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No SARS-CoV-2 reinfection among staff health-care workers: Prospective hospital-wide screening during the first and second waves in Paris

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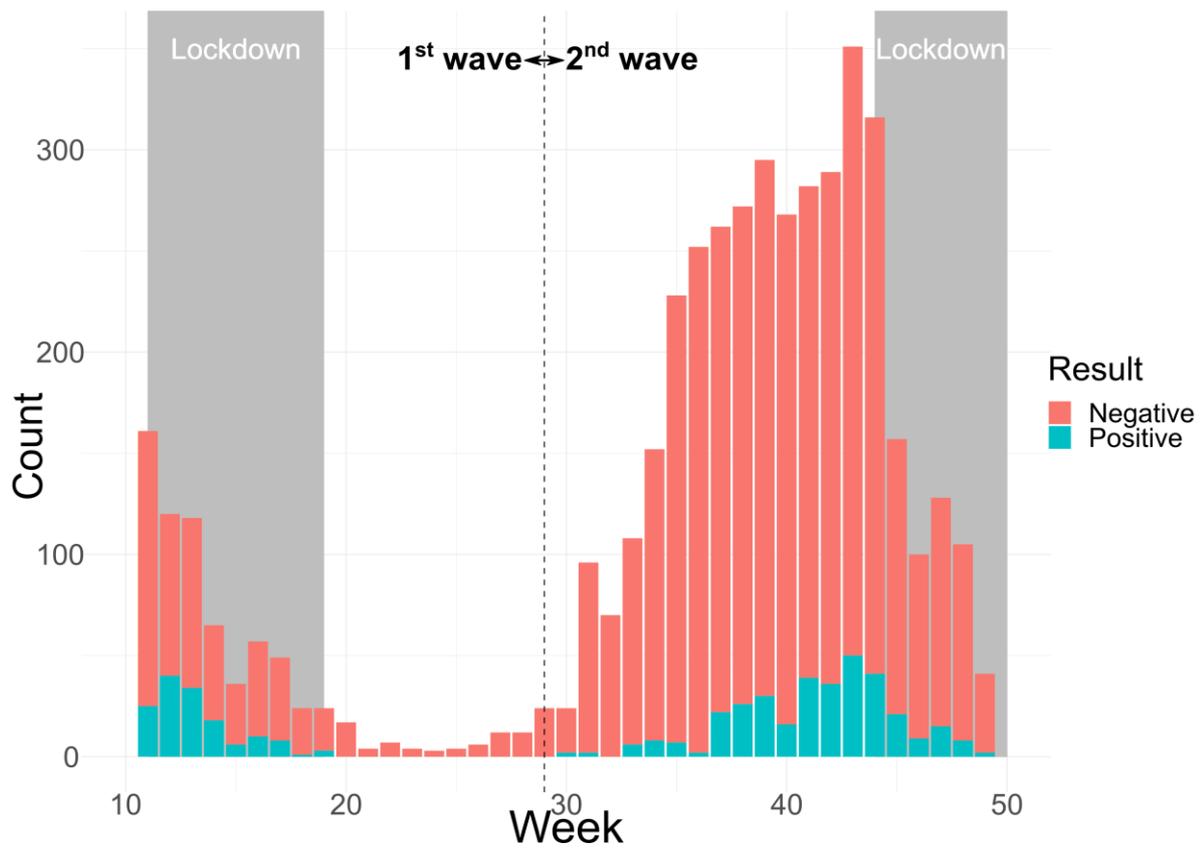
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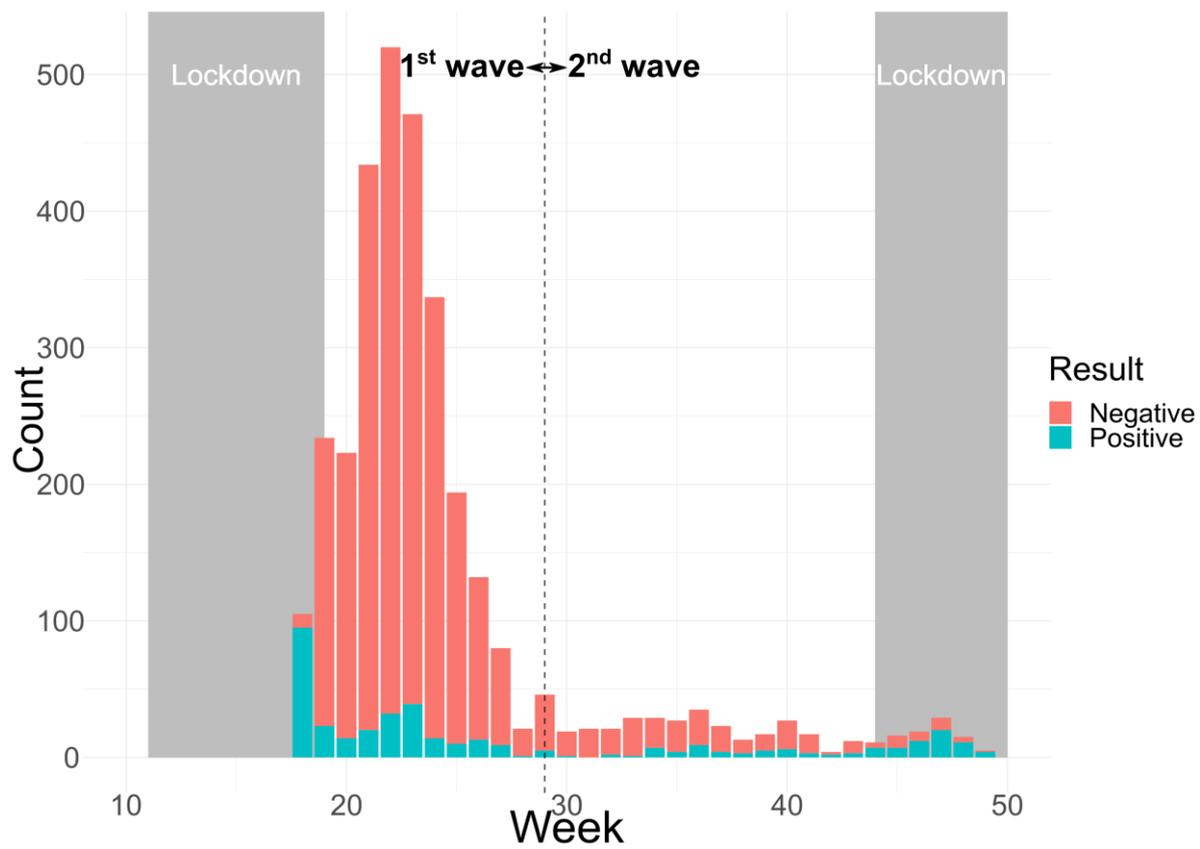
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A. Weekly PCR results for health-care workers



