

1      **Heterogeneity in transmissibility and shedding SARS-CoV-2 via droplets and aerosols**

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21    **Abstract**

22    A growing number of studies provide insight into how SARS-CoV-2 spreads<sup>1-7</sup>. Yet, many  
23    factors that characterize its transmissibility remain unclear, including mechanistic correlates of  
24    overdispersion, viral kinetics, the extent to which respiratory droplets and aerosols carry viable  
25    virus and the infectiousness of asymptomatic, presymptomatic and pediatric cases<sup>7</sup>. Here, we  
26    developed a comprehensive dataset of respiratory viral loads (rVLs) via systematic review and  
27    investigated these factors using meta-analyses and modeling. By comparing cases of COVID-19,  
28    SARS and influenza A(H1N1)pdm09, we found that heterogeneity in rVL was associated with  
29    overdispersion and facilitated the distinctions in individual variation in infectiousness among  
30    these emergent diseases. For COVID-19, case heterogeneity was broad throughout the infectious  
31    period, although rVL tended to peak at 1 day from symptom onset (DFSO) and be elevated for 1-  
32    5 DFSO. While most cases presented minimal risk, highly infectious ones could spread SARS-  
33    CoV-2 by talking, singing or breathing, which shed virions at comparable rates via droplets and  
34    aerosols. Coughing shed considerable quantities of virions, predominantly via droplets, and  
35    greatly increased the contagiousness of many symptomatic cases relative to asymptomatic ones.  
36    Asymptomatic and symptomatic infections showed similar likelihoods of expelling aerosols with  
37    SARS-CoV-2, as did adult and pediatric cases. Children tended to be less contagious by droplet  
38    spread than adults based on tendencies of symptomatology rather than rVL. Our findings address  
39    longstanding questions on SARS-CoV-2 transmissibility and present pertinent considerations for  
40    disease control.

41     **Main body**

42     The novel coronavirus SARS-CoV-2 has spread globally, causing the coronavirus disease 2019  
43     (COVID-19) pandemic with more than 38.0 million infections and 1.0 million deaths (as of 13  
44     October 2020)<sup>8</sup>. While the basic reproductive number has been estimated to be 2-3.6<sup>1,2</sup>,  
45     transmissibility of SARS-CoV-2 is highly overdispersed, with numerous instances of  
46     superspreading<sup>9-11</sup> and few cases (10-20%) causing many secondary infections (80%)<sup>4-6</sup>.  
47     Estimates indicate 40-87% of cases are asymptomatic or paucisymptomatic, which facilitates  
48     transmission<sup>2,3,12</sup>. Infectiousness begins around -3 to -2 DFSO and has been estimated to last 8-  
49     10 DFSO<sup>13-15</sup>. Hence, the temporal infectiousness profile of COVID-19 resembles that of  
50     influenza<sup>16</sup>, whereas its overdispersion is similar to that of severe acute respiratory syndrome  
51     (SARS)<sup>17</sup>.

52       For respiratory virus transmission, airway epithelial cells shed virions to the extracellular  
53       fluid before atomization (from breathing, talking, singing, coughing and aerosol-generating  
54       procedures) partitions them into a polydisperse mixture of droplets ( $>5 \mu\text{m}$ ) and aerosols ( $\leq 5 \mu\text{m}$ ) that are expelled to the ambient environment<sup>7</sup>. Based on mass, droplets tend to settle  
55       gravitationally, whereas aerosols remain suspended and travel based on airflow profiles.  
56       Although proximity has been associated with infection risk for COVID-19<sup>18</sup>, studies have also  
57       suggested that long-range aerosol spread occurs conditionally<sup>9-11</sup>.

59       Despite these analyses, key factors that characterize the transmissibility of SARS-CoV-2  
60       remain unclear. To investigate many of these factors, we synthesized evidence by systematic  
61       review, compared SARS-CoV-2 rVLs among subgroups, associated overdispersion, analyzed  
62       viral kinetics and modeled the likelihood of shedding viable virus via droplets and aerosols  
63       across respiratory activities, DFSO, case heterogeneity and subgroups. For inference on

64 transmissibility, we compared these analyses with those of SARS-CoV-1 (the most closely  
65 related human coronavirus) and A(H1N1)pdm09 (the most recent pandemic influenza virus),  
66 which spread by contact, droplets and aerosols<sup>19,20</sup>.

67

## 68 Systematic review

69 To develop the comprehensive dataset, we conducted a systematic review on quantitative VL  
70 measurements for respiratory specimens taken during the infectious periods of SARS-CoV-2 (-3  
71 to 10 DFSO)<sup>13-15</sup>, SARS-CoV-1 (0-20 DFSO)<sup>21</sup> and A(H1N1)pdm09 (-2 to 9 DFSO)<sup>16</sup>  
72 (Methods). The systematic search (Supplementary Tables 1-5) identified 4,274 results. After  
73 screening and full-text review, 63 studies met the inclusion criteria and were used for analysis  
74 (Fig. 1) ( $n=9,692$  total specimens), which included adult ( $n=5,124$ ) and pediatric ( $n=1,593$ ) cases  
75 and measurements for asymptomatic ( $n=2,378$ ), presymptomatic ( $n=28$ ) and symptomatic  
76 ( $n=7,231$ ) infections. According to a hybrid Joanna Briggs Institute critical appraisal checklist,  
77 risk of bias was low to moderate for included studies (Extended Data Table 1).

78

## 79 Meta-analysis and subgroup analyses of rVL

80 For each study in the systematic dataset, we used specimen concentrations to estimate rVLs  
81 (Methods). We then performed a random-effects meta-analysis (Extended Data Fig. 1), which  
82 showed that, during the infectious periods, the expected rVL of SARS-CoV-2 was comparable to  
83 that of SARS-CoV-1 ( $p=0.148$ , two-sided Welch's  $t$ -test) but lesser than that of A(H1N1)pdm09  
84 ( $p<0.0001$ ). We also performed random-effects subgroup analyses for COVID-19 (Fig. 2), which  
85 showed that expected SARS-CoV-2 rVLs were consistent between pediatric and adult cases  
86 ( $p=0.861$ ) and between symptomatic/presymptomatic and asymptomatic infections ( $p=0.951$ ).

87

88 **Association of heterogeneity in rVL with overdispersion**

89 Since few cases drive the transmission of SARS-CoV-2 (dispersion parameter  $k$ , 0.10-0.58)<sup>4-6</sup>  
90 and SARS-CoV-1 ( $k$ , 0.16-0.17)<sup>17</sup> whereas A(H1N1)pdm09 ( $k$ , 7.4-14.4)<sup>22,23</sup> spreads more  
91 homogeneously, we sought to find a mechanistic association for overdispersion. As an empirical  
92 estimate,  $k$  depends on myriad extrinsic (behavioral, environmental and invention) and host (host  
93 defenses) factors. However, since dispersion is similar across distinct outbreaks of a virus<sup>17</sup>, we  
94 hypothesized that an intrinsic virological factor mediates  $k$  for these emergent respiratory  
95 infections.

96 We assessed heterogeneity in rVL. For all three viruses, rVLs best conformed to Weibull  
97 distributions (Extended Data Fig. 2), and we fitted the entirety of individual sample data for each  
98 virus in the systematic dataset (Fig. 3a, Extended Data Fig. 2n). While COVID-19 and SARS  
99 cases tended to shed lesser virus than those with A(H1N1)pdm09 (Extended Data Fig. 1), broad  
100 heterogeneity in rVL inverted this relationship for highly infectious individuals (Extended Data  
101 Fig. 3a-c). At the 90<sup>th</sup> case percentile (cp), the estimated rVL was 8.91 (8.82-9.00, 95%  
102 confidence interval [CI]) log<sub>10</sub> copies/ml for SARS-CoV-2, whereas it was 8.62 (8.47-8.76) log<sub>10</sub>  
103 copies/ml for A(H1N1)pdm09. Moreover, heterogeneity in rVL was similar among adult,  
104 pediatric, symptomatic/presymptomatic and asymptomatic COVID-19 cases (Extended Data Fig.  
105 3d-g), with standard deviations (SDs) of 2.01-2.06 log<sub>10</sub> copies/ml (Extended Data Table 2).

106 To investigate the relationship between  $k$  and heterogeneity in rVL, we performed a meta-  
107 regression using each included study (Fig. 3b). The analysis showed a negative association  
108 ( $p=0.031$ , meta-regression slope  $t$ -test), indicating that heterogeneity in rVL intrinsically  
109 facilitated the distinctions in overdispersion among the emergent infections.

110

111 **Kinetics of SARS-CoV-2 rVL**

112 To investigate dynamics, we delineated SARS-CoV-2 rVLs by DFSO and fitted the mean  
113 estimates to a mechanistic epithelial cell-limited model for viral kinetics (Fig. 3c, Methods). The  
114 outputs indicated that, on average, each productively infected cell in the airway epithelium shed  
115 SARS-CoV-2 at 1.11 (0.51-1.71, 95% CI) copies/ml day<sup>-1</sup> and infected up to 10.6 susceptible  
116 cells (Extended Data Table 3). The turnover rate for infected epithelial cells was 0.55 (0.23-0.87)  
117 days<sup>-1</sup>, while the half-life of SARS-CoV-2 in the respiratory tract was 4.35 (2.23-97.8) hours. By  
118 extrapolating the model to an initial rVL of 0-1 log<sub>10</sub> copies/ml, the estimated incubation period  
119 was 5.38-4.52 days, which agrees with epidemiological findings<sup>1</sup>. Conversely, the expected  
120 duration of shedding was 26.8 DFSO. Thus, SARS-CoV-2 replicated exponentially in the  
121 respiratory tract based on a mean rate constant of 4.02×10<sup>-7</sup> (3.01×10<sup>-7</sup>-5.03×10<sup>-7</sup>) (copies/ml)<sup>-1</sup>  
122 day<sup>-1</sup> after infection. Around 1 DFSO, rVL peaked, as the number of infected epithelial cells  
123 reached equilibrium, and then diminished exponentially.

124 As SARS-CoV-2 rVLs showed widespread heterogeneity across the infectious period, we  
125 fitted distributions for each DFSO (Fig. 3d), which showed that high rVLs also increased from  
126 the presymptomatic period before decreasing towards the end of the first week of illness. At the  
127 90<sup>th</sup> cp, SARS-CoV-2 rVL peaked at 1 DFSO at 9.83 (9.12-10.61) log<sub>10</sub> copies/ml, an order of  
128 magnitude greater than the overall 90<sup>th</sup>-cp estimate (Extended Data Table 2). The estimate  
129 remained ≥9.33 log<sub>10</sub> copies/ml between 1-5 DFSO. At -1 DFSO, the 90<sup>th</sup>-cp rVL was 8.30  
130 (6.88-10.02) log<sub>10</sub> copies/ml, while it was 7.92 (7.34-8.55) log<sub>10</sub> copies/ml at 10 DFSO  
131 (Extended Data Fig. 3h-s).

132

133 **Likelihood of droplets and aerosols containing virions**

134 Since rVL is an intensive quantity, the volume fraction of virions is low and viral partitioning  
135 coincides with atomization, we used Poisson statistics to model likelihood profiles. To calculate  
136 an unbiased estimator of partitioning (the expected number of viable copies per particle), our  
137 method multiplied rVL estimates with the volumes of atomized particles and an assumed  
138 viability proportion of 0.1% after dehydration (Methods).

139 When expelled by the mean COVID-19 case across the infectious period, respiratory  
140 particles showed minimal likelihoods of carrying viable SARS-CoV-2 (Fig. 4a,b). Aerosols  
141 (dehydrated aerodynamic diameter [ $d_a$ ]≤5 μm) were <0.001% likely to contain a virion. Droplets  
142 also had low likelihoods: at  $d_a$ =40 μm, they were ≤0.4% likely to contain a virion.

143 COVID-19 cases with high rVLs, however, expelled particles with considerably greater  
144 likelihoods of carrying viable copies (Fig. 4a,b). For the 98<sup>th</sup> cp at 1 DFSO, 18.2% (8.8-27.6%)  
145 of aerosols ( $d_a$ =5 μm) contained at least one SARS-CoV-2 virion. For  $d_a$ >14.4 μm, droplets were  
146 >99% likely to contain virions, with large ones carrying tens to hundreds.

147

148 **Shedding SARS-CoV-2 via respiratory activities**

149 Using the partitioning estimates in conjunction with published profiles of the particles expelled  
150 by respiratory activities (Extended Data Fig. 4), we modeled the rates at which talking, singing,  
151 breathing and coughing shed viable SARS-CoV-2 across  $d_a$  (Fig. 4c-f). Among the non-  
152 presenting activities, singing emitted virions most rapidly followed by talking and then  
153 breathing, although talking loudly was similar to singing (Extended Data Fig. 4c,d). These  
154 activities produced more aerosols than droplets, but particle size correlated with the likelihood of  
155 containing virions. Thus, talking, singing and breathing shed SARS-CoV-2 at similar rates via

156 aerosols and droplets: aerosols mediated 25.2-43.4% of the virions expelled by the non-  
157 presenting activities (Fig. 4g). In comparison, coughing shed far greater quantities of virions  
158 (Fig. 4f), of which >99.9% were carried by droplets.

159 We further examined the influences of case heterogeneity and disease course on expelling  
160 SARS-CoV-2 (Fig. 4h, Extended Data Fig. 5). The estimated total shedding rates (over all  
161 particle sizes) for a respiratory activity spanned  $\geq 8.55$  orders of magnitude on each DFSO;  
162 cumulatively from -1 to 10 DFSO, they spanned 11.2 orders of magnitude. Hence, most cases  
163 expelled a negligible number of SARS-CoV-2 virions by talking, singing or breathing. Shedding  
164 occurred most rapidly at 1 DFSO: for the 98<sup>th</sup> cp, singing discharged 31.5 (3.26-379, 95% CI)  
165 virions/min to the ambient environment, while talking emitted 4.67 (0.48-56.1) virions/min and  
166 breathing exhaled 1.27 (0.13-15.2) virions/min; these estimates were two orders of magnitude  
167 greater than those for the 86<sup>th</sup> cp. For the 98<sup>th</sup> cp at -1 DFSO, singing shed 1.31 (0.01-406)  
168 virions/min and breathing exhaled  $5.24 \times 10^{-2}$  ( $5.28 \times 10^{-4}$ -16.3) virions/min. The estimates at 7-10  
169 DFSO were comparable to these presymptomatic ones (Fig. 4h, Extended Data Fig. 5).

170 At 1 DFSO, coughing expelled  $2.13 \times 10^6$  ( $2.20 \times 10^5$ - $2.56 \times 10^7$ ) virions/cough for the 98<sup>th</sup> cp,  
171 90.4 (24.6-372) virions/cough for the 50<sup>th</sup> cp and 2.66 (0.65-13.1) virions/cough for the 25<sup>th</sup> cp  
172 (Extended Data Fig. 5c). At -1 and 10 DFSO, these estimates were reduced by ~2 orders of  
173 magnitude. Thus, most symptomatic cases shed considerable quantities of SARS-CoV-2 by  
174 coughing; a single cough accounted for the virions emitted by weeks of singing for a case.

