

A viral perspective on worldwide non-pharmaceutical interventions against COVID-19

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Article

Keywords: COVID-19, non-pharmaceutical interventions, SARS-CoV-2

Posted Date: November 5th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-101080/v1>

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22 **Abstract:**

23 Quantifying the effectiveness of large-scale non-pharmaceutical interventions (NPIs)
24 against COVID-19 is critical to adapting responses against future waves of the
25 pandemic. Most studies of NPIs thus far have relied on epidemiological data. Here, we
26 report the impact of NPIs on the evolution of SARS-CoV-2, taking the perspective of the
27 virus. We examined how variations through time and space of SARS-CoV-2 genomic
28 divergence rates, which reflect variations of the epidemic reproduction number R_t , can
29 be explained by NPIs and combinations thereof. Based on the analysis of 5,198 SARS-
30 CoV-2 genomes from 57 countries along with a detailed chronology of 9 non-
31 pharmaceutical interventions during the early epidemic phase up to May 2020, we find
32 that home containment (35% R_t reduction) and education lockdown (26%) had the
33 strongest predicted effectiveness. To estimate the cumulative effect of NPIs, we
34 modelled the probability of reducing R_t below 1, which is required to stop the epidemic,
35 for various intervention combinations and initial R_t values. In these models, no
36 intervention implemented alone was sufficient to stop the epidemic for R_t 's above 2 and
37 all interventions combined were required for R_t 's above 3. Our approach can help
38 inform decisions on the minimal set of NPIs required to control the epidemic depending
39 on the current R_t value.

40 Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory
41 syndrome coronavirus 2 (SARS-CoV-2), emerged in China in late 2019¹⁻³. Facing or
42 anticipating the pandemic, the governments of most countries implemented a wide
43 range of large-scale non-pharmaceutical interventions, such as lockdown measures, in
44 order to reduce COVID-19 transmission⁴⁻⁶. Concerns have been raised regarding the
45 impact of such interventions on the economy, education, and, indirectly, the healthcare
46 system⁷.

47 Understanding the effectiveness of each non-pharmaceutical intervention against
48 COVID-19 is critical to implementing appropriate responses against current or future
49 waves of the pandemic. Comparative studies of interventions typically rely on
50 epidemiological data to estimate variations of the epidemic reproduction number, which
51 are then correlated with the implementation or relaxation of interventions^{5,6,8}. These
52 studies yielded conflicting conclusions. Depending on data sources and epidemiological
53 model design assumptions, some studies identified lockdown (stay at home order) as
54 the most effective intervention^{5,9} while others found little additional impact, if any,
55 compared to other interventions^{4,6,10}. Epidemiological studies of interventions against an
56 epidemic face several challenges. Models informed by counts of confirmed cases or
57 deaths ignore the relationships and transmission patterns between cases. Counts
58 themselves can vary in accuracy and timeliness depending on countries' health
59 facilities, surveillance systems, and the changing definitions of cases. Even when an
60 intervention immediately reduces the transmission rate, a detectable reduction of
61 disease incidence can be much delayed⁶, especially when testing and diagnoses are
62 restricted to specific patient populations. This delay from intervention to incidence
63 reduction, combined with the variety and simultaneous implementation of
64 interventions^{4,5}, complicates the identification of their individual effects.

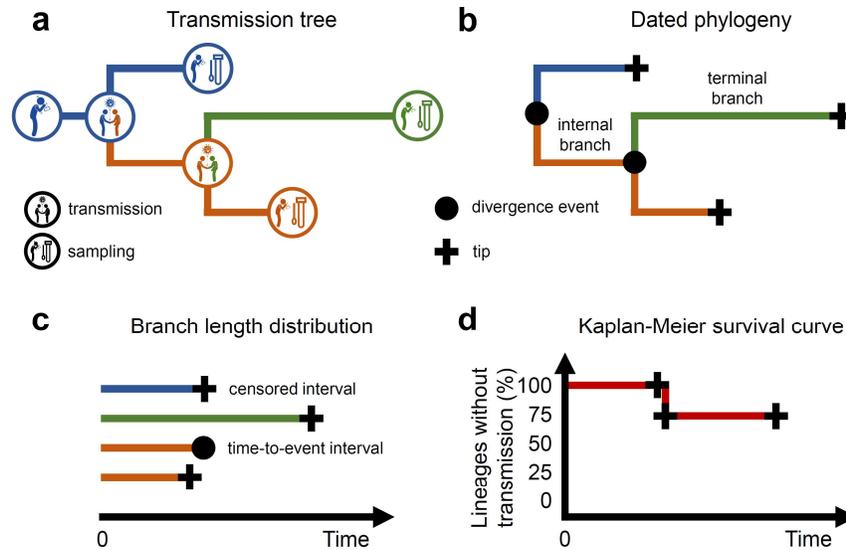
65 Unlike epidemiological case counts, viral genomes bear phylogenetic information
66 relevant to disease transmission. Extracting this information is the goal of
67 phylodynamics, which relies on evolutionary theory and bioinformatics to model the
68 dynamics of an epidemic¹¹. The dates of viral transmission events can also be inferred
69 from genome sequences to alleviate, at least in part, the problems of delayed detection

70 of an intervention's effect. Here, we conducted a phylodynamic analysis of 5,198 SARS-
71 CoV-2 genomes from 57 countries to estimate the independent effects of 9 large-scale
72 non-pharmaceutical interventions on the transmission rate of COVID-19 during the early
73 dissemination phase of the pandemic. We adapted an established phylogenetic
74 method^{12,13} to model variations of the divergence rate of SARS-CoV-2 in response to
75 interventions and combinations thereof. Building on known relationships between the
76 viral divergence rate and the effective reproduction number R_t ¹⁴, we quantified the
77 reduction of R_t independently attributable to each intervention, exploiting
78 heterogeneities in their nature and timing across countries in multivariable models. In
79 turn, these results enabled estimating the probability of stopping the epidemic ($R_t < 1$)
80 when implementing selected combinations of interventions.

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Fig. 1. Conceptual overview of phylodynamic survival analysis. Under the assumption that each viral lineage in a phylogeny belongs to an infected patient, the dates of viral transmission and sampling events in a transmission tree (a) coincide with the dates of divergence events (nodes) and tips, respectively, of the dated phylogeny reconstructed from the viral genomes (b). Treating viral transmission as the event of interest for survival modelling, internal branches connecting two divergence events are interpreted as time-to-event intervals while terminal branches, that do not end with a transmission event, are interpreted as censored intervals (c). Translating the dated phylogeny in terms of survival events enables visualizing the probability of transmission through time as a Kaplan-Meier curve (d) and modelling the transmission rate using Cox proportional hazards regression.

100 **Survival modelling of viral transmission**

101 The dissemination and detection of a virus in a population can be described as a
102 transmission tree (Fig. 1a) whose shape reflects that of the dated phylogeny of the
103 sampled pathogens (Fig. 1b). In a phylodynamic context, it is assumed that each
104 lineage, represented by a branch in the phylogenetic tree, belongs to a single patient
105 and that lineage divergence events, represented by tree nodes, coincide with
106 transmission events¹¹. Thus, branches in a dated phylogeny represent intervals of time
107 between divergence events interpreted as transmission events. This situation can be
108 translated in terms of survival analysis, which models rates of event occurrence, by
109 considering divergence as the event of interest and by treating branch lengths as time-
110 to-event intervals (Fig. 1c, d). Phylogenetic survival analysis was devised by E. Paradis
111 and applied to detecting temporal variations in the divergence rate of tanagers¹² or
112 fishes¹⁵, but it has not been applied to pathogens so far^{13,16,17}.

113 To quantify the effect of non-pharmaceutical interventions on the transmission
114 rate of COVID-19, we adapted the original model in the Paradis study¹² to account for
115 the specific setting of viral phylodynamics (see Methods). Hereafter, we refer to the
116 modified model as phylodynamic survival analysis. In survival analysis terms, we
117 interpret internal branches of the phylogeny (those that end with a transmission event)
118 as time-to-event intervals and terminal branches (those that end with a sampling event)
119 as censored intervals (Fig. 1c; see Methods).