B. Weekly serology results for health-care workers



2 **SARS-CoV-2 reinfection among staff health-care workers:**

3 **Prospective hospital-wide screening**

4 **during the first and second waves in Paris**

5
6 **Running title:** No SARS-CoV-2 reinfection among HCWs

7
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38 **Summary**

39 **Objectives.** Risk of reinfection with SARS-CoV-2 among health-care workers (HCWs) is unknown.

40 We assessed the incidence rate of SARS-CoV-2 reinfection in the real-life setting of a longitudinal
41 observational cohort of HCWs from the *Hôpital Européen Georges Pompidou, Assistance*
42 *Publique-Hôpitaux de Paris*, France, during the first and second waves of COVID-19 epidemic.

43 **Methods.** From March to December 2020, HCWs were subjected to molecular and serology testing
44 of SARS-CoV-2. Reinfection was defined as a positive test result during the first wave, either by
45 serology or PCR, followed by a positive PCR during the second wave. Evolution of COVID-19
46 status of HWCs was assessed by a Sankey diagram.

47 **Results.** A total of 7765 tests (4579 PCR and 3186 serology) were carried out and 4168 HCWs had
48 at least one test result during the follow-up period with a positivity rate of 15.9%. No case of
49 reinfection during the second wave could be observed among 102 positive HCWs of the first wave,
50 nor among 175 HCWs found positive by PCR during the second wave who were negative during
51 the first wave.

52 **Conclusions.** SARS-CoV-2 reinfection was not observed among HCWs, suggesting a protective
53 immunity against reinfection that lasts at least 8 months post infection.

54

55 **Keywords:** SARS-CoV-2; reinfection; health-care workers; vaccination; epidemiology

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58

59 **Introduction**

60

61 Health-care workers (HCWs) constitute a vulnerable population at high risk of SARS-CoV-
62 2 infection (1–3). During the first wave of COVID-19 epidemic in France, as of May 13, 2020,
63 more than 4,500 professionals were infected and 4 dead from COVID-19 in the *Assistance*
64 *Publique-Hôpitaux de Paris* (AP-HP, which represents the largest group of university hospitals in
65 Europe, accounting for about 100 000 employees).

66 SARS-CoV-2 infection elicits both humoral and cellular, mucosal and systemic specific
67 immunity (4–6). A key question yet to be addressed is whether SARS-CoV-2 infection induces
68 long-lasting protective or sterilizing immunity. Our understanding of the immune correlates of
69 protection for SARS-CoV-2 infection and their durability remains limited and depends mainly on
70 previous knowledge gained from SARS-CoV-1, the most closely related virus known to affect
71 humans (5,7). Furthermore, a number of cases of SARS-CoV-2 reinfection in humans have now
72 been reported a few months after initial infection (8,9), including HCWs (10), challenging the
73 possibility of durable protective immunity. These findings may have implications for the need of
74 continued protective measures and of further vaccination for persons previously infected with
75 SARS-CoV-2 (9).

76 In France, the SARS-CoV-2 epidemic officially began on January 24, 2020, with the first
77 confirmed case of COVID-19 imported from China. Early April, the number of deaths from
78 coronavirus increased dramatically, with more than 10,000 people dying during that period of time.
79 The first wave of the COVID-19 epidemic was contained due to the first national lockdown that
80 extended from March 17, 2020 until May 10, 2020, the peak of the first wave being reached on the
81 1st of April 2020. During August 2020, COVID-19 cases began to rise again. On October 28, France
82 entered a second nationwide lockdown with progressive lifting starting from December 15. The
83 peak of the second epidemic wave was reached on the 20th of November 2020, but the epidemic has

84 since remained at a high plateau level. The duration period between the peaks of the first and
85 second waves was 7.8 months (234 days).

86 Our institution, the *Assistance Publique-Hôpitaux de Paris*, has largely promoted both
87 molecular and serological testing for SARS-CoV-2 among healthcare staff, from the first wave of
88 the COVID-19 epidemic (1). Molecular testing for SARS-CoV-2 of symptomatic hospital
89 employees with COVID-19-related symptoms started on February 24, 2020. In addition, starting
90 early April 2020, the *Assistance Publique-Hôpitaux de Paris* offered HCWs serological screening
91 for SARS-CoV-2 to assess the prevalence of the infection during the first epidemic peak.

92 The intensity of COVID-19 epidemic in France in 2020 with a high risk of re-exposure to
93 SARS-CoV-2 infection for HCWs, as well as the availability of our centralized data-capture system
94 of all molecular and serological SARS-CoV-2 tests results, prompted us to assess the risk of SARS-
95 CoV-2 reinfections in a real-life setting in HCWs from our institution.

96

97 **Materiel and method**

98

99 **Study design and participants recruitment.**

100 The study was designed as an observational cohort with longitudinal analysis, focused on
101 molecular detection of SARS-CoV-2 RNA and immune response to SARSCoV-2 in volunteers
102 HCWs from the *Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris*,
103 tested during the first and second epidemic waves for suspected SARS-CoV-2 infection, contact
104 tracing and SARS-CoV-2 infection serological surveillance. Data included HCW ages, SARS-CoV-
105 2 PCR and SARS-CoV-2 serology sampling dates and results. HCWs gender was not available. All
106 molecular and serological results were fully pseudonymized. July 15 2020 was considered as the
107 limit between the first and second epidemic waves.

