New Approach to the Surveillance of Pediatric Infectious Diseases From Ambulatory Pediatricians in the Digital Era

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Background: Many ambulatory networks in several countries have established syndromic surveillance systems to detect outbreaks of different illnesses. Here, we describe a new Pediatric and Ambulatory Research in Infectious diseases network that combined automated data extraction from the computers of primary care pediatricians.

Methods: Pediatricians who used the same software, AxiSanté 5-Infansoft for electronic medical records were specially trained in infectious diseases, encouraged to comply with French treatments' recommendations, use of point-of-care tests and vaccination guidelines. Infectious disease diagnoses in children <16 years old in the records triggered automatic data extraction of complete records. A quality control process and external validation were developed.

Results: From September 2017 to February 2020, 107 pediatricians enrolled 57,806 children (mean age 2.9 ± 2.6 years at diagnosis) with at least one infectious disease diagnosis among those followed by the network. Among the 118,193 diagnoses, the most frequent were acute otitis media (n = 44,924, 38.0%), tonsillopharyngitis (n = 13,334, 11.3%), gastroenteritis (n = 12,367, 10.5%), influenza (n = 11,062, 9.4%), bronchiolitis (n = 10,531, 8.9%), enteroviral infections (n = 8474, 7.2%) and chickenpox (n = 6857, 5.8%). A rapid diagnostic test was performed in 84.7% of cases of tonsillopharyngitis and was positive in 44%. The antibiotic recommendations from French guidelines were strictly followed: amoxicillin was the most prescribed antibiotic and less than 10% of presumed viral infections were treated.

Conclusions: This "tailor-made" network set up with quality controls and external validation represents a new approach to the surveillance of pediatric infectious diseases in the digital era and could highly optimize pediatric practices.

Key Words: ambulatory network, automated data extraction, pediatric infectious disease

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Infectious diseases account for a large part of pediatric daily practice.[1–3] Colonization and infection with the same bacterial and/or viral species involved in pediatric community-acquired infections (CAIs) could be asymptomatic or paucisymptomatic or induce moderate or severe disease. Indeed, a continuum exists between first-line clinicians (pediatricians or general practitioners) and those working in emergency departments or hospital wards. The distribution of CAIs in ambulatory settings and the hospital is often presented in a pyramid shape, with noninvasive infections at the base and more severe invasive diseases such as meningitis or sepsis at the top.[4] This is true for many bacterial species such as pneumococcus but also viruses such as respiratory syncytial virus (RSV) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The overuse of antibiotics (ATBs) to treat these CAIs for outpatients and hospitalized patients plays an important role in the increase in ATB resistance, a worldwide threat.[5,6] Moreover, some previous data outlining the misuse of ATBs in the outpatient setting have justified the expansion of ATB stewardship programs into this healthcare setting.[7,8] Slowing the emergence and the spread of resistant bacteria implies that primary care physicians rigorously monitor CAIs.[7] Therefore, among the interventions to improve ATB use, clinician education appears challenging but essential.[4,9]

For CAIs, despite many efficient ambulatory networks in several countries, they are mainly based on diagnoses by first-line physicians not specifically trained in pediatric infectious diseases, despite some efforts to improve the quality.[10–13] In England, a primary care sentinel network, the Royal College of General Practitioners Research and Surveillance Centre, comprising more than 100 general practices,[14] is based on an automated and contemporaneous extraction from computerized medical records. However, the center observed disparities in diagnoses presenting to the practices within the network.[14] Other sentinel networks related to infectious diseases such as varicella, influenza or gastroenteritis are of interest.[10],[15–17] The results they generate are good indicators of the epidemiology of these diseases in the country, but some limitations counterbalance their performance.[14] First, often they involve generally supplementary work for the participating physicians, which consists of declaring the cases with a specific questionnaire dedicated to the study.[10,15] The second limitation is that the diagnoses usually relate to syndromic surveillance (influenza illness, gastroenteritis) or diseases for which there are few doubts about the diagnosis, such as varicella.[10,11],[16–21] Moreover, syndromic surveillance systems were established to detect outbreaks of different illnesses but not improve diagnostic performance nor use of appropriate ATBs.[16–21]

In this context, 3 years ago, we created a “tailor-made” national pediatric ambulatory network, Pediatric and Ambulatory Research in Infectious diseases (PARI). This surveillance network has 3 main characteristics: a major investment in teaching with specific training of participating pediatricians, increase in use of point-of-care tests and automated data extraction from pediatricians’ computers. Here, we present the set-up of the network, how it works and some results validating the quality of the surveillance.

