

# 1 Cryptic transmission of SARS-CoV-2 and the first COVID-19 wave in 2 Europe and the United States

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## 18 Abstract

19 Given the narrowness of the initial testing criteria, the SARS-CoV-2 virus spread through cryptic  
20 transmission in January and February, setting the stage for the epidemic wave experienced in March and  
21 April, 2020. We use a global metapopulation epidemic model to provide a mechanistic understanding  
22 of the global dynamic underlying the establishment of the COVID-19 pandemic in Europe and the  
23 United States (US). The model is calibrated on international case introductions at the early stage of  
24 the pandemic. We find that widespread community transmission of SARS-CoV-2 was likely in several  
25 areas of Europe and the US by January 2020, and estimate that by early March, only 1–3 in 100 SARS-  
26 CoV-2 infections were detected by surveillance systems. Modeling results indicate international travel  
27 as the key driver of the introduction of SARS-CoV-2 with possible importation and transmission events  
28 as early as December, 2019. We characterize the resulting heterogeneous spatio-temporal spread of  
29 SARS-CoV-2 and the burden of the first COVID-19 wave (February-July 2020). We estimate infection  
30 attack rates ranging from 0.78%-15.2% in the US and 0.19%-13.2% in Europe. The spatial modeling of  
31 SARS-CoV-2 introductions and spreading provides insights into the design of innovative, model-driven  
32 surveillance systems and preparedness plans that have a broader initial capacity and indication for  
33 testing.

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## 34 Introduction

35 The first confirmed case of COVID-19 in the United States (US) was diagnosed in Washington state on  
36 January 21, 2020 (1). In Europe, the first three COVID-19 cases were reported in France on January 24  
37 and had an onset of symptoms on January 17, 19 and 23, respectively (2; 3). In quick succession other  
38 cases were confirmed in the US (4; 5; 6) and in several European countries such as Germany (January  
39 27), Italy (January 30), Spain, and the United Kingdom (January 31). In Fig. 1A we include a timeline  
40 of initial confirmed cases and early containment and mitigation initiatives in the US and Europe. To  
41 study the cryptic spreading phase and the ensuing first wave of the COVID-19 pandemic, we use a  
42 data-driven, stochastic, spatial, and age-structured global epidemic model. We develop a mechanistic  
43 understanding of the epidemic evolution and estimate the time frame for the establishment of local  
44 transmission in different states and countries. The model provides a statistical picture of SARS-CoV-2  
45 introductions across US states and European countries. We quantify the association between the amount  
46 of international/domestic air travel and the model estimates of the arrival times of the virus in the US and  
47 Europe, showing that international and domestic travel patterns were a key driver in the establishment  
48 of SARS-CoV-2 local transmission. Furthermore, we use the model to estimate the COVID-19 disease  
49 burden across the two regions. We provide model estimates for the infection fatality ratios and the  
50 infection attack rates as of July 4, 2020. We find that our model-estimated infection attack rates are in  
51 good agreement with the results from serological studies of SARS-CoV-2 antibody prevalence conducted  
52 at different spatial resolutions (i.e., city, state, country). Additionally, the model highlights a strong  
53 statistical association between the number of cases reported at the time of issuing major mitigation  
54 policies in each country/state and the estimated number of infections at the end of the first wave. This  
55 is in agreement with statistical analysis showing that the effectiveness of mitigation policies is associated  
56 with the timing of their adoption (7; 8; 9; 10; 11; 12; 13; 14; 15). The unique, mechanistic understanding  
57 of the way in which the COVID-19 pandemic unfolded highlights that, in countries with confirmed local  
58 transmission, policies such as testing based on travel history and international travel restrictions are highly  
59 inefficient in preventing the development of local outbreaks. Wide spread testing would have detected  
60 transmission earlier and allowed for earlier implementation of interventions. Future preparedness plans  
61 must have broader, initial capacity and indication for testing to mitigate wide spread cryptic transmission.  
62 These findings are of particular relevance given that contrasting the spread of SARS-CoV-2 variants of  
63 concern presents similar dynamics and problems.

## 64 Results

65 We consider data concerning the continental US and the following list of 30 countries we will informally  
66 refer to as “Europe”: Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Fin-  
67 land, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta,  
68 Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, Switzer-  
69 land, and the UK. To study the spatial and temporal spread of SARS-CoV-2, we use the Global Epi-  
70 demic and Mobility Model (GLEAM), a stochastic, spatial, and age-structured metapopulation epidemic  
71 model (16; 17; 18). The model was previously used to characterize the early stage of the COVID-19 epi-  
72 demic in mainland China and the effect of travel restrictions on infections exported to other regions (19).  
73 The model divides the global population into more than 3,200 subpopulations in roughly 200 different  
74 countries and territories. A subpopulation is defined as the catchment area around major transportation  
75 hubs. The airline transportation data encompass daily origin-destination traffic flows from the Official  
76 Aviation Guide (OAG) database (20) reflecting actual traffic changes that occurred during the pandemic.  
77 Ground mobility and commuting flows are derived from the analysis and modeling of data collected  
78 from the statistics offices of 30 countries on five continents (17; 16). We set, as initial conditions, an  
79 epidemic starting date in Wuhan, China between November 15, 2019 and December 1, 2019, with 20

80 initial infections (21; 22; 23; 24; 19; 25). This considers that the virus could have emerged as early  
81 as mid October, 2019. The international travel data account for travel restrictions and government is-  
82 sued policies. Furthermore, the model accounts for the reduction of internal, country-wide mobility and  
83 changes in contact patterns in each country and state in 2020. To initially calibrate the global model, we  
84 use an Approximate Bayesian computation (ABC) method (26) that considers reports of international  
85 travelers carrying SARS-CoV-2 returning from China up to January 21, 2020, and accounts for different  
86 case detection capabilities (27; 19) among countries. The model details are reported in the Materials and  
87 Methods section and the Supplementary Information (SI).

88 Stochastic simulations of the global epidemic spread yield international and domestic infection impor-  
89 tations, incidence of infections, and deaths per subpopulation at a daily resolution. In Fig. 1B we show  
90 the model estimates for the median daily incidence of new infections up to February 21, 2020, for both the  
91 US and Europe. These values are much larger than the number of officially reported cases (see Fig.1A),  
92 highlighting the significant number of potential transmission events that may have already occurred before  
93 many states and countries had implemented testing strategies independent of travel history.