175 As indicated by similar mean rVLs (Fig. 2) and heterogeneities in rVL (Extended Data  
176 Table 2), asymptomatic, symptomatic/presymptomatic, adult and pediatric COVID-19 cases  
177 showed similar profiles for total shedding rates (Extended Fig. 6a-d). The estimates showed that  
178 the top 6.1%, 2.4% and 1.1% of pediatric cases shed  $\geq 1$  virion/min by singing, talking and

179 breathing, respectively, while 62.5% expelled  $\geq 10$  virions/cough. In general, highly infectious  
180 COVID-19 cases expelled virions more rapidly than did ones with A(H1N1)pdm09 (Extended  
181 Data Fig. 6f).

182

183 **Discussion**

184 This study provided comprehensive, systematic analyses of several factors characterizing the  
185 transmissibility of SARS-CoV-2. First, we evaluated the influence of heterogeneity in rVL. Our  
186 findings show that broad heterogeneity in rVL facilitates greater variation in individual  
187 infectiousness in the COVID-19 pandemic than was found in the 2009 H1N1 pandemic. For each  
188 respiratory activity, SARS-CoV-2 shedding rates span  $> 11$  orders of magnitude throughout the  
189 infectious period. While most COVID-19 cases present minimal transmission risk by talking,  
190 singing or breathing, highly infectious ones, including asymptomatic and presymptomatic  
191 infections, can spread SARS-CoV-2 through these activities. Our model estimates, when  
192 corrected to copies rather than virions, align with recent clinical findings for exhalation rates of  
193 SARS-CoV-2<sup>24</sup>. Moreover, the findings suggest that heterogeneity in rVL may be a virological  
194 factor generally associated with overdispersion for respiratory infections. In this case, rVL  
195 distribution may serve as an early correlate for transmission patterns, including superspreading,  
196 during outbreaks of novel respiratory viruses, providing insight for disease control before large-  
197 scale epidemiological analyses empirically characterize  $k$ .

198 Second, we analyzed SARS-CoV-2 kinetics during respiratory infection. While  
199 heterogeneity remains broad throughout the infectious period, the systematic dataset indicates  
200 that rVL tends to peak at 1 DFSO and be elevated for 1-5 DFSO, coinciding with the period of  
201 highest attack rates observed among close contacts<sup>25</sup>. These results indicate that transmission risk

202 tends to be greatest soon after illness rather than in the presymptomatic period, which concurs  
203 with large tracing studies (6.4-12.6% of secondary infections from presymptomatic  
204 transmission)<sup>26,27</sup> rather than early temporal models (~44%)<sup>14</sup>. Furthermore, our kinetic analysis  
205 suggests that, on average, SARS-CoV-2 reaches diagnostic concentrations 1.60-3.22 days after  
206 respiratory infection (-3.78 to -2.16 DFSO), assuming assay detection limits of 1-3 log<sub>10</sub>  
207 copies/ml, respectively, for nasopharyngeal swabs immersed in 1 ml of transport media.

208 Third, we modeled the likelihood of shedding SARS-CoV-2 via aerosols. Talking, singing  
209 and breathing shed SARS-CoV-2 at comparable rates through droplets and aerosols (up to tens to  
210 hundreds of virions/min). As airborne spread is recognized as a key mode of transmission for  
211 A(H1N1)pdm09<sup>20</sup>, our model estimates and comparative analyses support, particularly for highly  
212 infectious cases, airborne spread as a transmission mode for SARS-CoV-2. While our models  
213 delineated aerosols from droplets at the classical threshold ( $d_a=5\text{ }\mu\text{m}$ ), recent reports show that,  
214 based on emission vectors and environmental conditions, respiratory particles larger than 5  $\mu\text{m}$   
215 can also travel >2 m in air<sup>28,29</sup>, further supporting the plausibility of the airborne transmission of  
216 SARS-CoV-2. However, with short durations of stay in well-ventilated areas, the concentration,  
217 and exposure risk, of aerosols remains correlated with proximity to infectious cases<sup>18,28</sup>.

218 Fourth, we assessed the relative infectiousness of COVID-19 subgroups. Since rVL  
219 distributions are similar among subgroups and the predominant source of aerosols is the non-  
220 presenting respiratory activities (talking, singing and breathing), symptomatic and asymptomatic  
221 infections present similar risks for aerosol spread, as do adult and pediatric cases. However, most  
222 cases shed considerable numbers of virions via large droplets by coughing, a common symptom  
223 of COVID-19<sup>30</sup>. Thus, symptomatic infections tend to be significantly more contagious than  
224 asymptomatic ones, providing a reason as to why asymptomatic cases transmit SARS-CoV-2 at

225 lower relative rates<sup>3</sup>, especially in close contact<sup>31</sup>, despite similar rVLs and increased contact  
226 patterns. Accordingly, children (48-54% of symptomatic cases present with cough)<sup>32,33</sup> tend to be  
227 less contagious by droplet spread than adults (68-80%)<sup>30,33</sup> based on tendencies of  
228 symptomatology rather than rVL.

229 Our study has limitations. The systematic search found a limited number of studies reporting  
230 quantitative specimen measurements from the presymptomatic period, meaning these estimates  
231 may be sensitive to sampling bias. Although additional studies have reported semiquantitative  
232 metrics (cycle thresholds), these data were excluded because they cannot be compared on an  
233 absolute scale due to batch effects<sup>34</sup>, limiting use in compound analyses. Furthermore, our  
234 analyses considered population-level estimates of the infectious periods and viability  
235 proportions, which omit individual variation in the dynamics of virus viability. Some patients  
236 shed SARS-CoV-2 with diminishing viability soon after symptom onset<sup>13</sup>, while others produce  
237 replication-competent virus for weeks<sup>35</sup>. It remains unelucidated how case characteristics and  
238 environmental factors affect the viability dynamics of SARS-CoV-2.

239 Taken together, our findings provide a potential path forward for disease control. They  
240 highlight the disproportionate role of high-risk cases, settings and circumstances in propelling  
241 the COVID-19 pandemic. Since highly infectious cases, regardless of age or symptomatology,  
242 can rapidly shed SARS-CoV-2 via both droplets and aerosols, airborne spread should also be  
243 recognized as a transmission risk, including for superspreading. Strategies to abate infection  
244 should limit crowd numbers and duration of stay while reinforcing distancing and then  
245 widespread mask usage; well-ventilated settings can be recognized as lower risk venues.  
246 Coughing sheds considerable quantities of virions for most infections, while rVL tends to peak at  
247 1 DFSO and can be high throughout the infectious period. Thus, immediate, sustained self-

248 isolation upon symptom presentation is crucial to curb transmission from symptomatic cases.  
249 While diagnosing COVID-19, qRT-PCR can also help to triage contact tracing, prioritizing  
250 patients with higher specimen measurements: for nasopharyngeal swabs immersed in 1 ml of  
251 transport media,  $\geq 7.14$  (7.07-7.22, 95% CI)  $\log_{10}$  copies/ml corresponds to  $\geq 80^{\text{th}}$  cp. Doing so  
252 may identify asymptomatic and presymptomatic cases more efficiently, a key step towards  
253 mitigation as the pandemic continues.

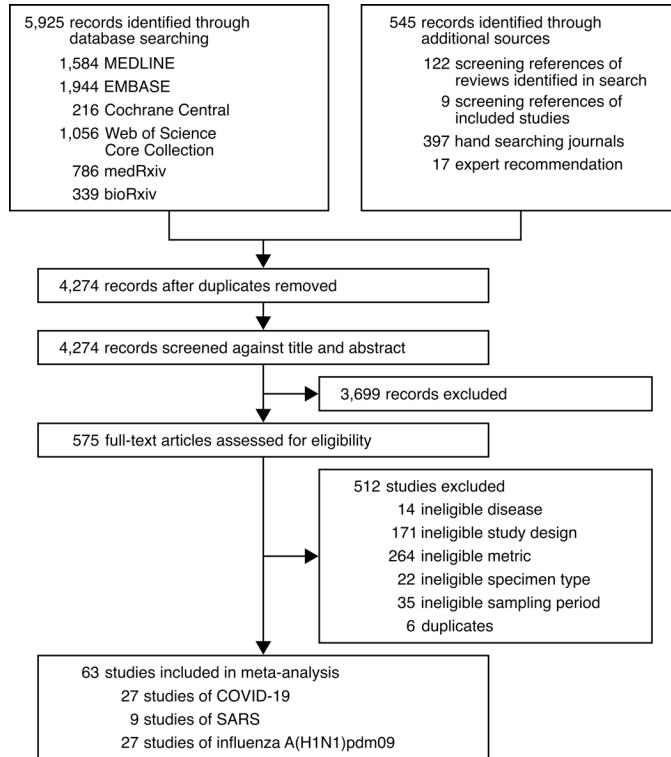
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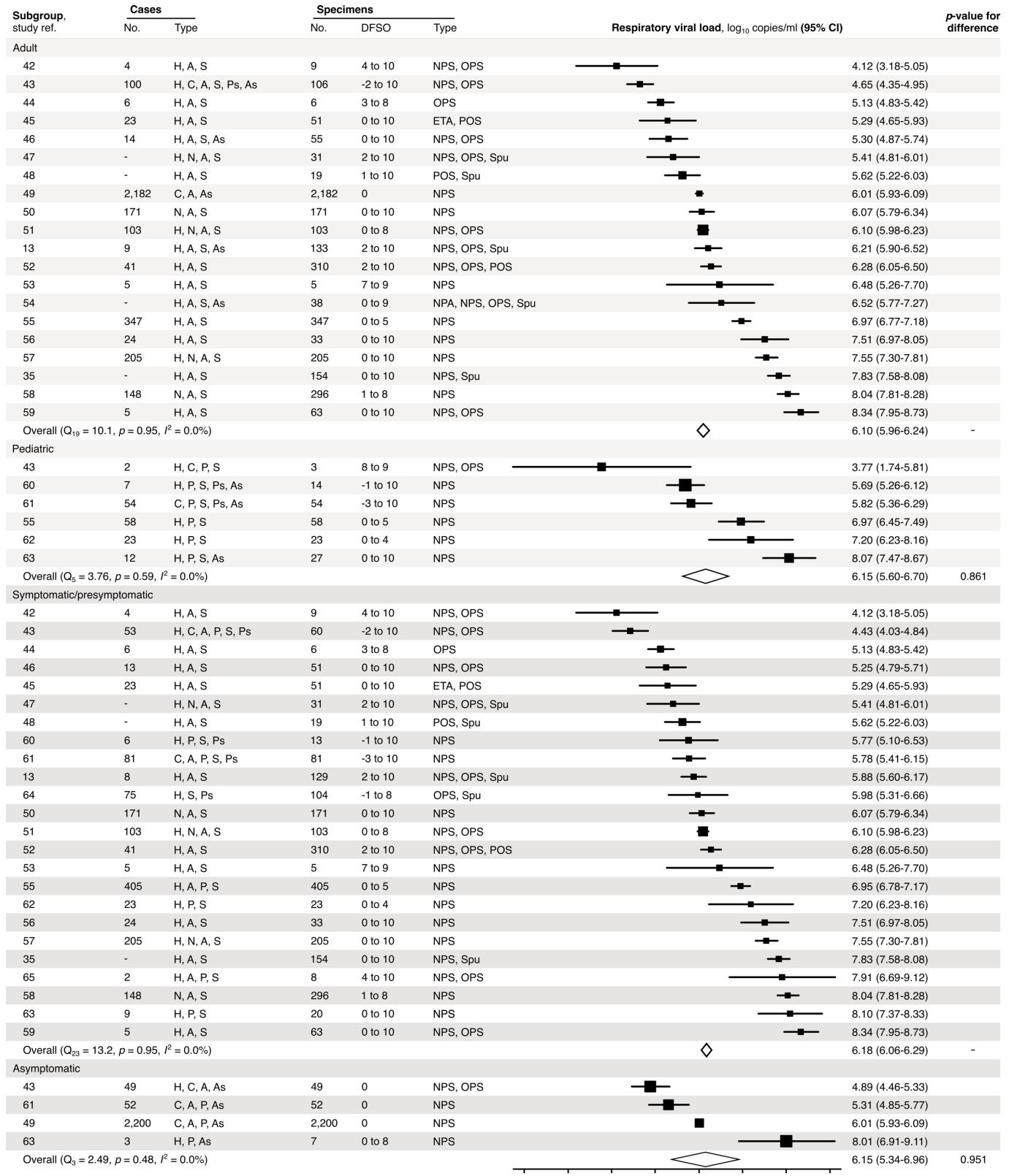
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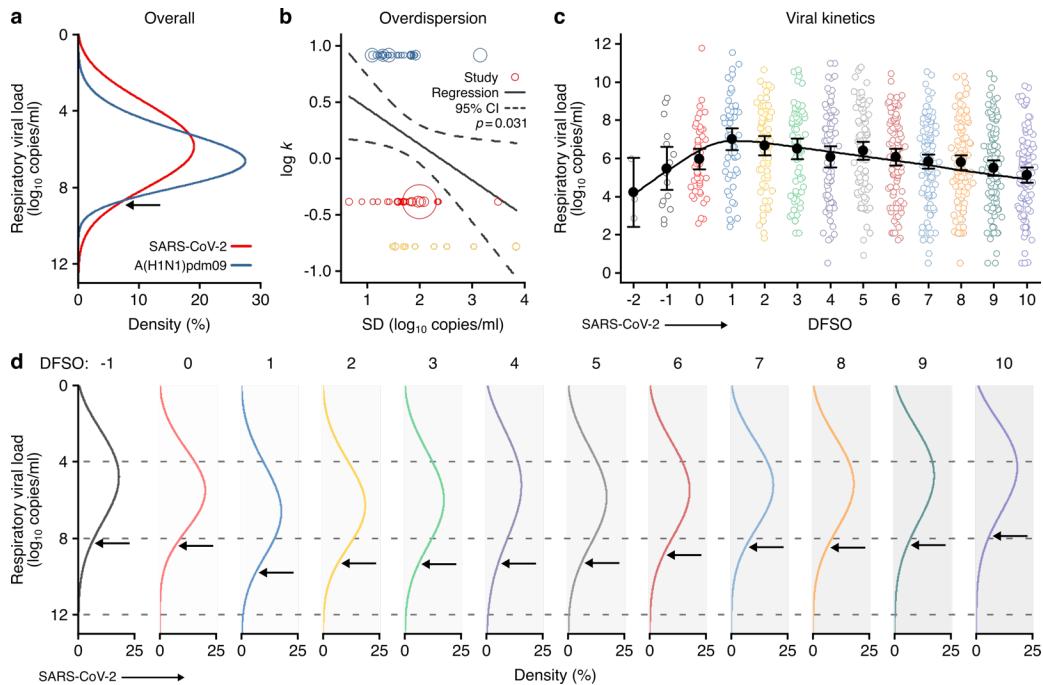


