**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 the modern civilization 1. By the end of March 2020, 136 countries all around the world have already implemented significant health measures facing the emerging pandemic Coronavirus infectious disease – 2019 (COVID-19) caused by SARS-CoV-2 2. Yearning for vaccine development governments focused their efforts in secondary prevention and non-pharmaceutical solutions 3 to reduce the transmission of the virus. Most countries adapted similar steps: Isolating suspected people following an exposure to a confirmed case, closure of working places and schools, wearing a face-mask in enclosed spaces and in some cases even large scale quarantines 4. The steps taken were determined by the rate of viral spread, yet their effectiveness was strongly associated to citizen's level of cooperation 5.

Local interventions aimed to contain the emerging outbreaks by ‘flattening the curve’ and reducing the spread of the pandemic, to allow health systems the capability to handle the increasing burden, in face of increasing demand of resources and intensive care units 6. In a retrospect, it is now possible to associate delays and avoidance of non-SARS-CoV-2 medical treatments during the peak of the pandemic to excess deaths and higher mortality rates 7. The Centers of Diseases Control and Prevention (CDC) addressed an issue of major decreases in Emergency Department (ED) visits due to chest pain and acute myocardial infarction 8, suggesting that some people could be delaying care for conditions that might result in increased mortality.

During the pandemic, many health systems around the world reported a dramatic decline in rates of admissions due to various medical conditions: respiratory diseases 9 including pneumonias 10, neurological conditions 11,12, gastrointestinal conditions 13 as well as chronic diseases 14. While some of the variance in the number of admissions and diagnosis rates could be contributed to avoidance of patients approaching health systems, some could be associated to changes in the spread of seasonal and non-seasonal diseases due to non-pharmaceutical measures taken 15.

The non-pharmaceutical interventions such as social distancing and universal masking, were associated with global decrease in the incidence of seasonal infectious disease; respiratory diseases, including influenza 16 upper, and lower respiratory diseases of all ages 17,18. Strict 'stay-at-home' regimes were also found associated to decrease in rates of food-borne infections and diseases transmitted by close physical contact such as sexually transmitted diseases (STD's) 19.

Like many countries, during the early phases of SARS-CoV-2 spreading (March 2020), incidence rates in Israel surged in a short period of time; In less than 30 days from the first confirmed case (February 21,2020), the doubling period of the disease in Israel was less than 3 days 20, leading the ministry of health to implement restrictive non-pharmaceutical intervention. Strict physical restrains implemented on 17 March 2020, and were followed by universal masking in and out-doors (12 April), and two major lockdowns (8 April – 4 May; 17 September -18 October), when Israelis had to remain within 500 meters of their homes.

The first lockdown was followed by a five months period in which population's compliance decreased, and a relatively early easing in most restrictions has occurred except of masking, and few limitations regarding public gathering 21, the 'second wave' of the pandemic followed by 218,000 new cases by the time the second lockdown has started 22. The sequence of events in Israel lead to a unique epidemiological study: where a couple of prolonged and strict lockdowns, separated by a five months period of loose restrictions and steep increase in morbidity.

Up until this point, many studies regarding the impact of non-pharmaceutical interventions and social distancing regulations were mainly focused on respiratory diseases including SARS-CoV-2 17,18,23, seasonal diseases 16 and general admissions to EDs and hospitals 10. Only few studies focused on the epidemiology of common infectious diseases in community 15, yet the number of diseases inspected was small and endemic for several areas. Hence, the questions regarding the impact of intervention itself on common infectious diseases in community left unsolved.

Our study aims to investigate the impact of non-pharmaceutical interventions during SARS-CoV-2 pandemic on epidemiology of community acquired infectious diseases that are mostly diagnosed based on clinical symptoms. The study conducted based on accumulative CID data from 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 registries of 445,640 patients, in 209 primary care clinics in southern district of CHS. The study approved by CHS institutional ethics committee, and did not require informed consent.

***Data source and inclusion criteria***

Data extracted from CHS using Clalit's Data sharing platform powered by 'MDClone' (<http://www.mdclone.com>). Our primary database included all medical records of patients from all ages living in the Southern district of Israel, who attended to CHS primary care clinics or considered their physician via CHS telemedicine services - and diagnosed with any infectious disease (supplementary table.I) between 1 January 2017 and 31 December 2020. Each register in our final data was a new diagnosis of a patient within the previously mentioned range of dates. In order to avoid multiple counting of same patient's diagnosis, a diagnosis considered 'new' only if it was not reoccurred and documented in the medical record of a patient within seven days. Diagnosis of any symptoms that turned to be diagnosed as CVOID-19 within seven days, were excluded from our data.