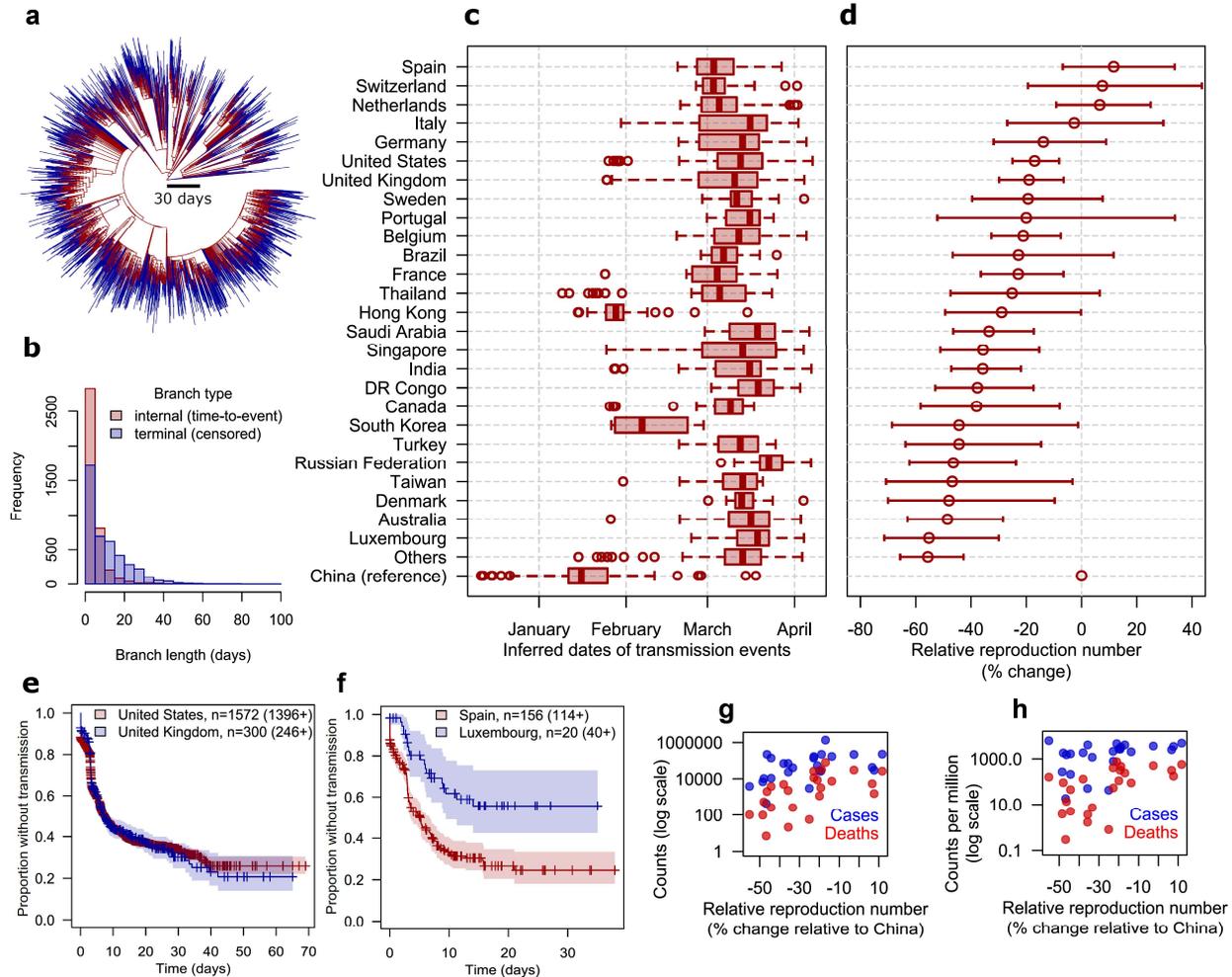
120 The predictors of interest in our setting, namely, the non-pharmaceutical
121 interventions, vary both through time and across lineages depending on their
122 geographic location. To model this, we assigned each divergence event (and
123 subsequent branch) to a country using maximum-likelihood ancestral state
124 reconstruction. Each assigned branch was then associated with the set of non-
125 pharmaceutical interventions that were active or not in the country during the interval
126 spanned by the branch. Intervals containing a change of intervention were split into
127 subintervals¹⁸. These (sub)intervals were the final observations (statistical units) used in

128 the survival models. Models were adjusted for the hierarchical dependency structure
129 introduced by interval splits and country assignments (see Methods).

130 **Phylogenetic survival models estimate variations of the reproduction number**

131 The evolution of lineages in a dated viral phylogeny can be described as a birth-death
132 process with a divergence (or birth) rate λ and an extinction (or death) rate μ ¹⁹. In a
133 phylodynamic context, the effective reproduction number R_t equals the ratio of the
134 divergence and extinction rates¹⁹. Coefficients of phylodynamic survival models (the so-
135 called hazard ratios of divergence; see Methods) act as multiplicative factors of the
136 divergence rate λ , independent of the true value of λ which needs not be specified nor
137 evaluated. As $R_t = \lambda/\mu$, multiplying λ by a coefficient also multiplies R_t , independent of
138 the true value of μ . Thus, coefficients of phylodynamic survival models estimate
139 variations of R_t in response to predictor variables without requiring external knowledge
140 or assumptions about λ and μ .

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Figure 2. Timing and reproduction numbers of the COVID-19 epidemic in 74 countries based on a dated phylogeny. **a**, Dated phylogeny of 5,198 SARS-CoV-2 genomes where internal (time-to-event) and terminal (time-to-censoring) branches are colored red and blue, respectively. **b**, Histogram of internal and terminal branch lengths. **c**, Box-and-whisker plots of the distribution over time of the inferred transmission events in each country, where boxes denote interquartile range (IQR) and median, whiskers extend to dates at most 1.5x the IQR away from the median date, and circle marks denote dates farther than 1.5 IQR from the median date. **d**, Point estimates and 95% confidence intervals of the relative effective reproduction number, expressed as percent changes relative to China, in 27 countries with ≥ 10 assigned transmission events. Countries with < 10 assigned transmission events ($n=32$) were pooled into the ‘Others’ category. **e, f**, Representative Kaplan-Meier survival curves of the probability of transmission through time in countries with comparable (**e**) or contrasting (**f**) transmission rates. ‘+’ marks denote censoring events. Numbers denote counts of internal branches and, in brackets, terminal branches. **g, h**, Scatter plots showing correlations between the relative reproduction number and the reported cumulative numbers of COVID-19 cases (blue marks) and deaths (red marks) per country up to May 12, 2020 (53), in absolute values (**g**) and per million inhabitants (**h**).

160 **Variations in COVID-19 transmission rates across countries**

161 We assembled a composite dataset by combining a dated phylogeny of SARS-CoV-2
162 (Fig. 2a), publicly available from Nextstrain²⁰ and built from the GISAID initiative data²¹,
163 with a detailed timeline of non-pharmaceutical interventions available from the Oxford
164 COVID-19 Government Response Tracker (OxCGRT)²². Extended Data Fig. 1 shows a
165 flowchart outlining the data sources, sample sizes and selection steps of the study.
166 Phylogenetic and intervention data covered the early phase of the epidemic up to May
167 4, 2020.

168 The 5,198 SARS-CoV-2 genomes used to reconstruct the dated phylogeny were
169 collected from 74 countries. Detailed per-country data including sample sizes are shown
170 in Extended Data Table 1. Among the 10,394 branches in the phylogeny, 2,162
171 branches (20.8%) could not be assigned to a country with >95% confidence and were
172 excluded, also reducing the number of represented countries from 74 to 59 (Extended
173 Data Fig. 1; a comparison of included and excluded branches is shown in Extended
174 Data Fig. 2). The remaining 4,025 internal branches had a mean time-to-event (delay
175 between transmission events) of 4.4 days (Fig. 2b). These data were congruent with
176 previous estimates of the mean serial interval of COVID-19 ranging from 3.1 days to 7.5
177 days²³. The 4,207 terminal branches had a mean time-to-censoring (delay from infection
178 to detection) of 10.6 days (Fig. 2a, b). This pattern of longer terminal vs. internal
179 branches is typical of a viral population in fast expansion¹¹.