342

343 **Fig. 1. Development of the systematic dataset.**

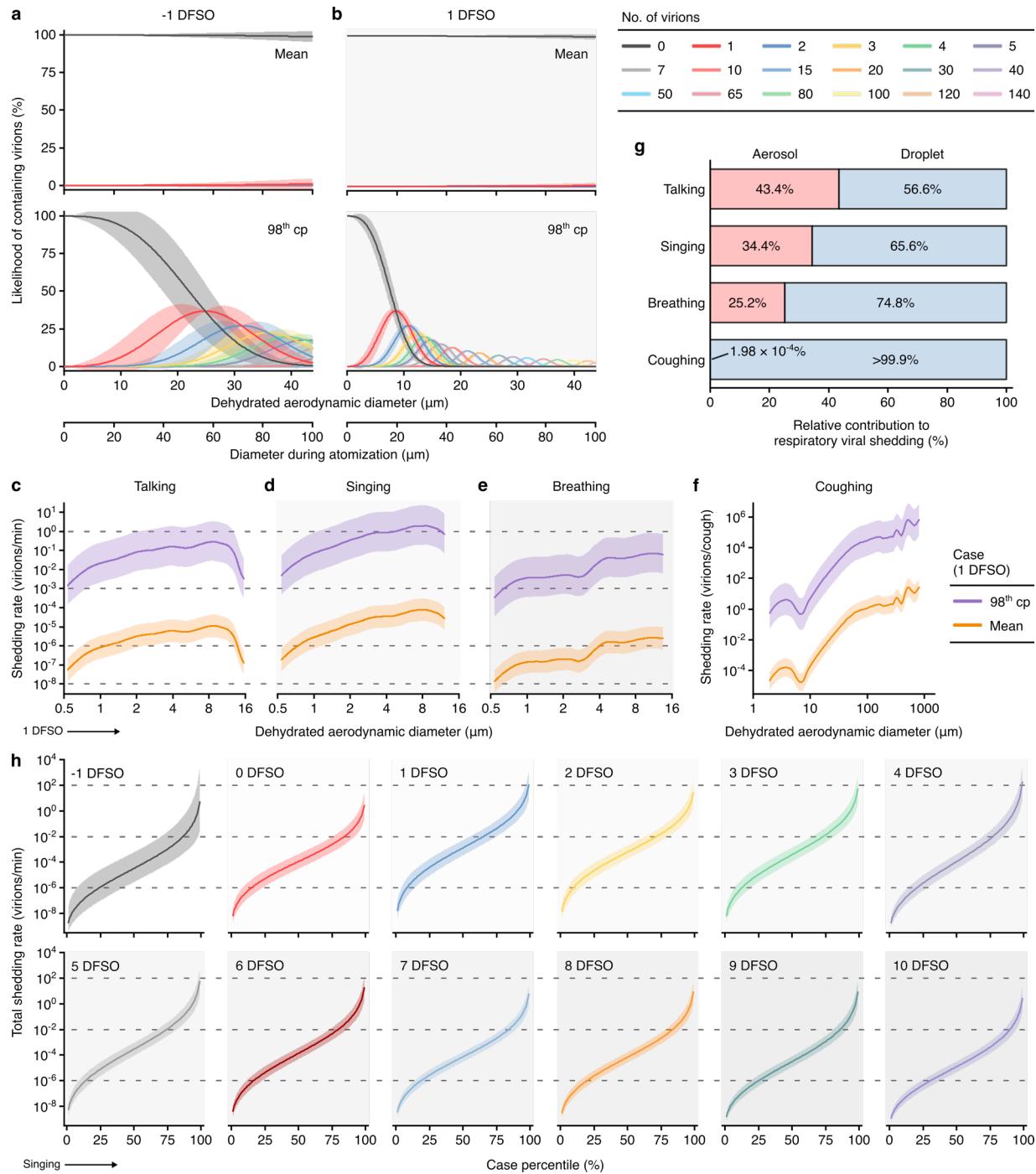


345 **Fig. 2. Subgroup analyses of SARS-CoV-2 respiratory viral load during the infectious**  
346 **period.** Random-effects meta-analyses comparing the expected rVLs of adult (>18 years old)  
347 COVID-19 cases with pediatric ( $\leq 18$  years old) ones (top) and symptomatic/presymptomatic  
348 infections with asymptomatic ones (bottom) during the infectious period. Quantitative specimen  
349 measurements were used to estimate rVLs, which refer to virus concentrations in the respiratory  
350 tract. Case types: hospitalized (H), not admitted (N), community (C), adult (A), pediatric (P),  
351 symptomatic (S), presymptomatic (Ps) and asymptomatic (As). Specimen types: endotracheal  
352 aspirate (ETA), nasopharyngeal aspirate (NPA), nasopharyngeal swab (NPS), oropharyngeal  
353 swab (OPS), posterior oropharyngeal saliva (POS) and sputum (Spu). Studies after ref. 35 are  
354 listed in Methods. Dashes denote case numbers that were not obtained. Box sizes are  
355 proportional to weighting in the overall estimates. Two-sided Welch's *t*-tests, non-significance  
356 ( $p > 0.05$ ).



357

358 **Fig. 3. Heterogeneity and kinetics of SARS-CoV-2 respiratory viral load. a,** Estimated  
359 distribution of rVL for SARS-CoV-2 ( $n=3,778$  samples from  $n=24$  studies) and A(H1N1)pdm09  
360 ( $n=512$  samples from  $n=10$  studies) throughout the infectious periods. **b,** Meta-regression of  
361 dispersion parameter ( $k$ ) with the standard deviation (SD) of rVLs from included studies ( $r=-$   
362 0.27). Estimates of  $k$  were pooled from the literature. Red, yellow and blue circles denote  
363 COVID-19 ( $n=27$ ), SARS ( $n=9$ ) and A(H1N1)pdm09 ( $n=27$ ) studies, respectively. Circle sizes  
364 are proportional to weighting in the meta-regression. The  $p$ -value was obtained using the meta-  
365 regression slope  $t$ -test. **c,** SARS-CoV-2 rVLs fitted to a mechanistic model of viral kinetics  
366 ( $r^2=0.88$ ). Filled circles and bars depict mean estimates and 95% CIs. Open circles  
367 show the entirety of individual sample data over DFSO (left to right,  $n=3, 15, 48, 59, 69, 71, 81,$   
368 87, 102, 125, 119, 117 and 110 samples from  $n=19$  studies). **d,** Estimated distributions of SARS-  
369 CoV-2 rVL over DFSO. Earlier DFSO were excluded based on limited data. Weibull  
370 distributions were fitted on the entirety of individual sample data for the virus (a) or DFSO (d) in  
371 the systematic dataset. Arrows denote 90<sup>th</sup> case percentiles for SARS-CoV-2 rVL.



372

373 **Fig. 4. Heterogeneity in shedding SARS-CoV-2 via droplets and aerosols. a,b,** Likelihood of  
 374 respiratory particles containing viable SARS-CoV-2 when expelled by the mean (top) or 98<sup>th</sup>  
 375 case percentile (cp) (bottom) COVID-19 cases at -1 (a) or 1 (b) DFSO. The models considered  
 376 virus viability within dehydrated particles. Diameters during atomization were included to show

377 their size relationship with dehydrated aerodynamic diameter ( $d_a$ ), but not likelihood of  
378 containing virions during atomization. For higher no. of virions, some likelihood curves were  
379 omitted to aid visualization. When the likelihood for 0 virions approaches 0%, particles are  
380 expected to contain at least one viable copy. **c-f**, Rate that the mean and 98<sup>th</sup>-cp COVID-19 cases  
381 at 1 DFSO shed viable SARS-CoV-2 by talking (**c**), singing (**d**), breathing (**e**) or coughing (**f**)  
382 over  $d_a$ . **g**, Relative contribution of aerosols ( $d_a \leq 5 \mu\text{m}$ , red bar) and droplets ( $d_a > 5 \mu\text{m}$ , blue bar)  
383 to shedding virions for the respiratory activities. **h**, Case heterogeneity in the total shedding rate  
384 (over all particle sizes) of virions via singing across the infectious period. Earlier  
385 presymptomatic days were excluded based on limited data. Data range between the 1<sup>st</sup> and 99<sup>th</sup>  
386 cps. Lines and bands represent estimates and 95% CIs, respectively, for likelihoods or Poisson  
387 means.

388    **Methods**

389    **Search strategy, selection criteria and data collection**

390    We undertook a systematic review and prospectively submitted the systematic review protocol  
391    for registration on PROSPERO (registration number, CRD42020204637). Other than the title of  
392    this study, we have followed PRISMA reporting guidelines<sup>36</sup>. The systematic review was  
393    conducted according to Cochrane methods guidance<sup>37</sup>.

394       The search included papers that (i) reported positive, quantitative measurements (copies/ml  
395    or an equivalent metric) of SARS-CoV-2, SARS-CoV-1 or A(H1N1)pdm09 in human  
396    respiratory specimens (ETA, NPA, NPS, OPS, POS and Spu) from COVID-19, SARS or  
397    A(H1N1)pdm09 cases; (ii) reported data that could be extracted from the infectious periods of  
398    SARS-CoV-2 (defined as -3 to +10 DFSO for symptomatic cases and 0 to +10 days from the day  
399    of laboratory diagnosis for asymptomatic cases), SARS-CoV-1 (defined as 0 to +20 DFSO or the  
400    equivalent asymptomatic period) or A(H1N1)pdm09 (defined as -2 to +9 DFSO for symptomatic  
401    cases and 0 days to +9 days from the day of laboratory diagnosis for asymptomatic cases); and  
402    (iii) reported data for two or more cases with laboratory-confirmed COVID-19, SARS or  
403    A(H1N1)pdm09. Quantitative specimen measurements were considered after RNA extraction for  
404    diagnostic sequences of SARS-CoV-2 (*Ofr1b*, *N*, *RdRp* and *E* genes), SARS-CoV-1 (*Ofr1b*, *N*  
405    and *RdRp* genes) and A(H1N1)pdm09 (*HA* and *M* genes).

406       Studies were excluded, in the following order, if they (i) studied an ineligible disease; (ii)  
407    had an ineligible study design, including those that were reviews of evidence (e.g., scoping,  
408    systematic, narrative), did not include primary clinical human data, reported data for less than  
409    two cases due to an increased risk of selection bias, were incomplete (e.g., ongoing clinical  
410    trials), did not report an RNA extraction step before measurement or were studies measuring

411 environmental samples; (iii) reported an ineligible metric for specimen concentration (e.g.,  
412 qualitative RT-PCR or cycle threshold [Ct] values without calibration included in the study); (iv)  
413 reported quantitative measurements from an ineligible specimen type (e.g., blood specimens,  
414 pooled specimens or self-collected POS or Spu patient specimens in the absence of a healthcare  
415 professional); (v) reported an ineligible sampling period (consisted entirely of data that could not  
416 be extracted from within the infectious period); or (vi) were duplicates of an included study (e.g.,  
417 preprinted version of published paper or duplicates not identified by Covidence). We included  
418 data from control groups receiving standard of care in interventional studies but excluded data  
419 from the intervention group. Patients in the intervention group are, by definition, systematically  
420 different from general case populations because they receive therapies not being widely used for  
421 treatment, which may influence virus concentrations. Interventional studies examining the  
422 comparative effectiveness of two or more treatments were excluded for the same reason. Studies  
423 exclusively reporting semiquantitative measurements (e.g., Ct values) of specimen concentration  
424 were excluded, as these measurements are sensitive to batch inconsistencies and, without proper  
425 calibration, cannot be compared on an absolute scale across studies<sup>34</sup>.

426 We searched, without the use of filters or language restrictions, the following sources:  
427 MEDLINE (via Ovid, 1946 to 7 August 2020), EMBASE (via Ovid, 1974 to 7 August 2020,  
428 Cochrane Central Register of Controlled Trials (via Ovid, 1991 to 7 August 2020), Web of  
429 Science Core Collection (including: Science Citation Index Expanded, 1900 to 7 August 2020;  
430 Social Sciences Citation Index, 1900 to 7 August 2020; Arts & Humanities Citation Index, 1975  
431 to 7 August 2020; Conference Proceedings Citation Index - Science, 1990 to 7 August 2020;  
432 Conference Proceedings Citation Index - Social Sciences & Humanities, 1990 to 7 August 2020;  
433 and Emerging Sources Citation Index, 2015 to 7 August 2020), as well as MedRxiv and BioRxiv

434 (both searched through Google Scholar via the Publish or Perish program, to 7 August 2020).  
435 We also gathered studies by searching through the reference lists of review articles identified by  
436 the database search, by searching through the reference lists of included articles, through expert  
437 recommendation (by Epic J. Topol, Akiko Iwasaki and A. Marm Kilpatrick on Twitter) and by  
438 hand-searching through journals (*Nature*, *Nat. Med.*, *Science*, *NEJM*, *Lancet*, *Lancet Infect. Dis.*,  
439 *JAMA*, *JAMA Intern. Med.* and *BMJ*). A comprehensive search was developed by a librarian,  
440 which included subject headings and keywords. The search strategy had 3 main concepts  
441 (disease, specimen type and outcome), and each concept was combined using the appropriate  
442 Boolean operators. The search was tested against a sample set of known articles that were pre-  
443 identified. The line-by-line search strategies for all databases are included in Supplementary  
444 Tables 1-5. The search results were exported from each database and uploaded to the Covidence  
445 online system for deduplication and screening.

446 Two authors independently screened titles and abstracts, reviewed full texts, collected data  
447 and assessed risk of bias via Covidence and a hybrid critical appraisal checklist based on the  
448 Joanna Briggs Institute (JBI) tools for case series, analytical cross-sectional studies and  
449 prevalence studies<sup>38-40</sup>. To evaluate the sample size in a study, we used the following calculation:

$$450 \quad n^* = \frac{z^2 \sigma}{d^2}, \quad (1)$$

451 where  $n^*$  is the sample size threshold,  $z$  is the z-score for the level of confidence (95%),  $\sigma$  is the  
452 standard deviation (assumed to be  $3 \log_{10}$  copies/ml, one quarter of the full range of rVLs) and  $d$   
453 is the marginal error (assumed to be  $1 \log_{10}$  copies/ml, based on the minimum detection limit for  
454 qRT-PCR across studies)<sup>41</sup>. The hybrid JBI critical appraisal checklist is shown in the  
455 Supplementary Notes. Inconsistencies were resolved by discussion and consensus.

456        The search found 27 studies for COVID-19<sup>13,35,42-66</sup>, 9 studies for SARS<sup>67-75</sup> and 27 studies  
457        for A(H1N1)pdm09<sup>76-102</sup>. Quantitative specimen measurements were collected directly if  
458        reported numerically or using WebPlotDigitizer 4.3 (<https://apps.automeris.io/wpd/>) if reported  
459        graphically. For included studies, we also collected the relevant numbers of cases, types of cases,  
460        volumes of transport media, pharmacotherapies, DFSO (for symptomatic cases) or day relative to  
461        initial laboratory diagnosis (for asymptomatic cases) on which each specimen was taken and  
462        numbers of tested specimens. Hospitalized cases were defined as those being tested in a hospital  
463        setting and then admitted. Non-admitted cases were defined as those being testing in a hospital  
464        setting but not admitted. Community cases were defined as those being tested in a community  
465        setting. Symptomatic, presymptomatic and asymptomatic infections were defined as in the study.  
466        Based on rare description in the included studies, paucisymptomatic infections, when defined in  
467        a study, were included with symptomatic ones. Pediatric cases were defined as those of 18 years  
468        of age or lower or as defined in the study. Adult cases were defined as those above 18 years of  
469        age or as defined in the study.

