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Article

Hospital and population-based evidences for COVID-19 early circulation in the East of France

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Abstract: Background: Understanding the SARS-CoV-2 dynamics and transmission is a major issue to model and control its propagation. The Alsace region in the East of France has been among the first French COVID-19 clusters in 2020. **Methods:** We confront evidences from three independent and retrospective sources: a population-based survey through internet, an analysis of the medical records from hospital emergency care services and the review of medical biology laboratory data. We also check the role played in the virus propagation by a large religious meeting which gathered over 2000 participants from all over France mid-February in Mulhouse. **Results:** SARS-CoV-2 was circulating several weeks before the first officially recognized case in Alsace on February 26th 2020 and the sanitary alert on March 3rd. The religious gathering played a role for secondary dissemination of the epidemic in France, but not in creating the local outbreak which was in place much earlier. **Conclusions:** Our results illustrate how the integration of data coming from multiple sources could help trigger an early alarm in the context of an emerging disease. Good information data systems, able to produce earlier alerts, could have avoided a general lockdown in France

Keywords: COVID-19; SARS-Cov-2; epidemic surveillance; emerging infectious disease; epidemic threshold

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1. Introduction

The coronavirus disease COVID-19 was labelled a pandemic by World Health Organization (WHO) on March 12th 2020 [1]. At that time, there were more than 20,000 confirmed cases and almost 1,000 deaths in Europe according to WHO statistics. The first three cases of COVID-19 in France were confirmed on January 24th 2020 [2]. The Oise department north of Paris was among the first COVID-19 clusters in France where SARS-CoV-2 was actively circulating weeks before the country lockdown on March 17th 2020 [3]. Alsace is a cultural and historical region located East of France in the “Grand Est” administrative region, on the border between France and Germany. In the southern part of Alsace, the Haut-Rhin department and especially Mulhouse, a city of 110,000 inhabitants, was also identified among the earliest COVID-19 clusters in France. The first official case of coronavirus in the Grand Est region, a traveler coming back from Lombardi (Italy), was identified on February 26th 2020 [4]. Beginning of March, the number of cases increased rapidly, particularly among the participants

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to a religious gathering at Porte Ouverte Chrétienne (POC) Church in Mulhouse which took place from February 17th to 21st 2020.

To understand the characteristics of the outbreak, the particular role played by the POC gathering in the virus transmission in Haut-Rhin and to see if the alert could have been triggered earlier, an online population-based survey was launched April 22nd 2020 with the support of general physicians and emergency unit health professionals of the Haut-Rhin department [5].

In this paper, we confront the results of this population-based survey to those of a retrospective study led by an emergency unit located in Mulhouse in order to check their coherence. Indeed, emergency services have been on the front line of the pandemic, especially during the first weeks of March 2020 when they had to handle a massive increase of COVID-19 cases. Retrospective analysis of medical files in a French hospital North of Paris allowed to identify patients with COVID-19 symptoms as early as December 2019 ([6]).

Before March 2020, the hospital biological laboratories were still performing PCR tests for influenza while PCR tests for SARS-CoV-2 coronavirus were restricted to persons coming back from regions at risk. If COVID-19 was already circulating in the Haut-Rhin population at that time, a number of early COVID-19 cases should have been tested negative for influenza. As a consequence, the number of negative tests should also provide a useful piece of information to understand the beginning of the COVID-19 epidemic.

So, the objective of our study is to draw a coherent picture of COVID-19 epidemic history in the Haut-Rhin department from January to April 2020 by confronting data coming from these three independent sources: an online population-based survey, an emergency care service retrospective study and influenza PCR laboratory tests.

2. Materials and Methods

2.1. Data sources

2.1.1. Online population-based survey

A population-based survey using anonymous questionnaire was conducted online to evaluate if people living in the Haut-Rhin department had symptoms commonly experienced in case of COVID-19 infection, when and which ones. In order to achieve a quick deployment to reduce memorization bias, we followed a fast track procedure to build protocol and get legal and ethical agreements.

After testing the questionnaire on four voluntary families in France and Switzerland, the study was approved by the legal and ethical agreements of Clermont Auvergne University Ethic Committee on April 10th 2020, and Clermont Auvergne University Personal Data Protection Management authorities and National Center for Scientific Research Personal Data Protection Management authorities both on April 21st 2020. Informed consent was obtained from all participants.

All families living in the Haut-Rhin department including POC meeting participants were invited to fill the online questionnaire. Thanks to the support of local media (local newspapers and radio) and to the POC meeting organizers, the survey was well advertised. There was no control nor deadline for participation.

The survey considers the family structure and the social relationships and networks of the household members. Respondents were then asked to document the occurrence among family members of the symptoms commonly observed in case of COVID-19 infection (see [7] and references therein). The intensity, duration and possible regrowth of each of the following clinical signs was documented: fever, cough, breathing difficulties, asthenia, loss of taste and/or smell, diarrhea, aches, ENT, neurological and dermatological symptoms. Respondents were also asked if they had been diagnosed with COVID-19, either through PCR test or remotely, and if they had also been tested for influenza. Up to 5 suspicious cases could be described in the same household. In addition, they were invited to indicate whether a household member had participated to the POC gathering in February 2020 in Mulhouse.

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2.1.2. Emergency care service

The second source of information is the emergency care service of the Diaconat-Fonderie Hospital in Mulhouse. This private not for profit hospital is located in the center of Mulhouse and has a capacity of 200 beds. Its emergency care service, created in 2006, is staffed by 7 emergency physicians supported by 17 paramedics. In 2018, this emergency service received 28,317 patients, to be compared to 68,552 at Mulhouse public hospital emergency service the same year.

Detection of COVID-19 patients became simpler in May 2020 thank to the availability of PCR and serological tests combined with the clinical experience of the healthcare professionals. This experience was used to reevaluate retrospectively all the medical files of patients who visited the emergency care service from December 30th 2019 to May 18th 2020 in order to identify potential COVID-19 cases.