180 We compared the timing and dynamics of COVID-19 spread in countries
181 represented in our dataset (Fig. 2c, d), pooling countries with <10 assigned
182 transmission events into an 'others' category. The estimated date of the first local
183 transmission event in each country showed good concordance with the reported dates
184 of the epidemic onset (Pearson correlation = 0.84; Extended Data Fig. 3). The relative
185 effective reproduction number R_t per country, taking China as reference, ranged from -
186 55.6% (95%CI, -71.4% to -29.9%) in Luxembourg to +11.7% (95% CI, -6.7% to +33.8%)
187 in Spain (Fig. 2c). Notice that these estimates are averages over variations of R_t
188 through time in each country, up to May 4, 2020. Exemplary survival curves of

189 transmission events are shown in Fig. 2e, f. Relative R_t 's are not expected to
190 necessarily correlate with the reported counts of COVID-19 cases across all countries
191 due to the confounding effects of population sizes, case detection policies and the
192 number of genomes included. Nevertheless, the relative R_t 's across countries
193 substantially correlated with the reported cumulative counts up to May 12 (Fig. 2g, h),
194 including COVID-19 cases (Pearson correlation with log-transformed counts, 0.46, 95%
195 CI, 0.07 to 0.73), deaths (correlation 0.59, 95% CI, 0.24 to 0.80), cases per million
196 inhabitants (correlation 0.39, 95% CI, -0.01 to 0.69) and deaths per million inhabitants
197 (correlation 0.56, 95% CI, 0.21 to 0.79).
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Table 1. Selected large-scale non-pharmaceutical interventions against COVID-19.

Non-pharmaceutical intervention	OxCGRT identifier	Definition
Information campaign	H1	Coordinated public information campaign across traditional and social media
Restrict international travel	C8	Ban or quarantine arrivals from high-risk regions
Education lockdown	C1	Require closing for some or all education levels or categories, e.g., high schools, public schools, universities
Cancel public events	C3	Require cancelling of all public events
Restrict gatherings >100 pers.	C4	Prohibit gatherings over 100 persons
Close workplaces	C2	Require closing or working from home for some or all non-essential sectors or categories of workers
Restrict internal movements	C7	Require closing routes or prohibit most citizens from using them
Close public transport	C5	Require closing of public transport or prohibit most citizens from using it
Home containment	C6	Require not leaving house with or without exceptions for daily exercise, grocery shopping and essential trips

NOTE. OxCGRT, Oxford COVID-19 Government Response Tracker initiative, www.bsg.ox.ac.uk/covidtracker

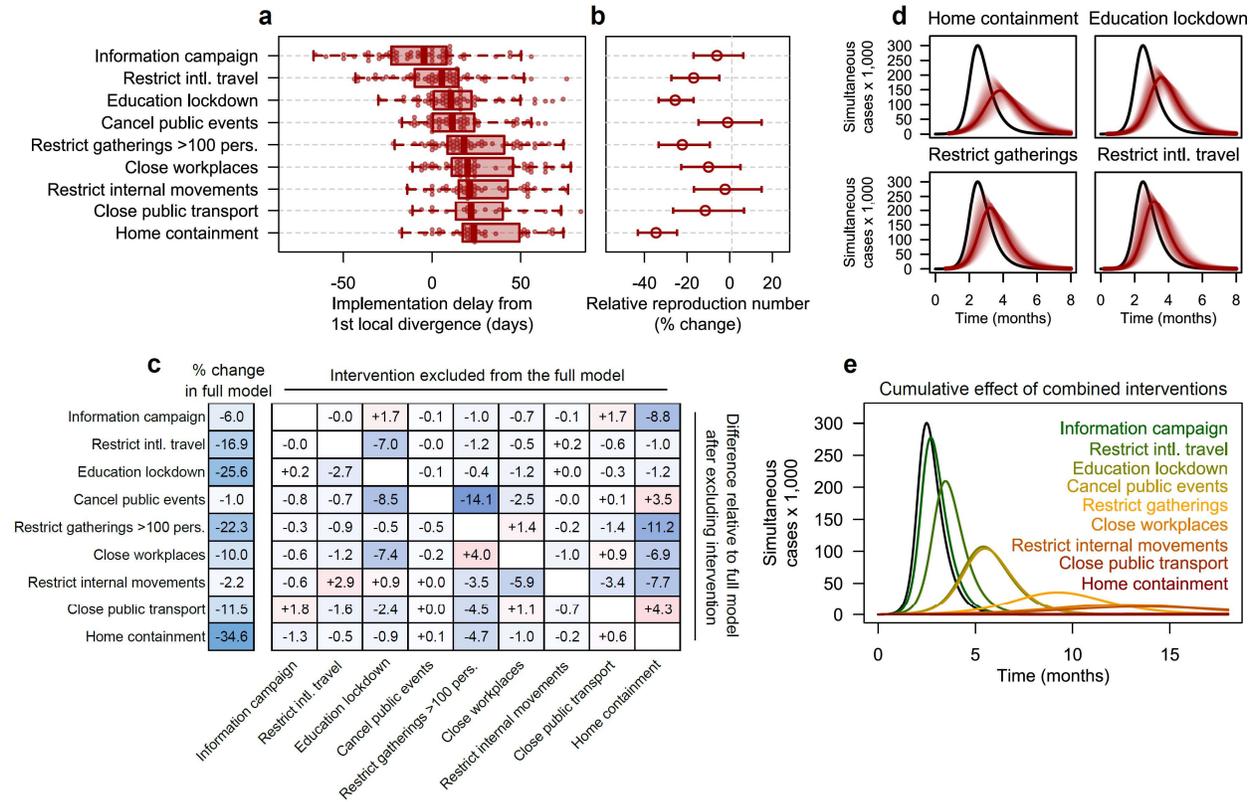


Figure 3. Non-pharmaceutical interventions variably reduce the reproduction number of COVID-19. Data derive from the phylogenetic survival analysis of 4,191 internal and 4,019 terminal branches of a dated phylogeny of SARS-CoV-2 genomes, combined with a chronology of interventions in 57 countries. **a**, Box-and-whisker plots of the delay between the 1st SARS-CoV-2 divergence event and the intervention. Plot interpretation is similar with Fig. 2c. **b**, Point estimates and 95% confidence intervals of the independent % change of the effective reproduction number predicted by each intervention in a multivariable, mixed-effect phylogenetic survival model adjusted for between-country variations. **c**, Matrix of pairwise interactions between the interventions (in rows) estimated using 9 multivariable models (in columns), where each model ignores exactly one intervention. Negative (positive) differences in blue (red) denote a stronger (lesser) predicted effect of the intervention in row when ignoring the intervention in column. **d**, **e**, Simulated impact of interventions implemented independently (**d**) or in sequential combination (**e**) on the count of simultaneous cases in an idealized population of 1 million susceptible individuals using compartmental SIR models with a basic reproduction number $R_0 = 3$ (black lines) and a mean infectious period of 2 weeks. Shaded areas in (**d**) denote 95% confidence bands.

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218 **Disentangling the individual effectiveness of non-pharmaceutical interventions**

219 The implementation and release dates of large-scale non-pharmaceutical interventions
220 against COVID-19 were available for 57 countries out of the 59 represented in the dated
221 phylogeny. Definitions of the selected interventions are shown in Table 1. Branches
222 assigned to countries with missing intervention data, namely, Latvia and Senegal, were
223 excluded from further analysis ($n=22/8,262$ (0.3%); see Extended Data Fig. 1). Up to
224 May 4, 2020, the interventions most universally implemented were information
225 campaigns, restrictions on international travel and education lockdown (>95% of
226 countries) (Extended Data Fig. 4). The least frequent were the closure of public
227 transportation (35%) and home containment (72%). Public information campaigns came
228 first and home containment came last (median delay across countries, 5 days before
229 and 24 days after the first local transmission event, respectively; Fig. 3a). Survival
230 curves for each intervention are shown in Extended Data Fig. 5. Most interventions
231 were implemented in combination and accumulated over time rather than replacing
232 each other (Extended Data Fig. 4; median delays between interventions are shown in
233 Extended Data Fig. 6; correlations in Extended Data Fig. 7; and a detailed timeline of
234 interventions in Extended Data Table 2). However, we observed a substantial
235 heterogeneity of intervention timing across the 57 countries (Fig. 3a), suggesting that
236 individual intervention effects can be discriminated by multivariable analysis given the
237 large sample size ($n=8,210$ subintervals).

238 A multivariable phylogenetic survival model, including the 9 interventions and
239 controlling for between-country R_t variations (see Methods), showed a strong fit to the
240 data (likelihood-ratio test compared to the null model, $P < 10^{-196}$). In this model, the
241 interventions most strongly and independently associated with a reduction of the
242 effective reproduction number R_t of SARS-CoV-2 were home containment (R_t percent
243 change, -34.6%, 95%CI, -43.2 to -24.7%), education lockdown (-25.6%, 95%CI, -33.4 to
244 -16.9%), restricting gatherings (-22.3%, 95%CI, -33.4 to -9.4%) and international travel
245 (-16.9%, 95%CI, -27.5 to -4.8%). We failed to detect a substantial impact of other
246 interventions, namely information campaigns, cancelling public events, closing

247 workplaces, restricting internal movement, and closing public transportation (Fig. 3b).
248 Based on coefficient estimates, all interventions were independently predicted to reduce
249 R_t (even by a negligible amount), in line with the intuition that no intervention should
250 accelerate the epidemic. Contrasting with previous approaches that constrained
251 coefficients⁵, this intuition was not enforced a priori in our multivariable model, in which
252 positive coefficients (increasing R_t) might have arisen due to noise or collinearity
253 between interventions. The absence of unexpectedly positive coefficients suggests that
254 our model correctly captured the epidemic slowdown that accompanied the
255 accumulation of interventions.