METHODS

To set up this network based on automated and contemporaneous extraction from computerized medical records, a dedicated scientific committee was created in 2014, 3 years before the start of the study. It was constituted by experts in pediatric infectious diseases, epidemiologists, methodologists and biostatisticians, as well as members of the Association Française de Pédiatrie Ambulatoire (AFPA), and the Association Clinique Thérapeutique Infantile du Val de Marne (ACTIV) research group. This committee planned the network priorities and developed a collaboration between the dedicated webmaster and the head of the electronic medical record (EMR) software. This study started without any external funding.

Participating Pediatricians

From June 2017 to June 2020, 107 pediatricians among the 1400 members of the French ambulatory pediatric association AFPA were recruited from all over France by co-optation, via email and/or during the annual AFPA meeting. This voluntary enrollment was based on high motivation and the willingness to improve their diagnostic performance for the benefit of children.

To belong to the PARI network, pediatricians had to use the same software, AxiSanté 5-Infansoft (developed by CompuGroup Medical in France) for EMRs of children. Moreover, they also had to attend to the PARI group meetings, training courses and a specific annual congress dedicated to ambulatory pediatric infectious diseases. Inappropriate use of the software and/or nonregular participation in training sessions and/or meetings could lead to their exclusion. Two face-to-face meetings were mandatory and the percentage of attendance should be at least 85%.

Diagnostic Performance Improvement

To avoid the heterogeneity of diagnosis for the same pathology among the different participants and improve diagnostic performance, the scientific committee set up several strategies. The goal was to harmonize the pediatricians’ daily practices. First, emphasis was placed on training face to face and with e-learning. A dedicated website (https://www.activ-france.com/fr/accueil-e-learning) was created to help pediatricians improve their skills and diagnoses in several infectious diseases such as otitis, pharyngitis, extrapharyngeal Group A *Streptococcus* (GAS) infections, enterovirus infections and ATB treatment duration. For otitis diagnosis, the use of digital otoscope was strongly recommended. Indeed, a tympanic picture could easily be shared in the PARI group for advice (https://www.engineeringforchange.org/solutions/product/oto/, https://doi.org/10.1177/0009922815593909). Moreover, the use of point-of-care tests such as urinary strips, rapid diagnostic tests (RDTs) for GAS, influenza and RSV, as well as C-reactive protein were part of the recommendations and distributed free of charge for participants. The use and interpretation of these tests were regularly discussed during the PARI training courses.[22,23] Finally, a Website presenting automatically generated graphs with the frequencies of each disease and a weekly newsletter were provided to all participants to allow them to monitor the epidemiology of the infectious diseases and to be informed in real time in the event of an outbreak.

Study Population and Data Collection

The study population consisted of all children under 16 years of age from the patient population of the pediatricians. The following infectious diseases diagnoses (complete list with International Statistical Classification of Diseases, 10th Revision, codes is in Figure [Supplemental Digital Content 1, http://links.lww.com/INF/E327]) triggered the automatic data extraction: GAS infections (tonsillopharyngitis, scarlet fever, perineal infections, paronychia), acute otitis media (AOM)/otorrhea, pneumonia, influenza/influenza syndromes, bronchiolitis, pertussis, urinary tract infections/pyelonephritis/cystitis, gastroenteritis, enteroviral infections (hand/foot/mouth diseases, herpangina, etc.), chickenpox/shingles and mononucleosis, etc. We prospectively collected demographic data from patients as well as details of point-of-care tests used, vaccination status and ATB consumption. A close collaboration with national reference centers for the different bacterial or viral species (enteroviruses, pertussis, pneumococcus, etc.) was set up to take advantage of their microbiology expertise (virulence, typing, resistance, etc.). Moreover, we could identify new visits for the same diagnoses. No additional data than those required in the daily practice of the pediatricians were requested. AxiSanté 5 is a medical software for patient record management that was developed and marketed by CompuGroup Medical and developed in partnership with AFPA. In particular, it allows for entering medical and vaccine data, producing biometrics, creating assisted and automated prescriptions, accounting management and tele-transmission. When the EMR of a child with an infectious disease targeted in the study is closed in AxiSanté 5, de-identified data are automatically collected and securely transferred to the PARI Medical Observatory operated within a secure technical environment accredited for hosting medical data. This routine information system provides real-time data, requires little additional work from participating pediatricians and complies with all regulations regarding clinical research and general data protection regulation. The participating pediatrician cannot prevent data from being extracted from the EMR to the PARI Medical Observatory, which can only be processed by the authorized research coordinating center (ACTIV).

