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The rapid rebound of invasive meningococcal disease in France at the end of 2022

Samy Taha, MD, Eva Hong, MS, Mélanie Denizon BS, Michael Falguières BS, Aude Terrade BS, Ala-Eddine Deghmane, PhD, and Professor Muhamed-Kheir Taha, MD, PhD*

Affiliations:

Institut Pasteur, Université Paris Cité, Invasive Bacterial Infections Unit and National Reference Centre for Meningococci and *Haemophilus influenzae*

***Corresponding Author:**

Muhamed-Kheir Taha, MD, PhD
Institut Pasteur,
28 rue du Dr Roux, 75724 Paris cedex 15
France
Tel +33 1 45 68 84 38
Email: muhamed-kheir.taha@pasteur.fr

1 **Research in context**

2 **Evidence before this study**

3 We conducted a PubMed search for articles published in any language until March 07, 2023 to
4 identify previous studies describing the evolution of invasive meningococcal disease (IMD)
5 before and during the COVID-19 pandemic and since the easing of COVID-19 containment
6 measures. The terms “COVID” AND “meningococcal” AND “invasive” were used. The search
7 identified 31 published papers and two preprints, of which 13 were excluded because they did
8 not address the overall evolution of IMD (case reports or evaluation of COVID-19
9 treatment/vaccines). The remaining 18 papers reported a decrease in the worldwide incidence
10 of IMD since the emergence of the COVID-19 pandemic. The data suggest that implementation
11 of stringent COVID-19 infection control measures in 2020 (lockdown, physical and social
12 distancing, and mask wearing) were associated with a substantial decrease in IMD prevalence
13 and vaccination uptake. Several other papers reported lower circulation and carriage of
14 *Neisseria meningitidis*, as well as that of influenzae viruses. A position paper hypothesized that
15 an immunity gap would result from lower natural and vaccine-dependent immunization,
16 possibly leading to a sharp re-emergence of IMD upon the easing of COVID-19 control
17 measures. Two papers from England and Wales and France have reported a trend towards
18 increasing IMD cases since the fall of 2021.

19 **Added value of this study**

20 Our study evaluated the very recent trend in IMD cases during the year 2022 and reports data
21 on the overall evolution of IMD, serogroup-specific trends, age-specific changes, and changes
22 in genotype, as well as the association with influenzae-like syndrome.

23 **Implications of all the available evidence**

24 Understanding the changing epidemiology of IMD offers the possibility to adapt protective
25 measures against IMD, with more relevant schemes, targeted serogroups, and targeted ages.

26 **Abstract**

27 **Background:** Invasive meningococcal disease (IMD) cases declined upon the implementation
28 of non-pharmaceutical measures to control the COVID-19 pandemic. A rebound in IMD cases
29 was feared upon easing these measures.

30 **Methods:** We conducted a retrospective cohort study using the French National Reference
31 Centre Database for meningococci between 2015-2022. We scored serogroups, sex, age groups,
32 and clonal complexes of the corresponding isolates.

33 **Findings:** Our data clearly show a decline in the number of IMD cases for all serogroups and
34 age groups until 2021. This decline was mainly due to a decrease in IMD cases provoked by
35 the hyperinvasive ST-11 clonal complex. However, since the fall of 2021, there has been an
36 increase in IMD cases, which accelerated in the second half of 2022. This rebound concerned
37 all age groups, in particular 16-24 years. The increase in cases due to serogroups B, W, and Y
38 were mainly due to the expansion of isolates of the ST-7460, the clonal complex ST-9316
39 strains and the clonal complex ST-23, respectively.

40 **Interpretation:** IMD epidemiology remains unpredictable and with profound epidemiological
41 changes have been observed. The surveillance of IMD needs to be enhanced using molecular
42 tools. Additionally, vaccination strategies need to be updated to acknowledge recent
43 epidemiological changes.

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45 **Funding:** Institut Pasteur and Santé Publique France.

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47 **Keywords:** invasive meningococcal disease, epidemiology; COVID-19, *Neisseria*
48 *meningitidis*; flu-like syndrome, rebound

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51 **Introduction**

52 Invasive meningococcal disease (IMD) is caused by *Neisseria meningitidis* (Nm), a
53 Gram-negative encapsulated bacterium. IMD has an epidemic spread potential that can be
54 linked to travel and mass gatherings.¹ The notification of IMD cases is therefore mandatory in
55 France under a well-established surveillance system that includes, in addition to mandatory
56 reporting, the sending of isolates to the National Reference Centre for meningococci at the
57 Institut Pasteur, Paris for extensive typing. This system has allowed the detection of several
58 changes in meningococcal epidemiology over the last two decades in France, such as the
59 emergence of IMD of serogroup W, which was associated with the Hajj pilgrimage of 2000,
60 the expansion of isolates belonging to the so called South American-UK strain since 2013, and
61 that of isolates belonging to ST-9316.^{2,3} The surveillance system also allowed detection of the
62 decline in IMD cases in 2020 upon the implementation of nonpharmaceutical control measures
63 to control the COVID-19 pandemic.^{4,5} The global carriage rate of *N. meningitidis* prior to the
64 COVID-19 pandemic was approximately 10% in the general population⁶ but data showed lower
65 carriage rates under containment measures.⁷ The decrease of IMD due to less bacterial
66 circulation may have been strengthened by the reduction in the circulation of influenza viruses,⁸
67 as the spatiotemporal association between flu and IMD has been consistently reported.⁹
68 Moreover, lower vaccine uptake during the COVID-19 pandemic may have further potentiated
69 the decline in anti-meningococcal immunity, referred to as an “immunity debt” or “immunity
70 gap”.¹⁰ A rebound in IMD cases was hypothesized upon the easing of control measures of the
71 COVID-19 pandemic.¹⁰ Indeed, early results from France and England and Wales from the end
72 of 2021 already suggested such a rebound.^{11,12}

73 We therefore aimed to follow up the evolution of IMD cases in 2022 to better describe this
74 rebound and compare this recent evolution to a longer period before the COVID-19 pandemic.
75 We thus studied IMD disease in France during the period of 2015 to 2022 by analysing the

76 number of cases, serogroup and age distribution, genotype distribution, and spatiotemporal
77 association with flu infection.