94 As validation we compare our model projections of the number of infections during the week of March  
95 8, 2020 to the number of cases reported during that week within each US state and European country  
96 that had at least 1 reported case (shown in Fig.1B inset). While we see a strong correlation between  
97 the reported cases and our model's projected number of infections (Pearson's correlation coefficient on  
98 log-values, US: 0.79,  $p < 0.001$ ; Europe: 0.80,  $p < 0.001$ ), many fewer cases had actually been reported by  
99 that time. If we assume that the number of reported cases and simulated infections are related through  
100 a simple binomial sampling process, we find that on average 9 in 1,000 infections (90%CI [1 – 35 per  
101 1,000]) and 35 in 1,000 infections (90%CI [4 – 90 per 1,000]) were detected by March 8, 2020 in the US  
102 and Europe respectively. As testing capacity increased that week, the ascertainment rate grows and our  
103 estimates increase to detecting 17 in 1,000 infections (90%CI [2 – 55 per 1,000]) by March 14, 2020 in  
104 the US and 77 in 1,000 infections (90%CI [5 – 166 per 1,000]) in Europe. The estimated ascertainment  
105 rates are in agreement with independent results based on different statistical methodologies (28; 29; 30).

106 In mid-February, other than travel-related restrictions, there were very few mitigation policies im-  
107 plemented for the purpose of reducing community transmission (i.e., social distancing guidelines, school  
108 closures, stay at home orders, etc.) in the US and Europe. Combined with the lack of testing capabilities,  
109 the virus was able to spread undetected and unhindered. In Fig.1C we show the probability that a city in  
110 the US or Europe had generated at least 100 infections by February 21, 2020. We see that the progression  
111 of the virus through the US and Europe is both temporally and spatially heterogeneous. While many  
112 cities had not yet experienced much community transmission by late February, a few areas such as New  
113 York City or London likely already had local virus spreading. As discussed in more detail in the following  
114 sections, the position of the cities within the global mobility network plays a critical role in the timing  
115 of the virus' introduction to the population and onset of local transmission.

116 **Onset of local transmission.** The model allows us to study the unfolding patterns compatible with  
117 the global importation of cases from China leading to the initial local outbreaks. It is important to stress  
118 that the model's realizations explore all possible paths of the epidemic. Thus rather than describing  
119 a specific, single causal chain of events, the results provide a statistical description of all the potential  
120 pandemic histories compatible with the initial evolution of the pandemic in China. For instance, some  
121 initial clusters, such as in Germany, have been effectively contained, possibly delaying the start of wide  
122 spread transmission (31). While the inclusion of these additional events in selecting epidemic paths would  
123 be computationally unfeasible, it is possible to assume, considering also recent evidence from models of  
124 genomic epidemiology (32; 31; 33), that Italy has been the first among European countries to experience  
125 substantial widespread transmission. Due to limited testing capacity during the early phases of the  
126 pandemic, confirmed SARS-CoV-2 deaths might be a better proxy for the relative start of the local  
127 outbreak in each country rather than reported cases. As of March 9, 2020, Italy reported 463 cumulative  
128 deaths, Spain 35, USA 26, France 25, Germany 2, the UK 7, and Italy was the first in the region to

129 impose a national lockdown. Therefore, throughout the paper, we constrain the ensemble of simulations  
130 focusing only on stochastic realizations where Italy is the first country, in the group under examination,  
131 to experience sustained local transmission. In the SI we report the analysis of the full unconstrained set  
132 of simulations.

133 Here, we define the onset of local transmission for a country or state as the earliest date when at least  
134 10 new infections are generated per day. This number is chosen because at this threshold the likelihood  
135 of stochastic extinction is extremely small (34; 35). In fact, the probability of disease extinction in a  
136 fully susceptible and well-mixed population exposed to  $n$  infected individuals can be approximated as  
137  $R_0^{-n}$ , which is approximately  $10^{-5}$  when  $R_0 = 2.7$ . As detailed in the SI, further calibration on the US  
138 states and European countries suggests values of  $R_0$  ranging from 2.4 – 2.8. These values are consistent  
139 with many other (country dependent) estimates (36; 37; 38; 39; 40; 8). At the same time, given the  
140 doubling time of COVID-19 before the implementation of public health measures, any variation of a  
141 factor 2 around the 10 infections/day threshold corresponds to a small adjustment of 3 – 5 days to the  
142 presented timelines.

143 In Fig. 2, we show the posterior distribution of onset of local transmission for different US states (A)  
144 and European countries (B). Among the US states, California and New York state are the earliest, with  
145 over a 50% estimated probability of local transmission by the end of January (California) or beginning  
146 of February (New York), 2020. In Europe, Italy, UK, Germany, and France are the first countries with  
147 a probability larger than 50% to have experienced local transmission by the end of January 2020. A  
148 majority of the states and countries analyzed have a median date of onset of local transmission by early  
149 March, with the large majority of them in February, 2020, a critical month for the cryptic spread of  
150 SARS-CoV-2 in the continental US and Europe. Remarkably, the plots for both Europe and the US  
151 indicate that while surveillance and testing in February and early March were focused on travel history,  
152 several European countries and US states were likely already experiencing local community transmission.  
153 This finding confirms that from late January to early March SARS-CoV-2 had been spreading across the  
154 US and Europe mostly undetected. However, the wide distribution of dates suggest that SARS-CoV-2  
155 cryptic transmission may have begun as early as December, 2019. The model also allows us to estimate  
156 possible COVID-19 related deaths during the undetected spreading phase. For instance by March 1,  
157 2020, the model suggests that the median cumulative number of deaths was 56 [90% CI 9 – 544] in the  
158 US and 120 [90% CI 21 – 1,177] in Europe. Although some US states and European countries launched  
159 investigations in search of evidence that COVID-19 was the cause of death as far back as December 2019,  
160 it is likely that most early deaths were not recorded (41).