Ethics

Before starting the electronic data capture, parents and children were informed of the study by a poster placed in the waiting room and an information leaflet in the pediatrician’s office. Any child or parent had the right to object to the data collection for this study. In this case, the pediatrician had to inform ACTIV to not use the patient’s data. To date, no one has opposed use of the data. The study was approved by the French National Commission on Informatics and Liberty (no. 1921226) and by an ethics committee (CHI Créteil Hospital, France). The study was registered at ClinicalTrials.gov (NCT04471493).

Quality Controls and External Validation

Several levels of internal and external validation were set up to ensure the high quality of data generated by the system. First, data exported from each participating pediatrician was internally checked each month and compared with other members of the network. Several parameters allowed to detect abnormal data extraction pattern, including a lack of data for several weeks, a particularly low variety of targeted diagnoses and an abnormal use of the prescription module. In this situation, pediatricians were contacted as potential outlier to understand and solved, if necessary, the difference in behavior.

Second, we monitored the appropriate use of point-of-care tests and concordance of ATB prescriptions (for AOM or GAS tonsillopharyngitis) with the national guidelines. In France, for children ≥3 years old with tonsillopharyngitis, it is recommended to perform an RDT. In case of positive result, the recommended treatment is amoxicillin. For children <2 years old with AOM, the recommended treatment is amoxicillin.[24,25] Amoxicillin-clavulanate is recommended only for conjunctivitis-otitis syndrome or nonresponsive AOM. Oral third-generation cephalosporins are recommended only in case of suspicion of penicillin allergy. According to these guidelines, the following outcomes were analyzed in our cohort to assess appropriateness of point-of-care tests and ATB use:

1. Rate of RDT use for tonsillopharyngitis in children ≥3 years old.
2. ATB prescription rate for tonsillopharyngitis according to RDT result, presumed viral acute respiratory tract infections (bronchiolitis, influenza illness) and AOM.

These parameters were analyzed for the overall cohort of patients, but also separately for each participating pediatrician, to identify unusual prescribing pattern. Thus, these controls allowed to confirm the high quality of the training of the participating pediatricians.[24,25]

Third, to externally validate the data process as well as the epidemiologic features, PARI weekly frequencies for influenza, bronchiolitis, gastroenteritis and varicella were compared with data from the French national institute for health, Santé Publique France, through their national surveillance network, Sentinelles and Geodes.[15,26]

Statistical Analysis

STATA 15 (StataCorp 2015, College Station, TX) was used for data management and statistical analysis. To evaluate the diagnostic methods, clinical characteristics, treatments and evolution of the pathologies, we computed frequencies and percentages for each infectious disease diagnoses from September 2017 to February 2020 (ie, before the coronavirus disease 2019 [COVID-19] pandemic) as well as vaccination status, ATB prescription and use of RDTs. For the graphs presenting the CAIs, we computed the data up to June 2020. The external validation of PARI network with Sentinelles/Geodes networks was performed using Pearson correlation coefficient.

RESULTS

Participating Pediatricians

The 107 pediatricians involved in the PARI network are distributed in all French metropolitan territories (see Figure, Supplemental Digital Content 1, http://links.lww.com/INF/E327). The mean age of pediatricians was 54.3 ± 9.9 years, and women accounted for 76.6% (n = 82). The mean number of overall visits per week per pediatrician was 90.0 ± 50.1 and the mean number of infectious diseases diagnoses followed by PARI was 10.1 ± 8.1 per week.

Population of Children

From September 2017 to February 2020, 57,806 children (58.6% male) had at least one infectious disease diagnosis from the 107 pediatricians. The mean age was 2.9 ± 2.6 years at diagnosis (see Figure, Supplemental Digital Content 2, http://links.lww.com/INF/E327).

