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Control of common viral epidemics but not of SARS-CoV-2 through the application of hygiene and distancing measures

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7

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26 **ABSTRACT**

27 **Background** We systematically survey respiratory and gastrointestinal infections of viral
28 origin in samples sent to our university hospital institute in Marseille, southern France. Here,
29 we evaluated whether the measures implemented to fight COVID-19 had an effect on the
30 dynamics of viral respiratory or gastrointestinal infections.

31 **Methods** We analysed PCR performed and positive for the diagnoses of viral respiratory and
32 gastrointestinal infections over five years (January 2017-February 2021). Data were collected
33 from our epidemiological surveillance system (MIDaS). Dates and contents of French
34 measures against SARS-CoV-2 were collected from: [https://www.gouvernement.fr/info-](https://www.gouvernement.fr/info-coronavirus/les-actions-du-gouvernement)
35 [coronavirus/les-actions-du-gouvernement](https://www.gouvernement.fr/info-coronavirus/les-actions-du-gouvernement).

36 **Results** Over the 2017-2021 period, 990,364 analyses were carried out for respiratory
37 infections not including SARS-CoV-2, 511,381 for SARS-CoV-2 and 27,719 for
38 gastrointestinal infections. During winter 2020–2021, when the most restrictive lockdown
39 measures were in place in France, a marked decrease of infections with influenza viruses (one
40 case versus 1,839-1,850 cases during 2017-2020 cold seasons) and with the RSV (56 cases
41 versus 988-1,196 cases during 2017-2020 cold seasons) was observed, demonstrating the
42 relative effectiveness of these measures on their occurrence. SARS-CoV-2 incidence seemed
43 far less affected. Rhinoviruses, parainfluenza 3 virus, and the NL63 coronavirus remained at
44 comparable levels. Also, the norovirus winter season positivity rates decreased continuously
45 and significantly over time from 9.3% in 2017–2018 to 2.0% in 2020–2021.

46 **Conclusion** The measures taken to control COVID-19 were effective against lower
47 respiratory tract infections viruses and gastroenteritis agents, but not on the agents of the
48 common winter cold and SARS-CoV-2. This suggests that more specific measures to prevent
49 COVID-19 and upper respiratory tract infections need to be discovered to limit the spread of
50 this epidemic.

51

52 **Key words:** Coronavirus; respiratory infections; gastrointestinal infections; SARS-CoV-2;

53 MIDaS

54

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61

62 **Competing interests**

63 The authors have no competing interests. Funding sources had no role in the design
64 and conduct of the study; collection, management, analysis, and interpretation of the data; and
65 preparation, review, or approval of the manuscript.

66

67 **Ethics**

68 All data have been generated as part of the routine work at Assistance Publique-
69 Hôpitaux de Marseille (Marseille university hospitals), and this study results from routine
70 standard clinical management. The study was approved by the ethical committee of the
71 University Hospital Institute Méditerranée Infection (N°: 2020-029 and 2022-015). Access to
72 the patients’ biological and registry data issued from the hospital information system was
73 approved by the data protection committee of Assistance Publique-Hôpitaux de Marseille
74 (APHM) and was recorded in the European General Data Protection Regulation registry under
75 number RGPD/APHM 2019-73.

76 **TEXT**

77

78 **BACKGROUND**

79 In December 2019, a new coronavirus named SARS-CoV-2 (for severe acute
80 respiratory syndrome coronavirus 2) emerged in Wuhan, Hubei region, China. It spread
81 rapidly to the rest of the world and was declared a pandemic in March 2020 [1]. As of
82 February 09, 2022 402,064,265 SARS-CoV-2 cases and 5,768,927 patient deaths from
83 COVID-19 (for coronavirus disease 2019) were reported [2]. SARS-CoV-2 variants have
84 emerged since summer of 2020 [3,4] and have each determined an epidemic of variable
85 intensity and duration. These variants have been revealed to be associated with differences
86 regarding viral loads, transmissibility, and clinical severity and they have been involved in
87 various degrees of escape to immunity elicited by vaccination or infection [5-8]. The
88 dynamics of SARS-CoV-2 epidemics at national and global scales proved to be unpredictable.

89 In order to reduce the spread of SARS-CoV-2, the French government decided to take
90 several health and social measures. This initially involved repeated risk prevention messages
91 on the use of protective measures including regularly hand washing with soap or alcohol-
92 based hand gel, social distancing of two meters between individuals, and wearing a mask [9].
93 These measures had already been used in prevention campaigns for other viruses, particularly
94 respiratory viruses such as influenza [10,11]. More restrictive measures on movement were
95 also taken, with the implementation of a number of lockdowns and curfews (Decree No.
96 2020–260; Decree No. 2020–1310) [12,13]. Thus, in addition to the fight against COVID-19,
97 these measures may also be effective at controlling other communicable respiratory and
98 digestive diseases.