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101 **Methods**

102 *Data sources*

103 The National Reference Centre for meningococci and *Haemophilus influenzae*
104 (NRCMHi) receives isolates and samples from IMD cases for full phenotyping and genotyping,
105 including whole genome sequencing (WGS). This typing is part of the national surveillance of
106 IMD in France based on mandatory reporting and sending of the isolates for typing to the
107 NRCMHi.¹³ Sending material to the NRCMHi is accompanied by a standardized clinical record
108 form (available at <https://www.pasteur.fr/fr/file/16390/download>) that is completed by the
109 clinician and microbiologist at the hospital where patients are admitted. The records include the
110 age and sex of the patient and clinical and biological findings. Typing of the isolates and
111 samples, including WGS (for culture-confirmed cases) and multilocus sequence typing, MLST,
112 (for non-culture-confirmed samples) were performed as previously described.¹⁴ Data on flu-
113 like syndromes for the 2015-2022 period were extracted from (<https://www.sentiweb.fr/>),
114 which is managed by the *Institut national de la santé et de la recherche medical* (Inserm),
115 Sorbonne University, and Santé Publique France.

116 *Data analysis*

117 Isolates and samples for the 2015-2022 period were extracted from the NRCMHi
118 database. Data were curated for duplicate entries. We used GraphPad PRISM 5.0.1 software
119 for statistical analysis. Chi-square tests were used to compare the observed number of cases to
120 the expected number. The significance level was $P < 0.05$ for single comparisons. Correlation
121 between IMD cases and flu-like syndromes were determined using Spearman's correlation for
122 nonparametric data. Descriptive analysis of the number of cases, age, sex, and serogroup and
123 clonal complex distribution by year was performed. Age groups (<1 years, 1–4 years, 5–9 years,
124 10–14 years, 15–19 years, 20–24 years, 24–44 years, and ≥ 65 years) were used according to
125 those used for the evaluation of vaccination coverage.

126 *Ethics Approval*

127 These data were collected anonymously as part of the mission of the National Reference Centre
128 for meningococci and *Haemophilus influenzae* (NRCMHi) for routine surveillance of IMD and
129 isolate identification and typing. The procedure for collecting samples and information was
130 submitted and approved by the CNIL N°1475242/2011 (*Commission Nationale de*
131 *l'Informatique et des Libertés*) and the requirement for consent was waived.

132 *Role of funding source*

133 The study was funded by the Institut Pasteur and Santé Publique France. The study design, data
134 collection, data analysis, data interpretation, and writing of the report were performed by the
135 authors of the study.

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151 **Results**

152 *Overall characteristics of invasive meningococcal diseases between 2015 and 2022*

153 The NRCMHi received samples for 2,719 cases of IMD between 2015 and 2022 that
154 were screened based on the date of reception by the NRCMHi in the Institut Pasteur (Paris) and
155 the date of isolation (for the cases that were isolated at the end of 2022 and received at the
156 beginning of 2023). This number varied between 106 cases at the lowest point in 2021 and 456
157 cases at the highest point in 2017.

158 The average sex ratio (male/female) was 0.96 and varied non-significantly between 0.78
159 in 2019 and 1.17 in 2022. The average median age for the entire period of the study was 21.75
160 years and varied non-significantly between 19.3 years in 2015 and 27.4 years in 2017. The
161 number of IMD cases per year was stable but declined sharply in 2020 across all serogroups
162 and age groups upon the implementation of COVID-19 control measures. This decline
163 continued into 2021 but showed a significant rebound to almost pre-pandemic levels, except
164 for serogroup C disease (Figure 1). The decrease in the number of cases of IMD due to the non-
165 pharmaceutical control measures against COVID-19 concerned all age groups to a varying
166 extent in 2020 and 2021. The rebound in 2022 was also observed in all age groups but
167 particularly among the 15-19-year age group, for which it surpassed pre-pandemic levels
168 (Figure 2).

169 Genotyping data (clonal complexes, cc) were available for 2,471 cases (91%). The
170 number and proportion of isolates belonging to hyperinvasive cc (cc11, cc32, cc41/44, and
171 cc269) significantly decreased overall from 241 (66.8%) in 2015 to 113 (40.8%) in 2022.
172 ($p < 0.0001$) (Supplementary Figure 1). The most prominent decrease in hyperinvasive cc
173 involved cc11, from 38.4% in 2017 to only 7.2% in 2022.

174 *Characteristics of serogroup B invasive meningococcal diseases between 2015 and 2022*

175 IMD due to serogroup B (IMDB) isolates remained the most prevalent (n=1354)
176 during the study period, representing an average of half of IMD cases, and varied between
177 42% in 2017 and 62% in 2021. The average median age of IMDB patients was 17.4 years and
178 the sex ratio (male/female) was 1.04, with no significant year per year variation. There was a
179 large decline in the number of IMDB cases from the beginning of 2020 after the first
180 lockdown (15 March 2020). The decline was uneven across age groups and was most
181 pronounced among children and adults but not for those 65 years of age or older. However,
182 we observed a decline in this group in 2021. The IMDB cases increased in 2022 in all age
183 groups, except 65 years of age or older. The increase was greatest among the 15-24 year age
184 group, exceeding the number of cases of the pre-pandemic period (Figure 3).