470

## 471        **Meta-analysis of rVLs**

472        Based on the search design and composition of included studies, the meta-analysis overall  
473        estimates were the expected SARS-CoV-2, SARS-CoV-1 and A(H1N1)pdm09 rVL when  
474        encountering a COVID-19, SARS or A(H1N1)pdm09 case, respectively, during their infectious  
475        period. To determine rVLs, data collected on positive, quantitative specimen measurements were  
476        converted to the RNA concentration in the respiratory tract. Viral concentrations in respiratory  
477        specimens were denoted as specimen measurements, whereas viral concentrations in the  
478        respiratory tract were denoted as rVLs. For example, measurements from swabbed specimens

479 (NPS and OPS) typically report the RNA concentration in viral transport media. Based on the  
480 expected uptake volume for swabs ( $0.128 \pm 0.031$  ml, mean  $\pm$  SD)<sup>103</sup> or reported collection  
481 volume for expulsed fluid in each study (e.g., 0.5 to 1 ml) along with the reported volume of  
482 transport media in each study (e.g., 1 ml), we calculated the dilution factor for each respiratory  
483 specimen to estimate the rVLs. If the diluent volume was not reported, then the dilution factor  
484 was calculated assuming a volume of 1 ml (NPS and OPS), 2 ml (POS and ETA) or 3 ml (NPA)  
485 of transport media<sup>43,45,71</sup>. Unless dilution was reported for Spu specimens, we used the specimen  
486 measurement as the rVL<sup>13</sup>. The non-reporting of diluent volume was noted as an element  
487 increasing risk of bias in the hybrid JBI critical appraisal checklist. Viral load estimates (based  
488 on instrumentation, calibration, procedures and reagents) are not standardized. While the above  
489 procedures (including only quantitative measurements after extraction, collecting assay detection  
490 limits, correcting for specimen dilution) have considered many of these factors, non-  
491 standardization is an inherent limitation in interpreting specimen measurements across studies.

492 Pooled estimates and 95% CIs for the expected rVL of each virus across their infectious  
493 period were calculated using a random-effects meta-analysis. The estimates for rVL assumed  
494 that each viral copy was extracted and quantified from the tested specimen aliquot. For studies  
495 reporting summary statistics in medians and interquartile or total ranges, we derived estimates of  
496 the mean and variance and calculated the 95% CIs<sup>104</sup>. All calculations were performed in units of  
497  $\log_{10}$  copies/ml. Between-study heterogeneity in meta-analysis was assessed using the  $I^2$  and  $\tau^2$   
498 statistics. The weighting for each study in its virus group was calculated as the reciprocal of the  
499 rVL variance.

500

501 **Subgroup analyses of rVLs**

502 Subgroup analyses were conducted to compare the expected rVLs of SARS-CoV-2 in adult,  
503 pediatric, symptomatic and asymptomatic COVID-19 cases, as previously defined, during the  
504 infectious period. The overall estimate for each subgroup was the expected rVL when  
505 encountering a case of that subgroup during the infectious period. Studies reporting data  
506 exclusively from a subgroup of interest were included in the analysis without modification. For  
507 studies in which data for these subgroups constituted only part of its dataset, rVLs from the  
508 subgroup were collected to calculate the mean, variance and 95% CIs. All calculations were  
509 performed in units of  $\log_{10}$  copies/ml. In the analysis, we excluded studies with only a single case  
510 in our subgroups of interest. Pooled estimates and 95% CIs for each subgroup were calculated  
511 using a random-effects meta-analysis, in which between-study heterogeneity was assessed using  
512 the  $I^2$  and  $\tau^2$  statistics. The weighting for each study in its subgroup was calculated as the  
513 reciprocal of the rVL variance.

514

## 515 **Distribution of rVL**

516 To analyze heterogeneity in rVLs, we pooled the entirety of individual sample data (reported as  
517 individual specimen measurements rather through descriptive statistics) in the systematic dataset  
518 by disease, COVID-19 subgroups and DFSO. For analyses of SARS-CoV-2 dynamics across  
519 DFSO, we included estimated rVLs from negative qRT-PCR measurements of respiratory  
520 specimens ( $n=3, 3, 6, 8, 12, 15, 13, 17$  and 14 negative specimens for 2, 3, 4, 5, 6, 7, 8, 9 and 10  
521 DFSO, respectively) for cases that had previously been quantitatively confirmed to have  
522 COVID-19. These rVLs were estimated based on the reported assay detection limit in the  
523 respective study. Probability plots and modified Kolmogorov–Smirnov tests were used to  
524 determine the suitability of normal, lognormal, gamma and Weibull distributions to describe the

525 distribution of rVLs for SARS-CoV-2, SARS-CoV-1 and A(H1N1)pdm09. For each virus, the  
526 data best conformed to Weibull distributions, which is described by the probability density  
527 function

$$528 \quad f(v) = \frac{\alpha}{\beta} \left( \frac{v}{\beta} \right)^{\alpha-1} e^{-(v/\beta)^\alpha}, \quad (2)$$

529 where  $\alpha$  is the shape factor,  $\beta$  is the scale factor and  $v$  is rVL ( $v \geq 0 \log_{10}$  copies/ml). In this  
530 distribution, the value of the rVL at the  $x^{\text{th}}$  percentile was determined using the quantile function,

$$531 \quad v_x = \beta [-\ln(1-x)]^{1/\alpha}. \quad (3)$$

532 For cp curves, we used eq. (3) to determine rVLs from the 1<sup>st</sup> cp to the 99<sup>th</sup> cp (step size, 1%).

533 Curve fitting to eq. (2) and calculation of eq. (3) and its 95% CI was performed using the  
534 Distribution Fitter application in Matlab R2019b (MathWorks, Inc., Natick, Massachusetts,  
535 USA).

536

### 537 **Meta-regression of $k$ and heterogeneity in rVL**

538 To assess the relationship between  $k$  and heterogeneity in rVL, we performed a univariate meta-  
539 regression ( $\log k = a(\text{SD}) + b$ , where  $a$  is the slope for association and  $b$  is the intercept)  
540 between pooled estimates of  $k$  (based on studies describing community transmission) for  
541 COVID-19 ( $k=0.409$ )<sup>4-6,105-108</sup>, SARS ( $k=0.165$ )<sup>17</sup> and A(H1N1)pdm09 ( $k=8.155$ )<sup>22,23</sup> and the SD  
542 of the rVLs in each study. Since the negative binomial distribution, from which  $k$  is derived<sup>17</sup>, is  
543 analogous to a compound Poisson distribution in which each random variable is Log( $k$ )-  
544 distributed, the meta-regression was performed with  $\log k$ . Based on negligible between-study  
545 heterogeneity, we used a fixed-effects model. This analysis assumes that the SD of rVLs in each  
546 study estimates SD of rVL for the disease. Thus, for weighting in the meta-regression, we used  
547 the proportion of rVL samples for each study relative to the entire systematic dataset ( $W_i =$

548  $n_i/n_{\text{total}}$ ). The regression line, its 95% CI and its Pearson correlation coefficient ( $r$ ) were  
549 presented along with the  $p$ -value for association (meta-regression slope  $t$ -test for  $a$ ) between the  
550 two variables. The meta-regression assumed that the viability proportion (for viruses exiting the  
551 respiratory tract) was similar across cases for a given respiratory infection; it could be a different  
552 value for different diseases. The meta-regression also assumed that the rate profile of particles  
553 expelled by respiratory activities (e.g., talking) is similar among the diseases. The limit of  
554 detection for qRT-PCR instruments used in the included studies did not significantly affect the  
555 analysis of heterogeneity in rVL, as these limits tended to be below the values found for  
556 specimens with low virus concentrations.

557

## 558 **Viral kinetics**

559 To model the kinetics of SARS-CoV-2 rVL, we used a mechanistic epithelial cell-limited model  
560 for the respiratory tract<sup>109</sup>, based on the system of differential equations:

561 
$$\frac{dT}{dt} = -\beta TV \quad (4)$$

562 
$$\frac{dI}{dt} = \beta TV - \delta I \quad (5)$$

563 
$$\frac{dV}{dt} = pI - cV, \quad (6)$$

564 where  $T$  is the number of uninfected target cells,  $I$  is the number of productively infected cells,  $V$   
565 is the rVL,  $\beta$  is the infection rate constant,  $p$  is the rate at which airway epithelial cells shed virus  
566 to the extracellular fluid,  $c$  is the clearance rate of the virus and  $\delta$  is the clearance rate of  
567 productively infected cells. Parameter units are summarized in Extended Data Table 3. Using  
568 these parameters, the viral half-life in the respiratory tract ( $t_{1/2} = \ln 2/c$ ) and the half-life of  
569 productively infected cells ( $t_{1/2} = \ln 2/\delta$ ) and their 95% CIs could be estimated. Moreover, the

570 cellular basic reproductive number (the expected number of secondary infected cells from a  
571 single productively infected cell placed in a population of susceptible cells) was calculated by

572 
$$R_{0,c} = \frac{p\beta T_0}{c\delta}, \quad (7)$$

573 where  $T_0$  is the initial number of susceptible cells<sup>109</sup>.

574 For initial parameterization, eqs. (4)-(6) were simplified according to a quasi-steady state  
575 approximation<sup>110</sup> to

576 
$$\frac{dT}{dt} = -\beta TV \quad (8)$$

577 
$$\frac{dV}{dt} = rTV - \delta V, \quad (9)$$

578 where  $r = p\beta/c$ , for a form with greater numerical stability. The system of differential equations  
579 was fitted on the mean estimates of SARS-CoV-2 rVL between -2 and 10 DFSO using the  
580 entirety of individual sample data in units of copies/ml. Numerical analysis was implemented  
581 using the Fit ODE app in OriginPro 2019b (OriginLab Corporation, Northampton,  
582 Massachusetts, USA) via the Runge-Kutta method and initial parameters  $V_0$ ,  $I_0$  and  $T_0$  of 4  
583 copies/ml, 0 cells and  $5 \times 10^7$  cells, respectively, for the range -5 to 10 DFSO. The analysis was  
584 first performed with eqs. (8)-(9). These output parameters were then used to initialize final  
585 analysis using eqs. (4)-(6), where the estimates for  $\beta$  and  $\delta$  were input as fixed and variable  
586 parameters, respectively. The fitted line and its coefficient of determination ( $r^2$ ) were presented.

587 To estimate the average incubation period, we extrapolated the kinetic model to 0 and 1  
588  $\log_{10}$  copies/ml pre-symptom onset. To estimate the average duration of shedding, we  
589 extrapolated the model to 0  $\log_{10}$  copies/ml post-symptom onset. Unlike experimental estimates,  
590 this estimate for duration of shedding was not defined by assay detection limits. These analyses  
591 had limitations. To estimate the average DFSO on which SARS-CoV-2 concentration reached

592 diagnostic levels, we extrapolated the model pre-symptom onset to the equivalent of 1 and 3  
593  $\log_{10}$  copies/ml in specimen concentration (chosen as example assay detection limits), as  
594 described by the dilution factor estimation above. The average time from respiratory infection to  
595 reach diagnostic levels was then calculated by subtracting these values from the incubation  
596 period for 0  $\log_{10}$  copies/ml. However, the extrapolated time for SARS-CoV-2 to reach  
597 diagnostic concentrations in the respiratory tract should be validated in tracing studies, in which  
598 contacts are prospectively subjected to daily sampling.

599

## 600 **Considerations for particle dehydration**

601 The desiccation time of a particle in air was described  $t_{des} = b^{-1}(d_i^2 - d_{des}^2)$ , where  $b$  is  
602 prefactor for dehydration rate which depends on the environmental conditions,  $d_i$  is the initial  
603 hydrated diameter and  $d_{des}$  is particle diameter after desiccation<sup>111</sup>. After desiccation, the  
604 remaining non-volatile matter (ions, molecules, viruses and cells) governs particle size, which is  
605 approximately 0.44 times the initial size of particles atomized in the respiratory tract<sup>112</sup>.

606 Dehydrated aerodynamic diameter was calculated by  $d_a = d_p(\rho/\rho_0)^{1/2}$ , where  $d_p$  is the  
607 dehydrated particle size,  $\rho$  is the material density of the respiratory particle and  $\rho_0$  is the  
608 reference material density (1 g/cm<sup>3</sup>). For conservative estimates, the value of  $b$  was taken to be  
609 64.9  $\mu\text{m}^2/\text{s}$ <sup>113</sup> based on conditions of room temperature and a relative humidity of 59% (near the  
610 upper limit of 60% for healthcare and typical indoor specifications)<sup>114</sup>. The equation for  
611 desiccation time indicated that respiratory particles begin to dehydrate immediately upon release  
612 to the ambient environment. Desiccation occurred rapidly, as the equation estimated that an 11.4-  
613  $\mu\text{m}$  particle desiccated to 5  $\mu\text{m}$  in 1.6 s within the model conditions, and this value was an upper  
614 limit for the desiccation times of aerosols ( $t_{des} \leq 1.6$  s).

615

616 **Likelihood of respiratory particles containing virions**

617 To calculate an unbiased estimator for viral partitioning (the expected number of viable copies in  
618 an expelled particle at a given size), we multiplied rVLs with the volume equation for spherical  
619 particles during atomization and the estimated viability proportion:

620 
$$\lambda = \frac{\pi \rho v_p \gamma v}{6} d^3, \quad (10)$$

621 where  $\lambda$  is the expectation value,  $\rho$  is the material density of the respiratory particle (997 g/m<sup>3</sup>),  
622  $v_p$  is the volumetric conversion factor (1 ml/g),  $\gamma$  is the viability proportion,  $v$  is the rVL and  $d$  is  
623 the hydrated diameter of the particle during atomization. The model assumed  $\gamma$  was 0.1% for the  
624 viruses. For influenza, approximately 0.1% of copies in particles expelled from the respiratory  
625 tract represent viable virus<sup>115</sup>, which is equivalent to one in 3 log<sub>10</sub> copies/ml for rVL or, after  
626 dilution in transport media, roughly one in 4 log<sub>10</sub> copies/ml for specimen concentration. Recent  
627 reports have detected culture-positive respiratory specimens with SARS-CoV-2 concentrations  
628 down to 4 log<sub>10</sub> copies/ml<sup>13</sup>, including from pediatric patients<sup>62</sup> and in the presymptomatic  
629 period<sup>15</sup>, suggesting the assumption was also suitable for SARS-CoV-2.

630 Likelihood profiles were determined using Poisson statistics, as described by the probability  
631 mass function

632 
$$P(X = k) = \frac{\lambda^k e^{-\lambda}}{k!}, \quad (11)$$

633 where  $k$  is the number of virions partitioned within the particle. For  $\lambda$ , 95% CIs were determined  
634 using the variance of its rVL estimate. To determine 95% CIs for likelihood profiles from the  
635 probability mass function, we used the delta method, which specifies

636 
$$\text{Var}(g(\boldsymbol{\theta})) \approx \sigma^2 \dot{g}(\boldsymbol{\theta})' \mathbf{D} \dot{g}(\boldsymbol{\theta}), \quad (12)$$

637 where  $\sigma^2 \mathbf{D}$  is the covariance matrix of  $\boldsymbol{\theta}$  and  $\dot{g}(\boldsymbol{\theta})$  is the gradient of  $g(\boldsymbol{\theta})$ . For the univariate  
638 Poisson distribution,  $\sigma^2 \mathbf{D} = \lambda$  and

639 
$$\dot{g}(\theta) = \frac{\lambda^{k-1} e^{-\lambda}}{k!} (k - \lambda). \quad (13)$$

640 Based on the relative relationship between the residence time of expelled particles before  
641 assessment ( $\sim 5$  s)<sup>116</sup> in the referenced study<sup>115</sup> and the estimated dehydration rates of expelled  
642 particles, we took the viability proportion (0.1%) to be for dehydrated particles. The model  
643 calculated partitioning of copies using the hydrated volume and then applied the viability  
644 proportion for number of virions in particles after emission and dehydration. Thus, we compared  
645 likelihoods among expelled, dehydrated particles. In Fig. 4, the comparison between hydrated  
646 and dehydrated diameters showed only the relationship in particle size and not the relationship in  
647 likelihood of containing viable virus. Based on the scope of the study, the model did not account  
648 for the virion half-life as particles deposit onto surfaces or remain suspended in air<sup>117</sup>.