99 At the Hospital University Institute Méditerranée Infection (IHU-MI), the work of the
100 virology and microbiology laboratory is monitored by a collection and surveillance system

101 known as MIDaS (for Méditerranée Infection Data Warehousing and Surveillance) [14,15].
102 This system enables us to monitor respiratory and digestive virus infections on a weekly
103 basis, and has included COVID-19 since its emergence in France [16]. The objective of this
104 paper was to analyse the epidemiological curves of respiratory and gastrointestinal viruses
105 since the emergence of SARS-CoV-2 and to evaluate if they changed under the measures
106 implemented against COVID-19 in France by comparing them during cold seasons over the
107 past five years.

108

109 **MATERIALS AND METHODS**

110 *Surveillance system*

111 Since 2003, the work of our clinical microbiology laboratory has involved massive
112 and unbiased monitoring of all clinical samples received for testing bacteria, viruses, parasites
113 and fungi (16,17). This followed recommendations one of the authors (DR) [18] made to the
114 French government in 2003 to set up surveillance systems of any abnormal events related to
115 infectious diseases based on our laboratory data, including through syndromic surveillance.
116 These are the only laboratories to diagnose infections for all public university hospitals
117 (Assistance Publique - Hôpitaux de Marseille (AP-HM)) in Marseille, which has a total of
118 3,288 beds with nearly 125,000 admissions and one million consultations per year. Our
119 laboratory conducts approximately eight million tests every year.

120 Since 2013 when the IHU-MI was established, our surveillance tools have expanded
121 further and have improved through our unique MIDaS (for Méditerranée Infection Data
122 Warehousing and Surveillance) collection and surveillance system, which consists of five
123 sub-systems [14]. We systematically collect all laboratory data (samples, tests, positive
124 diagnoses) from the Nexlab laboratory management system. All microbiological analysis
125 results (sample identification, requesting department, date, sampling, analysis, result,

126 antibiotic susceptibility testing, antibiotic resistance phenotype, bacterial co-identifications)
127 and patient information (anonymised patient identification, age, sex, home postal code,
128 anonymised hospital stay identification, date of stay within a department, death) are then
129 deposited in a dedicated data warehouse. All samples, tests and infectious agents are
130 monitored on a weekly basis throughout the year. MIDaS automatically detects any
131 aberrations in the statistical signal using the cumulative sum control chart (CUSUM)
132 algorithm and triggers alarms [19]. These alarms are discussed during a weekly
133 epidemiological staff meeting, which includes epidemiologists, biologists, infectiologists and
134 pharmacists.

135 Respiratory and gastrointestinal samples and infectious agents are some of the items
136 surveyed. Generally speaking, respiratory and gastrointestinal viruses are diagnosed in our
137 laboratory using commercial or in-house real-time Polymerase Chain Reaction (qPCR) tests
138 and adopting a syndromic approach using multiplex tests or simplex tests. These include
139 influenza A and B viruses, respiratory syncytial virus (RSV), rhinoviruses, enteroviruses,
140 adenoviruses, metapneumovirus, endemic coronaviruses (OC43, NL63, E229 and HKU1),
141 parainfluenza viruses 1 to 4 (HPIV1 to HPIV4) and SARS-CoV-2, over a period of time from
142 January 2017 to February 2021. For the detection of SARS-CoV-2 RNA, we used in house
143 RT-PCR procedures previously described [20]. To detect the other respiratory viruses, we
144 used the FTD Respiratory pathogens 21 (Fast Track Diagnosis, Luxembourg), the Biofire
145 FilmArray Respiratory panel 2 plus (BioMérieux, Marcy-l'Etoile, France), the Respiratory
146 Multi-Well System r-gene (Argene, BioMérieux), or the GeneXpert Xpert Flu/RSV (Cepheid,
147 Sunnyvale, CA) assays [21].

148 Data on diagnoses of influenza A and B viruses were also collected from a private
149 clinical microbiology and virology laboratory through the PACASurVE (for the Provence
150 Alpes-Côte d'Azur Surveillance Epidemiological System) network that extents our

151 surveillance system to private medical biology laboratories located in the Marseille
152 geographical area [22]. These diagnoses were reached by an immunochromatographic assay
153 in 2017 and then switched to the GeneXpert Flu/RSV assay between 2018 and 2021.

154 The gastrointestinal viruses diagnosed included adenoviruses, rotaviruses, sapoviruses,
155 noroviruses and astroviruses. The tests were performed using the Fast Track Diagnosis (FTD)
156 viral gastroenteritis pathogens assay.