185 We observed several genotypes of NmB isolates, which varied over the study period.
186 Hyperinvasive cc (cc11, cc32, cc41/44, and cc269) were most prevalent and accounted for
187 63% over the entire 2015-2022 period, with no significant variation, between 58% in 2017
188 and 70% in 2015. IMDB cases were strongly associated with cc32, which was detected in an
189 average of 35% of the cases with typing data and which remained stable, despite a lower
190 number of cases during the pandemic period. NmB isolates of cc32 were mostly related to
191 ST-7460. The number and proportion of cases consisting of cc41/44 decreased from 28% in
192 2015 to 9% in 2021 but rebounded to 26% in 2022 (p=0.004) (Supplementary Figure 2).

193 *Characteristics of serogroup C invasive meningococcal diseases between 2015 and 2022*

194 IMDC represented an average of 19% of IMD cases and ranked second for the 2015-2022
195 period (n=512). However, the proportion of IMDC cases drastically decreased from 27% in
196 2015 to 3% in 2021 and 2022. The average median age of IMDC patients over the studied
197 period was 28.5 years but varied from 19.8 years in 2015 to 51.5 in 2020. The average sex ratio
198 (male/female) was 1.22 and did not significantly vary (p=0.4). The reduction of IMDC cases in
199 2017 was observed mainly among patients ≤ 24 years of age, whereas the decrease from the

200 beginning of the COVID-19 pandemic involved all age groups. Only three cases of IMDC were
201 recorded in France in 2021, which increased to eight cases in 2022 (Figure 4), and IMDC ranked
202 fourth in 2022 behind the three other major serogroups B, W, and Y. The genotypes of NmC
203 isolates were dominated by cc11 (91% over the whole study period) and significantly varied
204 over the study period from 96% in 2015 to 25% in 2022 ($p<0.0001$).

205 *Characteristics of serogroup W invasive meningococcal diseases between 2015 and 2022*

206 IMDW represented an average of 15% of cases between 2015 and 2022 and varied from
207 6% in 2015 to 21% in 2019.

208 Over the studied period, the average median age of IMDW patients was 33 years but
209 varied between 20.9 years in 2015 and 57.9 years in 2021. The average sex ratio was 0.95 and
210 did not significantly vary ($p=0.5$).

211 IMDW has been increasing significantly since 2015 in all age groups, including <1-
212 year, but the number of cases decreased drastically during the pandemic. The easing of COVID-
213 19-related restrictions in 2022 was associated with an increase in IMDW cases in several age
214 groups, in particular, among <1 year-olds and adults of 45-64 years of age and exceeded the
215 level of the pre-pandemic period (Figure 5).

216 As for IMDC, cc11 isolates were the most prevalent during the overall study period
217 (68%) and they were the most prevalent in 2018 (84%). However, the proportion of this clonal
218 complex decreased significantly in 2022 to 31% ($p<0.0001$). On the contrary, the increase in
219 other clonal complexes was due to the increase in isolates related to the clonal complex cc9316
220 (Supplementary Figure 3).

221 *Characteristics of serogroup Y invasive meningococcal diseases between 2015 and 2022*

222 IMDY also represented an average of 15% of all IMD cases but varied from 12% in
223 2019 and 2020 to 25% in 2022, when it became the second most prevalent serogroup for the
224 first time in France. In contrast to the other three main serogroups, IMDY was less common

225 under the age of 15 and most common among patients 65 years of age and older, who accounted
226 for an average of 39% of all IMDY cases between the end of 2015 and the end of 2021 (Figure
227 6). The number of cases increased in the over-25 age group from 2015 until the end of 2018,
228 before declining in 2019 until the eve of the COVID-19 pandemic. It is also notable that while
229 IMDY, like other serogroups, experienced a decline in 2020 at the time of the COVID-19
230 pandemic and the resulting public health measures, this decline was quickly offset in 2021
231 among those aged 15-44 years. Furthermore, IMDY cases increased in 2022 for all age groups,
232 including even young children. They also doubled among 15-19 year-olds relative to pre-
233 pandemic levels, with an unprecedented number of cases (Figure 6).

234 Genotypes of NmY were highly heterogenous. They were significantly associated with
235 clonal complex cc23, which was identified in 70% of IMDY cases, with no significant year-
236 per-year variation. However, several variants of cc23 isolates were detected based on WGS,
237 which showed four distinct clades among the NmY cc23 isolates (Supplementary Figure 4).
238 The marked rebound in IMDY was observed in the second half of 2022 and concerned all NmY
239 genotypes, with age-specific clustering (Supplementary Figure 5).

240 Other serogroups and non-groupable isolates were rare, with little variation during the
241 study period (Figure 1).

242 *Spatiotemporal correlation of flu-like syndromes*

243 The marked increase in IMD cases in the second half of 2022, rebound in flu cases,^{15,16}
244 and described spatiotemporal association between the peak of flu-like syndromes and that of
245 IMD cases⁹ prompted us to explore this association during the study period by scoring weekly
246 cases of both diseases. There was a significant correlation between the peaks of flu-like
247 syndrome and a corresponding increase in the number of IMD cases ($p < 0.0001$).

248 The non-pharmaceutical measures to control the COVID-19 pandemic, in particular the
249 national lockdowns, had a clear effect on the number of flu-like syndrome cases and that of

250 IMD cases from the beginning of the first lockdown in March 2020. In 2022, there was a slow
251 increase in the number of flu-like syndrome cases, with a late moderate peak in April 2022,
252 along with an increase in the number of IMD cases. However, the rebound in IMD cases from
253 October 2022 reached an unprecedented peak by the end of 2022, with a total of 56 IMD cases
254 received between the last week of 2022 and the first week of 2023, shortly after a second peak
255 in the number of flu-like syndrome cases in December 2022 (Figure 7).