***Variables and definitions***

Each register contained an ICD-9 index of the disease, the date of diagnosis, the clinic's serial number, the visit's serial number, the age, gender and ethnicity of the patient. We than grouped the most frequent infectious diseases into seven main groups according to 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. We excluded equivocal diagnoses such as: "cough", "fever", and "unknown". For the further analysis, we recoded the continuous age variable into six discrete age groups: 0-4 years, 5-14 years, 15-34 years, 35-59 years, 60-79 years and 80 years and above.

In our analysis, we addressed the implementation dates of the main and major non-pharmaceutical interventions applied in Israel (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 diagnosis per each year (2017-2020). We than summed the daily number of diagnosis of each infections group into a calendric weekly (1-52) number of events, and compared the overall and age-specific weekly events through the years of surveillance. Since the number of outpatients registered to each clinic in Clalit's Southern district was not available, we were not able to estimate incidence rates, hence only counts were used.

 To determine the possible changes in diagnosis of common infections diagnosed during the pandemic compared to the prior surveillance time, we had to estimate the expected number of new diagnosis during the 'intervention' period. Hence, to estimate the expected number of weekly diagnosis per each infections group (counts) a quassi-Poisson regression was used 24 [due to over dispersion 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 treated using common trigonometrical harmonic functions. In this general model, we represented the whole period of strict NPIs using a binary '*limitations*'variable set as '0' for dates before 17 March 2020, and '1' for the rest (see Eq.1). Using this model, we calculated the intercepts, and implemented the best model achieved to investigate the overall expected weekly number of diagnosis for each infections group during the pandemic; assuming no change in limitations had occurred (*limitations = 0*).

In the analysis of the overall data, the trend found significant (P-value < 0.001) and the exponent of (the effect of limitations) was 0.414, hence the average decrease in number of diagnosis since the limitations had started was 58.6%. The season variable found to be significant (= -0.95, CI%95: 0.920-0.983), as well as 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 diagnosis during the pandemic period, we conducted a segmented regression model for the interrupted time series (ITSA). We added to Eq.1 binary variables describing the first and the second quarantines (Quarantine1/2), and related the time passed since intervention had started (Quarantinetime1/time2) 25. We also adjusted for autocorrelation using a one-step lagged counts variable (See Eq.2). A negative binomial regression performed and the best model chosen based on achieved Bayesian information criterion (BIC). The effect of each NPI estimated using the calculated constants.

Associations were considered statistically significant when p-value < 0.05. The data analysis 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 8 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 numbers of yearly diagnosis were: 540,945; 525,265 and 498,871 respectively – while in the pandemic year a significant reduction occurred among all age groups as 280,192 diagnosis were documented (F = 74.43, P-value < 0.001). It is less likely to assume that increase in ER diagnosis was the cause for the reduction in community diagnosis since number of visits to ERs 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. The significant reductions occurred among all age groups (supplementary table.III), but the most prominent were seen among the young children: a 61.32% decrease (CI%95 -53.59 to -69.04) among 0-4 years old, and 65.37% reduction (CI%95 -57.22 to -73.53) among 4-15 years old. According to the ITSA we performed, the effects contributed to the strict restrictions, and first lockdown were significant among all age groups. The intercept associated to the time passed since the first lockdown was mainly negative but found insignificant among 0-4 years old children. The effect of second lockdown and the time since it had started were mostly insignificant, but were positively associated to 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 48.06% (CI%95 -40.73 to -55.93) and 61.61% (CI%95 -52.42 to -70.20) respectively. Among other age groups, reduction in effect's magnitude has developed as age increased. The effects of restrictions and the first lockdown were negative and significant among all age groups, as the second increased with age. The time that followed the lockdown had a significant effect among all age groups: a slight positive among the youngest population, and negative for the rest. The effect of the second lockdown and the time that followed were negative and significant for children, but were inconsistent for the rest: while the second lockdown was associated with negative and significant effect for young adults (15-34) and the elderly (80+), the time followed was not significantly associated to the first, and showed positive and significant effect for all the rest.

***Gastrointestinal diseases***

Gastrointestinal diseases decreased significantly during 2020 among all age groups. Prominent differences compared to the expected morbidity detected among children of 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). The trend turned limited as age increased: -39.79% among young adults to -26.32% among 80+ years old. The effect of restrictions, as well as the first and the second lockdowns found negative and significant for most age groups except of two cases: (1) the first and the second lockdown didn't have any significant effect among 80+ years old. (2) The second lockdown didn't show significance for ages 4-15. An interesting trend observed for the time followed the first and the second lockdowns among all age groups: while the first had a positive significant effect for all, the second presented negative and significant effect.