161 **SARS-CoV-2 introductions.** As the model allows the recording of the origin and destination of SARS-  
162 CoV-2 carriers at the global scale, we can study the possible sources of infection importation for each US  
163 state and European country. More specifically, we record the number of introductions in each stochastic  
164 realization of the model. In Fig. 3 we visualize the origin of the introductions considering some key  
165 geographical regions (e.g., Europe and Asia) while keeping the US and China separate and aggregating  
166 all the other countries (i.e., Others). We show the directed importation flows from the aggregated source  
167 regions to the US states (A) and European countries (B). States and countries are ordered according to the  
168 date of the estimated establishment of local transmission. In both cases, the contribution from mainland  
169 China is barely visible and the local share (i.e., sources within Europe and US) becomes significantly  
170 higher across the board. Hence, while importation events in the early phases of the outbreak were key to  
171 start the local spreading (see details in the SI), the cryptic transmission phase has been sustained largely  
172 by internal flows. Domestic SARS-CoV-2 introductions through April 30, 2020, account for 71% [IQR  
173 61% – 82%] of the introductions in California, 79% [IQR 73% – 88%] in Texas, and 71% [IQR 61% – 82%]  
174 in Massachusetts. European origins account for 69% [IQR 60% – 80%], 84% [IQR 79% – 91%], and 58%  
175 [IQR 48% – 68%] of the introductions in Italy, Spain, and the UK, respectively. In the SI we report the  
176 full breakdown for all states and countries.

177 It is important to distinguish between the full volume of SARS-CoV-2 introductions and the introduc-

178 tion events that could be relevant to the early onset of local transmission in each stochastic realization  
179 of the model. In the model we can investigate these specific events by recording introduction events  
180 before the local transmission chains were established (defined as the median dates of Fig. 2). We report  
181 the results of this analysis in the SI, showing that importations from mainland China may be relevant  
182 in seeding the epidemic in January, but then play a small role in the COVID-19 expansion in the US  
183 and Europe due to the travel restrictions imposed to/from mainland China after January 23, 2020. In  
184 fact, about 74% [IQR 60% – 100%] and 45% [IQR 15% – 71%] of the virus introduction before the onset  
185 of local transmission in California and New York states, respectively, were from mainland China. The  
186 equivalent share of importations from China in Italy and the UK were 72% [IQR 50% – 100%] and 52%  
187 [IQR 31% – 71%].

188 Our results concerning SARS-CoV-2 introductions in different countries/states can be compared to  
189 analysis based on gene sequencing and travel volumes, showing a good degree of agreement with the  
190 temporal and geographical distribution of SARS-CoV-2 importations. For example, Ref. (42) estimates  
191 that the majority of importation events associated with onward transmissions in the UK, through April  
192 2020, came from Europe. Similar to our findings, the contributions from China are quantified below  
193 1% and limited to the very early phase. Furthermore, the seeding events from the US are estimated  
194 to be  $\sim 3\%$  which is in agreement with our estimate of 8% [IQR 3% – 9%]. However, their results  
195 point to a larger share from Europe ( $\sim 90\%$ ) compared to ours (58% [IQR 48% – 68%]). Conversely, we  
196 estimate a larger contribution from Asia (27% [IQR 19% – 35%]). The discrepancies might be due to  
197 biases in genomic sampling (43) and/or the fact that we sample all possible epidemic paths statistically  
198 possible rather than the single, observed occurrence. To this point, it is worth stressing that seeding  
199 importations are different from the actual number of times the virus has been introduced to each location  
200 with subsequent onward transmission. Even after local transmission has started, future importation  
201 events may give rise to additional onward transmission forming independently introduced transmission  
202 lineages of the virus(42). Ref. (44) confirms the key role of national importations in the US. In fact,  
203 by analyzing both genomic and travel data (national and international) it estimates that the outbreak  
204 in Connecticut was largely driven by domestic importations. Our results indicate an internal share of  
205 importations for that state of 64% [IQR 54% – 76%]. Furthermore, Ref. (33) confirms the key role of  
206 importations from China to Italy at the beginning of the pandemic. As shown in the SI and mentioned  
207 above, our results suggest that 72% of the early introductions before the start of the local outbreak in  
208 Italy are linked to China.

209 **COVID-19 burden.** The model allows us to estimate the disease burden in the US and Europe once  
210 COVID-19 has established local transmission. Starting in March 2020, the COVID-19 epidemic trajectory  
211 in each country and state is driven by the establishment and timing of non-pharmaceutical interventions  
212 (NPIs) as well as by the epidemiological relevant features (i.e., population size and density, age-structure  
213 etc.) which are spatially heterogeneous (45; 46; 47; 7). The model accounts for these features as detailed  
214 in the SI. To calibrate the model results for each individual US state and European country, we use the  
215 weekly number of new deaths reported from March 22, 2020 to June 27, 2020. Furthermore, we consider  
216 a uniform prior for the average infection fatality ratio (IFR) in the range from 0.4% to 2% that is age  
217 stratified proportional to the IFR values reported in Ref. (48). We also consider a uniform prior for  
218 reporting delays between the date of death and reporting ranging from 2 to 22 days in both Europe  
219 and the US (49). We provide the details of our calibration for each geographical unit (i.e., US state or  
220 European country) in the SI.

221 In Fig. 4(A-D, F-I), we report the projected results of the weekly deaths of the first wave for selected  
222 states and countries. Additional model results for all investigated regions including a sensitivity analysis  
223 of different calibration methods can be found in the SI. We find a strong correlation between the weekly  
224 model-estimated deaths and the reported values with a Pearson correlation coefficient of 0.99 ( $p < 0.001$ )  
225 for both Europe and the US (see Fig. S5). As the data suggest, many European countries and US states  
226 saw peaks in April and May with various decreasing trajectories that are dependent on the mitigation

227 strategies in place. Additionally, we report the estimated cumulative infection attack rates and IFRs as  
228 of July 4, 2020, in European countries experiencing more than 100 total deaths and the top 20 states  
229 ranked by infection attack rate in the US. The median infection attack rates vary from 0.19% – 13.2% in  
230 Europe and 0.78% – 15.2% in the US.