649

## 650 Rate profiles of particles expelled by respiratory activities

651 For the rate profiles of particles expelled during respiratory activities, we used distributions from  
652 the literature. For coughing, we considered the rate (particles/cough) of expelling particles at  
653 different sizes, as determined by Loudon and Roberts<sup>118</sup>, by calculating the mean number of  
654 respiratory particles expelled per cough based on subject tests RI, RII, LI, LII and EI (EI was  
655 presumed to be an outlier based on the relative rate when compared to EI). These particles were  
656 taken to be dehydrated based on the deposition time in the experiment relative to estimated  
657 dehydration rates. We compared this rate profile to that of Duguid<sup>119</sup>, which were taken to be  
658 hydrated particles based on experimental design. For talking, singing and breathing, we obtained  
659 data from Morawska et al<sup>120</sup>. Rate profiles (particles/min) were calculated by converting the

660 normalized concentration (particles/cm<sup>3</sup>) at each particle size based on normalization (32  
661 channels per decade) for the aerodynamic particle sizer (APS) used, unit conversion (cm<sup>3</sup> to L)  
662 and the sample flow rate (1 L/min). Rate profiles of talking and singing were isolated from  
663 breathing by subtracting the contribution of breathing to the combined data. Particles were taken  
664 to be dehydrated based on the minimum particle age in the measurements. Based on the APS  
665 used, the analyzed range for  $d_a$  was 0.3-20  $\mu\text{m}$ . While larger droplets may potentially be expelled  
666 by the respiratory activities, the data suggested that their emission rates were minimal, and there  
667 was a limited bias associated with instrumentation. We compared these data for talking with rate  
668 profiles of talking loudly and talking quietly from Asadi et al<sup>121</sup>. For data reported in a size  
669 channel, we took the particle size to be the median value. Curves based on discrete particle  
670 measurements were connected using the nonparametric Akima spline function.

671

## 672 **Shedding virions via respiratory droplets and aerosols**

673 To determine the respiratory shedding rate across particle size, rVL estimates and the hydrated  
674 diameters of particles expelled by a respiratory activity were input into eq. (10), and the output  
675 was then multiplied by the rate profile of the activity (talking, singing, breathing or coughing).  
676 Dehydration and viability considerations were continued from the likelihood models. The model  
677 used particle profiles from (coughing) Loudon and Roberts<sup>118</sup> or (talking, singing and breathing)  
678 Morawaska et al<sup>120</sup>.

679 To determine the total respiratory shedding rate for a given respiratory activity across cp, we  
680 determined the cumulative hydrated volumetric rate (by summing the hydrated volumetric rates  
681 across particle sizes for that respiratory activity) and input it into eq. (10). Using rVLs as

682 determined by the Weibull quantile functions, we then calculated the Poisson means and their  
683 95% CIs at different cps.

684 To assess the relative contribution of aerosols and droplets to mediating respiratory viral  
685 shedding for a given respiratory activity, we calculated the proportion of the cumulative hydrated  
686 volumetric rate contributed by aerosols ( $d_a \leq 5 \mu\text{m}$ ) or droplets ( $d_a > 5 \mu\text{m}$ ) for that respiratory  
687 activity. Since the Poisson mean was proportional to cumulative volumetric rate, this estimate of  
688 the relative contribution of aerosols and droplets to respiratory viral shedding was consistent  
689 among viruses and cps in the model.

690 In this study, the model for shedding virions via droplets and aerosols did not delineate  
691 particles generated in the upper respiratory tract from those generated in the lower respiratory  
692 tract, as the sites of atomization remain poorly understood. It also did not differentiate cases with  
693 significant expectoration from those without it. In addition, it did not account for individual  
694 variation in the profiles of expelled particles; superemitters can expel respiratory particles at  
695 rates ~3 times above median<sup>121</sup>.

696

## 697 Statistical analysis

698 For data collection, statistical analysis, coding and data visualization, we used Excel v16.40  
699 (Microsoft Corporation, Redmond, Washington, USA), OriginPro 2019b (OriginLab  
700 Corporation, Northampton, Massachusetts, USA) and Matlab R2019b (MathWorks, Inc., Natick,  
701 Massachusetts, USA). Between-study heterogeneity in the random-effects meta-analyses was  
702 assessed using the  $I^2$  and  $\tau^2$  statistics. Probability plots for normal, lognormal, gamma and  
703 Weibull distributions of rVLs were scored based on the Blom method. Modified Kolmogorov-  
704 Smirnov tests were used to determine the goodness of fits between rVLs (in  $\log_{10}$  copies/ml) and

705 normal, lognormal, gamma or Weibull distributions. By accepting the null hypothesis in the  
706 modified Kolmogorov–Smirnov test, the given distribution cannot be rejected to fit the data.  
707 Based on fitted Weibull distribution parameters, the Weibull quantile function was used to  
708 determine the rVL and its 95% CIs at a given cp. The association between  $k$  and rVL was  
709 assessed via meta-regression, and the  $p$ -value for association was based on the meta-regression  
710 slope  $t$ -test. Likelihood profiles were determined using the Poisson probability mass function and  
711 the unbiased estimator for the expected partitioning of virions at a given particle size. Variance  
712 on likelihood estimates was determined via the delta method. Since case variance or sample size  
713 may be unequal among the viral infections or subgroups, the two-sided Welch's  $t$ -test was used  
714 to compare the difference of expected rVLs in the meta-analysis and subgroup analyses. For all  
715 statistical analyses, the significance level ( $\alpha$ ) was taken to be 0.05.

716

## 717 **Data availability**

718 Data will be made available upon request. All raw data, code and model outputs from this study  
719 will be made publicly available in online repositories after peer review. Search strategies for the  
720 systematic review are shown in Supplementary Tables 1–5. The systematic review protocol was  
721 prospectively registered on PROSPERO (registration number, CRD42020204637).

722

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953

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961

962 **Author contributions**

963 P.Z.C. designed the study, performed analyses, interpreted results and drafted the manuscript.  
964 P.Z.C. and N.B. conducted screening, appraised studies and drafted the review protocol. Z.P.  
965 developed and conducted the systematic review search. M.K. and D.N.F. assessed methods,  
966 interpreted results and contributed to the discussion. All authors reviewed and revised the  
967 manuscript. F.X.G. secured funds, interpreted results and supervised the project.

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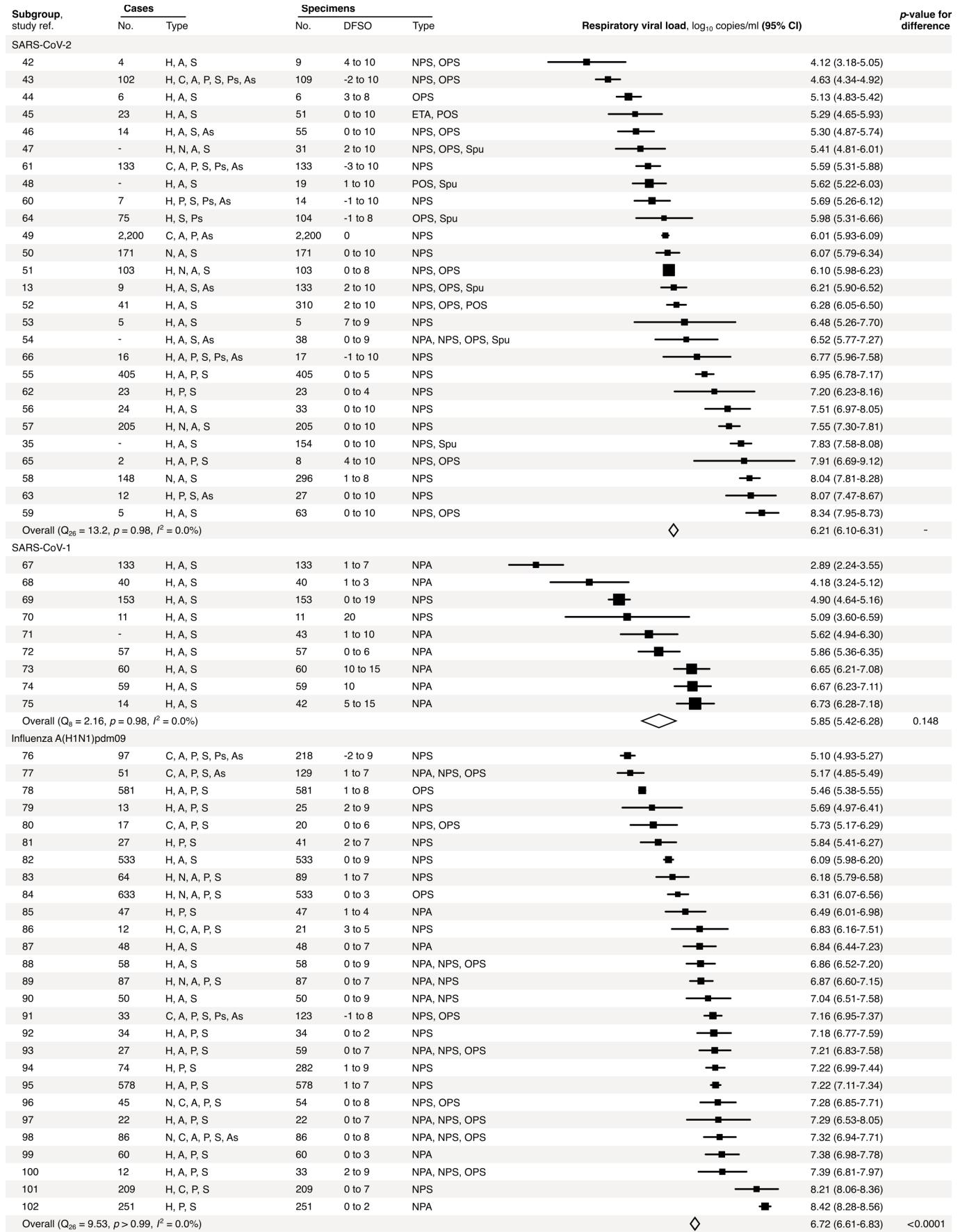
969    **Competing interests** The authors declare no competing interests.

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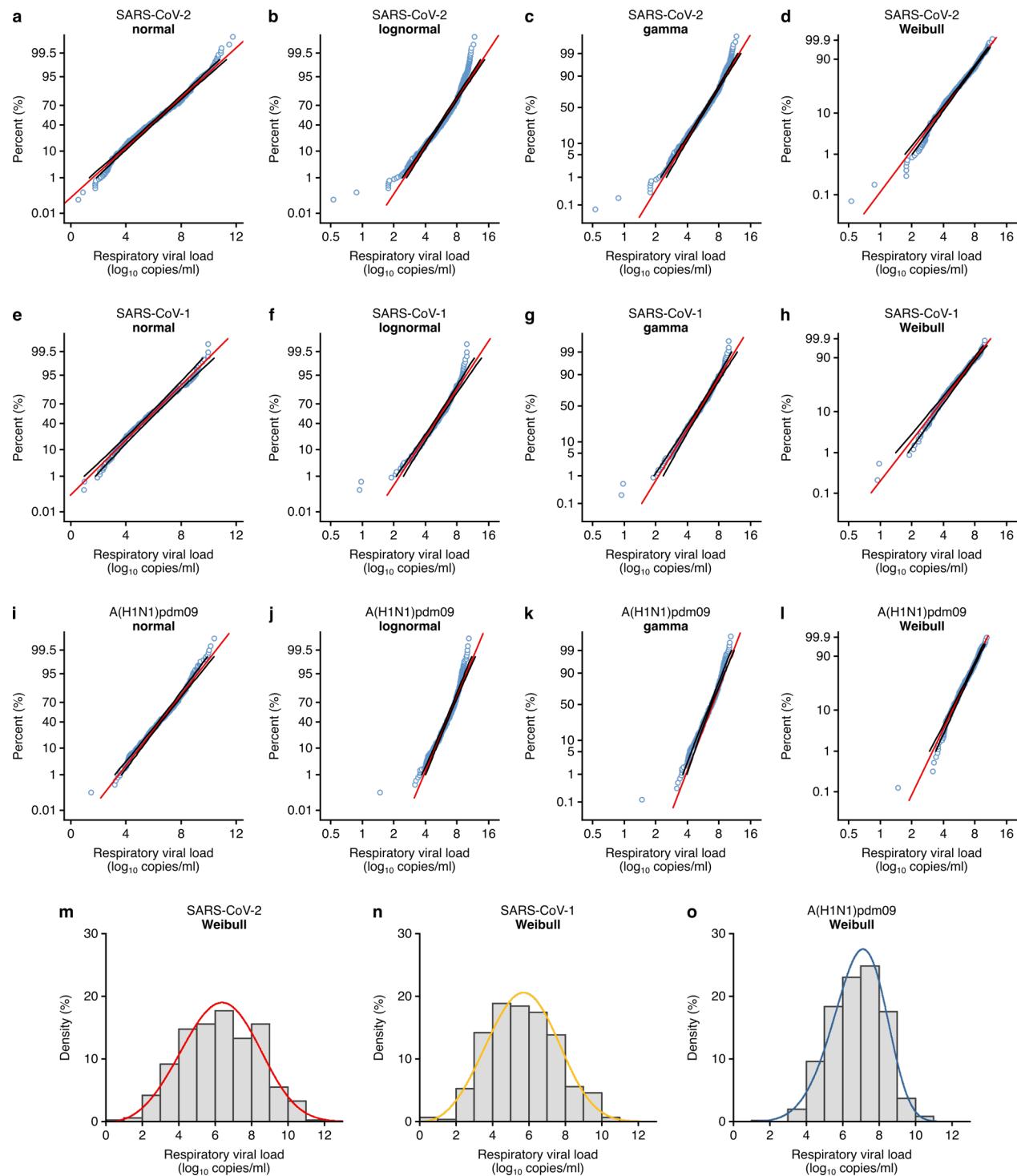
971    **Supplementary information** is available for this paper.

972

973    **Correspondence and requests for materials** should be addressed to F.X.G.