***Urinary infections***

urinary infections diagnosis was significantly lower in all age groups during the pandemic year, and ranged from reduction of 9.87% among 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). Nevertheless, the individual effect of each NPI seemed to be negligible. The restrictions period presented a negative and significant effect only for children from both age groups, and the first lockdown had a significant but negligible positive effect on the elderly. A significant but negligible positive effect was also associated to the time that followed the lockdown for all age groups. The effect of the second lockdown found negative and significant for 0-4, 35-59 and 80+ years old, and the time passed since the second lockdown had a negative and significant 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: ranged from -54.37% (CI%95: -46.87 to – 61.72) among youngest children to -10.69% (CI%95: -5.58 to – 15.80) for adults aged 60-79. The restrictions period showed a negative and significant effect among all age groups, most prominent among the children. This group was also negatively affected by the first lockdown, in contrast to the elderly that were positively affect by it. The time followed the first lockdown had a positive and significant effect among all age groups, effecting mostly the children aged 4-15 years old. The effect contributed by the second lockdown was negative and significantly associated only to both edges of aged: 0-15 year's old children, and the elderly. During the following period, a negative and significant effect existed among all age groups, again 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 of 0-4 years old, to -20.43% (CI%95: -14.53 to -20.06). Restrictions had a negative and significant effect for all age groups except of adults aged 60+. The first lockdown seemed to significantly affect only the youngest children, while the second one affected them and children aged 4-15 years old. The time that followed the first lockdown had a significant and positive effect among adults aged 60+, while the time that followed the second lockdown was negatively associated to all age groups except of the youngest children.

***Skin infections***

Children experienced the most prominent decrease in number of observed cases of skin infections compared to the expected: -44.96% for children aged 0-4 and -50.98% for 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, and young adults up to 39, and the elderly. The first lockdown had a negative and significant effect only for children (0-15 years old), and the second found negative only among adults of15-34 years old. The time that followed the first lockdown was positively and significantly associated to increase in morbidity among all except of the elderly. The time that followed the second lockdown had an opposite pattern: negative and significant effect among all age groups except of the elderly.

***Discussion***

The COVID-19 pandemic has had a significant and global effect on every aspect of health, and represented a turning point for global 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 the physical and non-physical aspects of outpatients. Alongside the meticulous management of acute and post-acute growing number of COVID-19 outpatients 27,29, nurse practitioners and family physicians in community clinics kept managing the treatment of chronic and acute non-COVID patients on a daily basis. 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. The burden of pandemic on community health was even more significant, as morbidity rates increased and medical teams have been suffering of continuous physical and psychological burnout 20. Hence health authorities implemented various control policies: including NPI's and strict limitations, in attempting to soften a possible surge in demand of health services 30. Beside their ability to change the course of 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 negative psychological effects 32.

Nevertheless there is a growing evidence 15,33, that alongside the negative impacts of NPIs, they can play a major role in reduction of COVID and non-COVID infectious diseases, hence might reduce the burden associated to seasonal and endemic infections in times of crisis. The reduction in infectious morbidity in Israel, a country ranked under the OECD average of physicians and nurses per 1000 patients 34, could be a major role player, enabled the local community health system to manage routine health tasks. And might even contributed to the management of the nationwide mass vaccination operation 35. our experience could shed light on the necessity of encouraging health promoting actions that can be easily implemented and eventually 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 meant to reduce the spread of the disease, but the early easing and the lockdown that followed created a unique outbreak situation. We aimed to examine the effects of NPIs on common infections, accounting for a great burden on community health 37 among the same population in three different time points: (1) During the period of strict restrains; (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 trace effective contagious disease reduction tools.

***Strict physical restrictions***

 Before the first lockdown has started, a series of strict restraints were adopted by the government: On 13 March 2020 Educational institutions and some daycares had been closed until further notice, while on 17 March 2020 a new regulation determined a person could exit to a public place only if it was necessary. This period of time is usually characterized by a moderate decrease in the incidence rates of community acquired infectious diseases, as upper and lower respiratory diseases account for most of diagnosis among all age groups during this period 38. The seasonal trend demonstrated in our analysis, but this year the observed number of diagnosis of respiratory diseases found significantly lower than expected by our model: 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 on 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. Immediate association between restrictions and major decrease of respiratory infections among children also reported by Haapanen et.al 39, but the magnitude reported was much moderate.

The restrictions including schools closure seemed to be effective in reducing the spread of other infectious diseases as well 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. In our study, some significant but less prominent effects among children also observed in eye infections, skin infections and urinary tract infections.

The young adults group (15-34) experienced the second most prominent reduction in infectious diseases since the restrictions had started; it was most considerable among respiratory, GI and ear infections. The impact of restrictions on this age group seemed to be closer to the effect it has among children, than the effect among 35+ years old. 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), schools closure attributed to this group too.

