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Original article

Impact of the COVID-19 pandemic on pediatric bacterial infection rates: A population-based study

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Abstract. *Background and aim:* During the COVID-19 pandemic a significant reduction of viral infections was observed in children probably due to the imposition of lockdown measures. The aim of this study was to compare the incidence of some common bacterial infections in children before and after COVID-19 pandemic in an Italian third-level pediatric hospital. *Methods:* We retrospectively reviewed medical records of patients evaluated at our Pediatric Clinic from October 2018 to April 2019 in comparison to those admitted from October 2022 to April 2023. All patients aged 0-16 hospitalized with a diagnosis of a bacterial infection were included in the analysis. *Results:* A total of 879 children was enroled. The 2 groups were comparable in terms of age and sex. No significant difference emerged, except for the presence of a concomitant acute viral illness, less frequently found in 2022-2023 than in 2018-2019. The incidence of bacterial infections resulted significantly higher in 2022-2023 than in 2018-2019 with an estimated OR of 2.92 (95%CI 1.88-4.48). *Conclusions:* The non-pharmacological measures adopted during the pandemic might have been a double-edged sword for young children, as delayed immune maturity might have increased susceptibility to infections and led to an increase in invasive bacterial infections. (www.actabiomedica.it)

Key words: pediatrics, bacterial infections, COVID-19, immunity debt, epidemiology

Introduction

Since 2020 the CoronaVirus Disease 19 (COVID-19) pandemic hit the world, with an estimated 242’688’319 human infections and about 4,932,928 deaths worldwide at the end of November 2021.

Initially, children appeared to be immune from COVID-19, but later pediatric cases grew, even if they globally accounted for a minority of infections; and we are not key drivers of transmission (1) However, they have borne some of the highest indirect burdens of the pandemic, including disrupted education and reduced social and developmental opportunities (2). Several public health and social measures (PHSMs) were imposed during the COVID-19 pandemic: in fact, personal protective mask, hands hygiene, social distancing and restrictions on contacts were adopted worldwide. These measures contributed to reduce the COVID-19 transmission but also had a significant impact on the spread of other pathogens. As largely demonstrated, community-acquired endemic pediatric infections exhibit distinct seasonal and longer-term cycles incidence (3, 4). While climate conditions may drive the seasonality of some diseases (5) other contagious infections, such as measles, are usually influenced primarily by seasonal cycles of people aggregation such as the timing of school semesters (6). For instance, a reduced measles transmission by 38% was reported during the 1918 Influenza pandemic (7). Indeed, the number of accesses to the pediatric emergency room for community-acquired infections decreased significantly during the lockdown periods (8). In parallel, a significant reduction of the number of severe disease cases due to Streptococcus pneumoniae, Haemophilus influenzae B o Neisseria meningitidis was observed during the pandemic time window (9). These infections are associated with mucosal carriage and human-to-human transmission through the respiratory tract, so it is not surprising their reduced incidence after the adoption of PHSM. On the other hand, the typical immune stimulation in children due to infections exposure has been reduced due to the PHSM application (10), thus leading to the development of an "immunity debt" and a subsequent negative impact once the restrictive measures were no longer needed and adopted. Some authors also suggested that some viral infections, such as those by Respiratory syncytial virus (RSV) and influenza virus with related-bacterial complications may be more intense in the coming years according to specific predictive mathematical models (5). The aim of this study was to retrospectively compare the incidence of some common bacterial infections in children before and after COVID-19 pandemic in a third-level-hospital in Italy.

Material and Methods

We retrospectively reviewed the medical records from the computerized database system of a tertiary level Pediatric Clinic, which covers an area of 530,000 residents with 70,000 children aged 0-16 years. To limit possible bias due to seasonal changes in the incidence of viral co-infections two time-periods were compared: the first from October 2018 to April 2019 (before COVID-19 pandemic), and the second from October 2022 to April 2023 (after COVID-19 pandemic). All patients aged 0-to-16 years admitted to the ward during the selected periods with a clinical diagnosis of a bacterial infection were included in the analysis. Immunocompromised patients or children with a severe chronic condition (cardiac, neurological, genetic, oncological) were excluded. We also examined demographic and clinical characteristics of the enrolled patients, including age, sex, discharge and admission diagnoses (codified according to ICD-9-CM nomenclature), clinical conditions, length of hospitalization, microbiological exams, vaccination status.