256 **Estimated intervention effects are robust to time-dependent confounders and** 257 **collinearity**

258 A reduction of R_t through time, independent of the implementation of interventions,
259 might lead to overestimate their effect in our model. Several potential confounders might
260 reduce R_t through time but cannot be precisely estimated and included as control
261 covariates. These included the progressive acquisition of herd immunity, the so-called
262 artificial diversification slowdown possibly caused by incomplete sampling, and time-
263 dependent variations of the sampling effort (see Methods). To quantify this potential
264 time-dependent bias, we constructed an additional model including the age of each
265 branch as a covariate (Extended Data Table 1). The coefficients in this time-adjusted
266 model only differed by small amounts compared to the base model. Moreover, the
267 ranking by effectiveness of the major interventions remained unchanged, indicating that
268 our estimates were robust to time-dependent confounders.

269 We also quantified the sensitivity of the estimated intervention effects to the
270 inclusion of other interventions (collinearity) by excluding interventions one by one in 9
271 additional models (Fig. 3c). This pairwise interaction analysis confirmed that most of the
272 estimated effects were strongly independent. Residual interferences were found for
273 gathering restrictions, whose full-model effect of -22.3% was reinforced to -33.5% when
274 ignoring home containment; and for cancelling public events, whose full-model effect of
275 -0.97% was reinforced to -15.1% when ignoring gathering restrictions. These residual

276 interferences make epidemiological sense because home containment prevents
 277 gatherings and gathering restrictions also prohibit public events. Overall, the absence of
 278 strong interferences indicated that our multivariable model reasonably captured the
 279 independent, cumulative effect of interventions, enabling ranking their impact on
 280 COVID-19 spread.

Table 2. Predicted reduction of the COVID-19 effective reproduction number under increasingly stringent combinations of non-pharmaceutical interventions.

Accumulated interventions	Relative R_t (cumulative % change)	Probability of reducing R_t below 1				
		$R_0=1.5$	$R_0=2.0$	$R_0=2.5$	$R_0=3.0$	$R_0=3.5$
Information campaign	-6.0 (-17.0 to +6.5)	<0.01	<0.01	<0.01	<0.01	<0.01
+ Restrict intl. travel	-21.9 (-35.0 to -6.1)	0.05	<0.01	<0.01	<0.01	<0.01
+ Education lockdown	-41.9 (-52.5 to -29.0)	0.91	0.07	<0.01	<0.01	<0.01
+ Cancel public events	-42.5 (-54.0 to -28.1)	0.90	0.11	<0.01	<0.01	<0.01
+ Restrict gatherings >100 pers.	-55.3 (-63.4 to -45.5)	1.00	0.86	0.14	<0.01	<0.01
+ Close workplaces	-59.7 (-67.6 to -50.0)	1.00	0.98	0.48	0.04	<0.01
+ Restrict internal movements	-60.6 (-67.9 to -51.6)	1.00	0.99	0.56	0.06	<0.01
+ Close public transport	-65.1 (-72.6 to -55.7)	1.00	1.00	0.87	0.36	0.05
+ Home containment	-77.2 (-81.5 to -71.9)	1.00	1.00	1.00	1.00	0.98

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283 **Simulating intervention effectiveness in an idealized population**

284 To facilitate the interpretation of our estimates of the effectiveness of interventions
 285 against COVID-19, we simulated each intervention's impact on the peak number of
 286 cases, whose reduction is critical to prevent overwhelming the healthcare system (Fig.
 287 3d and Extended Data Fig. 8). We used compartmental Susceptible-Infected-Recovered
 288 (SIR) models with a basic reproduction number $R_0 = 3$ and a mean infectious period of
 289 2 weeks based on previous estimates^{24,25}, in an idealized population of 1 million
 290 susceptible individuals (see Methods). In each model, we simulated the implementation
 291 of a single intervention at a date chosen to reflect the median delay across countries
 292 (Fig. 3a) relative to the epidemic onset (see Methods). On implementation date, the

293 effective reproduction number was immediately reduced according to the estimated
294 intervention's effect shown in Fig. 3b.

295 In this idealized setting, home containment, independent of all other restrictions,
296 only halved the peak number of cases from 3.0×10^5 to 1.5×10^5 (95% CI, 1.0×10^5 to
297 2.0×10^5) (Fig. 3d). However, a realistic implementation of home containment also
298 implies other restrictions including, at least, restrictions on movements, gatherings, and
299 public events. This combination resulted in a relative R_t of -50.8% (95% CI, -59.4% to -
300 40.2%) and a 5-fold reduction of the peak number of cases to 6.0×10^4 (95% CI, 1.9×10^4
301 to 1.2×10^5). Nevertheless, if $R_0 = 3$ then a 50% reduction is still insufficient to reduce R_t
302 below 1 and stop the epidemic. This suggests that even when considering the most
303 stringent interventions, combinations may be required. To further examine this issue, we
304 estimated the effect of accumulating interventions by their average chronological order
305 shown in Fig. 3a, from information campaigns alone to all interventions combined
306 including home containment (Fig. 3e). Strikingly, only the combination of all
307 interventions completely stopped the epidemic under our assumed value of R_0 . To
308 estimate the effectiveness of combined interventions in other epidemic settings, we
309 computed the probabilities of reducing R_t below 1 for values of R_0 ranging from 1.5 to
310 3.5 (Table 2; see Methods). The same probabilities for individual interventions are
311 presented in Table S2, showing that no single intervention would stop the epidemic if
312 $R_0 \geq 2$. These results may help inform decisions on the appropriate stringency of the
313 restrictions required to control the epidemic under varying transmission regimes.

314

315 **Discussion**

316 We present a phylodynamic analysis of how the divergence rate and reproduction
317 number of SARS-CoV-2 varies in response to large-scale non-pharmaceutical
318 interventions in 57 countries. Our results suggest that no single intervention, including
319 home containment, is sufficient on its own to stop the epidemic ($R_t < 1$). Increasingly
320 stringent combinations of interventions may be required depending on the effective
321 reproduction number.

322 Home containment was repeatedly estimated to be the most effective response
323 in epidemiological studies from China²⁶, France²⁷, the UK²⁸, and Europe⁵. Other studies
324 modelled the additional (or residual) reduction of R_t by an intervention after taking into
325 account those previously implemented^{4,6,10}. Possibly because home containment was
326 the last implemented intervention in many countries (Fig. 2a), these studies reported a
327 weaker or even negligible additional effect compared to earlier interventions. In our
328 study, home containment, even when implemented last, had the strongest independent
329 impact on epidemic spread (R_t percent change, -34.6%), which was further amplified (-
330 50.8%) when taking into account implicit restrictions on movements, gatherings and
331 public events.

332 We found that education lockdown substantially decreased COVID-19 spread (R_t
333 percent change, -25.6%). Contrasting with home containment, the effectiveness of
334 education lockdown has been more hotly debated. This intervention ranked among the
335 most effective ones in two international studies^{4,6} but had virtually no effect on
336 transmission in other reports from Europe^{5,10}. Young children have been estimated to be
337 poor spreaders of COVID-19 and less susceptible than adults to develop disease after
338 an infectious contact, counteracting the effect of their higher contact rate^{29,30}. However,
339 the relative susceptibility to infection was shown to increase sharply between 15 and 25
340 years, suggesting that older students might be more involved in epidemic spread³⁰.
341 Importantly, we could not differentiate the effect of closing schools and universities
342 because both closures coincided in all countries. Thus, our finding that education
343 lockdowns reduce COVID-19 transmission might be driven by contact rate reductions in

344 older students rather than in children, as hypothesized elsewhere⁴. This raises the
345 question of whether education lockdown should be adapted to age groups, considering
346 that: (1), education lockdown had a sizeable impact on COVID-19 transmission in our
347 study and others^{4,6}; (2), this impact might be preferentially driven by older students^{29,30};
348 and (3) autonomous distance learning might be more effective in university students³¹
349 compared to younger children who require parental presence and supervision following
350 school closure, possibly widening the gap for children from under-resourced
351 backgrounds³². Based on these elements, we speculate that closing universities, but not
352 elementary schools, might strike the right balance between efficacy and social impact.