157 *Statistical analyses*

158 In order to better understand the evolution of respiratory and gastrointestinal virus
159 infections over time, the proportion of positive results between October and the end of
160 February were compared for each virus for the 2017–2018, 2018–2019, 2019–2020 and
161 2020–2021 seasons. These evolutions were analysed using the log-linear model, and the
162 Fisher and Chi-square tests for point comparisons with a two-tailed statistical significance
163 threshold of 0.05. Statistical analyses were done using R version 4.1 [23].

164 *Government measures and policies*

165 Measures taken by the French government in the fight against the spread of SARS-
166 CoV-2 and dates these measures were implemented were collected from the government
167 website (<https://www.gouvernement.fr/info-coronavirus/les-actions-du-gouvernement>).

168

169 **RESULTS**

170 *Diagnoses of respiratory viral infections at IHU-MI from 2017 to 2021*

171 Over a period of five years (January 2017 to February 2021), 990,364 analyses were
172 performed for common respiratory viruses, with 37,915 positive results. Most of these cases
173 were due to influenza viruses (influenza A virus, 6,544; influenza B viruses, 2,459) followed
174 by rhinoviruses (7,379), RSVs (3,846), adenovirus (1,991), metapneumoviruses (1,482),
175 enteroviruses (790), HKU1 coronavirus (424), NL63 coronavirus (421), OC43 coronavirus

176 (227), E229 coronavirus (87), HPIV3 (340), HPIV4 (68), HPIV2 (18) and HPIV4 (9) (Table
177 1).

178 **Table 1** – Tests performed and positive for PCR detection of respiratory viruses in 2017, 2018, 2019, 2020 and 2021 at Hospital University Institute

179 Méditerranée Infection.

	2017	2018	2019	2020	2021	Total 2017-2021	2017	2018	2019	2020	2021	Total 2017-2021						
	N	N	N	N	N		N	%	N	%	N		%	N	%	N	%	
Adenovirus	5,656	14,881	17,636	32,237	5,283	75,693	160	2.8	449	3.0	652	3.7	600	1.9	130	2.5	1,991	2.6
Common coronaviruses	2,395	3,773	8,211	32,237	5,283	51,899	70	2.9	110	2.9	231	2.8	998	3.1	276	5.2	1,685	3.2
HCoV 229E	2,395	3,773	8,211	11,739	5,283	31,401	0	0.0	0	0.0	0	0.0	84	0.7	3	0.1	87	0.3
HCoV HKU1	2,395	3,773	8,211	11,736	5,283	31,398	0	0.0	0	0.0	0	0.0	423	3.6	1	0.0	424	1.4
HCoV NL63	3,791	3,773	8,211	11,739	5,283	32,797	0	0.0	0	0.0	0	0.0	252	2.1	169	3.2	421	1.3
HCoV OC43	9,007	3,773	8,211	11,74	5,283	38,014	0	0.0	0	0.0	0	0.0	175	1.5	102	1.9	277	0.7
Enterovirus	4,362	8,933	17,649	32,237	5,283	68,464	36	0.8	164	1.8	279	1.6	307	1.0	4	0.1	790	1.2
Influenza virus	12,992	14,856	17,844	32,237	5,283	83,212	1,737	13.4	1,708	11.5	2,427	13.6	3,119	9.7	0	0.0	8,991	10.8
Influenza A virus	12,608	14,859	17,847	32,237	5,283	82,834	1,525	12.1	936	6.3	2,397	13.4	1,686	5.2	0	0.0	6,544	7.9
Influenza B virus	13,088	14,858	17,847	32,237	5,283	83,313	222	1.7	772	5.2	30	0.2	1,435	4.5	0	0.0	2,459	3.0
Metapneumovirus	7,654	14,75	17,622	32,237	5,283	77,546	230	3.0	325	2.2	445	2.5	462	1.4	20	0.4	1,482	1.9
Human parainfluenza virus	9,007	3,771	8,268	32,237	5,283	58,566	15	0.2	200	5.3	438	5.3	129	0.4	322	6.1	1,104	1.9
HPIV1	3,791	3,771	8,268	9,268	5,283	30,381	0	0.0	0	0.0	0	0.0	9	0.1	0	0.0	9	0.0
HPIV2	3,791	3,771	8,268	9,268	5,283	30,381	0	0.0	0	0.0	0	0.0	17	0.2	1	0.0	18	0.1
HPIV3	2,395	3,771	8,268	9,268	5,283	28,985	0	0.0	0	0.0	0	0.0	41	0.4	299	5.7	340	1.2
HPIV4	2,395	3,771	8,268	9,268	5,283	28,985	0	0.0	0	0.0	0	0.0	48	0.5	20	0.4	68	0.2
Rhinovirus	4,305	14,057	17,637	32,237	5,283	73,519	401	9.3	1,771	12.6	2,264	12.8	2,494	7.7	449	8.5	7,379	10.0
Respiratory syncytial virus	12,756	14,849	17,851	32,237	5,283	82,976	923	7.2	1,024	6.9	1,347	7.5	498	1.5	54	1.0	3,846	4.6
SARS-CoV-2	710	0	0	420,12	90,551	511,381	0	0	0	0	0	0	26,723	6.4	8,236	9.1	34,959	6.8

