**The impact of COVID-19 pandemic and non-pharmaceutical measures on most common infectious diseases: Based on diagnoses documented in Israel during 2017-2020**

**Introduction**

Controlling the spread of infectious diseases has been an issue for humankind since the dawn of modern civilization 1. By the end of March 2020, 136 countries had implemented significant health measures in the face of the emerging Coronavirus infectious disease – 2019 (COVID-19) pandemic caused by SARS-CoV-2 2. While awaiting vaccine development, governments focused their efforts on secondary prevention and non-pharmaceutical solutions 3 to reduce viral transmission. Most countries adopted similar measures: Isolating people exposed to a confirmed case, closing workplaces and schools, wearing facemasks in enclosed spaces, and, in some cases, large-scale quarantines 4. The severity of the measures taken was determined by the rate of viral spread, and their effectiveness was strongly dependent upon citizen cooperation 5.

Local interventions aimed to contain the emerging outbreaks by ‘flattening the curve’ and reducing the pandemic spread to allow health systems to handle the increasing burden in the face of increased demand of resources and intensive care units 6. In retrospect, we can now associate treatment delays and cancellations of non-SARS-CoV-2 related medical issues during the peak of the pandemic to higher mortality rates 7. For example, the Centers of Diseases Control and Prevention (CDC) identified significant decreased Emergency Department (ED) visits due to chest pain and acute myocardial infarction 8, suggesting that some people were delaying care for conditions that might increase mortality.

During the pandemic, health systems worldwide reported a dramatic decline in admission rates due to various medical conditions such as respiratory diseases 9, including pneumonia 10, neurological 11,12 and gastrointestinal disorders 13, as well as chronic diseases 14. While the decreased number of admissions and diagnosis rates can be attributed to patient avoidance of the health systems, they may also be associated with changes in the spread of seasonal and non-seasonal diseases due to non-pharmaceutical measures taken, such as social distancing and mask-wearing 15. These interventions were associated with a global decrease in seasonal infectious diseases, respiratory diseases, including influenza 16, upper and lower respiratory diseases in all ages 17,18. In addition, strict 'stay-at-home' orders were also associated with a decrease in the rates of food-borne infections and diseases transmitted by close physical contact, such as sexually transmitted diseases (STDs) 19.

Like many countries, during the early phases of the SARS-CoV-2 pandemic (March 2020), incidence rates in Israel surged in a short period. In less than 30 days from the first confirmed case (February 21, 2020), the doubling period of the disease in Israel was less than three days 20, leading the Ministry of Health to implement restrictive non-pharmaceutical interventions (NPIs). Strict physical restraints were executed on March 17, 2020, and were followed by universal masking requirements inside and outdoors (April 12) and two major lockdowns (April 8 – May 4; September 17 – October 18), when Israelis had to remain within 500 meters of their homes.

The first lockdown was followed by a five-month period in which the population's compliance gradually decreased. Most restrictions were eased relatively early, except for masking, and few limitations regarding public gathering remained 21. This led to the 'second wave' of the pandemic, which included 218,000 new cases by the time the second lockdown was initiated 22. Thus, the sequence of events in Israel leads to a unique opportunity for an epidemiological study: two prolonged and strict lockdowns, separated by a five-month period of easing restrictions and a steep increase in morbidity.

Up until this point, many studies investigating the impact of non-pharmaceutical interventions and social distancing regulations were mainly focused on respiratory diseases, including SARS-CoV-2 17,18,23, seasonal conditions 16, and general admissions to EDs and hospitals 10. Only a few studies focus on the epidemiology of common infectious diseases in a given community 15 and the number of diseases inspected was small and endemic for several areas. Hence, the impact of the interventions themselves on common infectious diseases within a community is unknown.

Our study aims to investigate the impact of non-pharmaceutical interventions during the SARS-CoV-2 pandemic on the epidemiology of community-acquired infectious diseases that are mostly diagnosed based on clinical symptoms. This retrospective study was conducted on CID data accumulated over the past four years.

**Methods**

***Design and setting***

We analyzed data from Clalit Health Services (CHS), the largest of four health care organizations in Israel, which insures almost 53% of the population. The data included1,845,273 diagnoses from 445,640 patient registries in 209 primary care clinics in the southern CHS district. The study was approved by the CHS institutional ethics committee and did not require informed consent.