For patients admitted before the local sanitary alert on March 3rd 2020, the selection process involved several stages. Patient files were first preselected by the head nurse based on their motivation for consulting. Patients coming for reasons possibly related to a COVID-19 infection were kept, including fever, cough, dyspnea, headache, diarrhea, dizziness or unexplained discomfort. Files were excluded if medical evaluation recorded at both entrance and exit were not compatible with COVID-19 and if PCR tests for influenza were positive. The preselected patient files were then analyzed by the emergency physicians and classified as probable COVID-19 cases if several of the following clinical conditions were fulfilled:

- The patient interview revealed previous contacts with COVID-19 symptomatic persons
- The following clinical signs were present: significantly impaired general condition, fever or absence of fever, myalgia, arthralgia, dry cough, significant asthenia, shortness of breath desaturation, sibilant rales at auscultation, chest pain, headaches, unexplained discomfort, anosmia, diarrhea or abdominal pain. Symptom duration was considered. Productive cough was considered a symptom excluding COVID-19.
- Chest CT-scans suggested COVID-19: presence of Ground Glass Opacities [8]. Ambiguous CT-scan images were double checked by radiologists. A clear pneumonia spot excluded a COVID-19.
- Biological indicators were in favor of a COVID-19: lymphopenia, negative influenza PCR test or thrombocytopenia.

For patients admitted after March 3rd 2020, the head nurse reviewed all patient files and performed a first selection of potential COVID-19 cases based on respectively reason for consulting, nurse's clinical assessment, results of medical examinations, with a particular focus on imaging and biological tests. The selected patients were further evaluated by an emergency physician who established a list of probable or confirmed COVID-19 patients. This list was then revised by integrating data coming from the radiology service (scanner examinations) and the medical laboratory (biological tests).

At the end of this process, 552 patients were retained as COVID-19 probable or confirmed cases, out of the 7,184 patients admitted to the emergency care service from December 29th 2019 to May 18th 2020.

2.1.3. Medical biology laboratory

The Diaconat-Fonderie medical biology laboratory is a multi-purpose biological platform open 24 hours a day every day to provide a continuous support to emergency care services. Its team handles over 600 daily samples coming from more than 20 healthcare centers in the Haut-Rhin department. The laboratory performed influenza PCR tests of the samples sent by the Diaconat-Fonderie emergency care services between January 1st and March 15th 2020 using the Abbott Binax Now Influenza A&B Card kit [9]. After the sanitary alert on COVID-19 epidemic was raised and containment established by the government, PCR tests for influenza were not performed any more.

For the population-based survey respondents, only declarative information was available whether they had laboratory test for influenza (PCR) and whether it was positive or negative.

2.2. Data analysis

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Statistical analyses were conducted using SAS software v9.4 (SAS Institute, INC., Cary, NC, USA). Categorical variables were presented as frequencies and percentages. Continuous variables were presented as means and standard deviations (SD).

In the analysis of the population-based survey presented in this paper, we focused on the people living in the Haut-Rhin department and excluded the attendants to the POC gathering coming from other departments. Overall epidemic evolution was compared in the survey data and in the retrospective analysis of emergency care service medical records. For both data sources, we focused our work on the moment incidence crossed over the threshold defining the outbreak. We particularly looked at the delay between the beginning of the outbreak and the sanitary alert form local authorities on March 3rd [10].

The epidemic threshold was estimated first from the upper limit of the 95% confidence interval of the incidence moving mean on the last seven days. The December 15th 2019 to January 15th 2020 period was used as a reference to compute the seven days moving mean confidence interval. In a second step, we checked for stability in terms of consecutive days over or under the threshold: if the incidence was rapidly oscillating under and over the threshold, it meant that the threshold did not discriminate between outbreak and background noise. The signal was stable if each period under or over the threshold was larger than seven consecutive days. In order to complete the incidence curves analysis, we also computed the daily speed ($s_i = \Delta m_i/\Delta t_i$) and acceleration ($a_i=\Delta s_i/\Delta t_i$).

For the majority of cases documented in the population-based survey, biological proofs of SARS-CoV-2 infection are missing and there could be confounding epidemic events as documented for instance in [3]. To confirm the nature of the epidemic tracked and to measure its dynamic, we compared our results to the studies based on cohorts with proved biological infection. So, using the intra-household data, we computed the reproduction number (approximated by the number of cases induced in one family by the very first case) [11-13] and the generation interval (computed as the difference between the occurrence days of successive cases in the same family) [14,15]. Considering that children are more sensitive to other respiratory viruses than to COVID-19 [16,17], we also considered incidence moving mean among children under 15 years old and adults and children aged 15 years and older. In case of confusion with another virus, the curve should display the same pattern for adults and children. Among all the symptoms, we particularly focused on anosmia, which has been identified as a typical sign of COVID-19 symptoms with highest predictive values for SARS-CoV-2 infection [3 ,18, 19]. From [18], the predictive value could be as high as 80% in presence of other respiratory syndromes while prevalence is lower among children. Nevertheless, anosmia is experienced by 30 to 50% of the COVID-19 infected patients [3, 17, 18], some times less as shown by a recent meta-analysis [19]. In the population survey, participants documenting COVID-19 suspicious cases were invited to evaluate this symptom intensity on a scale from 0 (no modification) to 3 (complete loss).

3. Results

3.1. Epidemic evolution of suspicious COVID-19 cases

3.1.1. Population-based survey

From April 22nd to June 4th 2020, 1,427 households participated to the population-based survey. The 201 households not living in the Haut-Rhin department were excluded from the present analysis, leading to a population of 1,226 households representing 3,350 individuals. Among them, 883 households (72.0%), representing 2,502 individuals, reported at least one suspicious case of COVID-19 (Table 1). A total number of 1,516 individuals (including 26 of unknown age) experienced symptoms commonly attributed to COVID-19 infection, corresponding to 1,301 adults and children aged 15 years and older and 189 children less than 15 years old. First suspicious cases were declared as early as November 2019.

Table 1. Composition of the 883 households in the Haut-Rhin department with at least one suspicious case of COVID-19.

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	N=883
Household size, mean (SD)	2.8 (1.2)
Number of adults in the household, mean (SD)	2.2 (0.9)
Age of adults (years), mean (SD)	44.4 (16.9)
Children in the household, n (%)	
No	552 (62.5)
Yes	331 (37.5)
Number of children in the household, mean (SD)	1.7 (0.7)
Age of children (years), mean (SD)	7.5 (4.1)
Number of suspicious cases of COVID-19 infection in the household, mean (SD)	1.7 (0.9)

Adults are 15 years and older; Children are less than 15 years old.