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275 **Discussion**

276 The changing epidemiology of IMD has been extensively described and reviewed.
277 Changes have been shown to be due to bacterial factors, such as the emergence of new variants,
278 the implementation of vaccines, environmental conditions (flu in temperate countries, dry and
279 windy seasons in sub-Saharan Africa), and mass gatherings.^{1,17} A reduction in meningococcal
280 transmission due to non-pharmaceutical measures has not been previously observed. Such
281 measures, including the wearing of masks, and school closures, the closure of bars and other
282 places of entertainment, and the inhibition of group leisure activities, during the COVID-19
283 pandemic limited inter-human contact under the lockdowns. Indeed, a reduction in IMD cases
284 was almost immediately observed upon the implementation of the first lockdown in several
285 countries in the world.⁴ It is noteworthy that the diminution of circulation of bacterial isolates
286 is expected to reduce not only the incidence of the disease but also that of asymptomatic
287 carriage.⁷ A further decline in IMD may have also occurred subsequent to the reduction in the
288 circulation of influenza viruses,¹⁸ as also suggested by our data, which shows a significant
289 correlation between the number of IMD and flu-like cases. Secondary bacterial infections
290 (including IMD) generally occur a few days after the peak of flu-like cases⁹ and was already
291 described during the flu pandemic of 1918.¹⁹ Such secondary infections were responsible, at
292 least in part, for the high mortality of the flu during that pandemic.²⁰

293 The biological mechanisms underlying such effects could include the facilitation of
294 meningococcal colonization through synergistic damage to the nasopharyngeal epithelium by
295 influenza A neuraminidase⁹ and meningococcus²¹ or altered immune function following
296 influenza infection, with the facilitation of colonization by *N. meningitidis*²².

297 Anti-meningococcal herd immunity was expected to decrease due to lower carriage of
298 *N. meningitidis*. Moreover, lower vaccine uptake during restriction measures^{23,24} was also
299 expected to further reduce anti-meningococcal immunity.

300 In easing social and physical restrictions, transmission circuits can resume, and it was
301 expected that cases would rebound, mainly in the 16-24 year age group, as this group has the
302 highest carriage rate and drives transmission of the disease, in accordance with our data. It is
303 noteworthy that the increase in the 16-24 year age group was observed for all serogroups, in
304 contrast to data from England, which showed a rebound of IMDB among adolescents and young
305 adults following the easing of COVID-19 containment measures.¹² This difference between
306 England and France can be explained by vaccination using the quadrivalent ACWY vaccine in
307 England among adolescents,²⁵ unlike in France. IMDC showed a different evolution during the
308 studied period from that of IMD due to serogroups B, W, and Y. Indeed, the decrease in the
309 number of IMDC cases started in 2017, before the COVID-19 pandemic, and only slightly
310 increased in 2022 after the easing of containment measures. Such evolution of IMDC is
311 consistent with the positive impact of the vaccination strategy against serogroup C in France.¹⁴
312 Our data also suggest that the decrease observed under the containment measures preferentially
313 involved hyperinvasive isolates, in particular those of cc11, which were mainly of serogroups
314 C and W.

315 The immunity gap in the population may raise fears of the emergence of new genotypes.
316 Our data suggest that the rebound was mainly based on isolates related to ST-9316 and ST-
317 7460 for serogroups W and B, respectively. These isolates started to increase in France prior to
318 the COVID-19 pandemic and their rebound may have been potentiated by such an immunity
319 gap and the restriction of historical hyperinvasive isolates belonging to cc11 and other sequence
320 types of cc32. The rebound of IMDY is also consistent with this hypothesis, as it involved
321 several clonal complexes and even several variants within cc23.

322

323 **Conclusion**

324 The containment measures to control the COVID-19 pandemic had a profound impact
325 on IMD epidemiology that resembles the “pressing of a reset button”. Important quantitative
326 and qualitative changes occurred, with the restriction of historical genotypes and the expansion
327 of new genotypes, which may indicate major increases in the burden of IMD. Specific measures
328 may be required, including adapting vaccination strategies based on these epidemiological
329 changes. Targeting adolescents and adults with specific preventive policies, including the
330 promotion of vaccination against the ACWY and B serogroups, are needed. The upcoming mass
331 gathering events that are scheduled in the country (Rugby World Cup in 2023 and Olympic
332 Games in 2024) require attention, as mass gatherings are a risk a factor for IMD and its spread.¹

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Contributors

ST, AED, and MKT: conceptualization, methodology, formal analysis, data curation, writing of the first draft. EH, MD, MF, and AT: microbiological analysis and whole genome sequencing procedures, data curation, and review and editing of the manuscript.

Declaration of interests

MKT performs contract works for the Institut Pasteur funded by GSK, Sanofi and Pfizer outside the submitted manuscript, and MKT and AED have a patent with GSK, 630133. ST was a recipient of a fellowship from Pfizer that had no role in the data collection, interpretation, or writing of the manuscript. The other authors declare no conflicts of interest.

Data sharing

Genomic data are available at <https://pubmlst.org/neisseria/>. Applications for relevant anonymised and aggregated data can be submitted to the corresponding author for data release.

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Figure legends

Figure 1. Evolution of the number of IMD cases by serogroup in France from 2015 to 2022.

All cases and cases per serogroup (B, C, W, and Y) are shown. IMD due to non-groupable or other serogroups were referred to as “others”.

Figure 2. Evolution of the number of IMD cases by year and per age group in France from 2015 to 2022.