353 Restrictions on gatherings of >100 persons appeared more effective than
354 cancelling public events (R_t percent changes, -22.3% vs. -1.0%, respectively) in our
355 phylodynamic model, in line with previous results from epidemiological models⁴.
356 Notwithstanding that gathering restrictions prohibit public events, possibly causing
357 interferences between estimates (Fig. 3c), this finding is intriguing. Indeed, several
358 public events resulted in large case clusters, the so-called superspreading events, that
359 triggered epidemic bursts in France³³, South Korea³⁴ or the U.S.³⁵. A plausible
360 explanation for not detecting the effectiveness of cancelling public events is that data-
361 driven models, including ours, better capture the cumulative effect of more frequent
362 events such as gatherings than the massive effect of much rarer events such as
363 superspreading public events. This bias towards ignoring the so-called 'Black Swan'
364 exceptional events³⁶ suggests that our findings (and others¹⁴) regarding restrictions on
365 public events should not be interpreted as an encouragement to relax these restrictions
366 but as a potential limit of modelling approaches (but see³⁷).

367 There are other limitations to our study, including its retrospective design. Similar
368 to previous work⁶, we did not consider targeted non-pharmaceutical interventions that
369 are difficult to date and quantify, such as contact tracing or case isolation policies. Data
370 were analyzed at the national level, although much virus transmission was often
371 concentrated in specific areas and some non-pharmaceutical interventions were
372 implemented at the sub-national level³⁸. Our phylogeographic inferences did not
373 consider the travel history of patients, whose inclusion in Bayesian models was recently

374 shown to alleviate sampling bias³⁹. From a statistical standpoint, the interval lengths in
375 the dated phylogeny were treated as fixed quantities in the survival models. Ignoring the
376 uncertainty of the estimated lengths might underestimate the width of confidence
377 intervals, although this is unlikely to have biased the pointwise estimates and the
378 ranking of interventions' effects. The number of genomes included by country did not
379 necessarily reflect the true number of cases, which might have influenced country
380 comparison results in Fig. 2, but not intervention effectiveness models in Fig. 3 which
381 were adjusted for between-country variations of R_t . Finally, our estimates represent
382 averages over many countries with different epidemiological contexts, healthcare
383 systems, cultural behaviors and nuances in intervention implementation details and
384 population compliance. This global approach, similar to previous work^{4,6}, facilitates
385 unifying the interpretation of intervention effectiveness, but this interpretation still needs
386 to be adjusted to local contexts by policy makers.

387 Beyond the insights gained into the impact of interventions against COVID-19,
388 our findings highlight how phylodynamic survival analysis can help leverage pathogen
389 sequence data to estimate epidemiological parameters. Contrasting with the Bayesian
390 approaches adopted by most, if not all, previous assessments of intervention
391 effectiveness^{4,5,8}, phylodynamic survival analysis does not require any quantitative prior
392 assumption or constraint on model parameters. The method should also be simple to
393 implement and extend by leveraging the extensive software arsenal of survival
394 modelling. Phylodynamic survival analysis may complement epidemiological models as
395 pathogen sequences accumulate, allowing to address increasingly complex questions
396 relevant to public health strategies.

397

398

METHODS

399

Definitions and chronology of non-pharmaceutical interventions

400

The nature, stringency and timing of non-pharmaceutical interventions against COVID-

401

19 have been collected and aggregated daily since January 1, 2020 by the Oxford

402

COVID-19 Government Response Tracker initiative of the Blavatnik School of

403

Government, UK^{4,22}. As of May 12, 2020, the interventions are grouped into three

404

categories, namely: closures and containment (8 indicators), economic measures (4

405

indicators) and health measures (5 indicators). Indicators use 2- to 4-level ordinal scales

406

to represent each intervention's stringency, and an additional flag indicating whether the

407

intervention is localized or general. Details of the coding methods for indicators can be

408

found in⁴⁰. We focused on large-scale interventions against transmission that did not

409

target specific patients (for instance, we did not consider contact tracing) and we

410

excluded economic and health interventions except for information campaigns. This

411

rationale led to the selection of the 9 indicators shown in Table 1. To facilitate

412

interpretation while constraining model complexity, the ordinal-scale indicators in

413

OxCGRT data were recoded as binary variables in which we only considered

414

government requirements (as opposed to recommendations) where applicable. We did

415

not distinguish between localized and nation-wide interventions because localized

416

interventions, especially in larger countries, targeted the identified epidemic hotspots.

417

As the data did not allow to differentiate closures of schools and universities, we use the

418

term 'education lockdown' (as opposed to 'school closure' in²²) to avoid

419

misinterpretation regarding the education levels concerned.

420

Phylogenetic survival analysis in measurably evolving populations

421

The original phylogenetic survival model in¹² and its later extensions⁴¹ considered

422

intervals backward in time, from the tips to the root of the tree, and were restricted to

423

trees with all tips sampled at the same date relative to the root (ultrametric trees).

424

Censored intervals (intervals that do not end with an event) in¹² were used to represent

425

lineages with known sampling date but unknown age. In contrast, viral samples in

426 ongoing epidemics such as COVID-19 are typically collected through time. A significant
427 evolution of the viruses during the sampling period violates the ultrametric assumption.
428 To handle phylogenies of these so-called measurably evolving populations⁴², we
429 propose a different interpretation of censoring compared to¹². Going forward in time, the
430 internal branches of a tree connect two divergence events while terminal branches,
431 those that end with a tip, connect a divergence event and a sampling event (Fig. 1b).
432 Thus, we considered internal branches as time-to-event intervals and terminal branches
433 as censored intervals representing the minimal duration during which no divergence
434 occurred (Fig. 1c).

435 **SARS-CoV-2 phylogenetic data**

436 SARS-CoV-2 genome sequences have been continuously submitted to the Global
437 Initiative on Sharing All Influenza Data (GISAID) by laboratories worldwide²¹. To
438 circumvent the computational limits of phylogeny reconstruction and time calibration
439 techniques, the sequences of the GISAID database are subsampled before analysis by
440 the Nextstrain initiative, using a balanced subsampling scheme through time and
441 space^{20,43}. Phylogenetic reconstruction uses maximum-likelihood phylogenetic inference
442 based on IQ-TREE⁴⁴ and time-calibration uses TreeTime⁴⁵. See⁴⁶ for further details on
443 the Nextstrain bioinformatics pipeline. A dated phylogeny of 5,211 SARS-CoV-2
444 genomes, along with sampling dates and locations, was retrieved from
445 nextstrain.org/ncov on May 12, 2020. Genomes of non-human origin (n = 13) were
446 discarded from analysis. Polytomies (unresolved divergences represented as a node
447 with >2 descendants) were resolved as branches with an arbitrarily small length of 1
448 hour, as recommended for adjustment of zero-length risk intervals in Cox regression⁴⁷.
449 Of note, excluding these zero-length branches would bias the analysis by
450 underestimating the number of divergence events in specific regions of the phylogeny.
451 Maximum-likelihood ancestral state reconstruction was used to assign internal nodes of
452 the phylogeny to countries in a probabilistic fashion, taking the tree shape and sampling
453 locations as input data⁴⁸. To prepare data for survival analysis, we decomposed the
454 branches of the dated phylogeny into a set of time-to-event and time-to-censoring

455 intervals (Fig. 1c). Intervals were assigned to the most likely country at the origin of the
456 branch when this country's likelihood was >0.95. Intervals in which no country reached
457 a likelihood of 0.95 were excluded from further analysis (Extended Data Figs. 1, 2).
458 Finally, intervals during which a change of intervention occurred were split into sub-
459 intervals, such that all covariates, including the country and interventions, were held
460 constant within each sub-interval and only the last subinterval of an internal branch was
461 treated as a time-to-event interval. This interval-splitting approach is consistent with an
462 interpretation of interventions as external time-dependent covariates¹⁸, which are not
463 dependent on the event under study, namely, the viral divergence event.