Figure 1 shows the seven days moving incidence average based on the onset day of the first symptoms reported for these COVID-19 possible cases (blue line). .

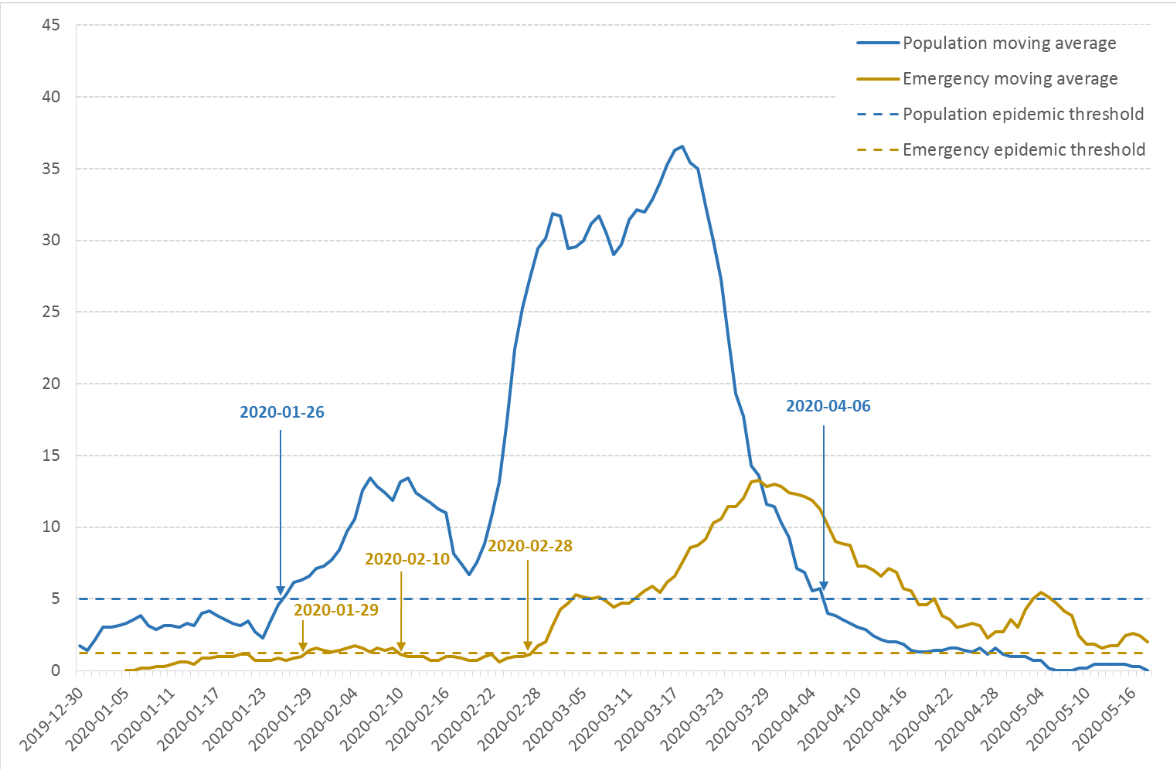

Figure 1. Dynamics of suspicious COVID-19 cases: seven days moving incidence average and epidemic threshold. The figure shows data coming from population-based survey (blue line) and emergency care services (yellow line) and corresponding epidemic thresholds (dashed blue and dashed yellow lines).

Based on the number of cases documented in the reference period (December 15th 2019 to January 15th 2020), the epidemic threshold (dashed blue line) was computed as 5 new cases per day. The curve shape indicates three waves in the epidemic development, which is confirmed by the speed and acceleration analysis (data not shown). From December 30th 2019 to January 22nd 2020, a first wave lasted 24 days, with the same one-week increase (January 1st to 7th) and decrease (January 17th to 24th) periods. However, the highest incidence remained under the epidemic threshold. The second wave also lasted 24 days from January 23rd to February 17th. It crossed the epidemic threshold on January

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26th and remained over this threshold despite a decrease after February 10th. The third wave of the outbreak began on February 17th, with an incidence increase leading to a first maximum on March 1st 3.6 times higher than the preceding wave. A partial and local lockdown started on March 3rd [10] and was extended to the whole country on March 17th. The incidence began to decrease after March 20th, 17 days after the beginning of the local lockdown.

Among households documenting at least one suspicious COVID-19 case, 47.6% indicate that the onset of the first COVID-19 symptoms occurred before March 1st 2020. On March 17th, first day of nationwide lockdown, 81.2% of these households have already reported a suspicious COVID-19 case. On the positive side, the lockdown was very efficient at stopping the epidemic as only 2.9% of the households reported their first case after March 31st, two weeks after entering the lockdown.

For the whole period, the mean reproduction number was 1.4 and the mean generation interval was 4 days, as computed using intra-household data.

3.1.2. Emergency care service

After analyzing the records of all the patients admitted into the Diaconat-Fonderie emergency care service from December 30th 2019 to May 18th 2020, 552 probable or confirmed COVID-19 cases were retained.

The seven days moving average of their admittance day is documented on Figure 1 (yellow line). We estimated the epidemic threshold at 1.2 cases a day (dashed yellow line). The first case occurred on January 6th and the threshold was crossed a first time on January 29th. The first outbreak wave remained flat, although the incidence stayed over the threshold until February 10th, with a first weak maximum on February 4th. Then, the incidence remained under but close to the threshold which was crossed once again on February 28th, showing an important outbreak, with a maximum on March 27th, which was 7.6 times higher than in February.

In order to check the possible role of emergency attendance, we also computed the fraction of the weekly attendance related to COVID-19 (Figure 2). The pattern observed on figure 2 is close to the yellow line on Figure 1, showing a little increase at the end of January and a major increase from February 24th on.