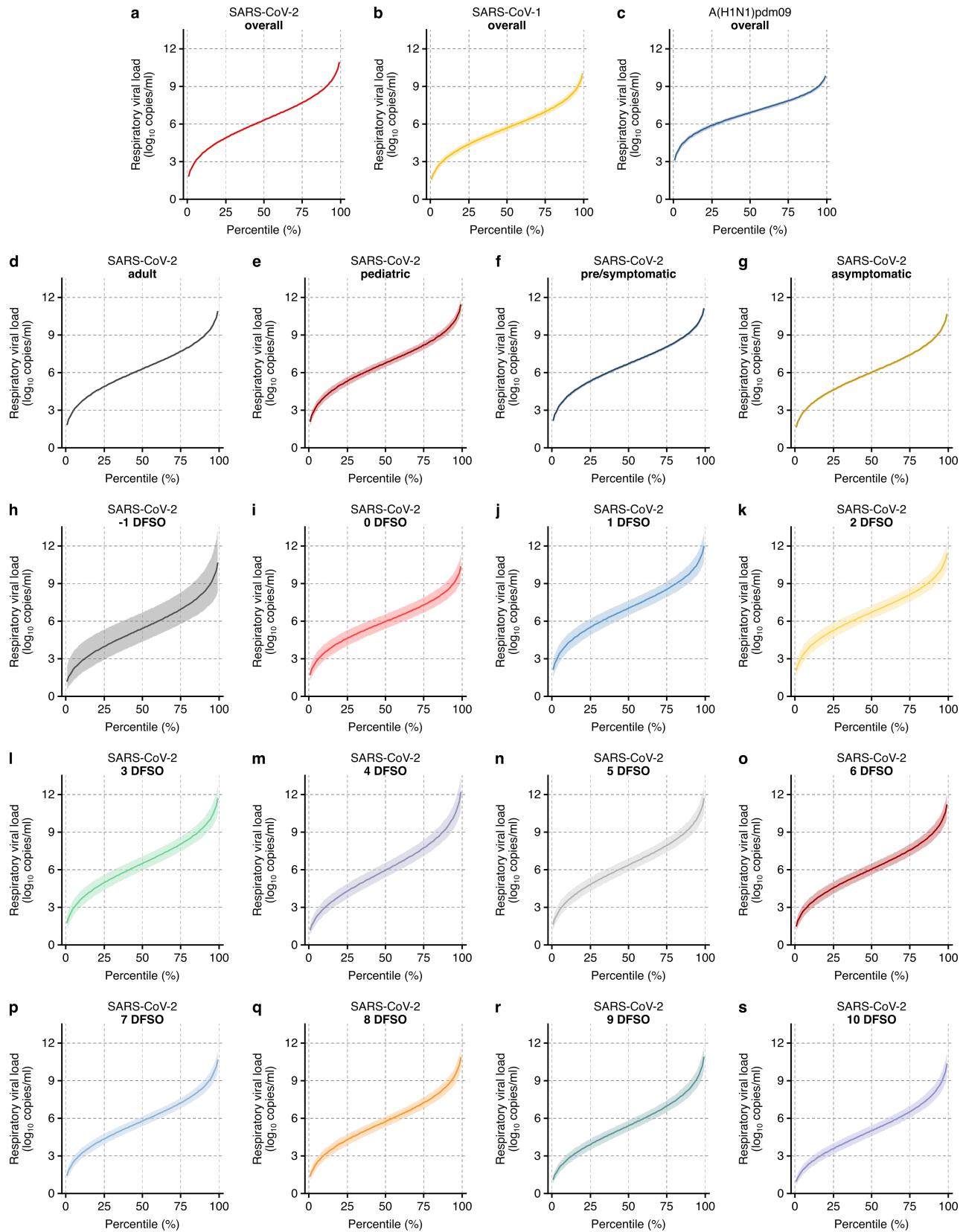
975 **Extended Data Fig. 1. Meta-analysis of respiratory viral loads of SARS-CoV-2, SARS-CoV-**  
976 **1 and influenza A(H1N1)pdm09 during the infectious period.** Random-effects meta-analyses  
977 comparing the expected rVLs for COVID-19, SARS and A(H1N1)pdm09 cases during the  
978 infectious period. Quantitative specimen measurements were used to estimate rVLs, which refer  
979 to virus concentrations in the respiratory tract. Case types: hospitalized (H), not admitted (N),  
980 community (C), adult (A), pediatric (P), symptomatic (S), presymptomatic (Ps) and  
981 asymptomatic (As). Specimen types: endotracheal aspirate (ETA), nasopharyngeal aspirate  
982 (NPA), nasopharyngeal swab (NPS), oropharyngeal swab (OPS), posterior oropharyngeal saliva  
983 (POS) and sputum (Spu). Studies after ref. 35 are listed in Methods. Dashes denote case numbers  
984 that were not obtained. Box sizes are proportional to weighting in the overall estimates. Two-  
985 sided Welch's *t*-test (relative to SARS-CoV-2), non-significance ( $p>0.05$ ).



986

987 **Extended Data Fig. 2. Respiratory viral loads for SARS-CoV-2, SARS-CoV-1 and**  
 988 **A(H1N1)pdm09 best conform to Weibull distributions. a-d, Normal ( $p \leq 0.01$ ) (a), lognormal**  
 989 **( $p \leq 0.01$ ) (b), gamma ( $p \leq 0.005$ ) (c) and Weibull ( $p > 0.10$ , not significant [NS]) (d) probability**

990 plots for individual sample data of SARS-CoV-2 rVLs across DFSO in the systematic dataset  
991 ( $n=916$  samples from  $n=19$  studies). **e-h**, Normal ( $p>0.10$ , NS) (**e**), lognormal ( $p\leq 0.01$ ) (**f**),  
992 gamma ( $p>0.05$ , NS) (**g**) and Weibull ( $p>0.10$ , NS) (**h**) probability plots for individual sample  
993 data of SARS-CoV-1 rVLs in the systematic dataset ( $n=303$  samples from  $n=5$  studies). **i-l**,  
994 Normal ( $p\leq 0.01$ ) (**i**), lognormal ( $p\leq 0.01$ ) (**j**), gamma ( $p\leq 0.005$ ) (**k**) and Weibull ( $p>0.10$ , NS) (**l**)  
995 probability plots for individual sample data of A(H1N1)pdm09 rVLs in the systematic dataset  
996 ( $n=512$  samples from  $n=10$  studies). These categories included only rVL data from positive  
997 (above the detection limit) qRT-PCR measurements. The  $p$ -values were determined using the  
998 modified Kolmogorov-Smirnov test for the goodness of fit of the distributions. When the null  
999 hypothesis is accepted (NS at  $p>0.05$ ), the probability density function cannot be rejected to  
1000 describe the distribution of the data. Blue circles, black lines and red lines represent individual  
1001 sample data, expected distributions and 95% CIs, respectively. **m-o**, Histograms and fitted  
1002 Weibull distributions of the above data for SARS-CoV-2 (**m**), SARS-CoV-1 (**n**) and  
1003 A(H1N1)pdm09 (**o**).



1005 **Extended Data Fig. 3. Respiratory viral loads across case percentiles for viruses, subgroups**

1006 **and days from symptom onset. a, b,** Estimated rVLs of SARS-CoV-2 (**a**), SARS-CoV-1 (**b**)

1007 and A(H1N1)pdm09 (**c**) across cp during the infectious periods. **d-g**, Estimated SARS-CoV-2

1008 rVLs across cp for adult (**d**), pediatric (**e**), symptomatic/presymptomatic (**f**) and asymptomatic

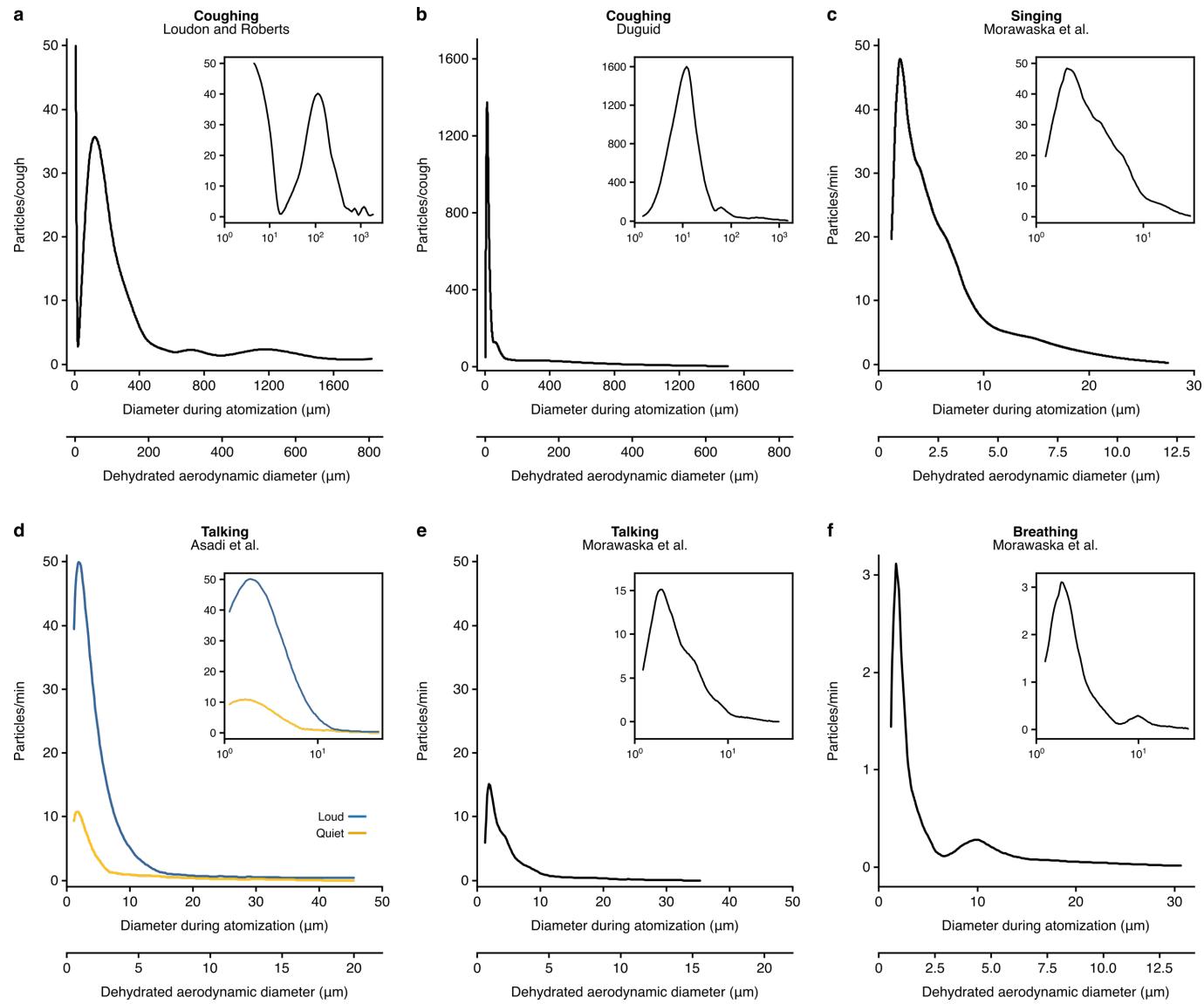
1009 (**g**) cases during the infectious period. **h-s**, Estimated SARS-CoV-2 rVLs across cp on different

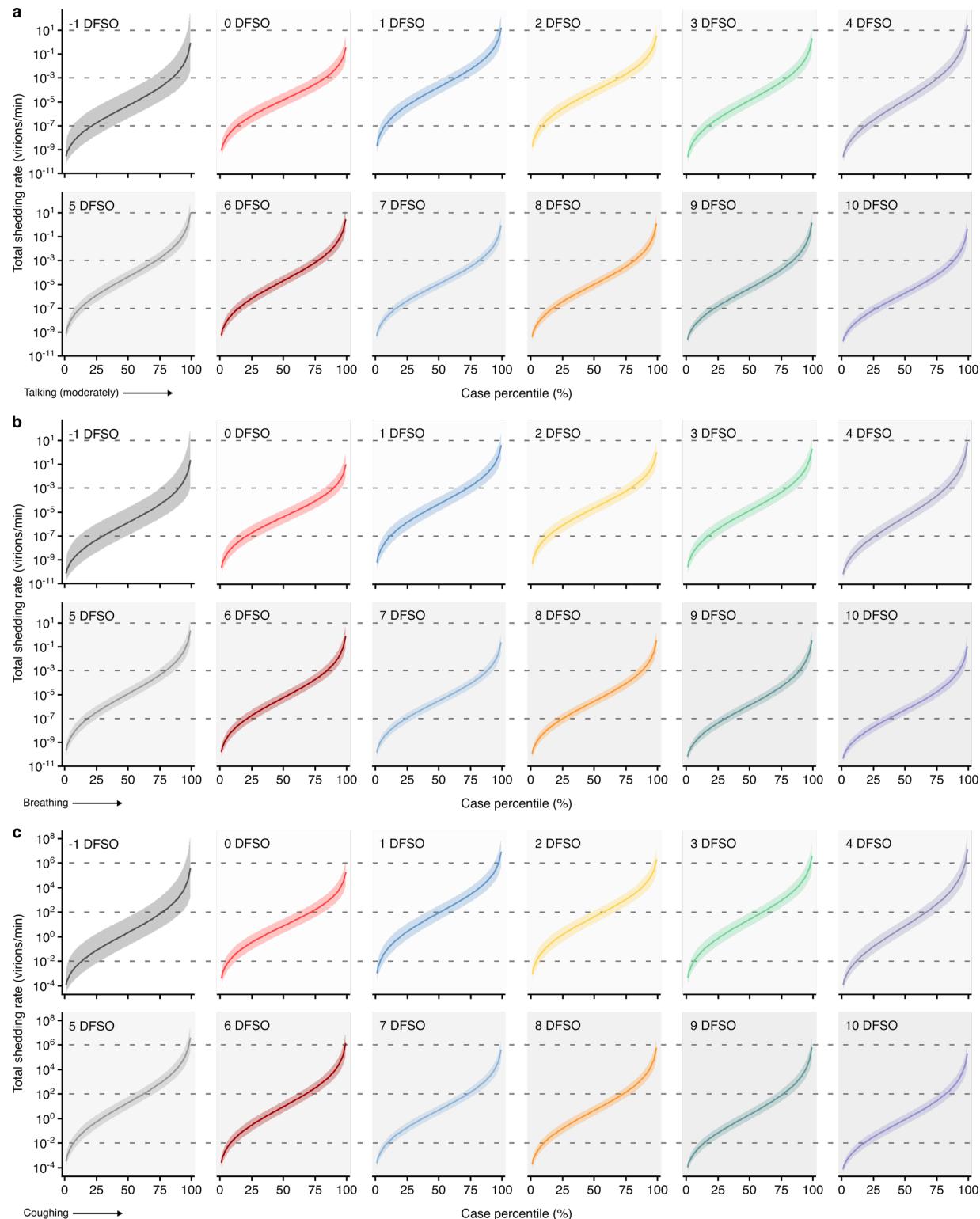
1010 days of the infectious period. Earlier presymptomatic days were excluded based on limited data.

1011 Data ranged between the 1<sup>st</sup> and 99<sup>th</sup> cps. Sample numbers, distribution parameters and

1012 descriptive statistics are summarized in Extended Data Table 2. Lines and bands represent

1013 estimates and 95% CIs, respectively.