180 HCoV, human coronavirus; HPIV, human parainfluenza virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

181

182

183 Slight yearly variations were observed from 2017 to 2019 with regards to the
184 respective prevalence of these viruses (Fig. 1). In 2017, the influenza A virus was the most
185 frequently identified respiratory viral agent (12.1%), followed by rhinovirus (9.3%) and RSV
186 (7.2%). In the same year, 1.7% of samples tested for influenza B virus were positive for this
187 agent. In 2018, the rhinovirus was the most commonly diagnosed (12.6%), compared to 6.9%
188 for RSV, 6.3% for influenza A virus and 5.2% for influenza B virus. 2019 was comparable to
189 2017 in terms of the ranking of respiratory viruses, although the proportions of respiratory
190 viruses' diagnoses were higher in 2019. The intensity of the epidemic peak for each of these
191 respiratory viruses therefore changed over the years, as did the date upon which they appeared
192 (Fig. 1).

197 Since February 2020, 511,381 samples have been analysed for SARS-CoV-2 and
198 34,959 tested positive (6.8%). Of 420,120 samples tested for SARS-CoV-2 in 2020, 6.4% (N
199 = 26,723) were positive while in 2021, out of 90,551 samples, 9.1% were positive. The
200 government introduced several restrictive measures in an attempt to mitigate the spread of
201 SARS-CoV-2 and to control the epidemic as effectively as possible. A first lockdown was
202 imposed between 17 March 2020 and 11 May 2020, recommendations have been in place on
203 wearing masks in enclosed spaces (particularly in the workplace) since 20 July 2020, a curfew
204 was introduced between 8pm and 6am between 17 October 2020 and 28 October 2020, a
205 second lockdown took place between 29 October 2020 and 15 December 2020, and a new
206 curfew was introduced on 16 January 2021 from 6pm to 6am. In addition to these actions,
207 individual preventive measures have also been recommended, including hand washing with
208 soap or alcohol-based hand gel, a distance of 1.5 metres between individuals and the
209 promotion of remote working. In 2020, the proportion of positive tests dramatically decreased
210 to 7.7% for rhinovirus, 5.2% for influenza A, 4.5% for influenza B and 1.5% for RSV. This
211 was also the case for the first two months of 2021, where no cases of influenza A or B were
212 observed. In the first two months of 2021, the most frequently diagnosed virus was SARS-
213 CoV-2 (9.1%), followed by rhinovirus (8.5%), parainfluenza virus (6.1%, mainly HPIV3:
214 5.7%) and other endemic coronaviruses (5.2%, mainly NL63: 3.2%). The same results were
215 observed from a private clinical microbiology and virology laboratory through the
216 PACASurVE network (Table 2).

217 **Table 2** – Results for influenza A virus and influenza B virus by year from a private clinical microbiology and virology laboratory through the
 218 PACASurvE (for the Provence Alpes-Côte d’Azur Surveillance Epidemiological System) network.
 219

Year	Number of samples tested	Influenza A virus diagnoses		Influenza B virus diagnoses	
		N	%	N	%
2017	547	67	12.2	2	0.4
2018	1,111	63	5.7	29	2.6
2019	2,410	681	28.3	32	1.3
2020	2,625	500	19.0	357	13.6
2021	106	0	0.0	1	0.9

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223 *Comparison of winter seasons for respiratory viral infections*

224 In order to avoid the Simpson effect, which is the presence of second order
225 interactions between all factors that inverse statistical relations when data are pooled [24], we
226 compared results during cold seasons (from October to mid-February). Over the last four such
227 seasons, the most significant variations were observed for influenza A virus, with a positivity
228 rate of 11.3% of the 9,819 tested samples (N= 1,106 cases) during the 2017–2018 winter
229 season, which increased to 18.6% of the 10,973 tested samples (N= 2,042 cases) during the
230 2018–2019 season, dropped to 9.6% of the 11,711 tested samples (N= 1,125 cases) in 2019–
231 2020 and accounted for 0% of the 8,786 tested samples in 2020–2021 (Fig. 1, Table 3). As of
232 24 February 2021, no cases of influenza A virus had been diagnosed during the 2020–2021
233 winter season. Influenza B virus is also absent for the 2020–2021 winter season, although this
234 had already been observed in 2018–2019. RSV also showed a considerable decrease in the
235 proportion of positive cases, reaching 0.6% (56 cases in 2020–2021 compared to between 9.4-
236 10.9% (N= 988-1,196 cases) in the other three cold periods (p-value <0.001).