Infectious Disease Diagnoses

Up to February 2020, 118,193 diagnoses were reported. The most frequent were AOM (n = 44,924, 38.0%), tonsillopharyngitis (n = 13,334, 11.3%), gastroenteritis (n = 12,367, 10.5%), influenza (n = 11,062, 9.4%) and bronchiolitis (n = 10,531, 8.9%), enteroviral infections (n = 8474, 7.2%) and chickenpox (n = 6857, 5.8%). We also recorded 1355 (1.2%) cases of pneumonia, 1354 (1.1%) of scarlet fever, 399 (0.3%) of perianal infections, 332 (0.3%) of paronychia/blister dactylitis, 86 (0.1%) of pertussis and 15 (0.01%) of measles.

Use of GAS RDT and ATB Prescriptions

For tonsillopharyngitis, an RDT was performed in 84.7% of cases: 52.0% for children <3 years old and 95.8% for those ≥3 years old. Among RDTs performed, the result was positive in 44.0% of cases: 23.3% for children <3 years old and 47.9% for those ≥3 years old ($P < 0.001$). Table 1 shows ATB prescriptions according to the disease. Amoxicillin was the most-prescribed ATB for respiratory tract infections. Few tonsillopharyngitis (5.3%, 278/5289) cases with negative RDT results were treated with ATBs, nor was bronchiolitis (10.3%, 720/6995) or influenza illness (7.6%, 679/8984).

Variability of Diagnoses: Identification of Outlier Pediatricians

Only 4 pediatricians among 107 could have been considered as outliers. However, the difference was due to a very high number of infectious diagnoses (>4000), but Figure (Supplemental Digital Content 3, http://links.lww.com/INF/E327) showed that their data remained in the overall network trends.

External Validation: Comparison With the Preexisting National Networks

Figure 1 shows the weekly frequencies of the influenza, gastroenteritis, bronchiolitis and varicella syndromic surveillances of the PARI network as compared with those of the Sentinelles and

TABLE 1. Antibiotics Prescriptions by Disease

Infectious Diseases	N Treated	Amoxicillin	Amoxicillin/ Clavulanate	Third-generation Cephalosporin	Macrolides
AOM (n = 34,667)	31,835 (91.8)	24,077 (75.6)	4503 (14.1)	1551 (4.9)	84 (0.3)
Tonsillopharyngitis					
RDT+ (n = 4753)	4688 (98.6)	4421 (94.3)	102 (2.2)	80 (1.7)	64 (1.4)
RDT– (n = 5289)	278 (5.3)	161 (57.9)	30 (10.8)	9 (3.2)	74 (26.6)
Influenza (n = 8984)	679 (7.6)	485 (71.4)	44 (6.5)	21 (3.1)	109 (16.1)
Confirmed A/B influenza (n = 1318)	101 (7.7)	75 (74.3)	12 (11.9)	2 (2.0)	11 (10.9)
Bronchiolitis (n = 6995)	720 (10.3)	516 (71.7)	49 (6.8)	9 (1.3)	130 (18.1)

+ indicates positive; –, negative.
This table does not report the patients with ≥2 diagnoses during the same visit.