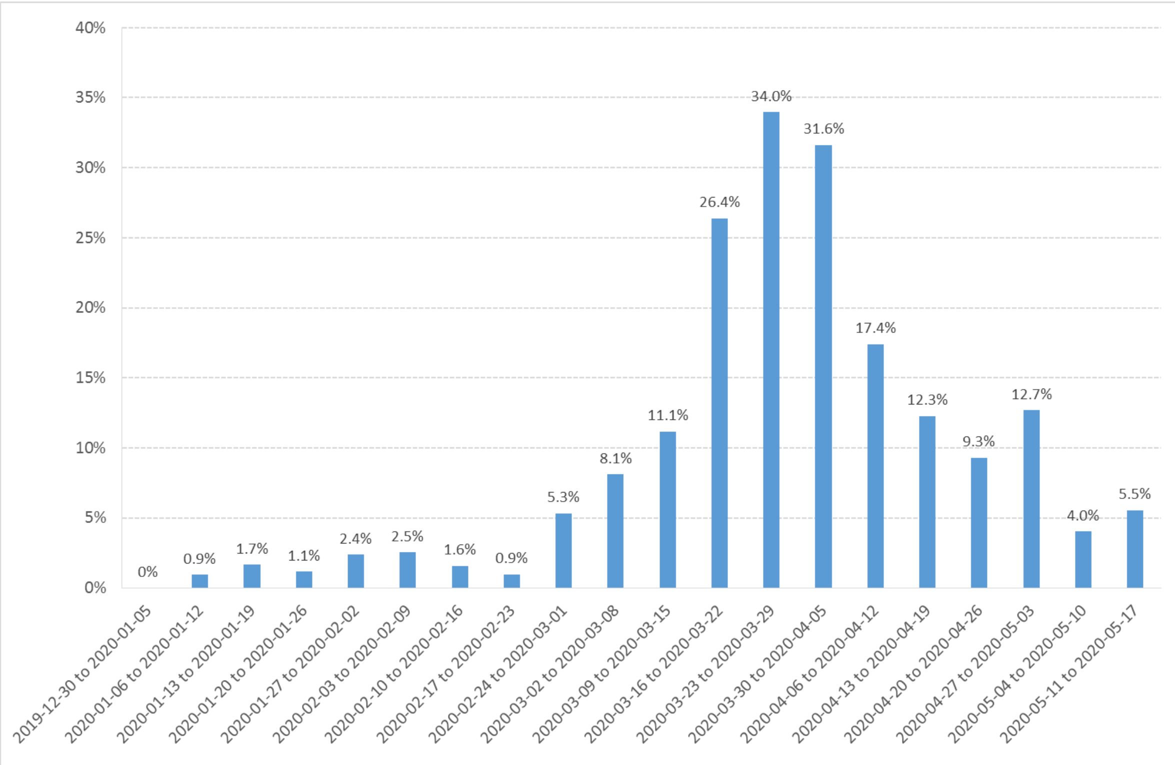

Figure 2. Fraction (expressed in %) of the Diaconat-Fonderie emergency care service weekly visitors with COVID-19 diagnosis from December 30th 2019 to May 17th 2020**.**

3.1.3. Evolution of influenza PCR tests

In the period preceding the sanitary alert, the circulation of COVID-19 in the population of the Haut-Rhin department was ignored. As a consequence, the persons visiting the emergency care service from January to mid-March 2020 with influenza-like syndrome were frequently given PCR tests for influenza.

The emergency care services sent to the Diaconat-Fonderie medical biology laboratory 59 samples for influenza PCR testing from January 1st to March 15th 2020: 37 of these samples (57.6%) turned out positive.

In the population-based survey, 3.2% of the cases (48 out of 1516) were tested for influenza. Three quarter of the tests were negative (n=36). Out of the 12 persons tested positive for influenza, 6 were also tested positive for COVID-19, showing the possibility of co-infection. As a consequence, we did not exclude from our population survey analysis the cases with influenza PCR positive tests.

Figure 3 shows the cumulative sum of the PCR tests performed by Diaconat Fonderie laboratory and documented in the population-based survey, and for both of them the cumulative sum of the positive ones. Although the statistics is small, the curves show a growing number of negative tests with a clear inflection of the curve after January 28th for the emergency patients and after January 30th for the population-based survey.

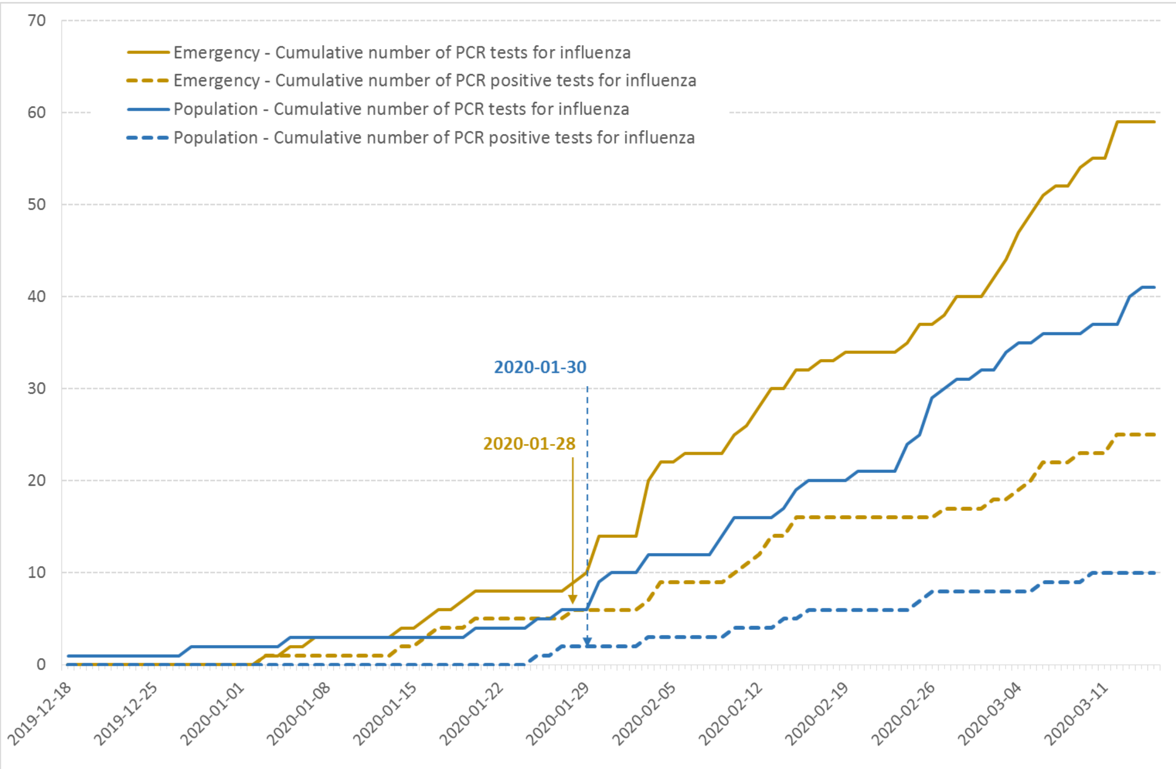

Figure 3. Time evolution of the cumulative sum of influenza PCR tests conducted by Diaconat-Fonderie biology laboratory (yellow line) and documented in the population-based survey (blue line). The dashed curves correspond to the cumulative sum of positive tests.

