Impact of COVID-19 pandemic and the lockdown on invasive meningococcal disease

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Data Note

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Abstract

Objective: Few data are available on the association between SARS-CoV-2 and secondary bacterial infections. Such an association was described for flu and invasive meningococcal disease (IMD). We aimed exploring such a correlation between COVID-19and IMD.

Results: We compared IMD cases received at the French National Reference Centre for meningococci and *Haemophilus influenzae* that are sent as part of the mandatory reporting of IMD. We compared these data during the period 01 January-15 May 2020 to those from the same period in 2019. IMD cases that were associated with respiratory presentations significantly increased in 2020, involved elderly and were due to unusual isolates. However, usual IMD cases due to highly transmissible isolates decreased during the lockdown. Enhancing IMD surveillance and anti-meningococcal vaccination in elderly should to be addressed.

Introduction

Neisseria meningitidis (Nm) is a Gram negative bacterium with airborne inter-human transmission. Nm is carried asymptomatically in the nasopharynx with 10% carriers in the general population (1). However, Nm is also responsible for invasive meningococcal disease (IMD) that is dominated by septicaemia and meningitis (2). Nm is highly diverse due to frequent DNA transfer between isolates followed by recombination and allelic exchanges (3). Genetic typing is crucial for epidemiological surveillance and is performed by DNA sequencing using multilocus sequence typing (MLST) and whole genome sequencing (WGS). The isolates are classified into genetic lineages called clonal complexes (CC) and those that are most frequently associated with IMD are referred to as hyperinvasive CC but other divers CC are more associated with carriage (1). Risk factors to develop IMD include bacterial virulence factors, host factors such as complement deficiencies and environmental factors such as viral infections where IMD can be associated with respiratory manifestations such as bacteremic pneumonia (2, 4). The association of viral infections and secondary bacterial infections has been described such as the association between flu and secondary bacterial infections including IMD (5, 6). During the 1918 pandemic flu, fatality records suggested large impact of secondary bacterial infection (5). Measures impacting airborne transmitted agents such as social and physical distancing are expected to reduce both flu and Nm transmissions and therefore to reduce the incidence of IMD. Indeed, it has been observed one century ago that bed distancing of 3 feet in military barracks reduced the risk of IMD outbreak among new recruits (7).

The implementation of lockdown to control COVID-19 pandemic may therefore interfere with the epidemiology of IMD. Moreover, sepsis was also observed as a common complication during COVID-19 (8). We therefore checked the impact of the lockdown period during the COVID-19 pandemic in France on IMD cases.

Main Text

We screened the database of the French National reference centre for meningococci and *Haemophilus influenzae* (NRCMHi) for biologically confirmed IMD cases (meningococci detected by culture and/or from a normally sterile site) and compared data for the period between 01 January and 15 May of 2019 and 2020. Meningococcal isolates are sent to the NRCMHi for full typing (MLST and WGS) as part of the mandatory reporting of IMD (9). A total of 305 cases of IMD were received at the NRCMHi for the two studied periods (176 in 2019 and 129 in 2020). The number of cases in 2020 decreased in 2020 compared to that of 2019 without any change in the vaccination strategies. This decrease occurred mainly during the lockdown period (16 March 2020-15 May 2020) with 23 IMD cases during the lockdown period in 2020 and 69 IMD cases during the same period in 2019 (P=0.0008). The number of IMD cases did not significantly differ between 2019 and 2020 before the period 16 March-15 May (Figure). Moreover, the decrease seems to mainly involve IMD cases due to serogroups B and C but not IMD due to serogroup Y and other unusual serogroups or non-serogroupable isolates which did not decreased significantly and which proportions increased during the lockdown 2020 (Figure). A special attention was drawn to IMD cases due to serogroup W that was continuing to increase in 2020 before the lockdown. The emergence of highly transmissible and hyperinvasive serogroup W isolates of the clonal complex CC11 in France as in other countries in Europe was reported since 2013 (10, 11). The serogroup W isolates showed a sharp decrease during the lockdown (3 cases in 2020 during the lockdown versus 22 cases during the corresponding period of 2019; P=0.001). Moreover, The decrease contrasted with the increasing number of IMD cases due to serogroup W before the lockdown period in 2020 compared to the same period in 2019 (31 cases before the lockdown in 2020 versus 19 cases for the corresponding period in 2019, P=0.01). The decrease during the lockdown involved mainly the highly transmissible and hyperinvasive isolates belonging to the clonal complex CC11(11).