231 Within Europe, Belgium has the highest estimated infection attack rate of 13.2% (90% CI [8.5% –  
232 28.3%]) by July 4, 2020, in agreement with the results detailed in Ref. (28). Furthermore, by that time  
233 Belgium reported the highest COVID-19 mortality rate out of the European countries investigated with  
234 8.5 deaths per 10,000 individuals. Italy is estimated to have the highest median IFR of 1.4% (90% CI  
235 [0.6% – 1.8%]), which aligns with other ranges reported in the literature (50; 51). The US states with the  
236 highest infection attack rates are located within the Northeast and experienced a significant first wave  
237 during March-April 2020. New York and New Jersey are the top two states with infection attack rates  
238 of 13.4% (90% CI [9.1% – 26.7%]) and 15.2% (90% CI [10.2% – 31.3%]) respectively. These numbers  
239 are aligned with estimates from New York City reported in Ref. (52). However, unlike many European  
240 countries, some states did not experience a significant initial wave until late summer 2020, after the time  
241 window considered here. The IFRs estimated for the US states range from 0.8% to 1.3%. In the SI we  
242 report summary tables with estimated IFRs, infection attack rates, as well as the reproductive number  
243 in the absence of mitigation measures for all calibrated US states and European countries.

244 **The drivers and impact of the cryptic transmission phase.** In the early stages of a pandemic,  
245 surveillance data are known to be unreliable due to under-detection. For each state in the US and  
246 each country in Europe we compared the order in which they surpassed 100 cumulative infections in the  
247 model and in total cases in the surveillance data (gathered from the John Hopkins University Coronavirus  
248 Resource Center (53)). In Fig. 5A we plot the ordering for states and compute the Kendall rank correlation  
249 coefficient  $\tau$  (see SI for details). The correlation is positive ( $\tau_{EU} = 0.71$ ,  $p < 0.001$  and  $\tau_{US} = 0.68$ ,  
250  $p < 0.001$ ) indicating that, despite the detection and testing issues, the expected patterns of epidemic  
251 diffusion are largely described by the model in both regions. The model, however, suggests that one  
252 major driver of this early diffusion pattern is air travel. We compare the ordering of states and countries  
253 according to their air travel volume to their epidemic order as previously defined (Fig. 5A). We consider  
254 both national and international traffic, and find a positive correlation ( $\tau_{EU} = 0.66$  with  $p < 0.001$  and  
255  $\tau_{US} = 0.66$  with  $p < 0.001$ ) between the epidemic ordering derived from surveillance data and air traffic,  
256 suggesting the passenger volume of both international and national traffic are key factors driving the  
257 early spreading of the outbreak across countries. Similar observations have been reported in China,  
258 where the initial spreading of the virus outside Hubei was strongly correlated with the traffic to/from  
259 the province (54). Population size is also correlated with both the traveling flows ( $\tau_{EU} = 0.59$ ,  $p < 0.001$   
260 and  $\tau_{US} = 0.7$ ,  $p < 0.001$ ) and the epidemic order of each state ( $\tau_{EU} = 0.46$ ,  $p < 0.001$  and  $\tau_{US} = 0.68$ ,  
261  $p < 0.001$ ) as discussed in the SI. In our model, it is not possible to exclude increased contacts in highly  
262 populated places before social distancing interventions and disentangle this effect from increased seeding  
263 due to the correlation between travel volume and population size.

264 As more cases were detected in countries and states, travel restrictions were implemented to/from  
265 high risk regions. Consequently, COVID-19 deaths started to rise along with hospitalizations and many  
266 governments began to issue social distancing guidelines, school closures, and community / country-wide  
267 lock downs. All NPIs were aimed at mitigating the spread of COVID-19 (8). In Fig. 5C (left) we report  
268 the correlation between the cumulative infections projected by the model on July 4, 2020, and the number  
269 of cases reported by the date of lockdown (reported data from Ref. (55)). Similarly, in the US (right:  
270 Fig. 5C) we show the correlation between the cumulative infection projections on July 4, 2020, and the  
271 number of cases reported by March 16, 2020, the date the “15 days to slow the spread” guidelines were  
272 released (56). At this point in time, many people were aware of the virus and altering their behavior (such  
273 as working from home or social distancing) (57; 58). In both cases we find a strong correlation (Pearson  
274 correlation coefficient,  $r = 0.92$ ,  $p < 0.001$  and  $r = 0.73$ ,  $p < 0.001$  in Europe and US respectively)  
275 indicating that the earlier NPIs had been issued with respect to the number of cases confirmed in each

276 specific state or country, the smaller the COVID-19 burden experienced during the first wave. This is  
277 in agreement with other analyses showing that the timing of NPIs is crucial in limiting the burden of  
278 COVID-19 (7; 8; 9; 10; 11; 12; 13; 14; 15).

279 By April-May 2020, after a month of *stay-at-home* orders and other NPIs coupled with travel re-  
280 strictions, many European countries and US states started to observed a decline in SARS-CoV-2 cases,  
281 deaths, and hospitalizations. This decline led to the relaxation of many social distancing policies, such  
282 as removing *stay-at-home* directives or opening workplaces and restaurants to in-person business. Even  
283 though at the end of the first wave the active prevalence of the virus may have been low within these  
284 regions, the relative low level of residual immunity left in a population has favored an epidemic resur-  
285 gence observed both in the US and Europe in October and November 2020. In Fig. 5D we report the  
286 correlation between our model-estimated infection attack rates and the prevalence of individuals with the  
287 SARS-CoV-2 antibody from 13 serological studies across the US and Europe. We find a remarkably good  
288 agreement between model estimates and seroprevalence studies at different point in times. Data from  
289 this figure can be found in the Table S7 in the SI.

## 290 Discussion

291 The model presented here captures the spatial and temporal heterogeneity of the early stage of the  
292 pandemic, going beyond the single country-level reconstruction. It provides a mechanistic understanding  
293 of the interconnected, underlying dynamics of the pandemic's evolution. The results of our analysis  
294 suggest that the first sustained local transmission chains took place as early as January and by the end of  
295 February 2020 the virus was spreading in a majority of European countries and US states. This timeline  
296 is shifted several weeks ahead with respect to the detection of cases in surveillance data and is consistent  
297 with the fact that, in January and February, no country had the capacity to do mass testing. The  
298 results also indicate that the sources of introduction of SARS-CoV-2 infections into Europe and the US  
299 changed substantially and rapidly through time. If testing had been more widespread and not restricted  
300 to individuals with a travel history from China, there would have been more opportunities for earlier  
301 detection and interventions.