3.2. Comparison of epidemics among adults and children

Existing COVID-19 epidemiological data show that children are significantly less affected than adults (see for instance [16-17]). Another study [18] conducted in one of the earliest French COVID-19 clusters in the department of Oise has documented that infection in young children (below 12 years old) was largely mild or asymptomatic, but also that other respiratory viruses were circulating concurrently with COVID-19 in the French population in February 2020.

To check whether other respiratory syndromes could explain the pattern observed on Figure 1, we analyzed the number of cases among children aged less than 15 years old in comparison to the rest of the population surveyed. Figure 4 shows the seven days moving incidence average of COVID-19 suspicious cases among adults and children aged 15 years and older (green line) compared to children under 15 years old (orange line) in the surveyed Haut-Rhin households. Although more exposed to respiratory viruses, children below 15 years old display significantly less symptoms than adults and teenagers over 15 years old. The outbreak existed but in a very tiny way, beginning at the second wave and stopping earlier. Moreover, there is no clear link between adults and children curves, showing that what we observe is mainly related to an adults' epidemic. Moreover, Figure 4 confirms that the epidemic threshold was crossed January 30th for individuals aged 15 years and older.

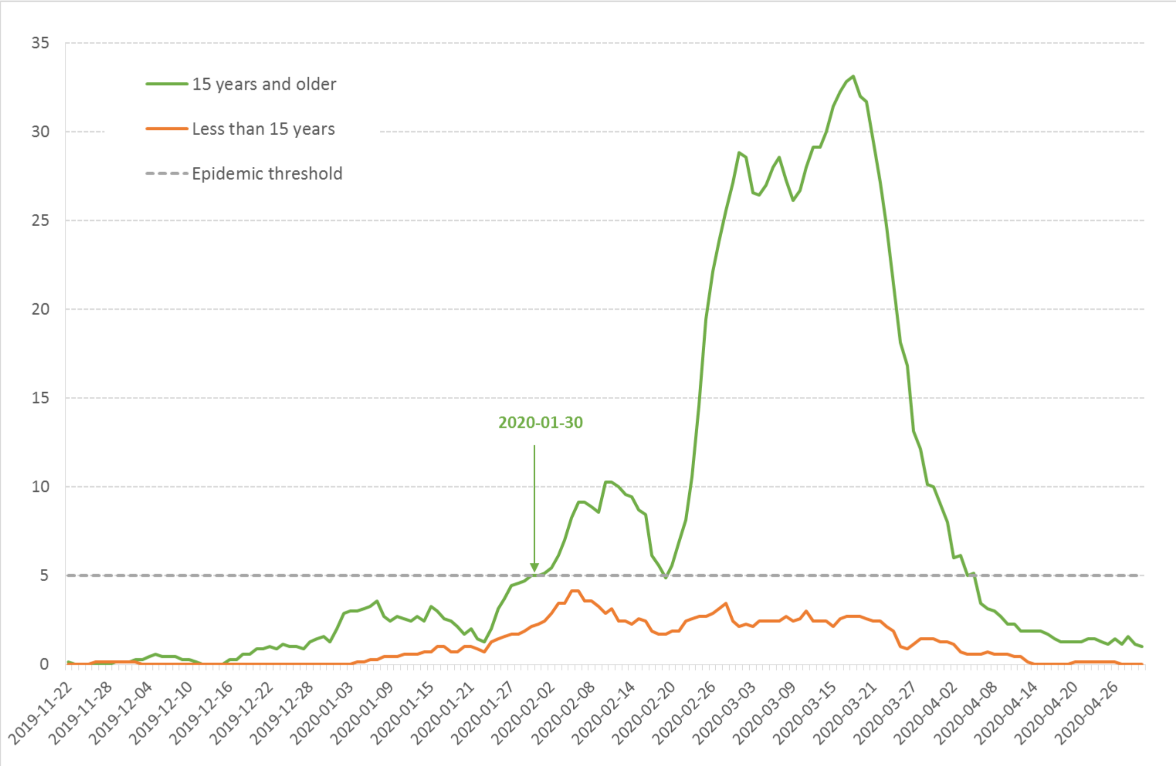

Figure 4. Seven days moving incidence average of the onset day of COVID-19 symptoms for children less than 15 years old (orange line) and adults and children above 15 (green line) from the population-based survey of Haut-Rhin households**.**

3.3. Prevalence of anosmia among COVID-19 symptoms

Out of the 1,516 suspicious cases documented by Haut-Rhin households, 13 out of 158 children below 11 years old (8.2%), 19 out of 67 children (28.4%) between 12 and 18 years old and 506 out of 1,265 adults (40%) experienced anosmia at different degrees.

Figure 5 shows the seven days moving average incidence of the first symptom onset day for COVID-19 suspicious cases that documented different anosmia intensities from 1 (modification of smell) to 3 (total loss). If we considered the total curve (in blue), the three waves evolution could be seen, with a crossing of the epidemic threshold on February 2nd, a little later than what was measured until now. Nevertheless, the speed of the curve was positive since January 30th. The third wave was much more developed and crossed the epidemic threshold on February 19th, with a positive speed since the day before.

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The curves corresponding to partial (orange) and total (red) loss of smell display similar patterns, in particular a little increase at the end of January. The curve corresponding to smell modification (yellow) is less marked.