The MLST typing data were obtained for 288 cases (94% of all IMD cases of this report; 167 for 2019 and 121 for 2020). The distribution of genetic lineages differed mainly during the lockdown period in 2020 compared to the same period in 2019 with lower proportion (although not significantly), of hyperinvasive genetic lineages in 2020 during the lockdown period (45% in 2020 versus 65% for the same period in 2019). This proportion did not differ outside the period corresponding to the lockdown for the two years (Figure). The genotypes that did not changed or even increased in 2020 were CC23 and the isolates belonging to the unassigned clonal complexes (UA). These isolates were frequently of serogroup Y (Supplementary Table). Indeed, IMD due to serogroup Y is frequently observed in elderly and associated with flu and respiratory manifestations such as bacteremic pneumonia (4, 12). Secondary invasive meningococcal infections were reported to occur 7 to 10 days after flu infections (4, 6). Interestingly, sepsis was also observed as a common complication during COVID-19 and occurred at a median of 9.0 days (7.0–13.0) after illness onset although the bacterial aetiology was not explored (8). We therefore explored whether IMD (detectable meningococci in a normally sterile site) was more frequently detected in association with respiratory presentations since the emergence of SARS CoV-2. We screened the NRCMHi database for IMD cases that were associated with “pneumonia” or “bronchopneumonia” as clinical manifestations. A total of 25 cases were detected (7 in 2019 and 18 in 2020 representing 4% and

14% of all cases respectively; *P*=0.005). Several of the 2020 IMD cases were preceded by clinically suspected SARS-CoV-2 infection (Supplementary Table).. These cases were not reported elsewhere.

Age and sex distributions did not differ significantly during this period for the two years for IMD cases without respiratory manifestations (Table). However, the age distribution differed significantly when respiratory presentations were present compared to cases without respiratory manifestations for each year. Indeed, median ages for IMD cases without respiratory manifestations were 21.1 and 20.5 for 2019 and 2020 respectively (Table). These median ages for IMD cases with respiratory manifestations were 82.2 (*P*=0.016) and 70.7 (*P*<0.0001) for the two years respectively) (Table). It is noteworthy that more male were present among cases with respiratory manifestations in 2020 compared to 2019 (Table). Serogroup distribution also differed for cases with respiratory manifestations compared to cases without respiratory presentations. The proportions of serogroups W and Y isolates were significantly higher among IMD cases with respiratory presentations (Table) in both 2019 and 2020 underlining the role of these isolates in respiratory forms of IMD (4, 6). These isolates (in particular serogroup W isolates) belonged mainly to non hyperinvasive genetic lineages (Figure and Supplementary Table).

The lockdown seems to have reduced inter-human meningococcal transmission that was associated with significantly lower number of “usual” IMD cases compared to the corresponding reference period of 2019. This decrease involved hyperinvasive but not the non-hyperinvasive isolates further underlying that the former may show higher transmission rates. Moreover, clinical forms with respiratory manifestations seem to increase on the basis of the non-hyperinvasive isolates that may be carried for longer period although of lower virulence. Our data suggest that the increase in these respiratory forms of IMD was concomitant with the COVID-19 pandemic and was mainly observed among elderly. More investigations are required to explore whether these data reveal an enhanced susceptibility to IMD that may be directly linked to the SARS-CoV-2 infections (13). An additional interference between COVID-19 and IMD may originate from the use anti-complement drugs that are explored to control COVID-19 by lowering complement mediated pro-inflammatory response (14). These drugs such as anti-complement compounded 5 (C5) are known to increase the risk for IMD (15).

Limitations

Several of IMD cases with respiratory presentations corresponded to suspected COVID-19. However, no PCR or serological confirmations of COVID-19 were available for all these cases. Moreover, it is important to underline that or data do support using or not antibiotics in COVID-19 patients as these questions still require more investigations. Finally, our data correspond to a snapshot of the evolution of IMD epidemiology during a short period of time. Long-term surveillance is required. In the meanwhile, our data highlight the need to enhance surveillance of IMD and to consider large anti-meningococcal vaccination and prophylaxis not only in children but also in elderly.