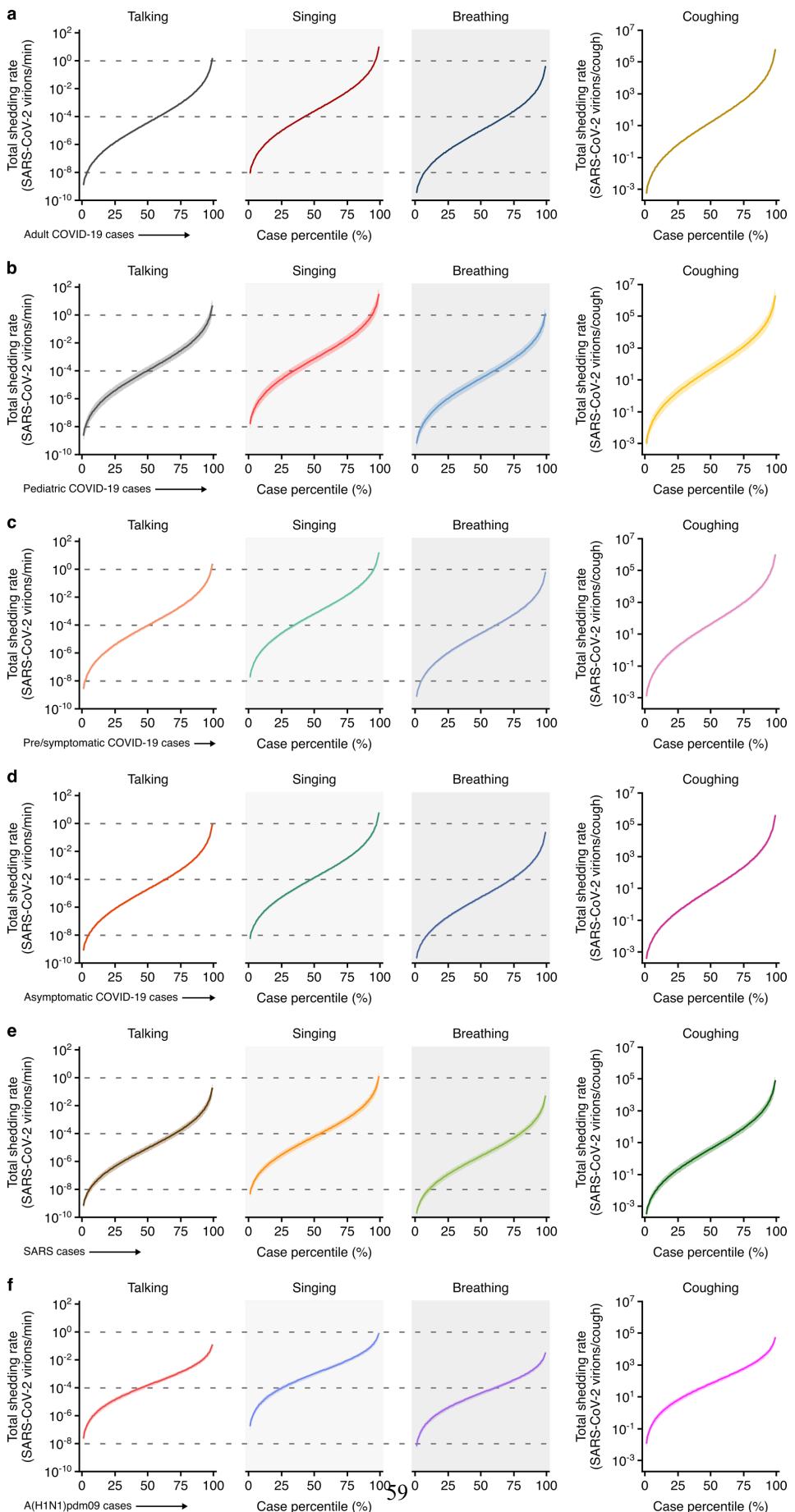




1022

1023 **Extended Data Fig. 5. Heterogeneity in shedding SAR-CoV-2 via talking, breathing and**  
1024 **coughing. a-c**, Case heterogeneity in the total SARS-CoV-2 shedding rate (over all particle

1025 sizes) by talking at a moderate level (**a**), breathing (**b**) or coughing (**c**) for COVID-19 cases  
1026 across the infectious period. Earlier presymptomatic days were excluded based on limited data.  
1027 Data represent estimated rates for viable virus and range between the 1<sup>st</sup> and 99<sup>th</sup> cps. Lines and  
1028 bands represent estimates and 95% CIs, respectively.



1030 **Extended Data Fig. 6. Heterogeneity in respiratory virus shedding for subgroup COVID-**  
1031 **19, SARS and A(H1N1)pdm09 cases. a-d,** Case heterogeneity in the total SARS-CoV-2  
1032 shedding rate for adult (**a**), pediatric (**b**), symptomatic/presymptomatic (**c**) and asymptomatic (**d**)  
1033 COVID-19 cases via talking, singing, breathing and coughing during the infectious period. **e,f,**  
1034 Case heterogeneity in the total SARS-CoV-1 (**e**) and A(H1N1)pdm09 (**f**) shedding rates via  
1035 talking, singing, breathing and coughing for SARS and A(H1N1)pdm09 cases, respectively,  
1036 during the infectious periods. Data represent estimated rates for viable virus and range between  
1037 the 1<sup>st</sup> and 99<sup>th</sup> cps. Lines and bands represent estimates and 95% CIs, respectively.  
1038

Study*	Country	No. of cases included (no. of specimens)	No. of pediatric cases (no. of specimens)	No. of asymptomatic cases (no. of specimens)	Disease caused by virus	Case definition (WHO)	Pharmaco-therapy (type)†	Individual data extracted (diluent volume reported)‡	Adjusted viral load§ (type of specimen)	Weight, % (meta-analysis category)¶	Weight, % (meta-regression)	Risk of bias¶
Argyropoulos et al. (2020) <sup>57</sup>	USA	205 (205)	0	0	COVID-19	Confirmed	No	No (no)	Yes (NPS)	2.3 (V), 2.9 (A), 2.5 (S/Ps)	2.12	*****
Baggio et al. (2020) <sup>55</sup>	Switzerland	405 (405)	58 (58)	0	COVID-19	Confirmed	No	Yes (no)	Yes (NPS)	2.1 (V), 2.7 (A), 11.5 (P), 2.2 (S/Ps)	4.18	*****
Fajnzylber et al. (2020) <sup>47</sup>	USA	- (31)	0	0	COVID-19	Confirmed	No	Yes (yes)	Yes (NPS, OPS) No (Spu)	2.8 (V), 3.5 (A), 3.0 (S/Ps)	0.32	*****
Han et al. (2020) <sup>65</sup>	South Korea	2 (8)	1 (6)	0	COVID-19	Confirmed	No	Yes (no)	Yes (NPS, OPS)	2.7 (V), 2.8 (S/Ps)	0.08	*****
Han et al. (2020) <sup>63</sup>	South Korea	12 (27)	12 (27)	3 (7)	COVID-19	Confirmed	No	Yes (no)	Yes (NPS)	3.2 (V), 18.5 (P), 3.2 (S/Ps), 31.0 (As)	0.28	*****
Hung et al. (2020) <sup>52</sup>	China	41 (310)	0	0	COVID-19	Confirmed	No (control group)	No (no)	Yes (NPS, OPS, POS)	2.0 (V), 2.4 (A), 2.1 (S)	3.20	*****
Hurst et al. (2020) <sup>61</sup>	USA	133 (133)	54 (54)	52 (52)	COVID-19	Confirmed	No	Yes (no)	Yes (NPS)	2.8 (V), 15.3 (P), 3.0 (S/Ps), 24.1 (As)	1.37	*****
Iwasaki et al. (2020) <sup>53</sup>	Japan	5 (5)	0	0	COVID-19	Confirmed	No	Yes (no)	Yes (NPS)	4.2 (V), 5.2 (A), 4.5 (S/Ps)	0.05	***
Kawasui et al. (2020) <sup>66</sup>	Japan	16 (16)	-	-	COVID-19	Confirmed	Yes (antivirals - type not reported)	Yes (no)	Yes (NPS)	2.8 (V)	0.18	****
L'Huillier et al. (2020) <sup>62</sup>	Switzerland	23 (23)	23 (23)	0	COVID-19	Confirmed	No	Yes (no)	Yes (NPS)	1.5 (V), 8.4 (P), 1.6 (S/Ps)	0.24	*****
Lavezzo et al. (2020) <sup>43</sup>	Italy	103 (110)	2 (3)	49 (49)	COVID-19	Confirmed	No	Yes (yes)	Yes (NPS, OPS)	3.2 (V), 4.0 (A), 14.4 (P), 3.3 (S/Ps), 27.9 (A)	1.13	*****
Lennon et al. (2020) <sup>49</sup>	USA	2,200 (2,200)	18 (18)	2,200 (2,200 <sup>#</sup> )	COVID-19	Confirmed	No	No (yes)	Yes (NPS)	2.0 (V), 2.5 (A), 17.0 (As)	22.70	*****
Lucas et al. (2020) <sup>56</sup>	USA	24 (33)	0	0	COVID-19	Confirmed	Moderate and severe patients (tocilizumab)	Yes (yes)	Yes (NPS)	3.3 (V), 4.0 (A), 3.5 (S/Ps)	0.34	*****
Mitja et al. (2020) <sup>58</sup>	Spain	148 (296)	0	0	COVID-19	Confirmed	No (control group)	No (no)	Yes (NPS)	1.9 (V), 2.3 (A), 2.0 (S/Ps)	3.05	*****
Pan et al. (2020) <sup>64</sup>	China	75 (104)	-	0	COVID-19	Confirmed	No	Yes (no)	Yes (OPS) No (Spu)	0.7 (V), 0.7 (S/Ps)	1.07	***

Peng et al. (2020) <sup>44</sup>	China	6 (6)	0	0	COVID-19	Confirmed	Yes (arbidol, lopinavir, ritonavir)	Yes (no)	Yes (OPS)	6.6 (V), 8.2 (A), 7.1 (S/Ps)	0.06	*****
Perera et al. (2020) <sup>54</sup>	China	- (36)	0	-	COVID-19	Confirmed	No	Yes (no)	Yes (NPA, NPS, OPS, Spu)	1.5 (V), 1.8 (A)	0.39	****
Shi et al. (2020) <sup>51</sup>	China	103 (103)	0	0	COVID-19	Confirmed	No	Yes (no)	Yes (NPS, OPS)	19.0 (V), 23.4 (A), 20.2 (S/Ps)	1.06	****
Shrestha et al. (2020) <sup>50</sup>	USA	171 (171)	0	0	COVID-19	Confirmed	No	Yes (no)	Yes (NPS)	2.4 (V), 3.0 (A), 2.6 (S/Ps)	1.76	*****
To et al. (2020) <sup>45</sup>	China	23 (51)	0	0	COVID-19	Confirmed	No	Yes (yes)	Yes (ETA, POS)	1.5 (V), 1.8 (A), 1.6 (S/Ps)	0.53	*****
van Kampen et al. (2020) <sup>55</sup>	The Netherlands	- (154)	0	0	COVID-19	Confirmed	No	Yes (yes)	Yes (NPS, Spu)	3.2 (V), 4.0 (A), 3.5 (S/Ps)	1.59	*****
Vetter et al. (2020) <sup>59</sup>	Switzerland	5 (63)	0	0	COVID-19	Confirmed	No	Yes (yes)	Yes (NPS, OPS)	3.3 (V), 4.1 (A), 3.5 (S/Ps)	0.65	*****
Wölfel et al. (2020) <sup>13</sup>	Germany	9 (136)	0	1 (4)	COVID-19	Confirmed	No	Yes (yes)	Yes (NPS, OPS) No (Spu)	2.5 (V), 3.0 (A), 3.2 (S)	1.37	*****
Xu et al. (2020) <sup>60</sup>	China	7 (14)	7 (14)	1 (1)	COVID-19	Confirmed	No	Yes (no)	Yes (NPS)	5.5 (V), 31.8 (P), 5.8 (S/Ps),	0.14	*****
Zhang et al. (2020) <sup>42</sup>	China	9 (9)	0	0	COVID-19	Confirmed	No	Yes (no)	Yes (NPS, OPS)	4.0 (V), 5.0 (A), 4.3 (S/Ps)	0.09	*****
Zheng et al. (2020) <sup>48</sup>	China	- (19)	0	0	COVID-19	Confirmed	No	Yes (no)	Yes (POS, Spu)	10.0 (V), 12.4 (A), 10.7 (S/Ps)	0.20	*****
Zou et al. (2020) <sup>46</sup>	China	14 (55)	0	1 (4)	COVID-19	Confirmed	No	Yes (no)	Yes (NPS, OPS)	3.0 (V), 3.7 (A), 3.1 (S/Ps)	0.57	*****
Chen et al. (2006) <sup>69</sup>	China	154 (154#)	0	0	SARS	Confirmed	Yes (oseltamivir, broad-spectrum antibiotics, ribavirin)	Yes (no)	Yes (NPS)	17.9 (V)	1.58	*****
Chu et al. (2004) <sup>67</sup>	China	133 (133)	0	0	SARS	Confirmed	No	No (yes)	Yes (NPA)	2.9 (V)	1.37	*****
Chu et al. (2004) <sup>70</sup> *	China	11 (11)	0	0	SARS	Confirmed	No (control group)	Yes (yes)	Yes (NPS)	6.7 (V)	0.11	*****
Chu et al. (2005) <sup>72</sup>	China	57 (57)	0	0	SARS	Confirmed	No	Yes (yes)	Yes (NPA)	11.6 (V)	0.59	*****
Cheng et al. (2004) <sup>74</sup>	China	59 (59)	0	0	SARS	Confirmed	Yes (ribavirin, hydrocortisone, prednisolone, methylpredni- solone)	Yes (yes)	Yes (NPA)	14.2 (V)	0.61	*****
Hung et al. (2004) <sup>73</sup>	China	60 (60)	0	0	SARS	Confirmed	Yes (ribavirin, hydrocortisone, prednisolone,	No (yes)	Yes (NPA)	14.7 (V)	0.62	*****