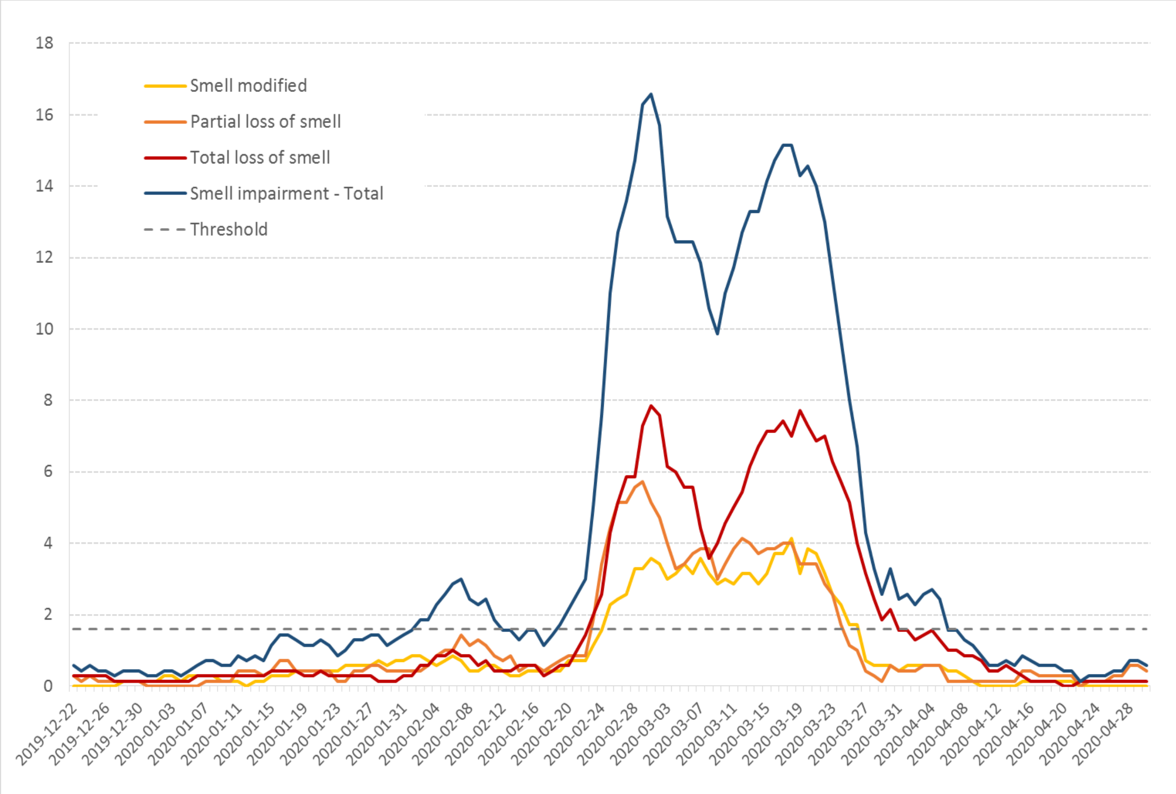

Figure 5. Curves of seven days moving average of the first symptom onset for COVID-19 suspicious cases that documented anosmia with intensities from 1 (modified smell) to 3 (total loss).

3.4. Impact of the POC gathering

Of particular interest in the case of the Haut-Rhin cluster is the role played by the POC gathering in the outbreak genesis and acceleration in February and beginning of March. The POC gathering began on February 17th and ended February 21st. In the population-based survey answers, 237 out of the 1,516 individuals who experienced symptoms commonly attributed to COVID-19 infection come from households in which one member at least participated to the POC gathering.

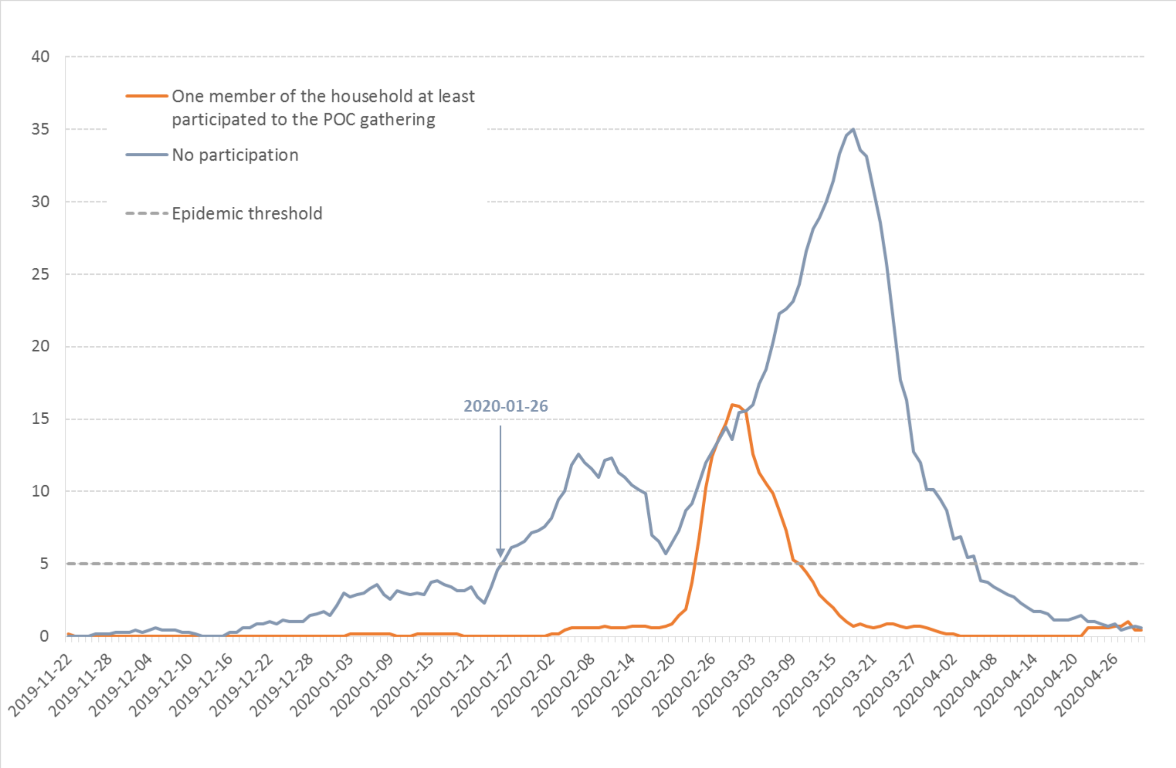

Figure 6. Seven days moving incidence average of the first symptom onset day for COVID-19 suspicious cases among Haut-Rhin households. Orange and grey lines correspond respectively to households with or without participants to the POC gathering in Mulhouse (February 17th to 21th 2020).