108 During the first epidemic wave, the HCW participants were categorized into two groups
109 according to their molecular and serological results: positive if any SARS-CoV-2 PCR test and/or
110 serology were positive, and negative if every SARS-CoV-2 PCR test and serology were negative.
111 During the second epidemic wave, the participants were categorized into two groups according to
112 their molecular results, as positive if any SARS-CoV-2 PCR test was positive, and negative if every
113 SARS-CoV-2 PCR test were negative. In addition, HCW participants included during the first wave
114 but not tested during the second wave, and those included during the second wave but not tested
115 during the first wave were categorized as participants with not available results (NA). Finally,
116 reinfection was defined as a positive result during the first wave, either by serology or PCR,
117 followed by a positive PCR during the second wave. If iterative PCR sampling occurred, reinfection
118 was considered if a negative result was surrounded by 2 positive results. Furthermore, if 2 PCRs
119 were positive with more than 30 days between the sample dates without any negative results in
120 between, results were individually assessed by a virologist to decide if reinfection was confirmed or
121 if remnant RNA from the original infection was still detected when the cycle threshold (C_t) value of
122 the PCR was over 33 (11). Positive serology during the first wave followed by positive PCR during
123 the second wave was also considered a reinfection.

124 **SARS-CoV-2 testing.** Molecular detection of SARS-CoV-2 was carried out from flocced
125 nasopharyngeal swab samples using Allplex™ 2019-nCoV Assay (Seegene, Seoul, Korea), a
126 multiplex real-time PCR assay that detects three coronavirus target genes (E gene, RdRP gene and
127 N gene) in a single tube, according to the manufacturer's instructions, as previously described (12).
128 Abbott SARS-CoV-2 IgG assay detecting IgG against SARS-CoV-2 nucleoprotein was used on
129 Architect analyzer (Abbott Architect™ i2000), according to manufacturer's instructions, as
130 previously described (13). Index value threshold for positivity was 1.4. Qualitative results were
131 used for analysis.

132 **Statistical analysis.** Categorical variables are presented as number (percentage and its [95%
133 confidence interval]), and numeric variables as median or mean (SD or IQR). The number of test
134 results was computed on a weekly basis. The evolution of the status for COVID-19 of HCWs
135 between the two waves was assessed using a Sankey diagram, as described (14).

136 **Ethics statement.** Our observational study was carried out in accordance with the Declaration of
137 Helsinki with no sampling addition to usual procedures. Swab and serum specimens were obtained
138 only for standard diagnostic following medical prescriptions in the service of occupational medicine
139 of our institution, and further eventual care. Under these conditions, the study was exempt from
140 informed consent application, according to the French public health code (*Code de la Santé*
141 *Publique*, article L 1121-1.1; <https://www.legifrance.gouv.fr/>). The dataset was completely
142 anonymous and did not contain any identifiable personal health information.

143

144 **Results**

145

146 A total of 7765 tests, including PCR and serology, were collected from March 5, 2020 to
147 December 4, 2020 by the occupational medicine service at the *Hôpital Européen Georges*
148 *Pompidou*, Paris.

149 As depicted in the Figure 1, the weekly number of PCR tests evolved in accordance to the
150 two waves of the epidemic of cases of SARS-CoV-2 infection in Paris. The number of serology
151 tests per week evolved according to the curve resembling the first wave of the epidemic due to an
152 institutional campaign for SARS-CoV-2 serology testing among HCWs between May and July.

153 Overall, 4579 PCR and 3186 serology tests were performed with positivity rates of 10.7%
154 and 12.1%, respectively. A total of 4168 HCWs (median age, 34.3 years; IQR, 20.9 years) had at
155 least one result, either PCR or serology, during the entire period with a positivity rate of 15.9%.
156 There were 690 HCWs with at least one PCR result during the first wave *versus* 2340 during the

157 second wave with a positivity rate of 21.3% and 14.1%, respectively. Conversely, 2737 HCWs had
158 a serology result during the first wave *versus* 417 during the second one, with a positivity rate of
159 9.8% and 27.8%, respectively (Table 1).