List Of Abbreviations

COVID-19: Corona virus disease 2019.

IMD: Invasive meningococcal disease.

MLST: Multilocus sequence typing.

NRCMHi: National reference centre for meningococci and *Haemophilus influenzae*.

SRAS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

WGS: Whole genome sequencing.

Declarations

Ethics approval and consent to participate

Meningococcal isolates were sent to the National Reference Centres for meningococci and *Haemophilus influenzae* (NRCMHi) for full typing as part of national laboratory surveillance systems and mandatory reporting for invasive meningococcal disease. The use of materials is performed according to the French public health code (Art L1211-2). https://www.lexbase.fr/texte-de-loi/57091269-art-l1211-2-code-de-la-sante-publique.

Consent for publication.

Not applicable.

Availability of data and materials.

Data on all cases and all isolates are provided in the Supplementary Table.

Competing interest.

The authors declare that they have no conflict of interest.

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Authors' contribution.

Both Authors contributed to extraction and analysis of data. MKT drafted the manuscript and both Authors reviewed and agreed on the manuscript.

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Table

Table. Characteristics of IMD cases

		2019	2020	*P**
IMD cases without respiratory presentations		169	111	0.369
Sex ratio (F/M)		96/73 (1.3)	61/50 (1.2)	0.171
Median Age (Interquartile range Q1-Q3) y		21.1 (2.4-54.3)	20.5 (3.3-55.8)	0.739
Serogroup				
	B	84	59	
	C	26	10	
	W	39	27	
	Y	16	14	
	Others	4	2	
		2019	2020	*P**
IMD cases with respiratory presentations		7	18	0.001
Sex ratio (F/M)		6/1 (6)	11/7 (1.6)	0.001
Median Age (Interquartile range Q1-Q3) y		82.2 (33.5-85.7)	70.7 (52.9-93.0)	0.607
Serogroup	B	0	3	
	C	0	1	
	W	2	7	
	Y	4	5	
	Others	1	2	

*Ki squared test

Figures

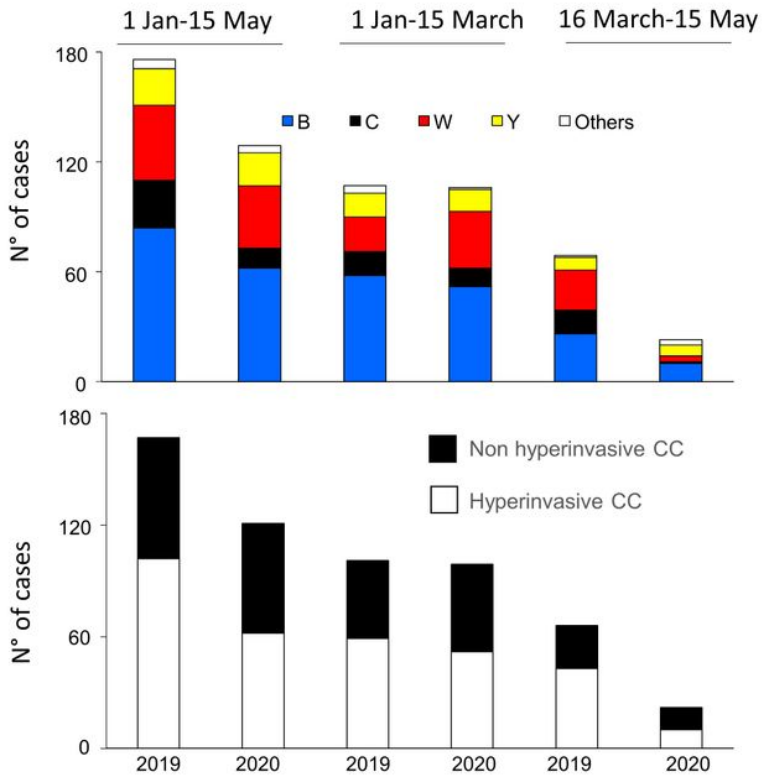

Figure 1

Distribution of isolates responsible for IMD according to serogroups (above) and genetic lineages (down) during the three periods of 2019 and 2020 as indicated. Hyperinvasive CC are CC11, CC32, CC41/44 and CC269 (3).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable.docx