302 The numerical simulations yield posterior distributions characterizing the timing of the onset of local  
303 transmission of SARS-CoV-2 across US states and European countries. These results generate a compre-  
304 hensive picture of the cryptic phase of the pandemic, especially for countries and states where genomic  
305 surveillance and testing capacity were not adequate. This is also relevant in the interpretation of many  
306 studies that are searching for SARS-CoV-2 traces in existing databases (ex. blood donors, sewage samples  
307 etc.).

308 The model can estimate the impact of the first wave through measuring the country and state level  
309 infection attack rates. These projections align with other sources and provide insights into the heteroge-  
310 neous progression of the pandemic across countries/states due to the timing and magnitude of different  
311 public health responses. We find that an early response is important in minimizing the burden of COVID-  
312 19 disease on a region. The first European country to implement a *cordon sanitaire* in response to the  
313 rise in SARS-CoV-2 related illness was Italy on February 23, 2020, for a few northern cities (59). How-  
314 ever, this is nearly one month after the median date of the onset of local transmission estimated by  
315 the model (see Fig. 2B). Many other countries followed suit and implemented national lock downs in  
316 March 2020 (45; 60), weeks after our model estimated that SARS-CoV-2 was introduced and subsequently  
317 spreading.

318 More generally, our results show that reactive response strategies, such as issuing travel restrictions  
319 targeting countries only after local transmission is confirmed, are highly inefficient. These strategies fail  
320 to prevent the establishment of local outbreaks because they do not recognize the critical importance  
321 of the cryptic phase. In addition, this finding parallels the emerging story of the cryptic spreading of  
322 variants of concern, pointing out the need of increased testing capacity not dependent on travel history,

323 contact tracing, and promoting the establishment of gene sequencing surveillance infrastructures.

324 As with all modeling analyses, results are subject to biases from the limitations and assumptions within  
325 the model as well as the data used in its calibration. The model's parameters, such as generation time,  
326 incubation period, and the proportion of asymptomatic infections are chosen according to the current  
327 knowledge of SARS-CoV-2. Although the model is robust to variations in these parameters (see the SI for  
328 the sensitivity analysis), more information on the key characteristics of the disease would considerably  
329 reduce uncertainties. The model calibration does not consider correlations among importations (i.e.,  
330 family travel) and assumes that travel probabilities are age-specific across all individuals in the catchment  
331 area of each transportation hub.

332 Although the modeling results should be interpreted cautiously in light of the assumptions and lim-  
333 itations inherent to modeling approaches, they are of interest in combination with sequencing data of  
334 SARS-CoV-2 genomes to reconstruct in greater detail the early epidemic history of the COVID-19 pan-  
335 demic. The methods used in this analysis offer a blueprint to identify the most likely early spreading  
336 dynamics of emerging variants and they can be used as a real-time risk assessment tool to inform policy  
337 makers. Anticipating the locations where the virus is most likely to spread to next could be instrumen-  
338 tal in guiding enhanced testing and surveillance activities, and complement phylogeographic inference  
339 approaches (33). The estimated SARS-CoV-2 importation patterns and the cryptic transmission phase  
340 dynamics are of potential use when planning and developing public health policies in relation to inter-  
341 national traveling and they could provide important insights in assessing the potential risk and impact  
342 of emerging SARS-CoV-2 variants in regions of the world with limited testing and genomic surveillance  
343 resources.

## 344 Methods

345 **SARS-CoV-2 transmission dynamic.** The transmission dynamics take place within each subpopulation and  
346 assume a classic SLIR-like compartmentalization scheme for disease progression similar to those used in several  
347 large scale models of SARS-CoV-2 transmission (29; 61; 62; 63; 64; 22). Each individual, at any given point in  
348 time, is assigned to a compartment corresponding to their particular disease-related state (being, e.g., susceptible,  
349 latent, infectious, removed) (19). This state also controls the individual's ability to travel (details in the SI).  
350 Individuals transition between compartments through stochastic chain binomial processes. Susceptible individuals  
351 can acquire the virus through contacts with individuals in the infectious category and can subsequently become  
352 latent (i.e., infected but not yet able to transmit the infection). The process of infection is modeled using age-  
353 stratified contact patterns at the state and country level (65; 66). Latent individuals progress to the infectious  
354 stage at a rate inversely proportional to the latent period, and infectious individuals progress to the removed stage  
355 at a rate inversely proportional to the infectious period. The sum of the mean latent and infectious periods defines  
356 the generation time. Removed individuals are those who can no longer infect others. To estimate the number of  
357 deaths, we use as prior the age-stratified infection fatality ratios from Ref (48). The transmission model does not  
358 assume heterogeneities due to age differences in susceptibility to the SARS-CoV-2 infection for younger children  
359 (1 – 10 years old). This is an intense area of discussion (67; 68; 69).

360 **Model calibration.** We assume a start date of the epidemic in Wuhan, China, that falls between November 15,  
361 2019 and December 1, 2019, with 20 initial infections (21; 22; 23; 24; 19). The model generates an ensemble of  
362 possible epidemic realizations and is initially calibrated using Approximate Bayesian computation (ABC) rejec-  
363 tion approach (26) based on the observed international importations from mainland China through January 21,  
364 2020 (19). Only a fraction of imported cases are generally detected at the destination (70; 27). According to the  
365 estimates proposed in Ref. (71), we stratify the detection capacity of countries into three groups: high, medium and  
366 low surveillance capacity according to the Global Health Security Index (72), and assume asymptomatic infections  
367 are never detected. The model calibration does not consider correlated importations (i.e., family travel) and as-  
368 sumes that travel probabilities are homogeneous across all individuals in each subpopulation. We perform for each  
369 state and country an additional ABC rejection analysis using as evidence the weekly reported deaths in the time  
370 window starting on March 22, 2020 through June 27, 2020. A full description of the model is provided in the SM file.

371



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379  
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382 K.M. and A.V. analyzed data; and M.C., J.T.D., N.P., M.A., C.G., M.L., S.M., A.P.P., K.M., N.E.D., L.R., K.S.,  
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389  
390 **Data Availability.** Proprietary airline data are commercially available from Official Aviation Guide (OAG)  
391 and IATA databases. The GLEAM model is publicly available at <http://www.gleamviz.org/>.