***Data source and inclusion criteria***

Data was extracted from CHS using Clalit’s Data sharing platform powered by ‘MDClone’ (<http://www.mdclone.com>). Our primary database included all patient medical records living in the Southern district of Israel, who visited CHS primary care clinics or consulted their physician via CHS telemedicine services, and was diagnosed with an infectious disease (supplementary table I) between January 1, 2017, and December 31, 2020. The final data list included only new patient diagnoses within the previously mentioned range of dates. A diagnosis was considered 'new' if it was not a reoccurrence documented in a patient's medical record in the previous seven days. Diagnoses of any symptoms that were confirmed as CVOID-19 within seven days were excluded from our data.

***Variables and definitions***

Each register contained an International Classification of Diseases (ICD)-9 disease index, date of diagnosis, clinic serial number, visit serial number, patient age, gender, and ethnicity. The most frequent infectious diseases were grouped into seven main groups according to the general site of infection (the specific diseases included in each group are presented in supplementary table I): (1) Upper respiratory diseases; (2) Lower respiratory diseases ; (3) Gastrointestinal diseases; (4) Ear infections; (5) Eyes infections; (6) Skin infections; (7) Urinary tracts infections. Diagnoses such as: "cough," "fever," and "unknown" were excluded. For further analysis, ages were divided into six discrete groups: 0-4 years, 5-14 years, 15-34 years, 35-59 years, 60-79 years, and 80 years and above.

Our analysis addressed the Israeli implementation dates of the central and major NPIs ( as described in supplementary table II).

No changes occurred in the definitions of any disease mentioned above between the years 2017 and 2021.

***Statistical Analysis***

First, we examined the overall and the age-stratified number of diagnoses per year (2017-2020). We then summed the daily number of diagnoses of each infection group into a calendric weekly (1-52) number of events and compared the overall and age-specific weekly events throughout the years of surveillance. Since the number of outpatients registered to each clinic in Clalit's Southern district was not available, we could not estimate incidence rates, and only counts were used.

To determine possible changes in the diagnosis of common infections occurring during the pandemic compared to the prior surveillance time, we had to estimate the expected number of new diagnoses during the 'intervention' period. To calculate the expected number of weekly diagnoses per infections group (counts), a quasi-Poisson regression was used 24 [due to overdispersion of the observed events].

We decomposed the variation of the time series into three components representing (1) trend, (2) seasonal variation, and (3) cyclic changes. Each year was divided into four seasons based on the local weather: Winter (December – February), spring (March-May), summer (June-September), and autumn (October-November). Cyclic changes were analyzed using standard trigonometrical harmonic functions. In this general model, the whole period of strict NPIs was represented using a binary '*limitations*'variable set as '0' for dates before March 17, 2020, and '1' for the rest (see Eq.1). Using this model, we calculated the intercepts and implemented the best model to investigate the overall expected weekly number of diagnoses for each infection group during the pandemic, assuming no change in limitations had occurred (*limitations = 0*).

In the overall data analysis, the trend was significant (P-value < 0.001) and the exponent of (the effect of limitations) was 0.414, hence the average decrease in the number of diagnoses since the country’s interventions started was 58.6%. The seasonal variable was also significant (= -0.95, CI%95: 0.920-0.983), as was the weekly cycle described by Cosine (= 1.094, CI%95: 1.054 – 1.135).

Next, to investigate the association between each NPI implemented to the number of weekly diagnoses during the pandemic, we conducted a segmented regression model for the interrupted time series (ITSA). We added binary variables describing the first and the second quarantines (Quarantine1/2) to Eq.1 and related the time passed since intervention started (Quarantinetime1/time2) 25. We also adjusted for autocorrelation using a one-step lagged counts variable (See Eq.2). A negative binomial regression was performed, and the best model was chosen based on the achieved Bayesian information criterion (BIC). Finally, the effect of each NPI was estimated using the calculated constants.

Associations were considered statistically significant when p-value < 0.05. Data analysis was performed using R (version 4.0.3) and the packages: *data.table, dplyr, lubridate, ggplot2*,and *MASS*.

***Findings***

We analyzed data of 445,640 children and adults diagnosed with eight common community-acquired groups of diseases and admitted to one of 209 primary care clinics in the south of Israel. During the years 2017-2019, the number of yearly diagnoses were: 540,945, 525,265, and 498,871, respectively. There was a significant reduction in diagnoses among all age groups during the pandemic year with a documented 280,192 diagnoses (F = 74.43, P-value < 0.001). It is unlikely that an increase in ER diagnoses was the cause for the community diagnosis reduction since number of ER visits also decreased 26. In the following analysis, no significant association was found to either gender or population size in cities or villages (i.e., less or more than 20,000 residents).