Figure 3. Evolution of the number of IMDB cases by year and per age groups in France from 2015 to 2022.

Figure 4. Evolution of the number of IMDC cases by year and per age group in France from 2015 to 2022.

Figure 5. Evolution of the number of IMDW cases by year and per age groups in France from 2015 to 2022.

Figure 6. Evolution of the number of IMDY cases by year and per age group in France from 2015 to 2022.

Figure 7. Invasive meningococcal infections and flu-like syndromes recorded in France by the Reference Center for Meningococci and the Sentinel Network from January 2015 to December 2022. Data are presented on a weekly basis. The number of IMD cases (right axis) and those of influenza-like syndrome (left axis) are represented on the same graph. The national lockdown periods are also shown by blue bars in the figure.

Supplementary Figure 1. Distribution of the clonal complexes identified by year in France from 2015 to 2022. Data are shown for isolates of cc11, other hyperinvasive and other ccs.

Supplementary Figure 2. Repartition of the clonal complexes of IMDB cases by year in France from 2015 to 2022.

Supplementary Figure 3. Evolution of the clonal complexes of IMDW cases by year in France from 2015 to 2022.

Supplementary Figure 4. Distribution of IMDY cases according to clonal complexes identified by year in France from 2015 to 2022. Data are shown for isolates of cc23 and other ccs. Neighbour-net network of all IMD culture-confirmed cases due to NmY cases in France for the 2015–2022 period. The major genotype (cc23) is indicated in the box and the four identified clades are mentioned. The other clonal complexes of NmY isolates are indicated. (A) The IMDY cases for the year 2022 are indicated by black dots and the IMDY cases from 2015 to 2021 are indicated by gray dots. (B) The IMDY cases are indicated by colored dots according to age groups. The genotypes sont as indicated in (A).