160 Among the 302 positive HCWs (either by serology or PCR) during the first wave, 102 were
161 tested by PCR at least once during the second wave (154 total PCRs), and all their PCR results were
162 negative (Figure 2). Furthermore, among the 330 PCR-positive HCWs during the second wave, 190
163 had a previous result from the first wave. Among those 190 that were tested in the first wave, there
164 were 9 positive PCRs and 14 positive serology (15 total HCWs), and 170 negative serology and 45
165 negative PCRs (175 HCWs). All those 15 positive HCWs in the first wave were only positive in
166 serology in the second wave. Among the 2657 negative HCWs during the first wave, 175 had a
167 positive PCR result (185 tests) and 965 (1859 tests) had a negative result during the second wave.
168 Overall, no case of reinfection during the second wave could be observed among the HCWs
169 population in our hospital. The observed reinfection incidence was thus 0% [95% CI: 0 - 3.55%].

170

171 **Discussion**

172

173 We herein assessed the incidence rate of SARS-CoV-2 reinfection in the real-life setting of a
174 longitudinal observational cohort of HCWs from one of the major university hospitals of the
175 *Assistance Publique-Hôpitaux de Paris*, France, during the first and second waves of COVID-19
176 epidemic in 2020. The longitudinal prevalence rates of SARS-CoV-2 infection among HCWs,
177 mostly symptomatic infections due to the design of the study, mimicked the curves of both waves of
178 the COVID-19 epidemics in France with an overall rate of SARS-CoV-2 infection around 16%,
179 demonstrating possible occupational risk for SARS-CoV-2 infection in HCWs despite barrier
180 protection measures within the community and hospital settings. Among the included SARS-CoV-2
181 infected HCWs tested for SARS-CoV-2 PCR swab and/or IgG serology in both the first and second

182 waves of the COVID-19 epidemic in Paris, no case of SARS-CoV-2 reinfection could be evidenced.
183 Thus, the risk of SARS-CoV-2 reinfection among HCWs appears negligible, despite the high level
184 of exposure to the virus during epidemic waves. Taken together, these observations demonstrate
185 that HCWs are at high risk of SARS-CoV-2 infection. SARS-CoV-2 reinfection was infrequent in
186 study HCWs, highly suggestive of a protective immunity against reinfection lasting at least 8
187 months following the primary infection.(1–3,15)

188 More than a seventh (15.9%) of HCWs showed at least one positive biological marker for
189 SARS-CoV-2 during the nearly 8 months of study inclusion. The risk of SARS-CoV-2 infection in
190 included HCWs strictly followed the waves of the COVID-19 epidemic in France, during which
191 between 3% and 7% of French people will have been infected by SARS-CoV-2 (16). Thus, our
192 findings suggest that HCWs are likely at supplementary risk for occupational SARS-CoV-2
193 infection, as previously reported in Paris and other settings (1–3,15).

194 The possibility of SARS-CoV-2 reinfection has raised important issues about the strength
195 and durability of the immune response to primary infection, which are key factors in predicting the
196 course of the pandemic (8). We herein show SARS-CoV-2 reinfection was infrequent or absent
197 among HCWs infected during the first wave of COVID-19 epidemic, despite their community and
198 occupational re-exposure during the second wave. Our observations are in agreement with the low
199 risk of SARS-CoV-2 reinfection generally reported (8,17), although the rates of reinfection with
200 SARS-CoV-2 can vary widely, depending on the criteria used, and also because it is difficult to
201 make the diagnosis with certainty, as previously pointed (18). By including the stringent criteria of
202 viral genomic data to distinguish reinfection from persistent viral carriage, only 16 documented
203 individual cases of reinfection confirmed by sequencing have been reported in the literature at the
204 end of 2020 (8,19). Recently in Qatar, the risk of SARS-CoV-2 reinfection was estimated to be as
205 low as 1 case of reinfection per 5000 infected individuals (17). However, a 2,800 person study
206 found no symptomatic re-infections over a ~118 days window (20), and a 1,246 person study

207 observed no symptomatic re-infections over 6 months (21). Overall, SARS-CoV-2 re-infection is
208 considered a possible but rare event (8), in keeping with our observational study based on field
209 results from a well-documented hospital cohort.