237 Metapneumovirus and enterovirus had a less marked decrease (N= 21 and 9 in 2020–2021 vs
238 N= 339 and 375 in 2019–2020, respectively; p-value < 0.001). The adenovirus positivity rate
239 has remained relatively constant over time, at about 3% (p-value > 0.05), as was the case for
240 endemic coronaviruses in 2017–2018 and 2018–2019. A significant decrease was
241 nevertheless observed in 2020–2021 (p-value < 0.001). Rhinovirus exhibited a significantly
242 higher positivity rate in 2020–2021 (12.9%) compared to 2017–2019 and 2018–2019 (9.9%
243 and 10.9% respectively, p-value < 0.001). The positivity rate of the HPIV3 parainfluenza
244 virus increased from 0.1% (N = 4) in 2019–2020 to 3.7% (N = 324) in 2020–2021 (p-value <
245 0.001).

246 **Table 3** - Tests performed and positive for PCR detection of respiratory viruses, during the same cold months in 2017–2018, 2018–2019,
 247 2019–2020 and 2020–2021

Viruses	Tests				Positive										
	2017-2018	2018-2019	2019-2020	2020-2021	2017-2018			2018-2019			2019-2020			2020-2021	
	N	N	N	N	N	%	p value	N	%	p value	N	%	p value	N	%
Adenovirus	8,876	10,831	11,687	8,786	262	3.0	0.51	416	3.8	0.006	355	3.0	0.74	274	3.1
Common coronaviruses	387	1,123	11,556	8,786	13	3.4	0.97	37	3.3	0.96	617	5.3	<0.001	292	3.3
HCoV 229E	387	1,123	6,357	8,786	0	0.0	1	0	0.0	1	31	0.5	<0.001	5	0.1
HCoV HKU1	387	1,123	6,357	8,786	0	0.0	1	0	0.0	1	236	3.7	<0.001	1	0.0
HCoV NL63	387	1,123	6,357	8,786	0	0.0	0.006	0	0.0	<0.001	114	1.8	0.49	171	1.9
HCoV OC43	657	1,123	6,357	8,786	0	0.0	0.003	0	0.0	<0.001	56	0.9	0.02	114	1.3
Enterovirus	900	10,83	11,688	8,786	13	1.4	<0.001	153	1.4	<0.001	375	3.2	<0.001	9	0.1
Influenza virus	9,819	10,973	11,711	8,786	1,839	18.7	<0.001	2,044	18.6	<0.001	1,85	15.8	<0.001	1	0.0
Influenza A virus	9,819	10,973	11,711	8,786	1,106	11.3	<0.001	2,042	18.6	<0.001	1,125	9.6	<0.001	0	0.0
Influenza B virus	9,819	10,973	11,711	8,786	743	7.6	<0.001	2	0.0	1	727	6.2	<0.001	1	0.0
Metapneumovirus	8,873	10,83	11,687	8,786	315	3.6	<0.001	258	2.4	<0.001	339	2.9	<0.001	21	0.2
Human parainfluenza virus	657	1,127	11,605	8,786	4	0.6	<0.001	42	3.7	0.68	226	1.9	<0.001	350	4.0
HPIV1	387	1,127	6,001	8,786	0	0.0	1	0	0.0	1	2	0.0	0.16	0	0.0
HPIV2	387	1,127	6,001	8,786	0	0.0	1	0	0.0	1	4	0.1	0.17	1	0.0
HPIV3	387	1,127	6,001	8,786	0	0.0	<0.001	0	0.0	<0.001	4	0.1	<0.001	324	3.7
HPIV4	387	1,127	6,001	8,786	0	0.0	0.62	0	0.0	0.1	14	0.2	0.73	23	0.3
Rhinovirus	5,15	10,833	11,683	8,786	511	9.9	<0.001	1,194	11.0	<0.001	1,42	12.2	0.11	1,134	12.9
Respiratory syncytial virus	9,912	10,973	11,707	8,786	988	10.0	<0.001	1,196	10.9	<0.001	1,104	9.4	<0.001	56	0.6
SARS-CoV-2	183	0	5,628	244,31	0	0.0	-	0	0.0	-	0	0.0	-	20748	8.5

248 HCoV, human coronavirus; HPIV, human parainfluenza virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

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250

251 *Total gastrointestinal viral infections at IHU-MI in 2017–2021*

252 Between 2017 and 2021, 27,719 tests were performed resulting in approximately
253 1,098 diagnoses of gastrointestinal infections (Table 4). Rotavirus (5.6% for 6,612 samples
254 analysed) was the most frequently diagnosed gastrointestinal virus over the study period,
255 followed by adenovirus (5.2% for 6,227 samples analysed) and norovirus (4.2% for 7,791
256 samples analysed). As was previously observed for respiratory viruses, the intensity of the
257 epidemic peak as well as the date of its onset varied over the years (Fig. 2). In 2017, 2018 and
258 2020, adenovirus was the most frequently identified virus (5.0%, 7.6% and 4.1% respectively)
259 while in 2019, rotavirus (8.6%) was the virus most commonly identified.