Figure 1

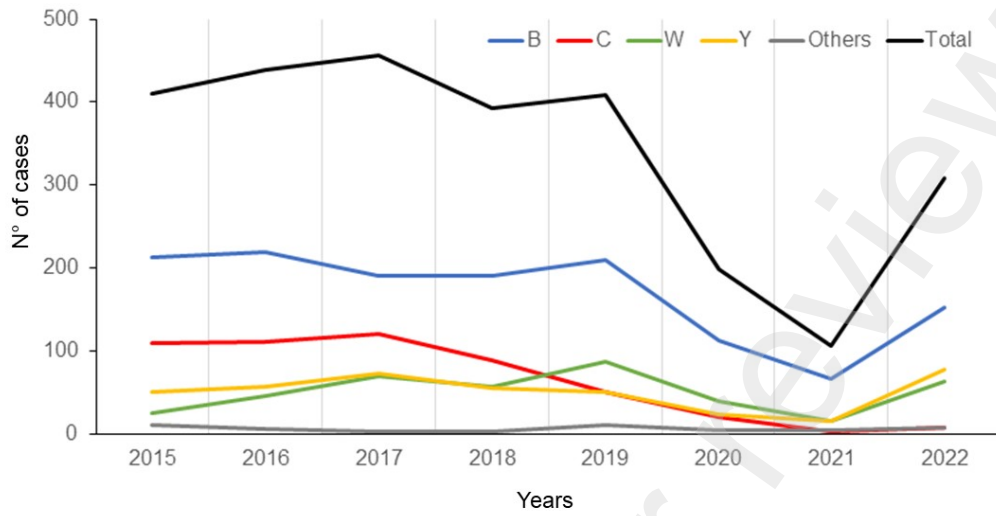


Figure 2

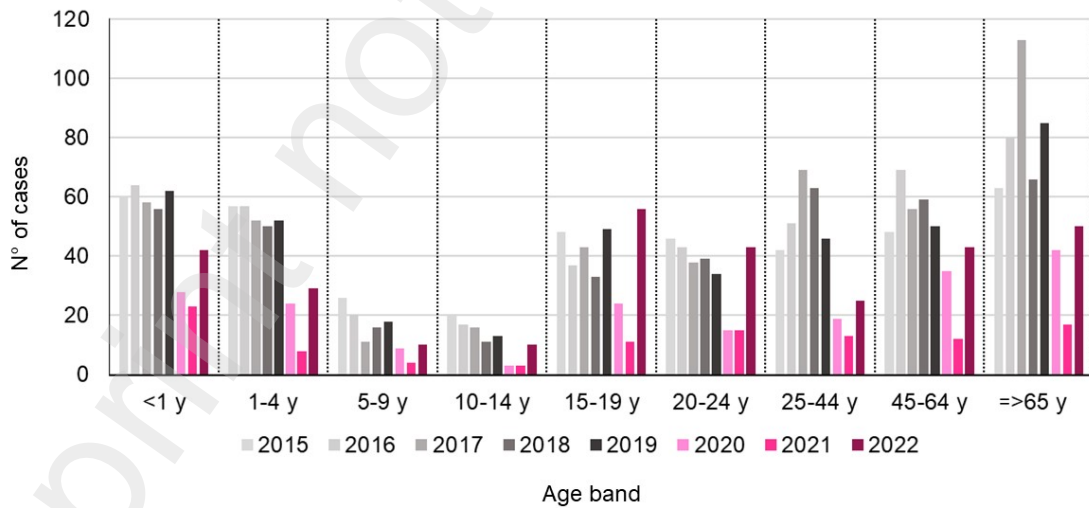


Figure 3

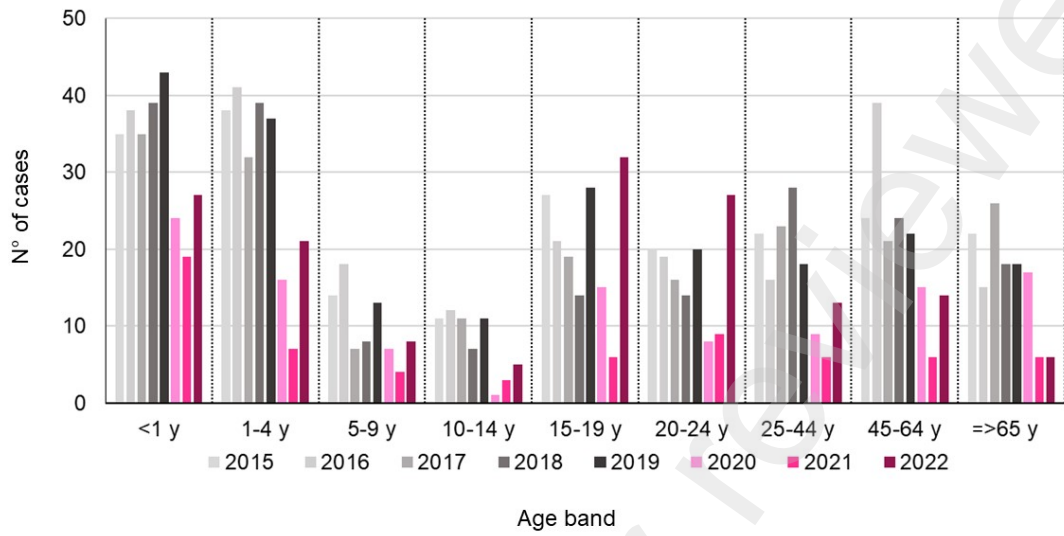


Figure 4

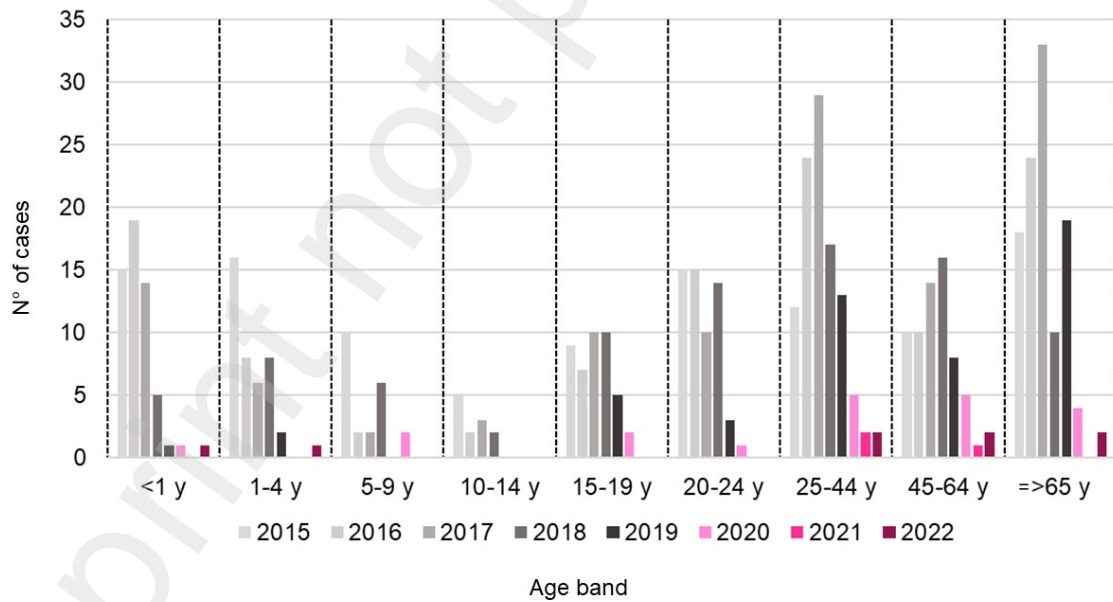