464 **Mixed-effect Cox proportional hazard models**

465 Variations of the divergence rate λ in response to non-pharmaceutical interventions
466 were modelled using mixed-effect Cox proportional hazard regression (reviewed in⁴⁹).
467 Models treated the country and phylogenetic branch as random effects to account for
468 non-independence between sub-intervals of the same branch and between branches
469 assigned to the same country. The predictors of interest were not heritable traits of
470 SARS-CoV-2, thus, phylogenetic autocorrelation between intervals was not corrected
471 for. Time-to-event data were visualized using Kaplan-Meier curves with 95% confidence
472 intervals. The regression models had the form

$$473 \quad \lambda_i(t) = \lambda_0(t) \cdot \exp(X_i \cdot \beta + \alpha_j + \gamma_k)$$

474 where $\lambda_i(t)$ is the hazard function (here, the divergence rate) at time t for the i th
475 observation, $\lambda_0(t)$ is the baseline hazard function, which is neither specified or explicitly
476 evaluated, X_i is the set of predictors of the i th observation (the binary vector of active
477 non-pharmaceutical interventions), β is the vector of fixed-effect coefficients, α_j is the
478 random intercept associated with the j th phylogenetic branch and γ_k is the random
479 intercept associated with the k th country. Country comparison models (Fig. 2d), in
480 which the country was the only predictor and branches were not divided into
481 subintervals, did not include random intercepts. Raw model coefficients (the log-hazard
482 ratios) additively shift the logarithm of the divergence rate λ . Exponentiated coefficients

483 $\exp \beta$ (the hazard ratios) are multiplicative factors (fold-changes) of the divergence rate.
484 To ease interpretation, hazard ratios were reported as percentage changes of the
485 divergence rate or, equivalently, of the effective reproduction number R_t , equal to
486 $(\exp \beta - 1) \times 100$. Analyses were conducted using R 3.6.1 (the R Foundation for
487 Statistical Computing, Vienna, Austria) with additional packages *ape*, *survival* and
488 *coxme*.

489 **Estimating the effect of combined interventions**

490 Pointwise estimates and confidence intervals of combined interventions were estimated
491 by adding individual coefficients and their variance-covariances. Cox regression
492 coefficients have approximately normal distribution with mean vector m and variance-
493 covariance matrix V , estimated from the inverse Hessian matrix of the likelihood
494 function evaluated at m . From well-known properties of the normal distribution, the
495 distribution of a sum of normal deviates is normal with mean equal to the sum of the
496 means and variance equal to the sum of the variance-covariance matrix of the deviates.
497 Thus, the coefficient corresponding to a sum of coefficients with mean m and variance V
498 has mean $\sum m$ and variance $\sum V$, from which we derive the point estimates and
499 confidence intervals of a combination of predictors. Importantly, summing over the
500 covariances captures the correlation between coefficients when estimating the
501 uncertainty of the combined coefficient.

502 **Probability of stopping an epidemic**

503 A central question regarding the effectiveness of interventions or combinations thereof
504 is whether their implementation can stop an epidemic by reducing R_t below 1 (Table 2).
505 Suppose that some intervention has an estimated log-hazard ratio $\hat{\beta}$. $\hat{\beta}$ has
506 approximately normal distribution with mean β and variance σ^2 , written $\hat{\beta} \sim N(\beta, \sigma^2)$.
507 For some fixed value of R_0 , the estimated post-intervention reproduction number $\widehat{R}_t =$
508 $R_0 \cdot \exp \hat{\beta}$. The probability p that $\widehat{R}_t < 1$ is $\int_{-\infty}^1 d(\widehat{R}_t) d\widehat{R}_t$ where d denotes the probability
509 density function. To solve the integral, remark that $\log \widehat{R}_t = \log R_0 + \hat{\beta} \sim N(\log R_0 +$

510 $\hat{\beta}, \sigma^2$). Using a change of variables in the integral and noting that $\log 1 = 0$, we obtain
511 the closed-form solution

512
$$p = \int_{-\infty}^0 d(\log \widehat{R}_t) d \log \widehat{R}_t = \Phi(0 | \log R_0 + \hat{\beta}, \sigma^2),$$

513 where Φ is the cumulative density function of the normal distribution with mean $\log R_0 +$
514 $\hat{\beta}$ and variance σ^2 . By integrating over the coefficient distribution, this method explicitly
515 considers the estimation uncertainty of $\hat{\beta}$ when estimating p .

516 **Potential time-dependent confounders**

517 Time-dependent phylodynamic survival analysis assumes that variations of branch
518 lengths though time directly reflect variations of the divergence rate, which implies that
519 branch lengths are conditionally independent of time given the divergence rate. When
520 the phylogeny is reconstructed from a fraction of the individuals, as is the case in
521 virtually all phylodynamic studies including ours, this conditional independence
522 assumption can be violated. This is because incomplete sampling increases the length
523 of more recent branches relative to older branches⁵⁰, an effect called the diversification
524 slowdown^{51,52}. Noteworthy, this effect can be counteracted by a high extinction rate^{17,50},
525 which is expected in our setting and mimicks an acceleration of diversification.
526 Moreover, whether the diversification slowdown should be interpreted as a pure artifact
527 has been controversial^{52,53}. Notwithstanding, we considered incomplete sampling as a
528 potential source of bias in our analyses because a diversification slowdown might lead
529 to an overestimation of the effect of non-pharmaceutical interventions. Additionally, the
530 selection procedure used by Nextstrain to collect genomes included in the dated
531 phylogeny possibly amplified the diversification slowdown by using a higher sampling
532 fraction in earlier phases of the epidemic⁴³. To verify whether the conclusions of our
533 models were robust to this potential bias, we built an additional multivariable model
534 including the estimated date of each divergence event (the origin of the branch) as a
535 covariate. The possible relation between time and the divergence rate is expectedly
536 non-linear⁵⁰ and coefficient variations resulting from controlling for time were moderate

537 (Extended Data Table 1), thus, we refrained from including a time covariate in the
538 reported regression models as this might lead to overcontrol. Further research is
539 warranted to identify an optimal function of time that might be included as a covariate in
540 phylodynamic survival models to control for sources of diversification slowdown.

541 **Compartmental epidemiological models**

542 Epidemic dynamics can be described by partitioning a population of size N into three
543 compartments, the susceptible hosts S , the infected hosts I , and the recovered hosts R .
544 The infection rate b governs the transitions from S to I and the recovery rate g governs
545 the transitions from I to R (we avoid the standard notation β and γ for infection and
546 recovery rates to prevent confusion with Cox model parameters). The SIR model
547 describes the transition rates between compartments as a set of differential equations
548 with respect to time t ,

$$549 \quad \frac{dS}{dt} = -bSI, \quad \frac{dI}{dt} = bSI - gI, \quad \frac{dR}{dt} = gI.$$

550 The transition rates of the SIR model define the basic reproduction number of the
551 epidemic, $R_0 = b/g$. From a phylodynamic standpoint, if the population dynamics of a
552 pathogen is described as a birth-death model with divergence rate λ and extinction rate
553 μ , then $R_t = \lambda/\mu$ or, alternatively, $R_t = \frac{\lambda-\mu}{g} + 1$ ⁵⁴. We simulated the epidemiological
554 impact of each individual intervention in SIR models with $R_0 = 3$ and $g^{-1} = 2$ weeks
555 based on previous estimates^{24,25}, yielding a baseline infection rate $b = gR_0 = 6$. In each
556 model, the effective infection rate changed from b to $b \cdot \exp \beta$ on the implementation
557 date of an intervention with log-hazard ratio β . To determine realistic implementation
558 delays, the starting time of the simulation was set at the date of the first local divergence
559 event in each country and the implementation date was set to the observed median
560 delay across countries (see Fig. 3a). All models started with 100 infected individuals at
561 $t = 0$, a value assumed to reflect the number of unobserved cases at the date of the
562 first divergence event, based on the temporality between the divergence events and the
563 reported cases (Extended Data Fig. 3) and on a previous estimate from the U.S.

564 suggesting that the total number of cases might be two orders of magnitude larger than
565 the reported count⁵⁵. Evaluation of the SIR models used the R package *deSolve*.

566 **Data and software availability**

567 All data and software code used to generate the results are available at
568 github.com/rasigadelab/covid-npi.

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752 **Acknowledgements:** We thank Philip Supply, François Vandenesch, Jean-Sébastien
753 Casalegno, Vanessa Escuret, and Christophe Ramière for fruitful discussions and
754 reviews of our work. We thank the GISAID, Nextstrain and OxCGRT teams for making
755 their high-quality datasets available to the community. A list of authors and laboratories
756 contributing SARS-CoV-2 genome sequences is shown in Extended Data Table 3.

757 **Funding:** JPR received support from the FINOVI Foundation (grant R18037CC).

758 **Author contributions:** JPR, LJ, TW designed research. JPR, ABarray, JTS, CQ, YV,
759 GD, LJ conducted research. JPR, TW analyzed the data. JPR created figures. JPR, Abal,
760 GD, LJ, PV, BL, TW interpreted the data. All authors wrote the paper.