Figure 6 shows the seven days moving incidence average of the first symptom onset day for COVID-19 suspicious cases among Haut-Rhin households which participated (orange line) or not (grey line) to the POC gathering. The two curves display very different shapes: the grey line (households with no participants to the POC gathering) shows the three waves evolution previously described (see figure 1) with epidemic thresholds crossed at very similar times. Among the POC gathering attendants, some COVID-19 suspicious cases are declared at the beginning of February, but there was no clear outbreak. After February 21st, the last day of the gathering, the POC curve is typical of a one-time and one-place outbreak, very close to the pattern observed in the high school cluster in the Oise department in February-March 2020 [3]. The cluster created by the POC gathering participants did not change the speed and acceleration of the non-attendant population during the increasing as well as the decreasing periods. This shows that the two events were concomitant but not strongly linked. Independent of the POC gathering, the outbreak in the Haut-Rhin population began on January 26th and developed by its own. As more than 2,000 persons coming from various places of the French territory - including overseas departments and territories - attended the POC meeting, it is clear that it played a role in disseminating SARS-CoV-2 to other regions in France.

Anosmia was observed more frequently (56.5%) in the households involved in the POC meeting than in the other households (32,0%), $p<0.0001$. Figure 7 shows the seven days moving incidence average for COVID-19 suspicious cases with anosmia among Haut-Rhin households that either were involved in the POC gathering (orange line) or not (grey line). Compared to figure 1 or figure 5, it also points to a first epidemic wave end of January.

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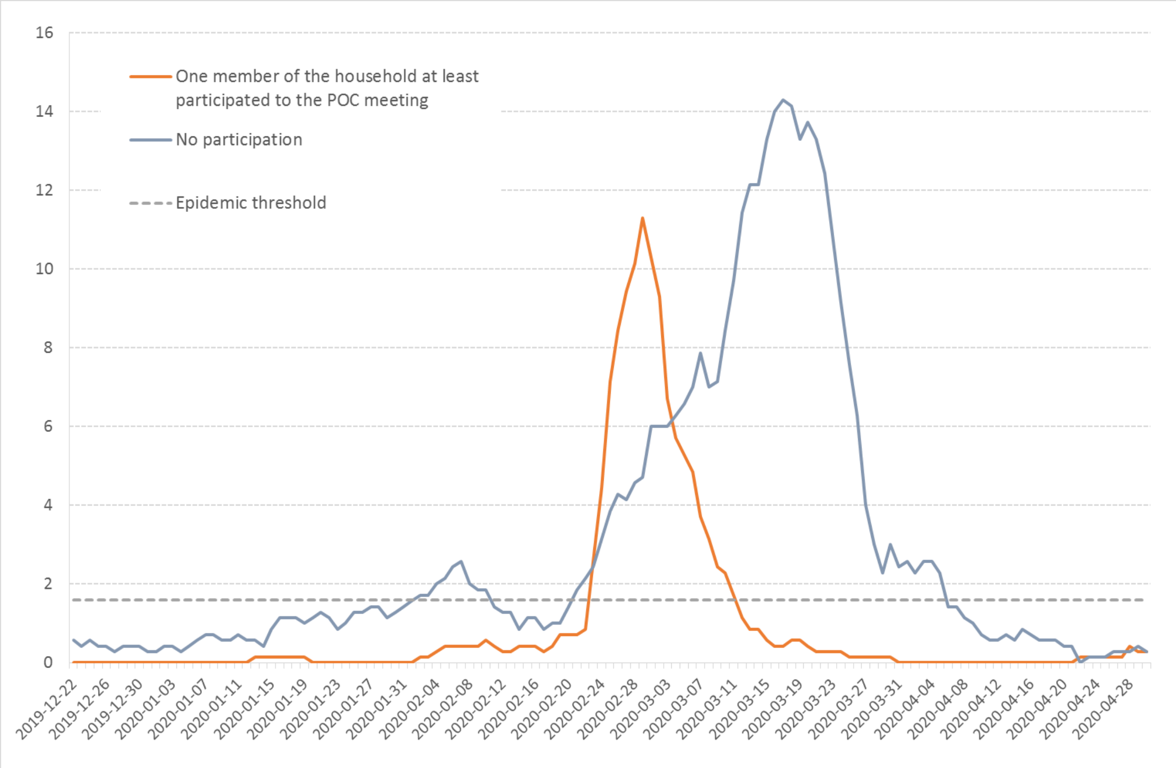

Figure 7. Seven days moving average of the first symptom onset for COVID-19 suspicious cases that documented anosmia among Haut-Rhin households. Orange and grey lines correspond respectively to households with or without participants to the POC gathering in Mulhouse (February 17th to 21th 2020)**.**

4. Discussion

The results presented in the previous section have been obtained from three independent sources: a population-based survey of the households living the Haut-Rhin department, a retrospective analysis of the Diaconat-Fonderie private not for profit hospital emergency care unit in Mulhouse and influenza PCR test data from the Diaconat-Fonderie biological laboratory. They all point toward an early circulation of the COVID-19 in the Haut-Rhin population, much earlier than the first official case identified on February 26th 2020 in the Grand Est region [4] and the epidemic alert on March 3rd [22].

The converging evidences for an epidemic starting end of January 2020 can be summarized as follows:
- the consistency of the epidemic threshold crossings for our three independent data sources
- the speeds of increase of incidence approximately at the same time (between January 26th and January 30th) among Haut-Rhin households (data not shown),
- the continuous flow of patients with COVID-19 clinical signs visiting Diaconat-Fonderie emergency care services in that period
- the significant increase of the number of negative PCR influenza tests performed by Diaconat-Fonderie laboratory
- and the early occurrence of anosmia among Haut-Rhin inhabitants.