***Lower respiratory infections***

During the pandemic year, respiratory diseases had the most dramatic change compared to the expected number of diagnoses. A significant reduction occurred among all age groups (supplementary table III), but the most prominent was seen among younger children: a 61.32% decrease (CI%95 -53.59 to -69.04) among 0-4 years old, and a 65.37% reduction (CI%95 -57.22 to -73.53) among 4-15 years old. According to the ITSA we performed, these decreases are attributed to the strict restrictions, and the first lockdown was significant among all age groups. The intercept associated with the time passed since the first lockdown was mainly negative but not significant among 0-4 year-old children. The effect of the second lockdown and the time since it had started were mostly insignificant but were positively associated in adults aged 35-59.

***Upper respiratory infections***

Upper respiratory diseases showed a significant decrease compared to the expected morbidity based on our model. Children aged 0-4 and 4-15 years old presented the most prominent reduction of 48.06% (CI%95 -40.73 to -55.93) and 61.61% (CI%95 -52.42 to -70.20), respectively. Among other age groups, there was a reduction in effect magnitude with age. The effects of the restrictions and the first lockdown were negative and significant among all age groups, as the second increased with age. The time following the lockdown had a significant effect among all age groups: slightly positive among the youngest population and negative for the rest. The impact of the second lockdown and the time that followed were significantly negative for children but inconsistent for the rest. While the second lockdown was associated with a significantly negative effect in young adults (15-34) and the elderly (80+), the time followed was not significantly associated with the first and showed a positive and significant effect on all the rest.

***Gastrointestinal diseases***

Gastrointestinal diseases significantly decreased during 2020 among all age groups. Compared to the expected morbidity, prominent differences were detected among children 0-4 years old: 53.35% (CI%95 -46.95 to -59.74) and 4-15 years old: 58.15% (CI%95 -51.00 to -65.29). This trend continued with increased age but was less pronounced: -39.79% among young adults to -26.32% among 80+ years old. The effect of restrictions, the first and the second lockdowns, was negative and significant for most age groups. The exceptions were: (1) the first and the second lockdown didn't have any significant effect among 80+ years old, and (2) The second lockdown was not significant for ages 4-15. There was an interesting trend in the time following the first and the second lockdowns among all age groups: while the first lockdown had a significant positive effect for all, the effect of the second lockdown was negative.

***Urinary infections***

Urinary infections diagnosis was significantly lower in all age groups during the pandemic year and ranged from a reduction of 9.87% among the elderly (CI%95 -5.38 to -14.37) to 39.30% among children of 4-15 years old (CI%95 -32.05 to -46.54). However, the individual effect of each NPI seems negligible. The restrictions period presented a significant negative effect only for children, and the first lockdown had a significant but negligible positive effect on the elderly. A significant negligible positive effect was also associated with the time following the lockdown in all age groups. The effect of the second lockdown was negative and significant for 0-4, 35-59, and 80+ year-olds, and the time passed since the second lockdown had a significant negative effect among all age groups.

***Ear infections***

In contrast to the diagnosis based on our model, the observed number of ear infections diagnosed during the pandemic was significantly lower: ranging from -54.37% (CI%95: -46.87 to – 61.72) among the youngest children to -10.69% (CI%95: -5.58 to – 15.80) in adults aged 60-79. The restrictions period showed a significant negative effect among all age groups and was most prominent among children. This group was also negatively affected by the first lockdown, in contrast to the elderly that were positively affected. The time following the first lockdown had a significant positive effect in all age groups, primarily affecting children aged 4-15 years old. The effect contributed by the second lockdown was negative and significantly associated only with the youngest and oldest aged groups: 0-15 year-old children and the elderly. During the period following lockdowns, a significant negative effect was found among all age groups, again the most prominent among children aged 4-15 years old.

***Eye infections***

Eye infections showed a significant decrease during the pandemic in all age groups: from -58.50% (CI%95: -50.25 to -65.77) among children 0-4 year-olds to -20.43% (CI%95: -14.53 to -20.06). Restrictions had a significant negative effect in all age groups, except in adults aged 60+. The first lockdown significantly affected only the youngest children, while the second one also children aged 4-15 years old. The time after the first lockdown had a significant positive effect among adults aged 60+, while the time following the second lockdown was negatively associated in all age groups except for the youngest children.

***Skin infections***

Children experienced the most prominent decrease in the number of observed cases of skin infections compared to the expected: -44.96% in children aged 0-4 and -50.98% in children aged 4-15 (CI%95: -38.67 to -51.24; -44.30 to – 56.47 respectively). In the other groups, differences were significant but moderate. The effect of restrictions was negative and significant among children, young adults up to 39, and the elderly. The first lockdown had a significant negative effect only in children (0-15 years old), and the second lockdown was negative only among adults of 15-34 years old. The time after the first lockdown was positively significantly associated with increased morbidity among all age groups, except the elderly. The time following the second lockdown showed an opposite pattern: negative and significant among all age groups except for the elderly.