Figure 5

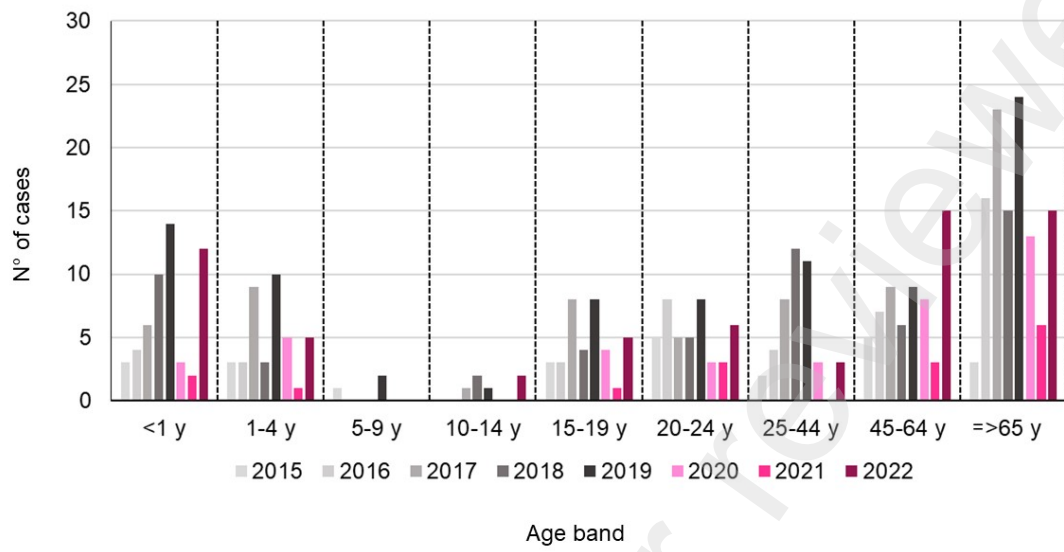


Figure 6

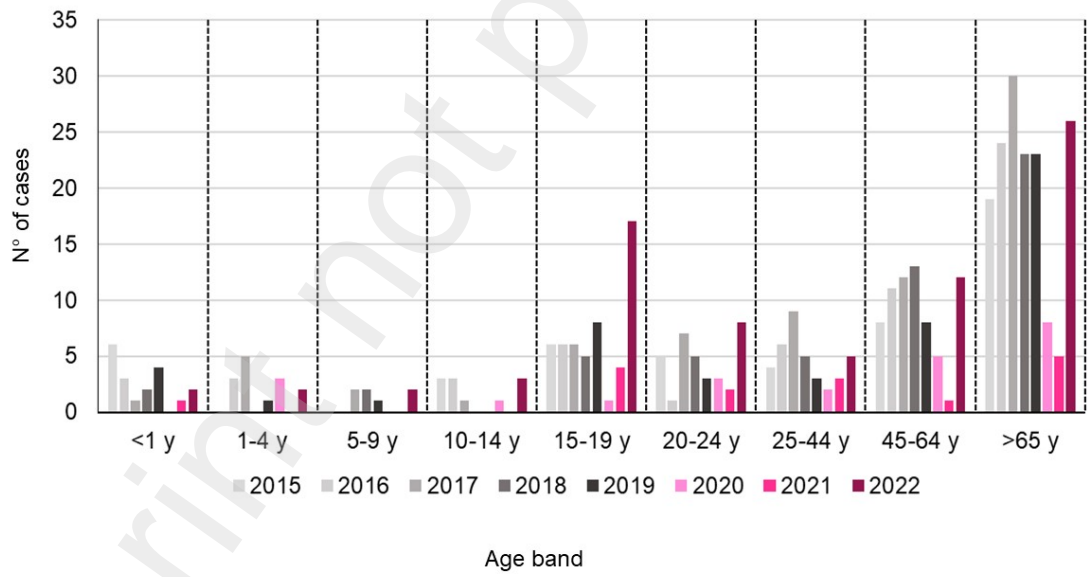
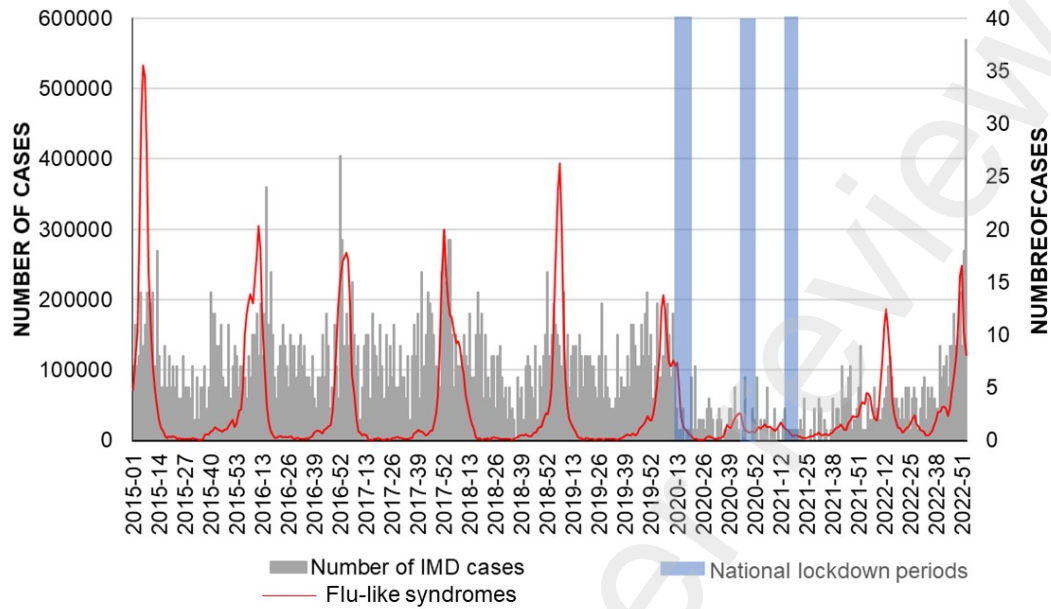
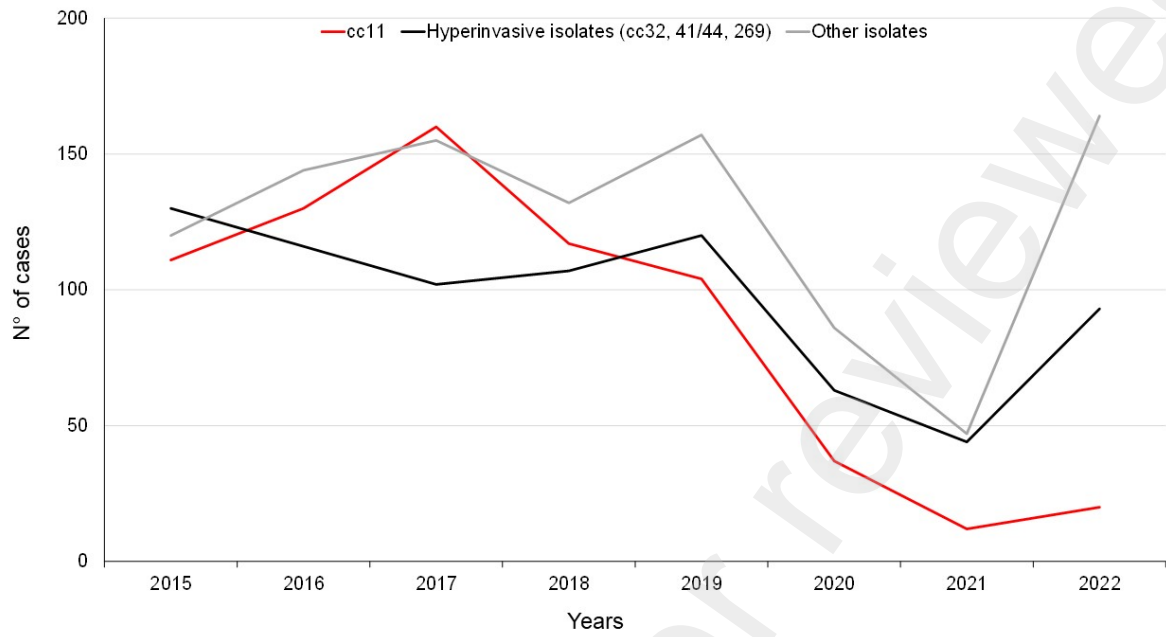