Significant but smaller effect sizes compared to the other age groups, computed for the age groups of 35-59 and 60-79. Compare to the other groups, these had the highest labor force participation rates 43, hence up until the third week of limitations when only 30% of the market allowed to operate, most of these people kept attending to their working places, exposing themselves to common infectious diseases. It is possible that the reduction in diagnosis among this age group was partially contributed to the steep decline in children's morbidity, particularly in respiratory and gastrointestinal infections, since children had been described before as a major source of secondary transmissions 44.

 The average weekly reduction in number of infections diagnosed among the 80+ years old was 30% less than any other year – yet It is noteworthy that year 2020 has started with a lower number of weekly infectious diagnoses among this age group, this finding could be contributed to a significant decrease in seasonal Influenza, due to successful vaccination operation 45. According to our ITSA model restrictions contributed significantly to reduction in respiratory and GI diseases, but barley effected the rest. 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 to a slight reduction in number of diagnoses among 80+ years old; a population that found most susceptible to negative changes in life-style and avoidance behaviors 46.

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

The first lockdown has started at 8 April 2020, three weeks after the strict restrictions had implemented. A gradual easing had started on April 19, until a complete cancelation of travel restrictions, and opening of education institutions on May 4th. The immediate effect of lockdown observed for most infectious diagnosis (except of urinary infections) among children can be explained by additional 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 the older the patients were, the more they were prone to skip medical appointments, and avoid visiting in community clinics, hence a reduction in the number of new diagnosis could occur. 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 in most age groups, except of children aged 0-4. This reduction of airborne transmitted diseases can be explained by the obligation to wear face-masks in public 49,50. Yet face-masks obligation and social distancing were not feasible among 0-4 years old children when daycares reopened, leading to slight increase in infectious morbidity of most kinds. The partially increase presented in GI, skin and ears infections among ages 4-79 reflects the major role social distancing has played before, as young children struggled to follow social distancing restrictions, and young adults had lower compliance compared to others 51: the effect of social-distancing decreased among younger population, hence raising a question regarding the burden of non-respiratory infectious diseases could potentially be reduced by basic hygiene principals only.

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

For many economical and sociological reasons the second lockdown started with lower public willingness to comply 21. We hypothesized that these factors could contribute to a great variability in the lockdown's effect, which eventually did found to be inconsistent among different age groups

Since universal masking continued, no significant effect among respiratory infections was expected. We did however observe a positive effect of lockdown and the time that followed on respiratory diseases among 35-59 years old. This finding is in line with a significant increase in SARS-Cov-2 Incidence rate ratios (IRR) among this group during this period, observed by Somekh et al. 52, and might be associated to reduced compliance related to income assurance considerations 53 that could have influenced this group more than the rest. Age groups that characterized with greater avoidance and willing to self-isolate 48 seemed to gain less from the second lockdown. Compared to the first lockdown, the easing of restrictions was more gradual during the time followed the second lockdown. The measures taken reflected in our results: as the effect contributed to this period was significant in most infectious diseases. While this time the effect among the children aged 5-14 years old seemed to be more prominent compared to the younger children. We found the pattern observed among other ages interesting, as it seemed to follow the one of the first lockdown: the older the adults were, the more they seemed to keep the social distancing and follow previous restrictions, hence effected less by changes in regime.

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. What will actually increase public satisfaction, reduce illness, and will eventually promote maintaining restrictions during an epidemic and reduce morbidity complications.

***Limitations***

Our study has several limitations. The data collected from CHS based on diagnosis documented by physicians in community clinics, either in-person or telemedicine visits. Unfortunately we were unable to retrieve accurate information regarding visit type, influencing to some extent the physician diagnostic capability. We are aware that primary physicians use their clinical basics skills especially physical examination, along lab and imaging tests to make infection disease diagnosis. Therefor the statistic power of our findings could be more accurate by further examination of lab tests conducted during this period, and possible changes in treatment regimens. Since data regarding socioeconomic status, and zip codes of patients were not available, we could not adjust our analysis to these confounders associated to transmission of infectious diseases. Nevertheless, based on clinic patients registereion we compared the data separately for towns with more than 20000 resident, or settlements with less. Though we did estimate the possible effect of different NPIs on morbidity while adjusting for changes related with time, the observational study we conducted can not draw causal relations between the covariates and changes associated to each intervention.

***Conclusion***

As the incidence rates of COVID-19 are globally increasing again, resolutions regarding possible elimination and eradication of the pandemic are back on decision maker's tables. Various measures and non-pharmaceutical interventions are available, including face-masks and physical distancing; all can be implemented by governments. But their effectiveness to mitigate the spread of disease remained unclear 54, and mostly relays on degree of compliance of the population and societal impact. Nevertheless, our analysis suggests rational use and careful management of NPIs can contribute to some extent to 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 manpower in times of routine or crisis, without the need for far-reaching policy decisions.

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