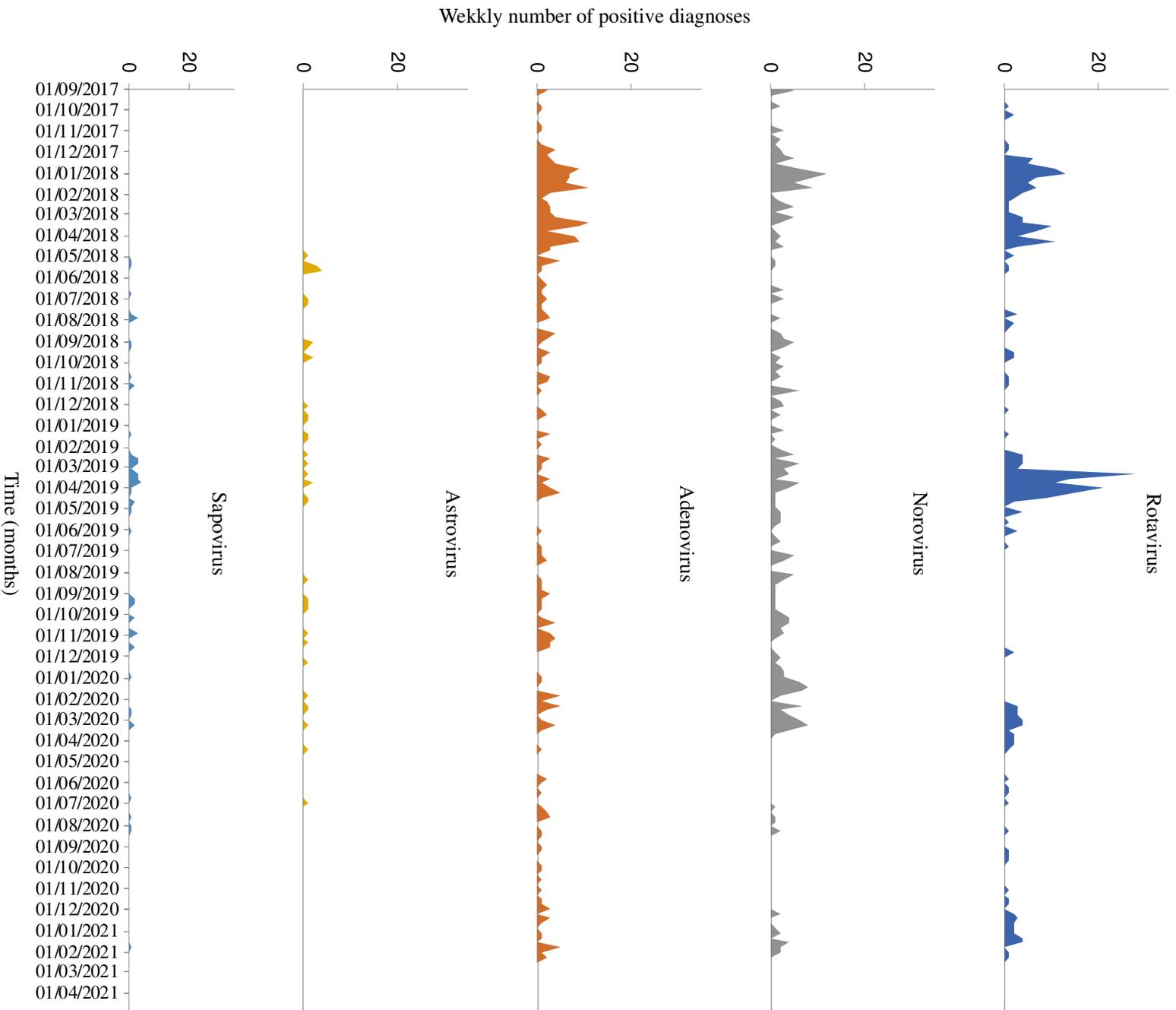
260 In the first two months of 2021, of the 255 samples analysed, rotavirus was again the
261 most frequently identified virus (N = 12, 4.7%) followed by norovirus (N = 10, 3.9%) and
262 adenovirus (N = 10, 3.9%).