Our results identify two waves over the epidemic threshold that has been computed to account for the background noise. The events mainly took place among adults, something specific of COVID-19 epidemic in comparison to the usual winter respiratory syndromes. Focused analysis of anosmia, one of COVID-19 most specific symptoms, does not change our main conclusion. Even if the data collected through the population-based survey include other respiratory syndromes, they trace an outbreak mainly due to COVID-19. Generation interval is close to what is published [12-13] while reproduction number is on the lower band of previously one published [10, 14-15]. This difference is

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certainly due to the fact that our evaluation takes only into account transmission inside families. A possible explanation is the rapid adoption of protective strategies inside families, as soon as the epidemic was known.

Our results show a very different pattern for the households concerned by the POC gathering or not. The curves corresponding to the households related to the POC gathering on figures 6 and 7 are very typical of a unique epidemic process, centered on one maximum. On the same figures, the curves corresponding to the households that are not related to POC gathering show three waves: the first two waves last for 24 days and the epidemic threshold is crossed during the second wave. If we consider stochasticity and heterogeneity in COVID-19 transmission dynamics [24], it shows that the transmission is not very important for most of the persons infected. But the transmission is dominated by a small number of individuals, and is driven by super-spreading events. As long as these super-spreading events are isolated, the epidemic threshold is not reached. But if some super-spreading events are combined in a short period of time, the outbreak is inescapable, progressing in a two waves rhythm that is commonly observed in the case of emerging diseases [25,26].

It is important to note that Diaconat-Fonderie emergency service is not a main line emergency service in Mulhouse (the main line is at the public hospital). It is more activated when the public hospital is overcrowded: this could explain the flat epidemic in January and February, before the generalization of the outbreak, and a highest ratio between the January-February outbreak and the main wave, as compared to population-based data.

Our data confirm the minor role of children in COVID-19 epidemic. Only limited related virus infection was observed in January and February among children below 15 years old. On the other hand, the frequent occurrence of anosmia among COVID-19 suspicious cases, especially for individuals older than 15 years, strongly favors a unique epidemic process.

The population-based survey was also extremely helpful to receive testimonies of people who experienced frequently observed symptoms of COVID-19 as early as December 2019. It also provided the opportunity to get in contact with local physicians who witnessed cases of patients coming for influenza syndromes and whose influenza PCR tests turned out negative as early as end of January 2020. As the survey was opened on April 22nd and closed on June 4th 2020, new cases may have occurred in the households after the survey was filled so the statistics certainly underestimate the number of cases.

Our work has some limits. Possible biases include, for population-based survey, the exclusion of people without access to internet, dependency upon participant declarations, and voluntary participation. Nevertheless, the population of respondents was diverse and included families without symptoms. The studies are retrospective, leading to possible memorization bias for the population-based survey, and bias of missing data for the emergency patient cohort.

We had no biological proofs of infection for the population-based survey, and these proofs came very late in the emergency retrospective study, due to the fact that, in France, we were unable to perform PCR tests at large scale until the end of April 2020. So, respondents to the survey were free to declare symptoms not due to COVID-19. Only 121 (8.0%) of the 1,516 COVID-19 suspicious cases were tested for COVID-19: 34 tests were negative and 87 positive. Results of serological tests were not available when the datasets have been analyzed.

Although Diaconat-Fonderie emergency care services documented probable COVID-19 cases in January, the only biological data used to reach our conclusions are the results of influenza PCR tests. As the hospital laboratory observed a significant increase of negative influenza PCR tests at the end of January 2020, we can hypothesize that the growing number of undiagnosed COVID-19 infected patients resulted in a growing number of negative influenza tests that went unnoticed.

Also, due to privacy rules, information on patient localization is very limited, consisting only in the department where the household lives, excluding therefore a spatial chaining of cases.

To further document the virus history and propagation, collecting statistics on influenza PCR tests from other biological laboratories in Mulhouse and other cities in Alsace should help to document the epidemic onset. Of great interest are the data from the other emergency services in Mulhouse and particularly the public hospital which was in first line during the COVID-19 crisis.

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Imaging data from radiology units should also help trace the early cases that were unseen during the early days of 2020. Further analysis of the population-based survey should help understand if the early COVID-19 suspicious cases had common activities or social networks as households were also invited to document their social contacts.

The role of comorbidities has to be explored. It is also necessary to better understand how the attendants to the POC gathering contributed to the nationwide epidemic spread which lead to a complete French lockdown after march 17th, one month after the beginning of the POC gathering and seven weeks after the outbreak started being significant.

5. Conclusions

Population-based survey and hospital data are strongly consistent and support the hypothesis that the COVID-19 outbreak started as early as the end of January 2020 in the Haut-Rhin department. An efficient sanitary surveillance requires time to collect and analyze data, and to achieve enough convergence to give an alert. An efficient surveillance system requires about one week [27,28]. So, local alert should have taken place around February 4th, but the sanitary alert only occurred on March 3rd. This delay was probably due to the fact that surveillance was mainly based on resuscitation wards data, excluding data from general practitioners as well as data from emergency units, repeating the strategy implemented in 2002-2003 to face the SARS epidemic. However, during the 2002-2003 SARS epidemic, all patients were strongly ill, none was asymptomatic and there was no transmission of the disease during the incubation period. Surprisingly, the information networks created in France to combine all existing sources in order to monitor the seasonal influenza [29] were not activated for COVID-19. The lack of population-based information was crucial, leading to delayed decisions based on insufficient data. The example of the POC gathering is particularly dramatic: data coming from population-based survey and hospital services confirm that the insufficient sanitary surveillance resulted in a gathering that should have been cancelled two weeks before by local sanitary authorities. As about 2,000 attendants to this gathering went back to their home, everywhere in France, cancelling this event could have change the decision of a nationwide lockdown. But the POC gathering did not create or accelerate the outbreak evolution in the Haut-Rhin department. As local events kept being held in a context where the very beginning of the epidemic had remained unseen, the spread was inevitable. Lockdown in Haut-Rhin could have decreased quickly the incidence, but was decided too late.

Of course, it could be said that it is easy to re-write history when you know how it turns. Nevertheless, in order to face the COVID-19 epidemic return, our work emphasizes the need for population-based surveys crossed with emergency units' data, to give alert at the best possible time. Delayed decisions always lead to degraded health policies.

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