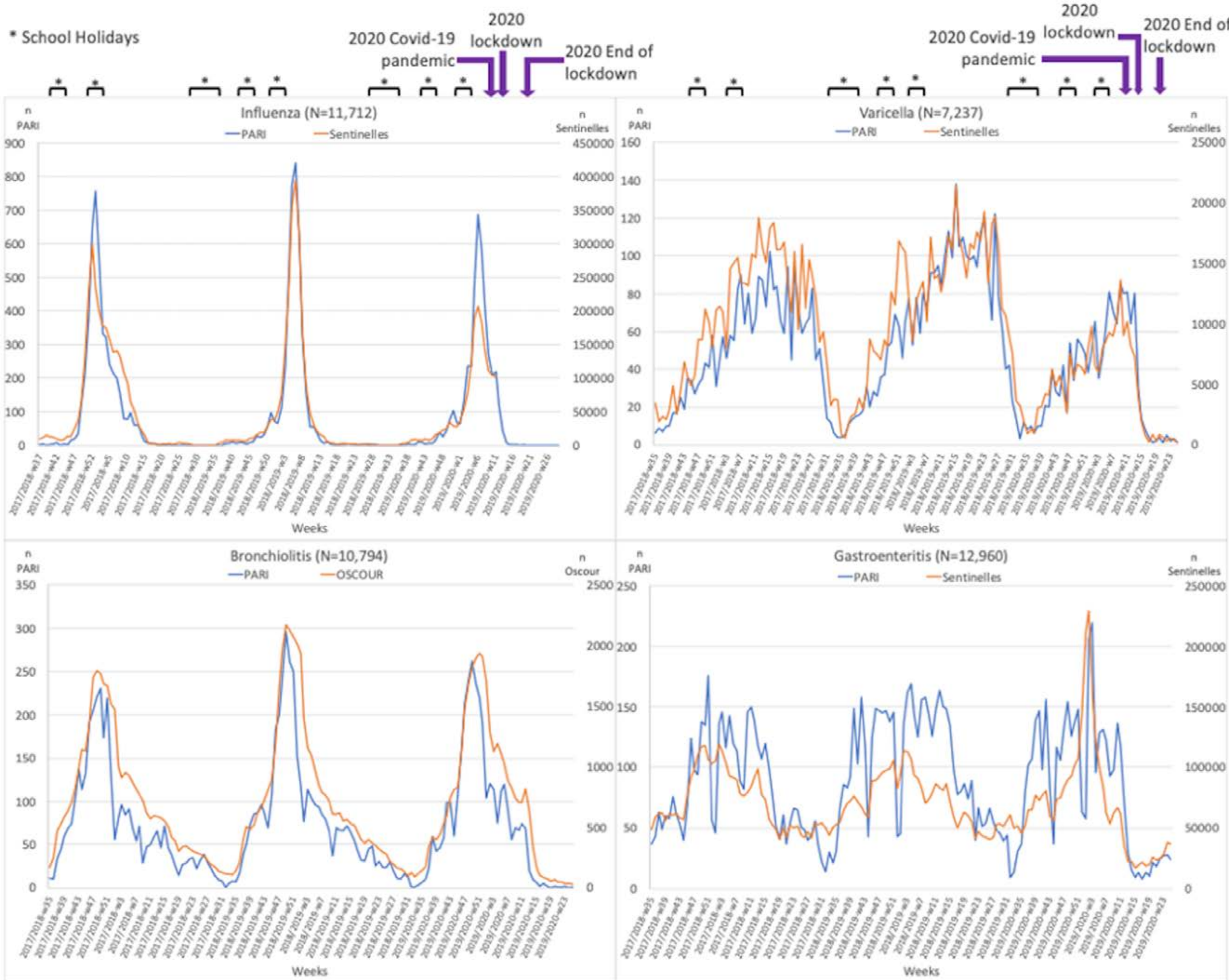

FIGURE 1. Distribution of influenza, varicella, gastroenteritis and bronchiolitis per week over 3 study years (June 2017 to June 2020) in children seen by 107 pediatricians in the Pediatric and Ambulatory Research in Infectious diseases network compared with Sentinelles and Geodes networks. OSCOUR indicates organization of coordinated surveillance of emergencies.

Geodes.[15,26] The curves were very similar for the 2 networks during the 3 study years and the seasonal peaks occurred exactly at the same time for the 4 diseases. Figure (Supplemental Digital Content 4, http://links.lww.com/INF/E327) shows the correlation between PARI network and Sentinelles/Geodes networks. All Pearson correlation coefficients were significant ($P < 0.0001$): 0.96, 0.68, 0.93 and 0.89 for influenza, gastroenteritis, bronchiolitis and varicella, respectively.

Annual Distribution of the Diseases

The distribution of AOM, bronchiolitis, influenza, gastroenteritis, tonsillopharyngitis, GAS tonsillopharyngitis, chickenpox and enterovirus diseases per week over the 3 study years (June 2017 to June 2020) is presented in Figure 2. For all these diseases, the reproducibility of the peaks each year was fully concordant, except for influenza, with a peak in 2017/2018 occurring earlier. Of note, for AOM, 2 peaks each year were observed. The first peak agreed with the bronchiolitis peak, whereas the second occurred with the influenza peak. As expected, for enteroviral infections, the main peak occurred each year at the end of spring and the beginning of summer. The curves over 3 years showed a decrease in the frequency of diseases during the COVID-19 pandemic.

DISCUSSION

The PARI network is a hybrid surveillance system combining automated data extraction from the computers of primary care pediatricians with specific and deep training in infectious diseases. Besides creating the network, with high computer constraints, the challenge was to find a group of pediatricians motivated to improve their diagnostic and therapeutic performance for infectious diseases. Moreover, pediatricians had to be sufficiently numerous to provide national representative data. They were trained to comply with treatments and vaccination guidelines and use point-of-care tests.