761 **Competing interests:** BL is currently active in groups advising the French government
762 for which BL is not receiving payment.

763 **Data and material availability:** Data and analysis code are available online at
764 <https://github.com/rasigadelab/covid-npi>.

765 **EXTENDED DATA**

766 Extended Data Figures 1 to 8 included below

767 Extended Data Tables 1 and 2 included below

768 **Other Supplementary Information for this manuscript include the following:**

769 Extended Data Table 3. Number of samples, phylogenetic branches, and dates of first
770 detected SARS-CoV-2 local transmission events and non-pharmaceutical interventions
771 in 74 countries. (.xlsx spreadsheet)

772 Extended Data Table 4. Detailed timeline of implementation and release of non-
773 pharmaceutical interventions against COVID-19 in 74 countries up to May 12, 2020.
774 (.xlsx spreadsheet)

775 Extended Data Table 5. Authors and laboratories having contributed SARS-CoV-2
776 genomes included in the dated phylogeny. (.xlsx spreadsheet)

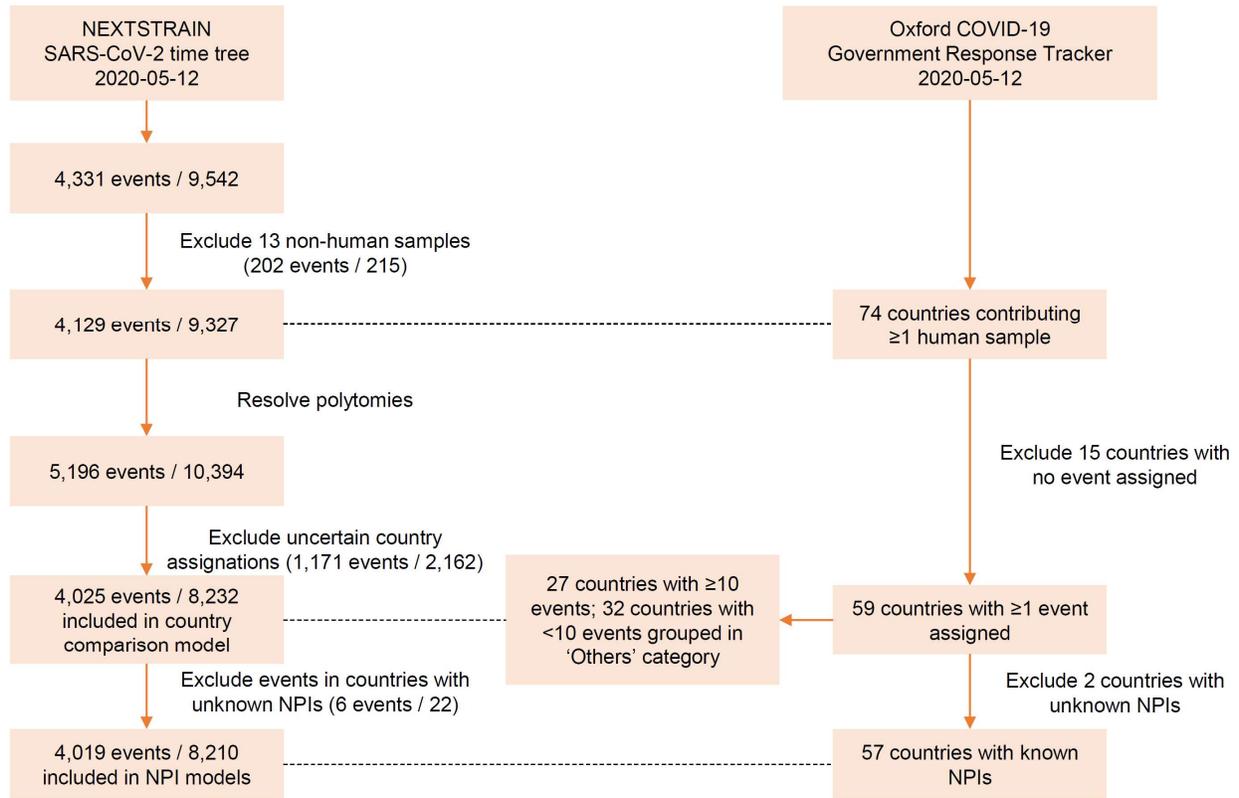
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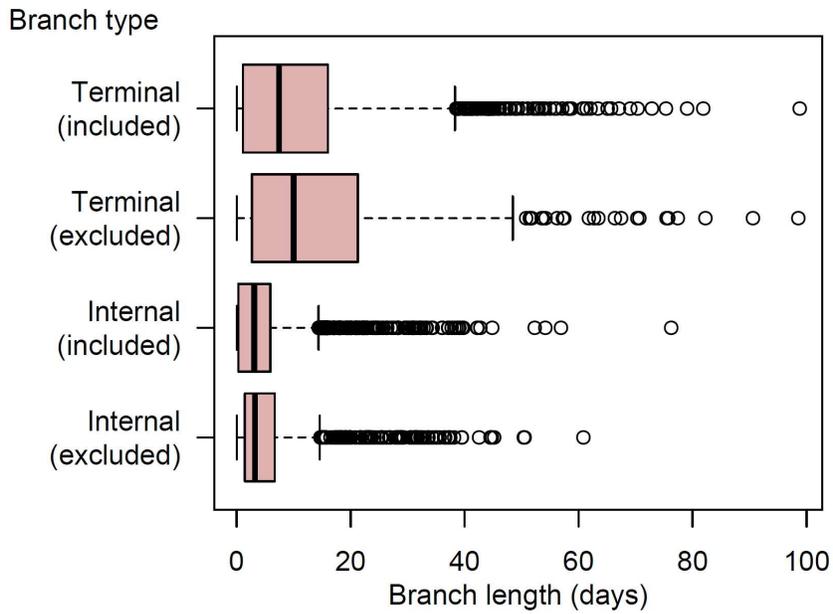
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784 **Extended Data Figure 1. Flowchart of data selection.** Events are phylogenetic divergences
785 (tree nodes in the SARS-CoV-2 phylogeny), excluding tree root. Polytomies are unresolved tree
786 nodes representing >1 divergence event. Polytomies were resolved into dichotomies (nodes
787 with exactly 1 divergence) with arbitrarily small interval length. NPI, non-pharmaceutical
788 intervention against COVID-19.
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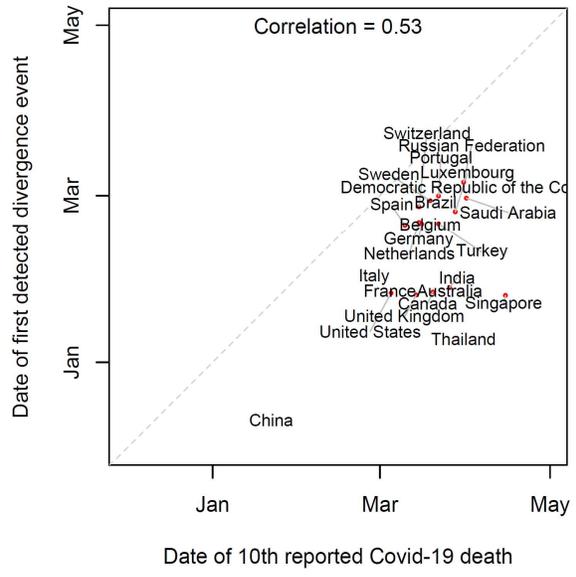
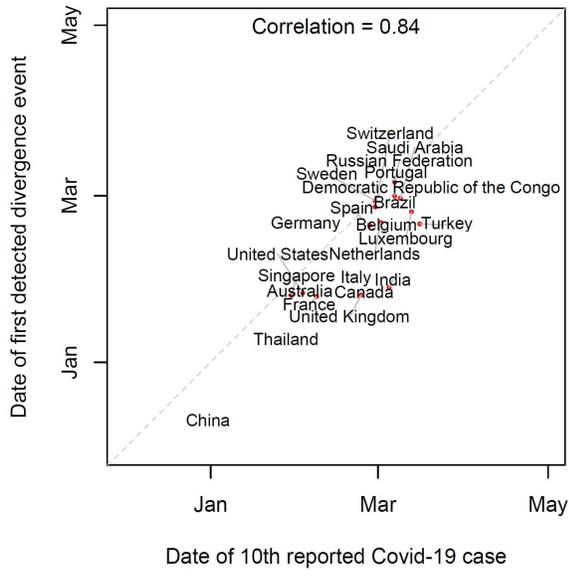
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Extended Data Figure 2. Length distribution in phylogenetic branches with uncertain country assignment. Shown are box-and-whisker plots of the lengths of internal and terminal branches, depending on branch exclusion due to uncertain (<95% confidence) country assignment. Boxes denote interquartile range (IQR) and median, whiskers extend to lengths at most 1.5x the IQR away from the median length, and circle marks denote lengths farther than 1.5 IQR from the median length.