210 SARS-CoV-2 infection consistently elicits neutralizing antibodies targeting the spike protein
211 (in addition to other viral antigens), as well as CD8+ and CD4+ T cell responses (4–6). However,
212 the duration of effective immunity to SARS-CoV-2 remains unknown, and the issue of waning
213 immunity and reversion to a SARS-CoV-2 susceptible state over months to years is raised (22). Our
214 observations of infrequent SARS-CoV-2 reinfection in hospital setting during the first and second
215 waves of COVID-19 epidemic in Paris are strongly suggestive of efficient and protective immunity
216 against reinfection that lasts at least 8 months post primary infection. These observations are in
217 keeping with measurable immune memory in the three major branches of adaptive immunity (CD4+
218 T cell, CD8+ T cell, and humoral immunity) in ~95% of subjects 5 to 8 months post symptom
219 onset, indicating that durable immunity against secondary COVID-19 disease is a possibility in
220 most individuals (23). Obviously, further follow-up of SARS-CoV-2-infected HCWs over time may
221 allow characterization of potential effects of SARS-CoV-2-specific immunity waning.

222 The need to vaccinate previously SARS-CoV-2-infected individuals remains the matter of
223 debate (9,24). It is possible that a fraction of the SARS-CoV-2-infected population with low
224 immune memory would become susceptible to re-infection relatively soon (23). Current
225 recommendations for COVID-19 vaccination from the World Health Organization (25) and the
226 Centers for Disease Control and Prevention (USA) (26) do not consider the fact of having been
227 infected with SARS-CoV-2. The National Health Service (UK) recommends to temporarily
228 postponing vaccination for 4 weeks after the onset of COVID symptoms (27). In France, the *Haute*
229 *Autorité de Santé*, Saint-Denis, has recommended that there is no need to systematically vaccinate
230 people who have already developed a symptomatic form of COVID-19 (28). Our observations of
231 HCWs infected by SARS-CoV-2 harboring durable protection against reinfection for at least 8

232 months indicate that COVID-19 vaccination does not *a priori* constitute a priority in case a previous
233 infection, especially if vaccine doses are limited. As vaccine candidates advance worldwide,
234 serostatus for COVID-19 could be relevant in HCWS before vaccination. If it is determined that a
235 single SARS-CoV-2 exposure induces long-lasting protective immunity, a positive serology test
236 could indicate that an individual does not require vaccination or should not receive priority for
237 vaccination (29). Finally, in case of vaccination in HCWS who have already been infected, the
238 vaccination schedule could also possibly be simplified to a single dose.

239 Our study has some limitations. Except for HCWs that were recently exposed to positive
240 patients or colleagues (contact tracing), only HCWs volunteering for testing were included and
241 probably most of them had symptomatic infection. Furthermore, the possibility could be that
242 reinfections (if they occur) would have been asymptomatic or well tolerated and that they went
243 unnoticed without a biological diagnosis. Finally, HCWs in our institution were exposed to the
244 SARS-CoV-2 variants circulating in France until December 2020, and our study does not evaluate
245 the possibility of reinfection by other variants, such as the new U.K. variant of SARS-CoV-2, which
246 various modeling exercises have estimated to be up to 70% more transmissible than the previously
247 circulating form of the virus (30).

248 In conclusion, SARS-CoV-2 reinfection appears to be a rare phenomenon, if it exists, in
249 HCWs despite their high level of exposure to the virus during epidemic peaks. This feature may
250 suggest that effective immunity against SARS-CoV-2 infection develops after primary infection and
251 lasts for at least 8 months, and that it is able to protect against reinfection. Finally, HCWs already
252 infected with SARS-CoV-2 do not constitute a priority population for vaccination, especially as
253 vaccine doses remain rationed.