***Discussion***

The COVID-19 pandemic has had a significant global effect on every aspect of health, threatening to become a burden that health systems would not be able to contain27. The pandemic has emphasized the role of primary and community health care 28 in diagnosing, treating, and monitoring outpatients aspects. Alongside the meticulous management of the growing number of acute and post-acute COVID-19 outpatients 27,29, nurse practitioners and family physicians in community clinics kept managing the treatment of chronic and acute non-COVID patients daily. Diagnosing and providing appropriate treatment became a challenge and increased the burden on medical teams, as patients avoided, and in some cases were prohibited, from visiting community clinics and hospitals. The burden of the pandemic on community health was even more significant, as morbidity rates increased with medical teams suffering from continuous physical and psychological burnout 20. Hence, health authorities implemented various control policies, including NPI's and strict limitations, in an attempt to minimize a possible surge in demand for health services 30. Besides their ability to control the pandemic spread 31, NPIs were associated with negative outcomes, including a significant decrease in hospital admissions due to heart diseases and other urgent medical conditions11,12,14, as well as adverse psychological effects 32.

Additionally, there is growing evidence 15,33 that NPIs can significantly reduce non-COVID infectious diseases and reduce the burden associated with seasonal and endemic infections during the pandemic. The reduction in infectious morbidity in Israel, a country ranked under the OECD average of physicians and nurses per 1000 patients 34, could enable the local community health system to manage routine health tasks better and contributed to the management of the nationwide mass vaccination operation 35. Israel’s experience could shed light on the necessity of encouraging easily implemented health-promoting actions that can influence the spread of COVID and non-COVID infections 36.

Like many other countries, the NPI measures taken by the Israeli government during the pandemic were meant to reduce the spread of COVID-19, but the early easing of restrictions and the following second lockdown created a unique situation. Therefore, we aimed to examine the effects of NPIs on common infections that account for the greatest burden on community health 37 among the same population at three different time points: (1) During the period of strict restraints; (2) during the first lockdown and the following period; and (3) during and after the second lockdown. By investigating the impact of NPIs on the epidemiology of these infectious diseases, we can evaluate practical contagious disease reduction tools.

***Strict physical restrictions***

Before the first lockdown has started, a series of strict restraints were adopted by the government. On March 13, 2020, educational institutions and some daycares were closed until further notice, while on March 17, 2020, new regulations only allowed people access to a public place if necessary. This type of restriction is usually associated with a moderate decrease in the incidence rates of community-acquired infectious diseases, as upper and lower respiratory diseases account for most diagnoses among all age groups 38. Analysis of the seasonal trend showed a significant decrease in the observed number of diagnoses of respiratory diseases: an average decrease of 50.1% among young children and 57.2% among children aged 5-14. While adjusting for seasonal changes and diagnosis documented the week before, the strict restrictions seemed to decrease 57% of potential morbidity of lower respiratory infections and an average of 40.4% among upper respiratory infections for both age groups. These results are in line with an association between restrictions and a major decrease of respiratory infections among children reported by Haapanen et al 39.

The restrictions seemed to effectively reduce the spread of other infectious diseases, including gastrointestinal diseases and ear infections. Similar effects were also described in other studies 40 and included drastic reduction in bronchiolitis, gastroenteritis, and otitis media 41. Less prominent effects among children were also observed in eye infections, skin infections, and urinary tract infections. The decreases observed in the young adults group (15-34) is also likely attributed to the educational system’s closing since teenagers aged 15-18 and adults in this group were probably in educational frameworks (the median age for obtaining an undergraduate in Israel is 27 42).

Significant but smaller effect sizes were also seen in the 35-59 and 60-79 age groups, the primary workforce 43, hence up until the third week of limitations when only 30% of the market was allowed to operate, most of these people kept attending to their workplaces, exposing themselves to common infectious diseases. The reduction in diagnoses among this age group may also be partially due to the steep decline in children's morbidity, particularly in respiratory and gastrointestinal infections, since children are a significant source of secondary transmissions 44.