To set up this surveillance, we previously performed a pilot study to verify the efficiency of the system. Indeed, we first described compliance with the immunization program according to the age recommended for each vaccination dose for children <2

FIGURE 2. Distribution of frequency of acute otitis media, tonsillopharyngitis (RDT-positive), bronchiolitis, tonsillopharyngitis (RDT-negative), influenza, varicella, gastroenteritis and enteroviral infections per week over 3 study years (June 2017 to June 2020).

years old.[27] This successful experience allowed us to develop the PARI network with confidence.

With data from only 107 well-trained pediatricians, we present epidemiologic curves highly similar (Pearson correlation coefficients: 0.96, 0.93, 0.89 and 0.68) to those of the Sentinelles and Geodes networks for influenza, bronchiolitis, varicella and gastroenteritis.[15,26] This observation could be considered an external validation. Other features underlying the high quality of the pediatrician training and the network efficiencies are the large use of point-of-care tests and appropriate prescriptions of ATBs. We tried to develop a framework for effective use of RDTs with an assessment of the pretest probabilities and good clinical examination to optimize practices. Therefore, in our study, according to the French guidelines, RDTs for tonsillopharyngitis was mainly performed for children >3 years old.[25] Positive RDT results accounted for 44.0% of cases of tonsillopharyngitis, which agreed with a recent meta-analysis showing the pooled prevalence of GAS at 37% (95% confidence interval 32%–43%) among children presenting sore throat.[28] Moreover, as recommended by the French guidelines amoxicillin was the most-prescribed ATB for GAS tonsillopharyngitis, and only 5.3% of tonsillopharyngitis cases with negative RDT results were treated with ATBs.[25] For AOM, amoxicillin prescription accounted for 75.6% of cases. Of note, amoxicillin-clavulanate represented 14.1% of the ATB prescriptions, which was consistent with the rate of conjunctivitis-otitis syndrome.[27,29] Again, these results fit with the French ATB guidelines for respiratory tract infections in children.[24] The overuse of ATBs for treating viral respiratory infections is a well-known factor in the development of ATB resistance.[5,6] In our study, according to the national guidelines, very few presumed viral infections such as bronchiolitis or GAS negative tonsillopharyngitis or influenza were treated with ATBs.[30] For example, only 7.6% of cases of influenza were treated with ATBs. This rate was lower than that reported in a recent study showing ATBs ordered for 33% of children with influenza in the outpatient setting (33%) and 93% of those hospitalized.[31]

In our study, for AOM, each year showed a first and main peak concurrent with the bronchiolitis peak and a second peak concurrent with the influenza peak. The importance of viruses in AOM is well known, particularly for RSV and influenza viruses.[32–34] The widespread use of pneumococcal conjugate vaccine was the first step to decrease the burden of AOM; the second one could be the use of viral vaccines such as routine influenza and RSV vaccines.[32–35] In the next few years, new vaccines and other methods for preventing respiratory pathogens will be developed (RSV vaccines, new generation pneumococcal conjugate vaccines, new influenza vaccines, SARS-CoV-2 vaccines, etc.). Our surveillance system with 3-year baseline data will allow us to quickly assess the effectiveness of all these interventions. Indeed, taking advantage of our baseline data before the COVID-19 pandemic, we were able to observe the disease's major impact on the sharp decrease in frequency of infectious diseases. The curves over 3 years allowed to see the absence of visits by children to pediatricians during the lockdown. With this observation, we started to implement a COVID-19 surveillance using this efficient network. We are now extending PARI to less frequent infectious diseases.

Our study has several limitations. Our highly motivated and trained pediatricians were not representative of the general population of health care provider. However, our objective was to have an evolutive picture of many primary cares acquired infections using the best diagnosis tools available for first-line pediatricians. They all had a high training in diagnoses of infectious diseases and they rigorously followed the guidelines for ATB prescriptions or RDT use.[36] In the coming months, other diagnostic tools must be deployed to improve the quality of diagnosis. These tools allow for adapted children management as well as improvement of the surveillance system. Hence, the need to have more diagnostic tools such as a rapid molecular test for acute respiratory tract infections combining SARS-CoV-2, influenza and RSV infections has become a priority.[37] A last limitation is the lack of information regarding children seeing another pediatrician not involved in the network. This bias is attenuated by the huge numbers (118,193 diagnoses) in our database, approaching big data in the coming years.

Despite these concerns, the involvement of the participating pediatricians and the first results plaid for the feasibility and the usefulness of such a network, which could easily be applied in other countries.

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