254

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257
258 **Author's contribution.** HP, LB, DV designed the research. NDG, KCN, LJ provided clinical care
259 and biological specimens. LB, DV, LI, BV analyzed the samples. MW, DV performed statistical
260 analysis. HP, MW, LB, DV drafted the manuscript. All authors read and approved the final
261 manuscript.

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361 **Table 1.** SARS-CoV-2 RNA PCR and SARS-CoV-2-specific IgG serology results carried out
 362 among HCWs in *Hôpital Européen Georges Pompidou*, Paris, France, during the first and second
 363 waves of the COVID-19 epidemic in 2020.

364

	First wave	Second wave	Total
HCWs tested by PCR and/or serology [n]	2902	2506	4168
Age of tested HCWs [median (IQR); years]	37.1 (20.6)	32.1 (19.5)	34.3 (20.9)
SARS-CoV-2 PCR and serology [n]	3510	4255	7765
PCR [n]	759	3820	4579
[percent of positive (CI)]	19.5% (16.7 – 22.5)	8.9% (8.0 – 9.8)	10.7% (9.8 – 11.6)
Serology [n]	2751	435	3186
[percent of positive (CI)]	9.8% (8.7 – 10.9)	26.7% (22.6 – 31.1)	12.1 % (11.0 – 13.3)
HCWs tested positive by PCR and/or serology [n]	302	379	666
[percent (CI)]	10.4% (9.3 – 11.6)	15.1% (13.7 – 16.6)	15.9% (14.9 – 17.1))
HCWs tested by both PCR and serology [n]	525	251	1565
[percent of positivity by PCR or serology (CIs)]	41.5% (37.3 – 45.9)	47% (40.7 – 53.4)	31.3% (29.0 – 33.7)
[percent of positivity by both PCR and serology (CIs)]	21.5% (18.1 – 25.3)	26.7% (21.3 – 32.6)	11.6% (10.1 – 13.3)
HCWs with at least one PCR result [n]	690	2340	2719
[percent of positivity (CI)]	21.3% (18.3 – 24.5)	14.1% (12.7 – 15.6)	17.5% (16.1 – 18.9)
PCR per HCW [mean (SD)]	1.10 (0.30)	1.63 (0.90)	1.68 (1.02)
HCWs with at least one serology result [n]	2737	417	3014
[percent of positivity (CI)]	9.8% (8.7 – 10.9)	27.8% (23.6 – 32.4)	12.3% (11.2 – 13.4)
Serology per HCW [mean (SD)]	1.01 (0.08)	1.04 (0.23)	1.06 (0.25)

365 CI: Confidence interval; IQR: Interquartile range; HCW: Health-care worker; n: number; SD: Standard deviation;

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369 **Figures Legends**

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371 **Figure 1.** PCR and serology results during the first and the second wave of the COVID-19

