sinusitis	19.069	18.671–19.476	<0.001
Urinary tract infection	16.929	16.593–17.265	<0.001
Skin and soft tissue	2.055	2.015–2.095	<0.001
COVID-19	0.219	0.211–0.227	<0.001
Other	0.851	0.833–0.869	<0.001

[3–5,20,21]. Moreover, some only evaluated the seasons as explanatory variables [3,4,20,22] and others assessed a limited number of explanatory variables [5,21].

The current study had several limitations. It was a retrospective, population-level study, based on secondary use of routine EMR data. Thus, some diagnoses might have been misclassified and could differ between periods. Based on the number of visits in each category, however, we do not believe this had a major effect on the results. Although COVID-19 could have potentially been mislabelled during a primary care visit as URTI or gastroenteritis, the percent positivity of SARS-CoV-2 among those ID aetiologies was extremely low (about 0.5% or less), which excludes the likelihood of these misdiagnoses (Table S2). The study included only community antibiotic prescriptions that were given during an ID-related visit. Therefore, antibiotics given in hospitals and other medical facilities were not included. However, the community is the major impetus behind antibiotic use as a whole [23]. A possible concern is that difficulty accessing care during the COVID-19 era might contribute to the observed decrease in antibiotic prescriptions. However, there was no change in primary care physician office hours during the COVID-19 era. Moreover, antibiotics in Israel are prescribed via a computerized system connected directly to the pharmacy, regardless of visit type. Another concern is failure to capture purchase of antibiotics in private pharmacies or through the internet. This is unlikely, because antibiotics can be purchased through HMOs at a minimal fixed rate. Over-the-counter purchase is illegal and, to the best of our knowledge, nearly non-existent. Lastly, we cannot exclude the presence of unexamined determinants explaining the decrease in antibiotic prescription.

In conclusion, this population-level study describes a major decrease in antibiotic prescription from March 1, 2020 to February 28, 2021—during the COVID-19 pandemic period. This was driven by a decrease in the incidence of ID, changes in their relative distribution, and a decrease in antibiotic prescriptions among physicians in the community. The effect of such a major change on antimicrobial resistance is still to be explored. Another unanswered question is whether the observed decrease in antibiotic prescription for diseases with viral aetiology will be maintained.

Transparency declaration

The authors declare that they have no conflicts of interest.

Author contributions

RA and MC contributed equally to this manuscript.

Conception and design: BG, MC, ML; acquisition of data: ML, DN; data analysis and interpretation: ML, RA, MC, BG; Drafting the article: MC, BG; revising it critically for important intellectual content: RA, ML, DN; final approval of the version to be submitted: BG, ML, DN, RA, MC.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.02.035.

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