Microbiological and clinical definition of included diagnosis

All children underwent microbiological investigations including body fluid cultures (from every kind of samples according to clinical conditions and suspicion: blood, cerebrospinal fluid, pleural effusion, skin/mucosal swabs, stools, urine), molecular swabs for respiratory virus and typical/atypical bacteria, rapid urine antigen assay for pneumococcal disease, virus DNA/RNA detection through polymerase chain reaction on blood samples. However, in most cases diagnosis was supposed by clinical and other laboratory characteristics.

Statistical analysis

Continuous variables were expressed as mean (SD), while categorical variables were expressed as percentages or frequencies. Unpaired t-test and Mann Whitney U test were used to compare the two time-periods as appropriate. Chi square test or Fischer's exact test were used to compare the differences between categorical variables. The differences were presented as odds ratio (OR) with 95% confidence interval (95% CI). A $p<0.05$ was considered as significant.

Results

A total of 483 children were admitted to our Pediatric Clinic from October 2022 to April 2023 and were included in this study. Among these, 73 patients (15.11%) were hospitalized with a diagnosis of bacterial infection, 49 (67%) were males, with mean age 5.1±4.0 years. From October 2018 to April 2019 (pre-COVID period) 396 patients were hospitalized and 27 (6.81%) (13 males, 48%, with mean age 4.4±3.9 years) were admitted with such a diagnosis. The incidence of bacterial infections resulted significantly higher in 2022-2023 than in 2018-2019 (0.66% per 10.000 children vs 0.19%, $p<0.001$), with an estimated OR of 2.92 (95%CI 1.88-4.48). Baseline characteristics were compared between the two time-periods (Table 1): the 2 groups were comparable in terms of age and sex. No significant difference emerged, except for the presence

Table 1. Baseline characteristics of children admitted for a bacterial infection in autumn/winter 2018-2019 and 2022-2023.

	2018-2019 N=27	**2022-2023 N=73**	***P***
Males (%)	13 (48)	49 (67)	0.105
Mean age (SD), years	4.4±3.9	5.1±4.0	0.44
Baseline chronic disease (%)	9 (33)	21 (29)	0.806
Concomitant acute viral illness (%)	**12 (44)**	**14 (19)**	**0.009***
Mean duration of hospitalization (SD), days	6.5±4.9	5.6±5.8	0.145
Complete antipneumococcal vaccination (%) 13v 7v	19 (70) **13 (48)** **6 (22)**	57 (78) **53 (70)** **6 (8)**	0.438 **0.029***

*Statistically significant.

of a concomitant acute viral illness, less frequently found in 2022-2023 than in 2018-2019 (13/73 vs 12/27, 28% vs 44%, respectively; p=0.009). Rates of complete anti-pneumococcal vaccination were otherwise similar (57/73, 78% in 2022-2023 vs 19/27, 70% in 2018-2019; p=0.438), even if 13-valent vaccine resulted prevalent in 2022-2023 (51/73, 70% vs 13/27, 48%, p=0.029). Discharge diagnosis of children with bacterial infections were also compared: orbital cellulitis was significantly more frequent in 2022-2023 than in 2018-2019 (10/73, 14% vs 0/27 in 2018-2019; p=0.042), while no other significant differences were reported. However, in 2022-2023 a total of 6 cases of severe and life-threatening infections were observed: 3/73 (4%) children were affected by cerebral empyema, 2/73 (3%) by sepsis and 1/73 (1%) by fulminant endocarditis, while in 2018-2019 only one child was reported with sepsis. Complete results are summarized in Table 2.

A specific bacterial pathogen was identified in 12/73 (16%) patients in 2022-2023 and in 7/27 (26%) in 2018-2019 (p=0.386). The number of infectious agents isolated in 2022-2023 was higher (8 species) than in the same period of 2018-2019 (3 species) without significant differences in the diagnostic techniques used. Furthermore, it is interesting to note that Streptococcus Pneumoniae was the most frequently identified agent in children hospitalized in 2022-2023 (5/12; 34%) but was never isolated in 2018-2019. Escherichia coli and Methicillin-resistant Staphylococcus aureus were found in both the time observation periods although in different rates (17% vs 29% for E. Coli and 17% vs 14% for MRSA in 2022-2023 vs 2018-2019, respectively) (Figure 1).