								methylpredni-solone)				
Peiris et al. (2003) <sup>75</sup> *	China	14 (42)	0	0	SARS	Confirmed	Yes (ribavirin, hydrocortisone, prednisolone, methylpredni-solone)	Yes (no)	Yes (NPA)	19.2 (V)	0.43	*****
Poon et al. (2003) <sup>68</sup>	China	40 (40)	0	0	SARS	Confirmed	No	No (yes)	Yes (NPA)	4.6 (V)	0.41	****
Poon et al. (2004) <sup>71</sup>	China	- (43)	0	0	SARS	Confirmed	-	No (yes)	Yes (NPA)	8.2 (V)	0.44	****
Alves et al. (2020) <sup>98</sup>	Brazil	86 (86)	-	15 (15)	Influenza A(H1N1)pdm09	Confirmed	No	No (yes)	Yes (NPA, NPS, OPS)	2.4 (V)	0.89	****
Chan et al. (2011) <sup>88</sup>	China	58 (58)	0	0	Influenza A(H1N1)pdm09	Confirmed	No (pretreatment)	Yes (no)	Yes (NPA, NPS, OPS)	4.6 (V)	0.60	*****
Cheng et al. (2010) <sup>99</sup>	China	60 (60)	-	0	Influenza A(H1N1)pdm09	Confirmed	No (pretreatment)	No (no)	Yes (NPA)	3.3 (V)	0.62	*****
Cowling et al. (2010) <sup>96</sup>	China	45 (54)	22 (31)	0	Influenza A(H1N1)pdm09	Confirmed	Yes (22 cases on oseltamivir)	Yes (yes)	Yes (NPS, OPS)	3.1 (V)	0.56	*****
Duchamp et al. (2010) <sup>101</sup>	France	209 (209)	209 (209)	0	Influenza A(H1N1)pdm09	Confirmed	Yes (oseltamivir, zanamivir)	No (yes)	Yes (NPS)	2.4 (V)	2.16	****
Esposito et al. (2011) <sup>94</sup>	Italy	74 (282)	74 (282)	0	Influenza A(H1N1)pdm09	Confirmed	No	Yes (yes)	Yes (NPS)	2.2 (V)	2.91	*****
Hung et al. (2010) <sup>89</sup>	China	87 (87)	-	0	Influenza A(H1N1)pdm09	Confirmed	Yes (oseltamivir)	Yes (no)	Yes (NPA, NPS)	4.7 (V)	0.90	*****
Ip et al. (2016) <sup>80</sup>	China	17 (20)	7 (-)	0	Influenza A(H1N1)pdm09	Confirmed	No	Yes (no)	Yes (NPS, OPS)	5.0 (V)	0.21	*****
Ito et al. (2012) <sup>92</sup>	Japan	34 (34)	-	0	Influenza A(H1N1)pdm09	Confirmed	No (pretreatment)	Yes (yes)	Yes (NPS)	5.5 (V)	0.35	****
Killingley et al. (2010) <sup>86</sup>	United Kingdom	12 (21)	-	0	Influenza A(H1N1)pdm09	Confirmed	Yes (oseltamivir)	Yes (yes)	Yes (NPS)	3.3 (V)	0.22	*****
Launes et al. (2012) <sup>85</sup>	Spain	47 (47)	47 (47)	0	Influenza A(H1N1)pdm09	Confirmed	No (pretreatment)	No (no)	Yes (NPA)	3.0 (V)	0.48	*****
Lee et al. (2011) <sup>87</sup>	China	48 (48)	0	0	Influenza A(H1N1)pdm09	Confirmed	No (pretreatment)	No (no)	Yes (NPA)	4.1 (V)	0.50	*****
Lee et al. (2011) <sup>95</sup>	Singapore	578 (578)	231 (231)	0	Influenza A(H1N1)pdm09	Confirmed	No (pretreatment)	No (no)	Yes (NPS)	4.1 (V)	5.96	*****
Li et al. (2010) <sup>78</sup>	China	581 (581)	522 (522)	0	Influenza A(H1N1)pdm09	Confirmed	No (pretreatment)	No (no)	Yes (OPS)	6.7 (V)	5.99	*****
Li et al. (2010) <sup>93</sup>	China	27 (59)	-	0	Influenza A(H1N1)pdm09	Confirmed	No (non-treated group)	No (no)	Yes (NPA, NPS, OPS)	3.8 (V)	0.61	*****
Loeb et al. (2012) <sup>76</sup>	Canada	97 (218)	-	- (17)	Influenza A(H1N1)pdm09	Confirmed	No	No (no)	Yes (NPS)	4.9 (V)	2.25	*****

Lu et al. (2012) <sup>79</sup>	China	13 (25)	-	0	Influenza A(H1N1)pdm09	Confirmed	Yes (oseltamivir, zanamivir)	Yes (no)	Yes (NPS)	2.4 (V)	0.26	*****
Meschi et al. (2011) <sup>82</sup>	Italy	533 (533)	0	0	Influenza A(H1N1)pdm09	Confirmed	No (pretreatment)	No (no)	Yes (NPS)	4.8 (V)	5.50	*****
Ngaosuwankul et al. (2010) <sup>100</sup>	China	12 (33)	-	0	Influenza A(H1N1)pdm09	Confirmed	No (pretreatment)	No (yes)	Yes (NPA, NPS, OPS)	2.8 (V)	0.34	*****
Rath et al. (2012) <sup>81</sup>	Germany	27 (41)	27 (41)	0	Influenza A(H1N1)pdm09	Confirmed	Yes (oseltamivir)	Yes (yes)	Yes (NPS)	4.1 (V)	0.42	*****
Suess et al. (2010) <sup>77</sup>	Germany	51 (129)	12 (-)	1 (1)	Influenza A(H1N1)pdm09	Confirmed	Yes (oseltamivir)	No (no)	Yes (NPA, NPS, OPS)	2.4 (V)	1.33	*****
Thai et al. (2014) <sup>91</sup>	Vietnam	33 (123)	16 (-)	5 (28)	Influenza A(H1N1)pdm09	Confirmed	Yes (oseltamivir)	Yes (yes)	Yes (NPS)	5.8 (V)	1.27	*****
To et al. (2010) <sup>90</sup>	China	50 (50)	0	0	Influenza A(H1N1)pdm09	Confirmed	Yes (oseltamivir, nebulized zanamivir)	No (no)	Yes (NPA, NPS)	2.2 (V)	0.52	*****
To et al. (2010) <sup>97</sup>	China	22 (22)	-	0	Influenza A(H1N1)pdm09	Confirmed	No (pretreatment)	No (no)	Yes (NPA, NPS, OPS)	2.5 (V)	0.23	****
Watanabe et al. (2011) <sup>102</sup>	Japan	251 (251)	251 (251)	0	Influenza A(H1N1)pdm09	Confirmed	No (pretreatment)	No (yes)	Yes (NPA)	6.6 (V)	2.59	*****
Wu et al. (2012) <sup>83</sup>	China	64 (89)	-	0	Influenza A(H1N1)pdm09	Confirmed	Yes (oseltamivir)	No (yes)	Yes (NPS)	2.3 (V)	0.92	*****
Yang et al. (2011) <sup>84</sup>	China	251 (251)	-	0	Influenza A(H1N1)pdm09	Confirmed	N/A	No (yes)	Yes (OPS)	0.8 (V)	6.53	*****

\*References 13 and 35 are listed in the main body while those 42 and after are listed in Methods. Data shown as “-” were not obtained from the paper or authors.

<sup>†</sup>Responses of “no” for pharmacotherapy are based on no pharmacotherapy given to any patients or none reported in the study.

<sup>#</sup>For studies reporting specimen measurements as individual sample data (either in numerical or graphical formats), the sample data was extracted for analysis.

<sup>§</sup>Specimen measurements were converted to rVLs based on the dilution factor for specimens immersed in transport media.

<sup>||</sup>Abbreviations: viral meta-analysis (V), adult subgroup (A), pediatric subgroup (P), symptomatic/presymptomatic subgroup (S/Ps), asymptomatic subgroup (As).

<sup>¶</sup>The hybrid JBI Critical Appraisal Checklist was used, with more stars indicating lower risk of bias. Results from each study are shown in Supplementary Table 6.

<sup>#</sup>For these studies, only 2,147 (Lennon et al.) and 134 (Chen et al.) individual specimen measurements were obtained for the individual sample datasets.

<sup>\*</sup>For Chu et al., only specimen measurements at 20 DFSO were extracted, as 5-15 DFSO were equivalent specimens as those reported in Peiris et al.

Extended Data Table 2 | Descriptive parameters for subgroups of respiratory viral loads based on individual sample data

Category			Weibull distribution parameters		Respiratory viral load, log <sub>10</sub> copies/ml				
	n * (specimens)	n * (studies)	Scale factor (95% CI)	Shape factor (95% CI)	Mean (95% CI) <sup>†</sup>	SD <sup>†</sup>	90 <sup>th</sup> percentile (95% CI) <sup>‡</sup>	95 <sup>th</sup> percentile (95% CI) <sup>‡</sup>	99 <sup>th</sup> percentile (95% CI) <sup>‡</sup>
SARS-CoV-2 (overall) <sup>§</sup>	3,778	24	7.01 (6.94-7.07)	3.47 (3.38-3.56)	6.28 (6.22-6.35)	2.04	8.91 (8.82-9.00)	9.61 (9.51-9.71)	10.88 (10.75-11.02)
SARS-CoV-1 (overall) <sup>§</sup>	303	5	6.34 (6.12-6.56)	3.37 (3.09-3.68)	5.69 (5.48-5.90)	1.86	8.11 (7.83-8.40)	8.77 (8.45-9.11)	9.96 (9.54-10.41)
A(H1N1)pdm09 (overall) <sup>§</sup>	512	10	7.39 (7.27-7.51)	5.43 (5.07-5.81)	6.81 (6.69-6.94)	1.45	8.62 (8.47-8.76)	9.04 (8.88-9.21)	9.79 (9.59-10.00)
SARS-CoV-2 (adult) <sup>§</sup>	3,532	18	6.99 (6.92-7.06)	3.47 (3.38-3.56)	6.27 (6.20-6.34)	2.04	8.89 (8.80-8.98)	9.59 (9.49-9.70)	10.86 (10.72-11.00)
SARS-CoV-2 (pediatric) <sup>§</sup>	185	7	7.47 (7.17-7.79)	3.65 (3.26-4.08)	6.73 (6.43-7.02)	2.06	9.39 (9.01-9.79)	10.09 (9.65-10.56)	11.36 (10.78-11.97)
SARS-CoV-2 (symptomatic/presymptomatic) <sup>§</sup>	1,503	20	7.39 (7.28-7.49)	3.79 (3.64-3.94)	6.66 (6.56-6.76)	2.01	9.21 (9.08-9.34)	9.87 (9.72-10.02)	11.06 (10.86-11.26)
SARS-CoV-2 (asymptomatic) <sup>§</sup>	2,212	6	6.72 (6.63-6.81)	3.32 (3.22-3.44)	6.01 (5.93-6.09)	2.02	8.64 (8.52-8.75)	9.35 (9.21-9.48)	10.64 (10.46-10.81)
SARS-CoV-2 (all DFSO) <sup>§</sup>	916	19	7.04 (6.90-7.18)	3.47 (3.30-3.65)	6.32 (6.19-6.45)	2.04	8.95 (8.78-9.13)	9.66 (9.45-9.86)	10.93 (10.66-11.21)
SARS-CoV-2 (-3 DFSO) <sup>¶</sup>	1	1	-	-	10.34	-	-	-	-
SARS-CoV-2 (-2 DFSO) <sup>¶</sup>	3	2	-	-	4.22 (2.41-6.02)	1.59	-	-	-
SARS-CoV-2 (-1 DFSO)	15	5	6.17 (5.11-7.47)	2.82 (1.89-4.19)	5.48 (4.25-6.70)	2.21	8.30 (6.88-10.02)	9.11 (7.44-11.16)	10.62 (8.38-13.45)
SARS-CoV-2 (0 DFSO)	48	10	6.63 (6.08-7.23)	3.46 (2.81-4.26)	5.97 (5.43-6.51)	1.85	8.43 (7.75-9.18)	9.10 (8.32-9.96)	10.31 (9.29-11.43)
SARS-CoV-2 (1 DFSO)	59	10	7.79 (7.23-8.40)	3.58 (2.91-4.40)	7.00 (6.42-7.59)	2.26	9.83 (9.12-10.61)	10.58 (9.75-11.49)	11.93 (10.84-13.14)
SARS-CoV-2 (2 DFSO) <sup>¶</sup>	69	13	7.42 (6.93-7.95)	3.61 (2.97-4.39)	6.67 (6.15-7.19)	2.17	9.35 (8.72-10.03)	10.06 (9.32-10.85)	11.33 (10.35-12.40)
SARS-CoV-2 (3 DFSO) <sup>¶</sup>	71	15	7.27 (6.74-7.84)	3.25 (2.69-3.93)	6.50 (5.96-7.04)	2.29	9.39 (8.71-10.14)	10.19 (9.38-11.06)	11.63 (10.54-12.82)
SARS-CoV-2 (4 DFSO) <sup>¶</sup>	81	15	6.84 (6.27-7.45)	2.66 (2.22-3.17)	6.08 (5.52-6.63)	2.51	9.36 (8.58-10.21)	10.34 (9.40-11.36)	12.15 (10.87-13.59)
SARS-CoV-2 (5 DFSO) <sup>¶</sup>	87	14	7.16 (6.67-7.68)	3.14 (2.65-3.72)	6.40 (5.91-6.89)	2.29	9.33 (8.69-10.02)	10.15 (9.40-10.96)	11.64 (10.63-12.74)
SARS-CoV-2 (6 DFSO) <sup>¶</sup>	102	14	6.81 (6.37-7.27)	3.09 (2.63-3.62)	6.07 (5.63-6.51)	2.24	8.92 (8.34-9.53)	9.71 (9.03-10.44)	11.16 (10.24-12.17)
SARS-CoV-2 (7 DFSO) <sup>¶</sup>	125	18	6.50 (6.13-6.89)	3.10 (2.69-3.58)	5.82 (5.45-6.19)	2.10	8.50 (8.01-9.03)	9.26 (8.67-9.88)	10.63 (9.84-11.49)
SARS-CoV-2 (8 DFSO) <sup>¶</sup>	119	18	6.49 (6.09-6.91)	2.99 (2.59-3.46)	5.79 (5.40-6.18)	2.14	8.57 (8.04-9.13)	9.35 (8.73-10.02)	10.80 (9.96-11.71)
SARS-CoV-2 (9 DFSO) <sup>¶</sup>	117	18	6.18 (5.76-6.63)	2.72 (2.35-3.15)	5.51 (5.11-5.91)	2.20	8.40 (7.82-9.01)	9.25 (8.57-9.98)	10.83 (9.90-11.85)
SARS-CoV-2 (10 DFSO) <sup>¶</sup>	110	16	5.76 (5.34-6.20)	2.61 (2.25-3.03)	5.13 (4.73-5.53)	2.11	7.92 (7.34-8.55)	8.76 (8.07-9.51)	10.33 (9.38-11.37)

\*These two columns summarize the cumulative number of specimens (left) collected from the number of studies (right) for each category in the systematic dataset.

<sup>†</sup>The mean and sample SD were calculated on the entire set of individual sample data for each category.

<sup>‡</sup>The Weibull quantile distributions were used to determine rVLs at the 90<sup>th</sup>, 95<sup>th</sup> and 99<sup>th</sup> cps.

<sup>§</sup>These categories included only rVL data from positive (above the detection limit) qRT-PCR measurements.

<sup>¶</sup>Data for earlier DFSO were excluded from distribution fitting based on limited data, and empty cells were marked with “-“.

<sup>¶</sup>These categories included negative qRT-PCR measurements (set at the detection limit to estimate rVLs; n = 3, 3, 6, 8, 12, 15, 13, 17 and 14 specimens for 2-10 DFSO, respectively) for cases that tested positive at an earlier DFSO.

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Extended Data Table 3 | Model parameters describing SARS-CoV-2 kinetics in the respiratory tract

Parameter	Description	Value (95% CI)	Units
$\beta$	Infection rate constant	4.02 (3.01-5.03)	$\times 10^{-7}$ (copies/ml) $^{-1}$ day $^{-1}$
$p$	Cellular shedding rate of virus	1.11 (0.51-1.71)	copies/ml day $^{-1}$ cell $^{-1}$
$c$	Clearance rate of virus	3.82 (0.17-7.47)	day $^{-1}$
$\delta$	Clearance rate of infected epithelial cells	0.55 (0.23-0.87)	day $^{-1}$
$R_{0,c}$	Cellular basic reproductive number	10.6	unitless
$V_0^*$	Initial rVL parameter	4	copies/ml
$k^*$	Initial number of infected cells	0	cells
$T_0^*$	Initial number of uninfected cells	$5 \times 10^7$	cells

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\*Initial values were used as inputs for the numerical estimation of the model parameters.