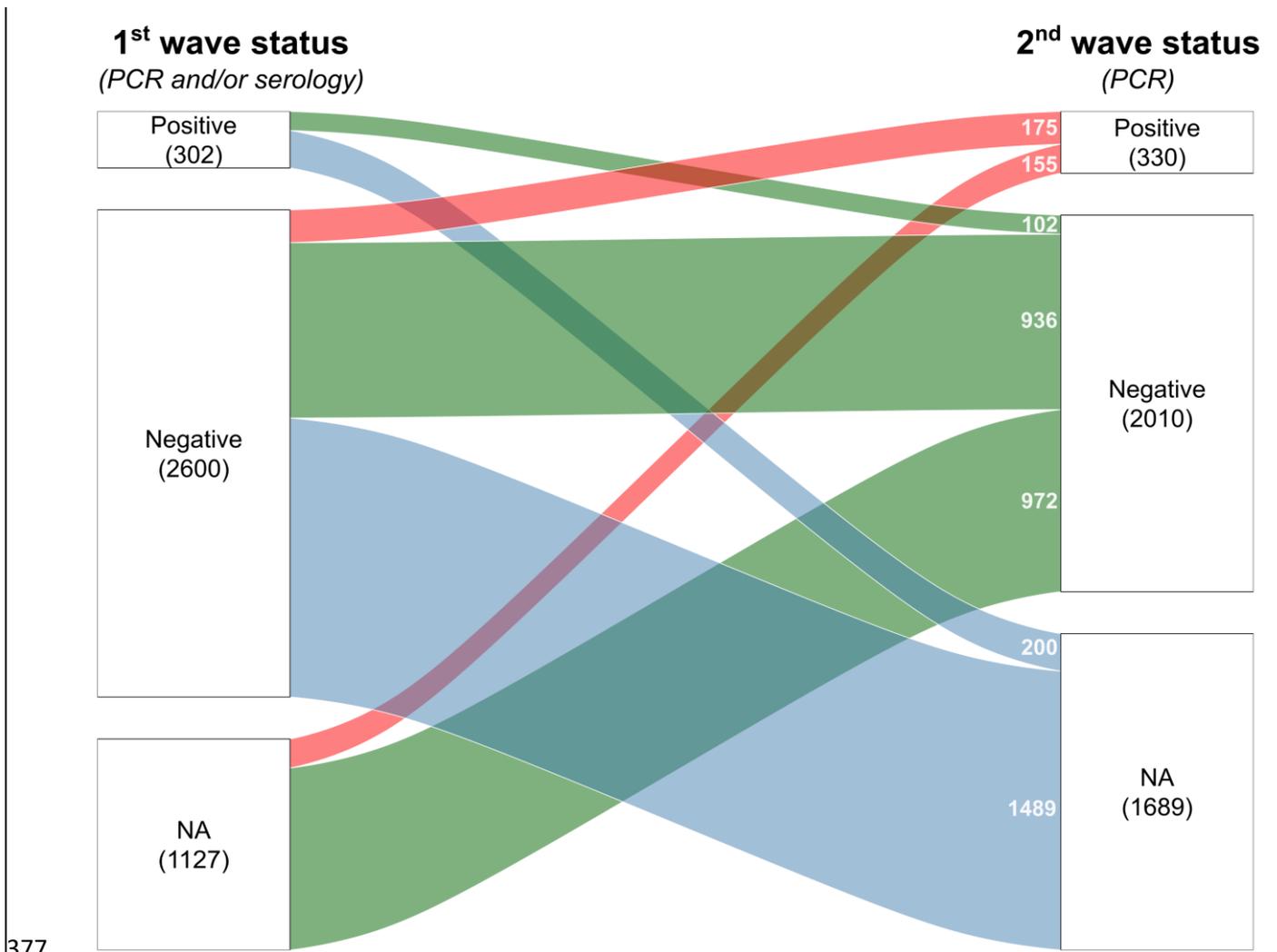
372 pandemic. Weekly SARS-CoV-2 RNA PCR results (A.) and SARS-CoV-2-specific IgG serology

373 results (B.) among staff HCWs in *Hôpital Européen Georges Pompidou*, Paris, France, during the

374 first and second waves of the COVID-19 epidemic in 2020. The dashed vertical line indicates the

375 separation between the first and second waves. The shaded areas correspond to the lockdown period

376 decided by the French government. Positive and negative results are in red and blue, respectively.



377

378 **Figure 2.** Health-care workers COVID-19 status evolution between the first and the second wave of

379 the COVID-19 pandemic. Sankey diagram showing the evolution of SARS-CoV-2 status among

380 HCWs in *Hôpital Européen Georges Pompidou*, Paris, France, between the first and the second

381 waves. Boxes on the left represent results either by PCR and/or serology during the first wave of the
382 SARS-CoV-2 epidemic, while those on the right represent results only by PCR during the second
383 wave. The different lanes show the status evolution with lane sizes proportional to the number of
384 HCWs. The blue lanes are for HCWs with no result during the second wave. The green lanes are for
385 HCWs with a negative result during the second wave. The red lanes are for HCWs with a positive
386 result during the second wave. NA: Results not available.

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