263 **Table 4** - Tests performed and positive for PCR detection of gastrointestinal viruses in 2017, 2018, 2019, 2020 and 2021 at Hospital University Institute
 264 Méditerranée Infection.

Viruses	Tests						Positive											
	2017	2018	2019	2020	2021	Total 2017-2021	2017		2018		2019		2020		2021		Total 2017-2021	
	N	N	N	N	N	N	N	%	N	%	N	%	N	%	N	%	N	%
Adenovirus	1,674	1,662	1,47	1,166	255	6,227	83	5.0	127	7.6	56	3.8	48	4.1	10	3.9	324	5.2
Astrovirus	0	886	1,458	1,146	255	3,745	0	0.0	18	2.0	16	1.1	6	0.5	0	0.0	40	1.1
Norovirus	1,386	1,666	2,368	2,116	255	7,791	60	4.3	91	5.5	101	4.3	63	3.0	10	3.9	325	4.2
Rotavirus	1,64	1,662	1,471	1,184	255	6,212	78	4.8	88	5.3	127	8.6	45	3.8	12	4.7	350	5.6
Sapovirus	0	886	1,46	1,143	255	3,744	0	0.0	12	1.4	38	2.6	8	0.7	1	0.4	59	1.6

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267

268 **Figure 2** – Gastrointestinal virus diagnosis between October 2017 and February 2021 at Hospital University

269 Institute Méditerranée Infection.

270 *Comparison of winter seasons for gastrointestinal viral infections*

271 The overall positivity rate of gastrointestinal infections decreased significantly over
272 time during the winter seasons (Table 5). Notably, the norovirus winter season positivity rates
273 decreased continuously and significantly over time (2017–2018: 9.3%; 2018–2019: 8.4%;
274 2019–2020: 5.5%; 2020–2021: 2.0%). In contrast, adenovirus and rotavirus showed stable
275 positivity rates between 2018–2019 (3.8% and 2.4% respectively) and 2020–2021 winter
276 seasons (3.4% and 3.6% respectively) (Fig. 2).

277

278 **Table 5** - Tests performed and positive for PCR detection of gastrointestinal viruses, during the same cold months in 2017–2018, 2018–2019, 2019–2020 and

279 2020–2021.

Viruses	Tests				Positive										
	2017-2018	2018-2019	2019-2020	2020-2021	2017-2018			2018-2019			2019-2020			2020-2021	
	N	N	N	N	N	%	p value	N	%	p value	N	%	p value	N	%
Adenovirus	661	369	380	642	61	9.2	<0.001	14	3.8	0.8	31	8.2	0.001	22	3.4
Astrovirus	0	369	368	619	0	0.0	-	6	1.6	0.003	5	1.4	0.01	0	0.0
Norovirus	636	369	1026	664	59	9.3	<0.001	31	8.4	<0.001	56	5.5	<0.001	13	2.0
Rotavirus	661	369	380	661	64	9.7	<0.001	9	2.4	0.3	5	1.3	0.03	24	3.6
Sapovirus	0	369	369	619	0	0.0	-	5	1.4	0.03	8	2.2	0.002	1	0.2

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DISCUSSION

In this paper, the systematic monitoring of our microbiology and virology laboratory work has enabled us to identify changes in the epidemiology of respiratory and gastro-intestinal viral communicable diseases during the spread of a new emerging virus, SARS-CoV-2.

These data show that the epidemiology of infection with SARS-CoV-2 is not at all similar to that of other respiratory infections. As observed in other countries and in France, flu viruses have decreased dramatically [25-27]. It should be noted that the number of infections by endemic coronaviruses and rhinovirus does not seem to be particularly affected by the preventive measures taken and may have, in common with COVID-19, modes of transmission that are different from those of influenza viruses, RSV and the other respiratory viruses studied. Curiously, in our region, a higher number of parainfluenza virus 3 (HPIV3) were observed. One of the explanations for these epidemiological figures could be that the viruses experiencing a decrease in their incidence are most often involved in pneumonia, while, conversely, the agents responsible for nasal infections and for causing colds, such as endemic coronaviruses or HPIV3, remain constant. Measures to control COVID-19 would then prevent pneumonia and gastroenteritis. From this hypothesis, it would be interesting to study the nasal and pneumonic forms in COVID-19 patients and assess their evolution in time.