The average weekly reduction in the number of infections diagnosed among the 80+ age group was 30% less than any other year. However, it is worth noting that 2020 started with a lower number of weekly infectious diagnoses among this age group, likely due to a significant decrease in seasonal Influenza following successful vaccinations 45. According to our ITSA model, restrictions significantly contributed to a reduction in respiratory and GI diseases but did not affect the remaining infectious diseases. It is possible that intensive media coverage regarding the spread of the SARS-CoV-2 and detection of new local cases in mid-February was associated with a slight reduction in the number of diagnoses among 80+ years old, a population that found most susceptible to negative changes in lifestyle and avoidance behaviors 46.

***The first lockdown and the time that followed***

The first lockdown started on April 8, 2020, three weeks after the strict restrictions were implemented. After that, a gradual easing began on April 19, up to a reversal of travel restrictions and the opening of education institutions on May 4. The immediate decrease of most infectious diagnoses (except for urinary infections) among children is due to the closure of all daycares and inclusive education frameworks.

In all other age groups, a pattern of declining effectiveness seemed to evolve with increasing age. As shown by Mehrotra et al. 47, it is possible that older patients were more prone to skip medical appointments, resulting in a reduction in the number of new diagnoses. It is also possible that older patients followed the lockdown restrictions more strictly and were willing to isolate, though previous results are inconsistent 48.

The time passed since the lockdown marked by a continuous decrease in upper and lower respiratory diseases due to the requirement to wear facemasks in public 49,50. Yet, facemask wearing and social distancing are not feasible among 0-4 years old children when daycares reopened, leading to a slight increase in infectious morbidity. The partially increase presented in GI, skin, and ears infections among ages 4-79 reflects the prominent role social distancing played, as young children struggled to follow social distancing restrictions, and young adults had lower compliance compared to others 51. The effect of social distancing on disease prevalence decreased among younger populations, suggesting that the burden of non-respiratory infectious diseases could be reduced using basic hygiene principles.

***The second lockdown and the time that followed***

For many economic and sociological reasons, the second lockdown started with a lower public willingness to comply 21. Thus, we attribute the inconsistency in the lockdown’s effect among the different age groups to differences in compliance.

Since universal masking continued, no significant effect among respiratory infections was expected. We did, however, observe a positive effect of lockdown and the following period on respiratory diseases among 35-59 years old. This is consistent with a significant increase in SARS-Cov-2 Incidence rate ratios (IRR) among this group during this period52 and might be associated with reduced compliance related to income assurance 53 that may have mainly influenced this group. Age groups characterized with more significant avoidance and willingness to self-isolate 48 gained less from the second lockdown. Compared to the first lockdown, the easing of restrictions was more gradual following the second lockdown. The measures taken are reflected in our results as the effect was significant in most infectious diseases. We found a pattern that the older the adults were, the more they followed social distancing and restrictions and were affected less by guideline changes.

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Identification of disease groups and their epidemiological characterization during an epidemic. Allows for better assessments of a health system for community or home diagnostic means and instruments ( e.g., UTI home kit diagnosis, telemedicine diagnostic video tools, etc.), as well as for more accessible and population-adapted means of treatment. This will increase public satisfaction, reduce illness, and eventually promote maintaining restrictions during an epidemic and reduce morbidity complications.

***Limitations***

Our study has several limitations. The data collected from CHS is based on diagnoses documented by physicians in community clinics, either in-person or via telemedicine visits. Unfortunately, we could not retrieve accurate information regarding visit type, which can influence the physician’s diagnostic capability since primary physicians use physical examinations, alongside lab and imaging results, for diagnosis. Therefore, the statistical power of our findings will be more accurate by further analysis of lab tests conducted and possible changes in treatment regimens. Since data regarding socioeconomic status and zip codes of patients were unavailable, we could not adjust our analysis to these confounders associated with infectious disease transmission. Nevertheless, based on clinic patients registration, we compared the data separately for towns with more than 20,000 residents, or settlements with fewer. Though we did estimate the possible effect of different NPIs on morbidity while adjusting for changes related to time, the observational study we conducted cannot draw causal relations between the covariates and changes associated with each intervention.

***Conclusion***

As the global incidence rates of COVID-19 are increasing again, resolutions regarding possible elimination and eradication of the pandemic are being reconsidered. Various measures and NPIs are available, including facemasks and social distancing, which governments can implement. However, their effectiveness to mitigate the spread of disease remained unclear 54 and primarily relies on the degree of population compliance and societal impact. Nevertheless, our analysis suggests rational use and careful management of NPIs can contribute to the reduction of common infectious diseases spread and indirectly reduce the burden on community health.It is possible that using these tools in collaboration with a local population can compensate for a medical shortage of workforce in times of routine or crisis without the need for far-reaching policy decisions.

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