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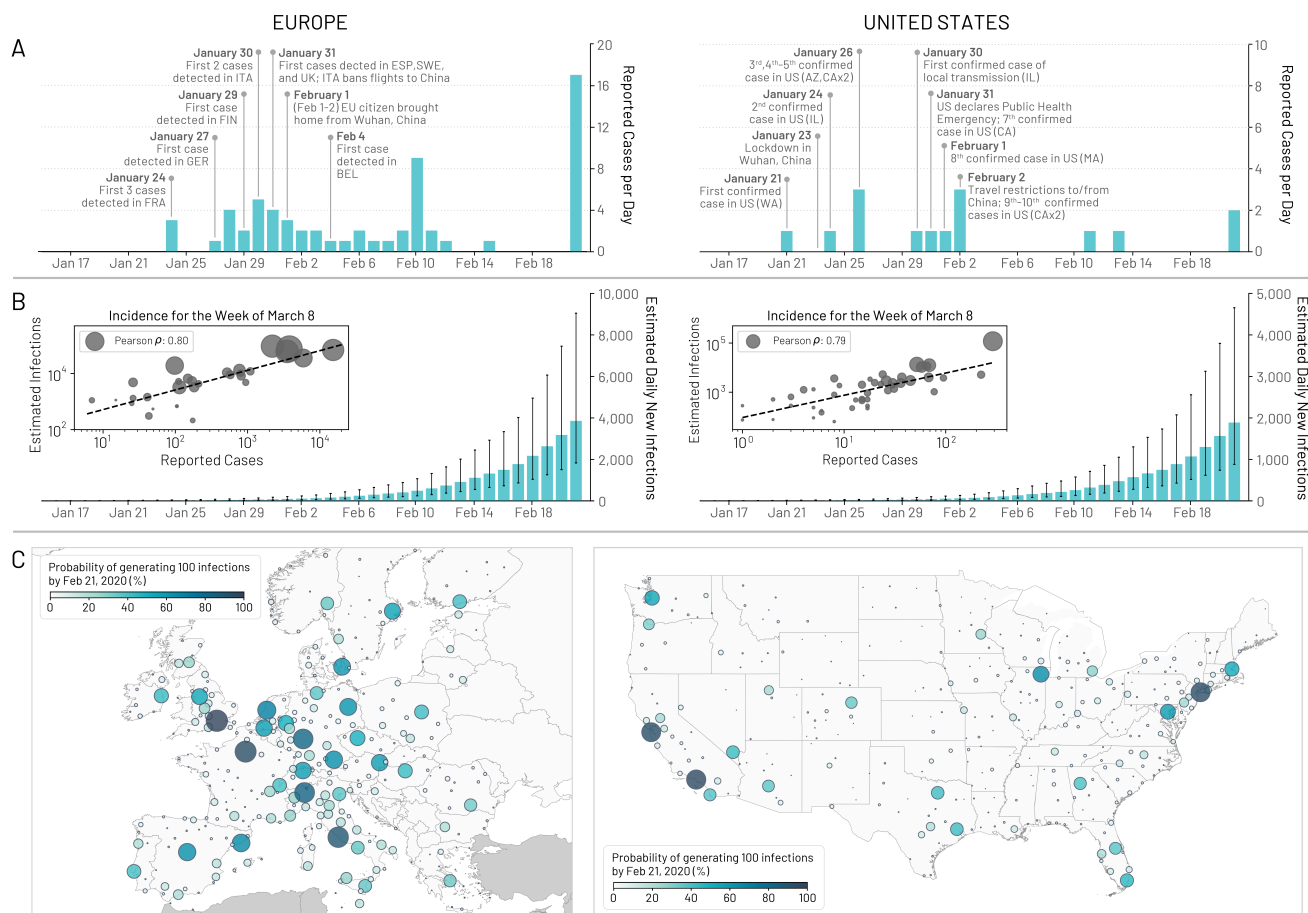


Figure 1: **Early picture of the COVID-19 outbreak in Europe and the United States.** (A) Timelines of the daily reported and confirmed cases of COVID-19 in Europe and US including information on initial reported cases and other significant events related to the outbreak. (B) Model-based estimates for the daily number of new infections in Europe and US. The inset plot compares the weekly incidence of reported cases with the weekly incidence of infections estimated by the model for the week of March 8 – 14, 2020 for the continental US-states and European countries that reported at least 1 case. Circle size corresponds to the population size of each state and country. (C) The probability that a city in Europe and the US had generated at least 100 cumulative infections by February 21, 2020. Color and circle size are proportional to the probability.