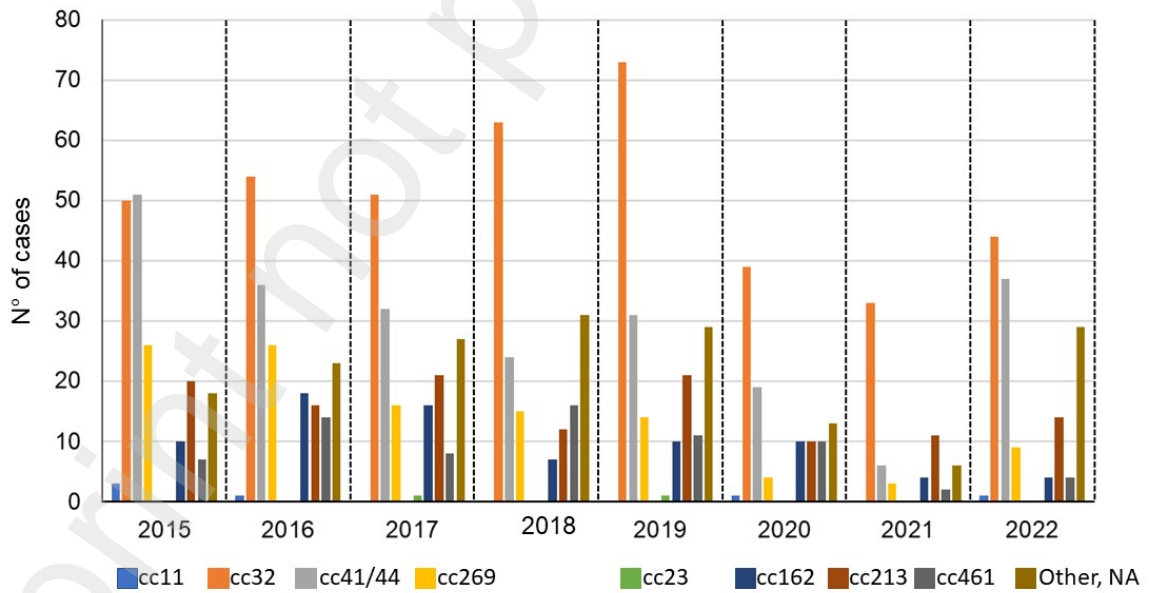
Figure 7



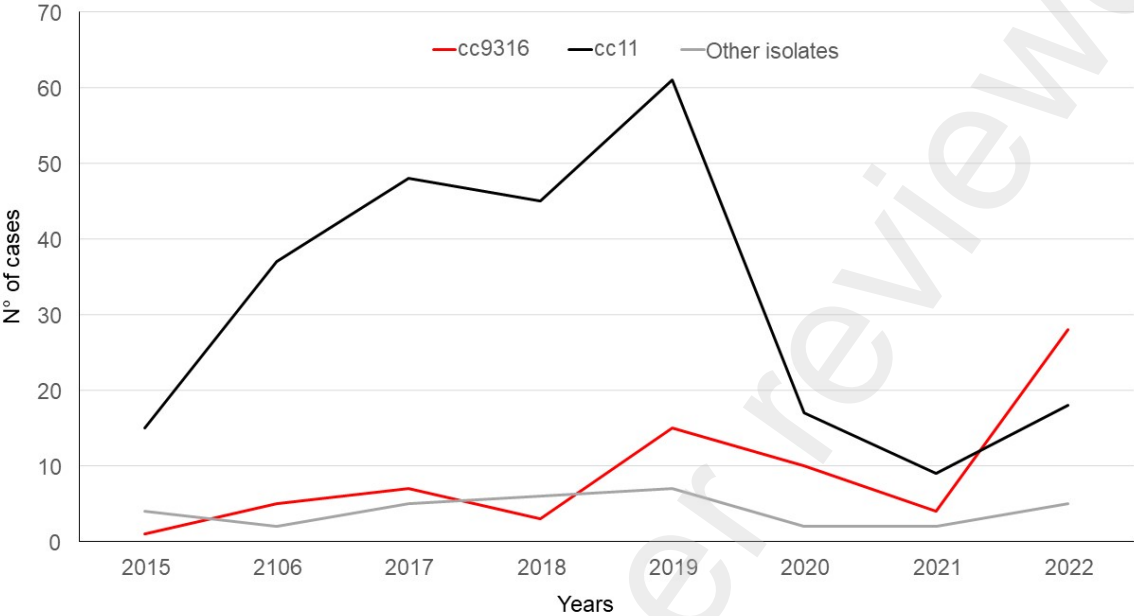
Supplementary Figure 1



Supplementary Figure 2



Supplementary Figure 3



Supplementary Figure 4