Discussion

The present study, although with the limitation of being retrospective, demonstrated a significant increase in the incidence of bacterial infections requiring hospitalization in post- COVID era in comparison to pre- COVID period. The epidemiological rebound of several infectious diseases after the COVID-19 pandemic is poorly understood and still controversial. Some authors hypothesized that the lack of immune stimulation and the reduction of vaccinations programs (11) experienced during the COVID lockdown may have produced a sort of "immunity debt" or an "immunity gap" in the pediatric population (10). The adoption of PHSM probably decreased some children's adaptative immunity to specific pathogens preventing them from "natural" exposure and contributed to the decline of herd immunity, making children more vulnerable to infections. This phenomenon has been particularly analyzed for viral infections, while it appears less clear for bacterial diseases. After barrier measures were lifted, several countries reported unusual viral outbreaks, with peaks exceeding those of the pre-pandemic period, in particular for respiratory syncytial virus (RSV) and other respiratory viruses (12-14). Transmission of RSV occurs by large droplets and

Table 2. Distribution of bacterial infections diagnosed in autumn/winter 2018-2019 and 2022-2023.

	2018-2019 N=27	%	2022-2023 N=73	%	*p*
Orbital cellulitis	0	0	10	13	0.05*
Mastoiditis	5	18	9	12	0.514
Pneumonia	6	22	20	27	0.798
Lymphadenitis	6	22	7	9	0.1
Sepsis	1	4	3	4	>0.99
Urinary tract infection	1	4	3	4	>0.99
Osteomyelitis	0	0	2	3	0.563
Skin infection	3	11	5	7	0.433
Cerebral empyema	0	0	3	4	0.563
Endocarditis	0	0	1	1	0.541
Acute otitis media	2	7	3	4	0.5
Meningitis	1	4	1	1	0.459
Peritonsillar abscess	0	0	5	7	0.163
Tooth abscess	1	4	2	3	0.8
Bacterial gastroenteritis	0	0	1	1	0.541
Pharyngitis	1	4	0	0	0.098

*Statistically significant.

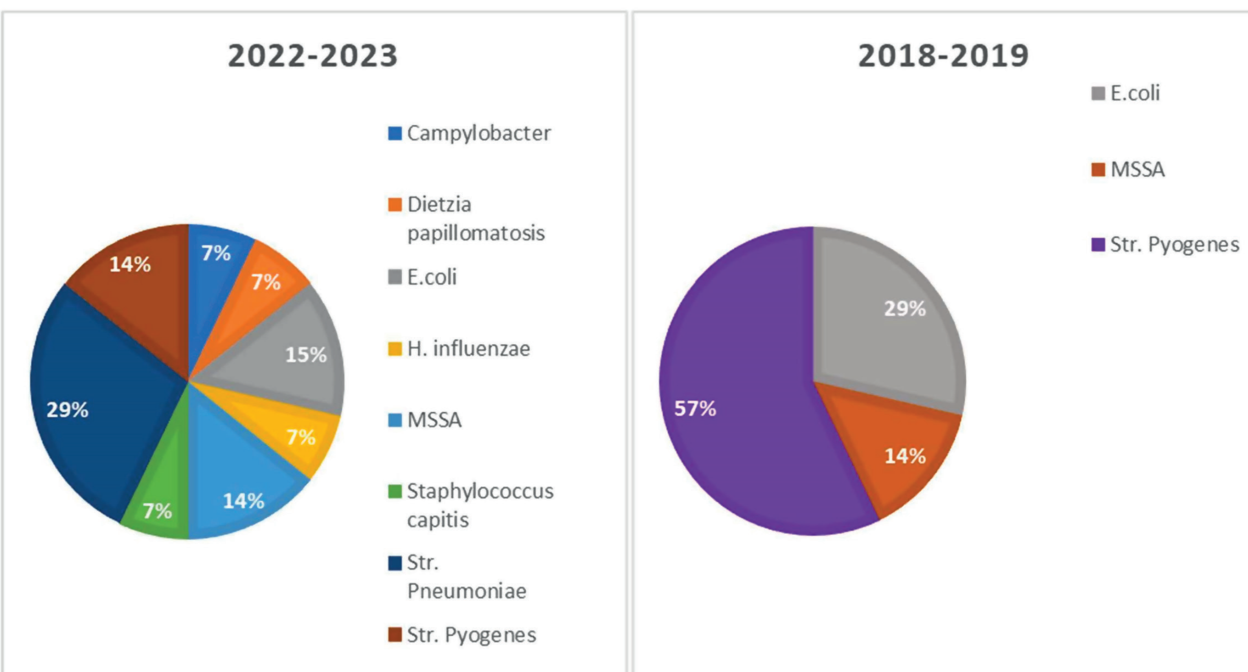

Figure 1. Most commonly isolated microbiological strains in children hospitalized with a bacterial infection.