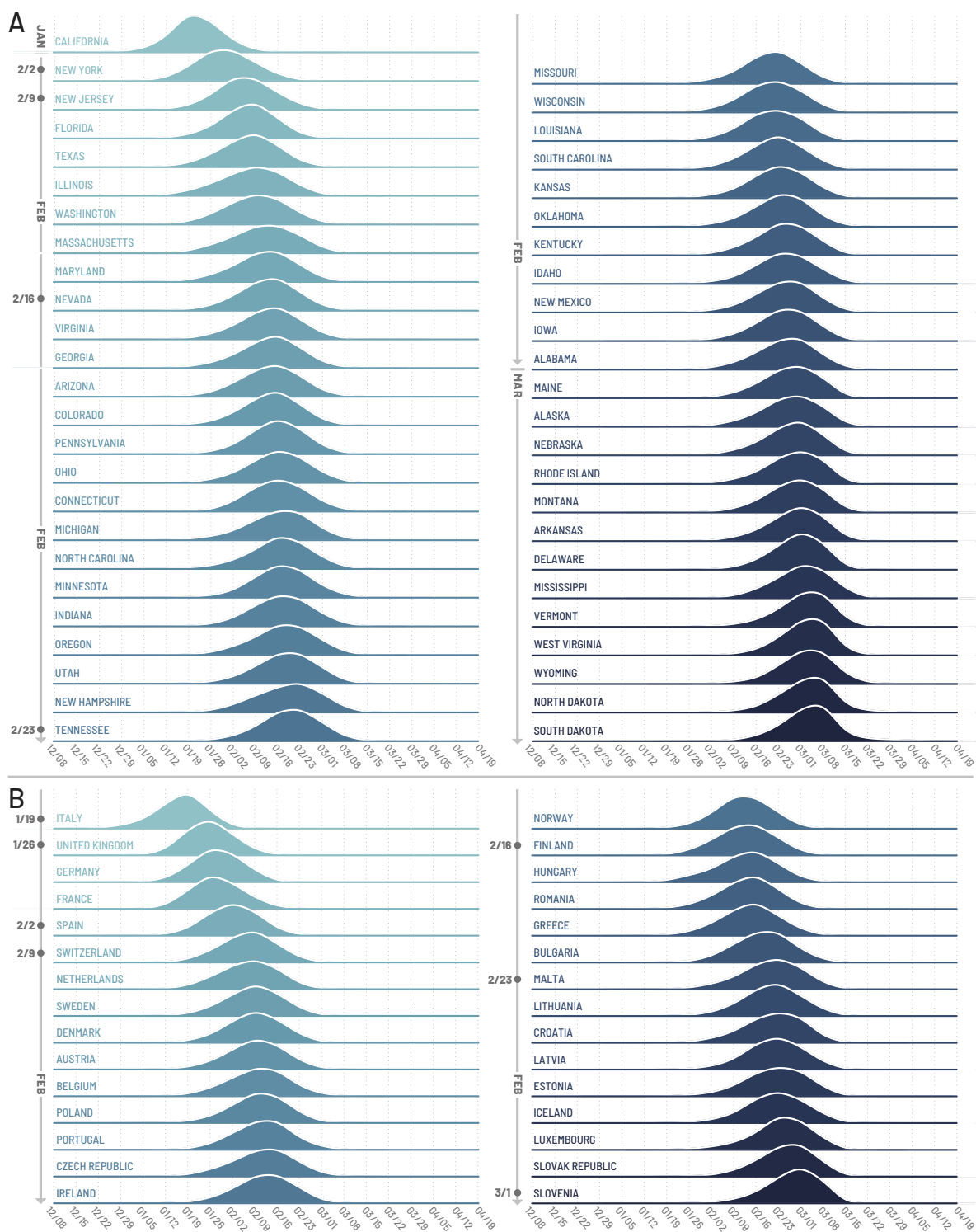


Figure 2: **Timing of the onset of local transmission.** We plot the posterior distributions of the week when each US state (A) or European country (B) first reached 10 locally generated SARS-CoV-2 transmission events per day. Countries/states are ordered by the median date of their posterior distribution. The week of this date corresponds to the dates reported on the the vertical axis.

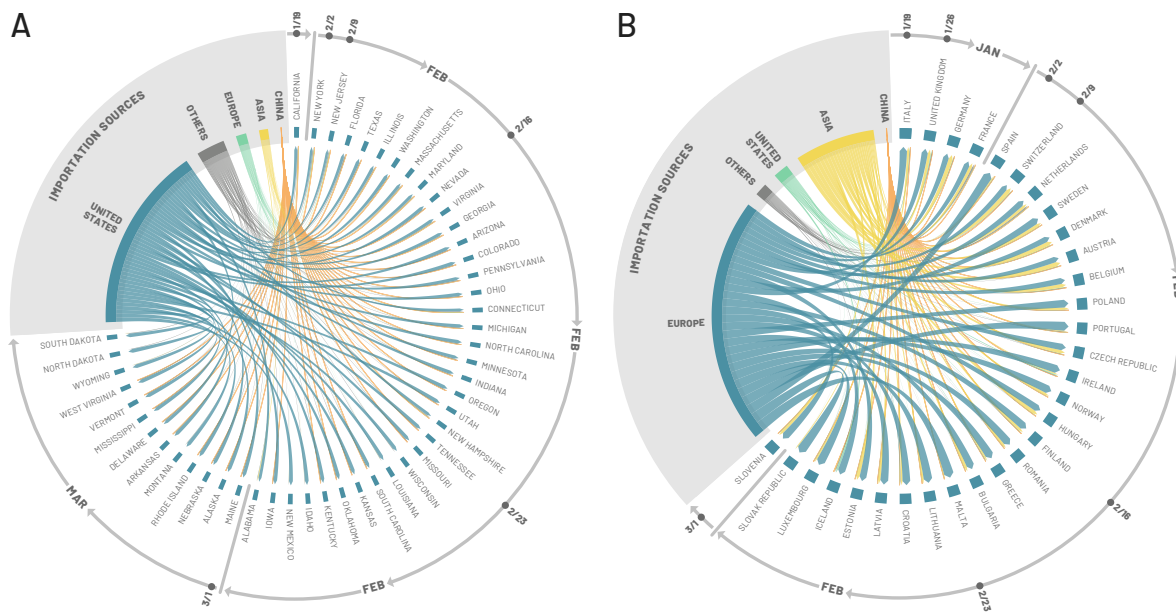


Figure 3: **Importation sources.** Each US state (A) and European country (B) is displayed in a clockwise order with respect to the start of the local outbreak (as seen in Fig. 2). Importation flows are directed and weighted. We normalize links considering the total in-flow for each state so that the sum of importations flows, for each state, is one. In the SM we report the complete list of countries contributing, as importation sources, in each group (i.e., geographical region).