The impact of measures to control COVID-19 probably played a major role in these epidemiological changes [28]. These measures included both repeated recommendations on risk prevention measures such as hand washing with soap or alcohol-based hand gel, disinfecting surfaces, and social distancing, but also actions which were legally enforced, including wearing masks and the implementation of lockdown or curfews [9,29]. Hand washing and disinfection was probably the main factor having an impact upon the usual respiratory and gastrointestinal viral infections [30], and have been key elements of influenza prevention campaigns for several years [11]. It is not clear from the literature that lockdown measures and other social control measures have really had an impact on the spread of SARS-CoV-2 or on other respiratory infections [31]. For example, Sweden has issued very few social control measures while other countries such as France have implemented relatively strong measures without significantly differences in the number of cases or mortality [32].

The lack of effectiveness of these measures on the COVID-19 epidemic raises several questions. The first is the existence of infection outbreaks in animals which are distinct from outbreaks in humans. It has been demonstrated that the emergence of new variants could be promoted by the intensive captive breeding of certain animals such as mink, which are likely to contaminate humans by being potentially more contagious or more pathogenic for humans [34-36]. Furthermore, it seems likely that a certain number of treatments, including serotherapy with hyper-human sera and antivirals such as remdesivir, can promote the appearance of mutations [37].

Strong reductions in the incidence of some but not all respiratory viruses, and of viral agents of gastrointestinal infections have been also reported in several countries worldwide. This has been particularly noticed for influenza virus infections [28]. Tanislav and Kostev reported fewer non-SARS-CoV-2 respiratory tract infections and gastrointestinal infections during the SARS-CoV-2 pandemic [38]. They collected data from 994 general practitioners and 192 pediatricians in Germany and compared the prevalence of these infections between April 2020-March 2021 and April 2019-March 2020. Substantial falls (-71% for general practices and -90% for paediatrician practices) were observed for influenza virus infections, which was accompanied by a 40% fall of intestinal infections for general practices. Agca et al. reported, in a study on 319 nasopharyngeal samples in Turkey, a 7.5-fold reduction of the proportion of positive testing for influenza virus during March 2020-February 2021 compared to the previous year [2.3% (n= 9 cases) versus 17.3% (133), respectively] [39]. A significant reduction was also observed for other respiratory viruses including RSV but not for rhinoviruses/enteroviruses and metapneumovirus. Ippolito et al. also reported in Italy a strong decrease during the SARS-CoV-2 pandemic of the diagnoses of several seasonal respiratory viruses among hospitalized children younger than two years [40]. Indeed, the number of positive tests was 80% lower during the September 2020-February 2021 period compared to between the same periods of years 2019-2020 and 2018-2019, with a disappearance of influenza viruses and RSV as well as disappearance or strong decreases of other respiratory viruses except rhinoviruses and endemic coronaviruses. In the Southern hemisphere, Yeoh et al., reported decreases by 99% and 98% of diagnoses of influenza viruses and RSV, respectively, in children in Western Australian through winter 2020 [41]. In

Singapore, influenza virus positivity rate decreased by 64% during weeks 5–9 of 2020 compared with the preceding years [42].

The present study has several limitations. We focused on the epidemiology of respiratory and gastrointestinal viruses only over the last four cold seasons in our institute. We analyzed here a limited number of seasons but notwithstanding these data further support the unpredictability of the epidemiology of these viruses. We observed considerable variations from season to season throughout the respiratory virus epidemic period regarding the predominant viruses, the time of emergence and duration of winter epidemics, the level of incidence reached at the epidemic peaks, and the time at which this peak occurred [15]. Also, we acknowledge that estimating hospitalization pattern in the typical pre-SARS-CoV-2 season may be the subject of large random variation. Here, we have not analyzed the impact of respiratory viruses on hospital admissions, but their impact on hospital mortality has been the subject of previous studies [15,33]. Finally, the present work has been conducted in a single institution, and the results could therefore display local specificities.

In conclusion, this study confirms that it is futile to try to make predictions about a disease for which the level of knowledge is limited [43]. The course of the epidemic over the past year was unpredictable and could not be integrated into any predictive models. Caution should be taken when using such models. Furthermore, this leads to the search for different modes of transmission of most respiratory diseases, as had already been mentioned in relation to SARS-CoV, where infections were retrospectively detected at a significant distance from the heart of the SARS-CoV outbreak, with no reasonable explanation [44]. Broad epidemiological surveillance of respiratory and gastrointestinal infections should be pursued in the future, as many changes occur during this pandemic among which public health policies and population behaviours including mask wearing or social distancing [31]. Also, in France, the issue of carriage and transmission by domestic pets has not been resolved and should be the subject of intense research to really understand the reservoirs, transmission and epidemiology of this very atypical virus. A new study on the 2021-2022 winter season should be carried out to better understand the epidemiology of these respiratory and gastrointestinal viruses and the impact of barrier measures on the spread of new SARS-CoV-2 variants with different transmissibility [45].

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