contact with contaminated surfaces, and it is more frequent among children in day-care centers and schools. Therefore, the effect on RSV epidemiology after the adoption of the PHSM was not surprising, as the absence of strong RSV epidemic likely increased the proportion of RSV-susceptible children (15). Moreover, it should be also considered that partial and transient immunity is naturally achieved each year by direct infection or transplacental transfer of maternal RSV antibodies (10) but, due to the decreased spread of RSV in 2020, the natural protection of the whole adult and pediatric population against RSV at the end of winter became lower than usual (5). Other proposed mechanisms of the changing epidemiology of RSV include potential COVID-19-induced immune dysregulation, viral interactions between COVID-19 and RSV, and modifications in health-seeking behaviors as well as heath systems factors (16). Viral infections, mainly RSV and influenza, also play a role in triggering specific invasive bacterial infections, such as pneumococcal disease (invasive pneumococcal disease – IPD) (17). However, as shown by our data, the increased number of hospitalized bacterial infections was not related to a concomitant increase in viral co-infections in most cases. Some studies (18, 19) have suggested that this viral coinfection was important for serotypes with low disease potential but less important for serotypes with high disease potential, which may be virulent enough to generate disease without a viral trigger. On the other hand, a decrease in pediatric IPD incidence occurred after the implementation of PHSM, and this decrease was associated with a decrease in viral infection cases rather than pneumococcal carriage rate (11). The association between pneumococcal carriage and IPD was potentially modified by changes in the number of RSV and influenza cases, suggesting that interventions targeting respiratory viruses, such as immunoprophylaxis or vaccines for RSV and influenza, may be able to prevent a large proportion of pediatric IPD cases. In our study two cases of invasive Group A Streptococcus (iGAS) requiring hospitalization were observed in the 2022-2023 period. Since September 2022 a number of European countries (including Ireland, France, the Netherlands, Sweden, United Kingdom and Italy) also indicated an increase in the number of cases of iGAS disease among children less than ten years of age (20). Although investigations are still ongoing, early data suggested that the surge of cases was not related to a specific or new strain, nor an increase in antibiotic resistance of GAS. These data could be related to the theory of immunity debt on trained immunity. Several authors suggest that the stimulation by exposure to several pathogens works as a "training" of innate immunity that could increase its effectiveness. The theory is related to the functional reprogramming of innate immune cells stimulated by pathogens, and which would lead to a reinforced response during subsequent exposures (21). Therefore, this trained immunity becomes effective in children particularly exposed to viral infections in the first years of life and even more effective in them than later in adulthood. The reduction of the number of infections related to PHSMs may have led to a decreased immune training in children. Therefore, we can hypothesize that if bacterial infections are somehow favorite by the co-presence of viral infections, the decrease in the incidence of the latter may determine a higher number of immunological "naïve" children to more severe bacterial infections with high invasive potential. Our study showed no significant difference in vaccination coverage between pre- and post-COVID periods, except for the 13-valent pneumococcal vaccine, which resulted more frequently administered in 2022-2023 than before. The COVID-19 pandemic had an impact on all vaccination coverage rates as they all decreased, sometimes even sharply, particularly during the lockdown periods and were not fully restored afterwards (1). However, according to recent reports vaccinations rates are improving in post-COVID era, in contrast to the downward trend continued into early 202, so the current raising incidence of severe bacterial infections may not be related to the previous decline in vaccine coverage.

Our study is limited by the retrospective methodology and relatively small numbers of patients. However, our experience may be representative of Italy setting. In conclusion the non-pharmacological measures adopted during the pandemic were essential to contain COVID-19 spreading. However, they might have been a double-edged sword especially for young children, as delayed immune maturity might have increased susceptibility to infections and led to an explosion not only in high-virulent diseases such as influenza and RSV infections, but also in invasive bacterial infections.

Ethic Approval: The study was approved by the local Institutional Review Board (Prot. IRB: 264/2023)

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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