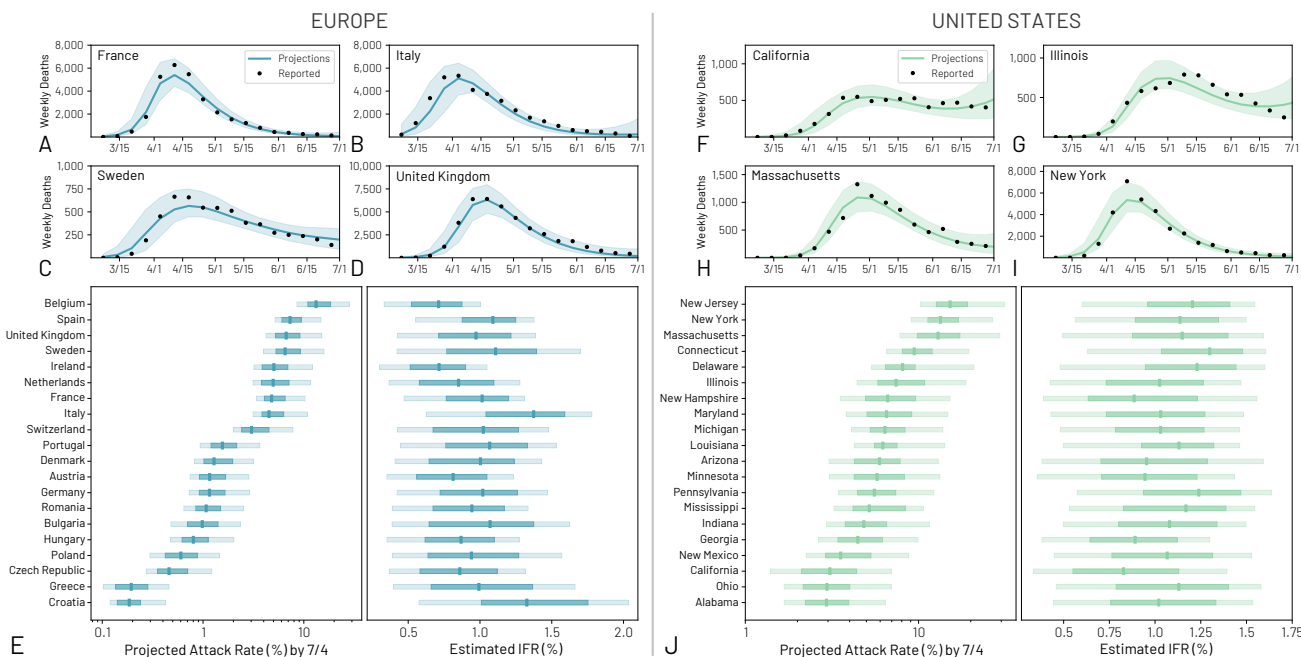
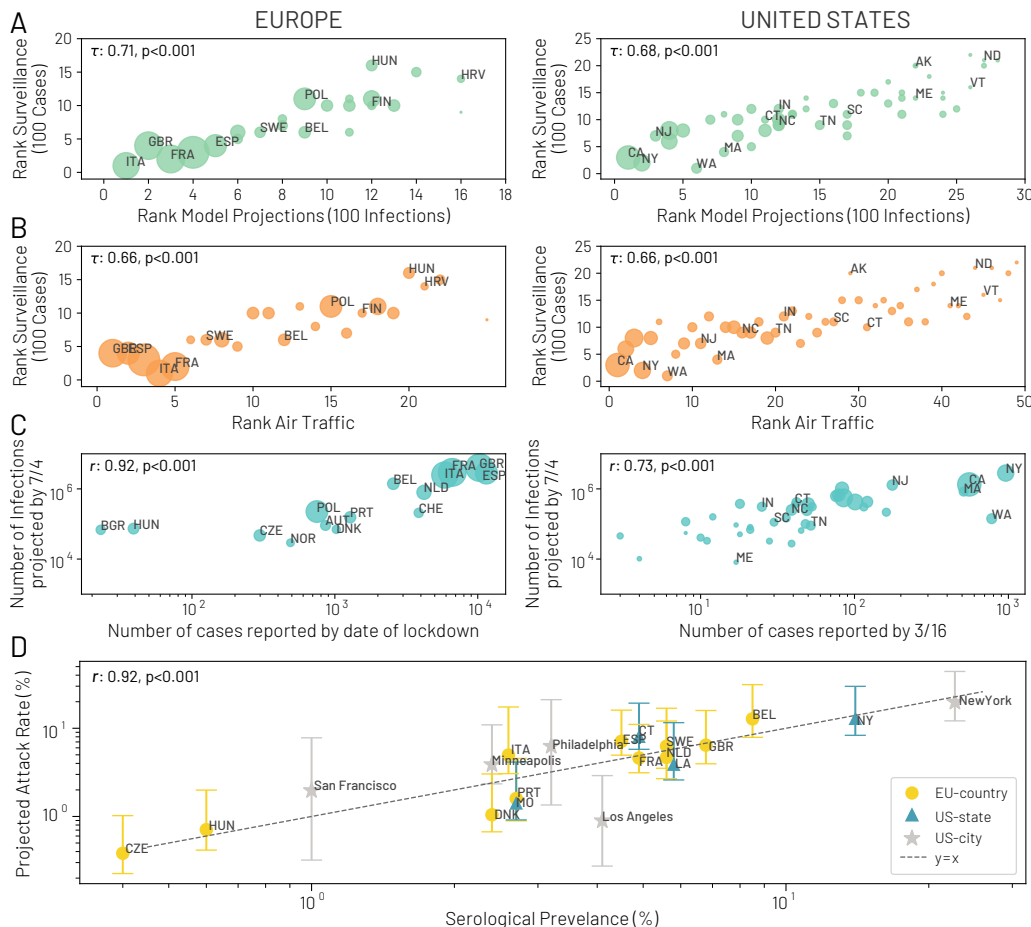


Figure 4: **The burden of the first wave in Europe and the US (A-D)** Model projection results of the weekly deaths for selected countries in Europe. (E) Estimated infection attack rates and infection fatality rates by July 4, 2020 for European countries where there were at least 100 reported deaths. (F-I) Model projection results of the weekly deaths for selected states in the US. (J) Estimated infection attack rates and infection fatality rates by July 4, 2020 for 20 US states.





**Figure 5: Correlation Analysis for European countries and US states.** (A) The correlation between the ordering of each country/state to reach 100 infections in the model projections and to reach 100 reported cases in the surveillance data. Correlation is computed considering the Kendall rank correlation coefficient,  $\tau$ . (B) The correlation between the ordering of each country/state considering the time needed to reach 100 reported cases in the surveillance data and the ranking of the combined international and domestic air traffic. (C) Left: the correlation between the number of cases reported by the date of lockdown for selected European countries (from Table 4 in (55)) and the projected total number of infections by July 4, 2020. Right: the correlation between the number of cases reported by March 16, 2020 for each US state and the projected total infections by July 4, 2020. (D) The correlation between the model-projected infection attack rate and the serological prevalence collected from studies. Data points refer to different dates and locations (table with values and dates reported in the SI). The correlations are calculated using the Pearson correlation coefficient  $r$  in (C-D).