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Extended Data Figure 3. Correlation of reported and estimated epidemic onset dates. Dates of first estimated autochthonous SARS-CoV-2 transmission per country relative to the dates of the 10th reported case (left panel) and the 10th reported death (right panel) in countries with at least 15 assigned internal branches.

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	No. of countries (%)	Information campaign	Restrict intl. travel	Education lockdown	Cancel public events	Restrict gatherings >100 pers.	Close workplaces	Restrict internal movements	Close public transport	Home containment
Information campaign	57 (100.0)	1.00	0.96	0.96	0.93	0.89	0.93	0.79	0.35	0.72
Restrict intl. travel	55 (96.5)	1.00	1.00	0.96	0.93	0.89	0.93	0.79	0.36	0.72
Education lockdown	55 (96.5)	1.00	0.96	1.00	0.96	0.91	0.96	0.82	0.36	0.75
Cancel public events	53 (93.0)	1.00	0.96	1.00	1.00	0.94	0.98	0.85	0.38	0.77
Restrict gatherings >100 pers.	51 (89.5)	1.00	0.96	0.98	0.98	1.00	0.98	0.83	0.38	0.76
Close workplaces	53 (93.0)	1.00	0.96	1.00	0.98	0.94	1.00	0.83	0.38	0.76
Restrict internal movements	45 (78.9)	1.00	0.96	1.00	1.00	0.94	0.98	1.00	0.43	0.87
Close public transport	20 (35.1)	1.00	1.00	1.00	1.00	0.98	1.00	0.98	1.00	0.93
Home containment	41 (71.9)	1.00	0.96	1.00	1.00	0.94	0.98	0.96	0.45	1.00

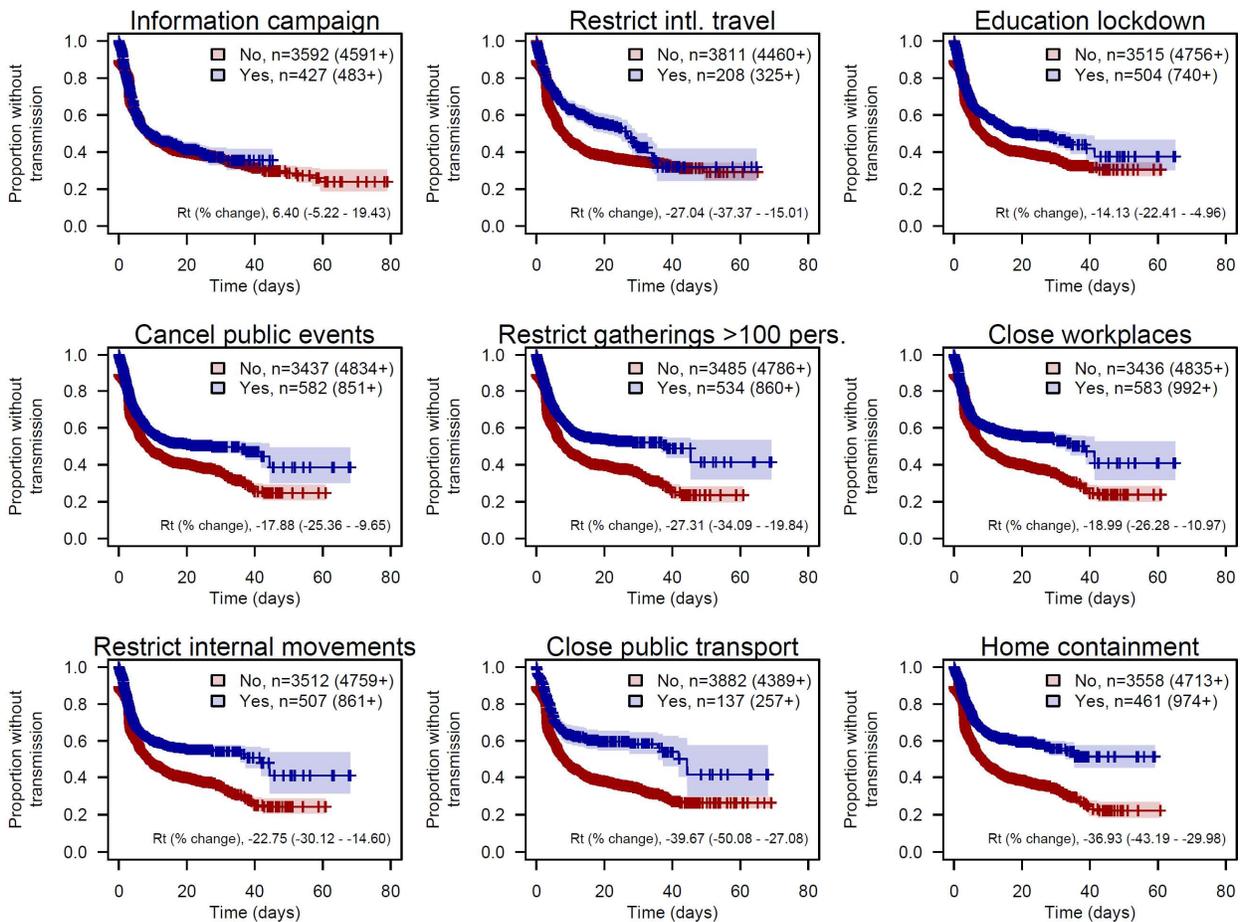
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808 **Extended Data Figure 4. Frequency and timing of implementation of non-pharmaceutical**
 809 **interventions in 57 countries.** The first column shows the number and percentage of countries
 810 implementing each intervention, independent of other interventions. Matrix cells show the
 811 proportion of countries implementing the intervention in column conditional on the
 812 implementation of the intervention in row.

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Extended Data Figure 5. Non-pharmaceutical interventions against COVID-19 correlate with reduced effective reproduction numbers. Data derive from a dated phylogeny of SARS-CoV-2 genomes from 57 countries, with 4,191 internal branches interpreted as time-to-event intervals, and 4,019 terminal branches interpreted as censored intervals, after exclusion of branches with uncertain country assignment. Shown are Kaplan-Meier survival curves of the waiting time without a viral transmission event, stratified on the presence of nine non-pharmaceutical interventions active or not in each country. Sample sizes denote, for each stratum, the no. of time-to-event subintervals (possibly resulting from splitting intervals containing a change of intervention) and, in brackets, the no. of censored subintervals. Percent changes of the effective reproduction number R_t were derived from separate time-dependent mixed-effect Cox regression models treating the country and the branch as random effects.

	Information campaign	Restrict intl. travel	Education lockdown	Cancel public events	Restrict gatherings >100 pers.	Close workplaces	Restrict internal movements	Close public transport	Home containment
Information campaign	0.0	8.0	14.0	19.0	21.0	25.0	27.0	24.5	28.0
Restrict intl. travel	-8.0	0.0	1.0	3.0	9.0	10.0	13.0	10.5	13.0
Education lockdown	-14.0	-1.0	0.0	0.0	1.0	5.0	8.0	11.5	9.0
Cancel public events	-19.0	-3.0	0.0	0.0	0.0	5.0	7.0	11.5	10.0
Restrict gatherings >100 pers.	-21.0	-9.0	-1.0	0.0	0.0	3.0	4.0	5.0	4.5
Close workplaces	-25.0	-10.0	-5.0	-5.0	-3.0	0.0	0.0	1.0	1.0
Restrict internal movements	-27.0	-13.0	-8.0	-7.0	-4.0	0.0	0.0	3.0	0.0
Close public transport	-24.5	-10.5	-11.5	-11.5	-5.0	-1.0	-3.0	0.0	1.0
Home containment	-28.0	-13.0	-9.0	-10.0	-4.5	-1.0	0.0	-1.0	0.0

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Extended Data Figure 6. Median delay between implementation of non-pharmaceutical interventions. Shown are the median days elapsed between the implementation of the intervention in the row and that of the intervention in the column, where median is taken across countries that implemented both interventions.

	Information campaign	Restrict intl. travel	Education lockdown	Cancel public events	Restrict gatherings >100 pers.	Close workplaces	Restrict internal movements	Close public transport	Home containment
Information campaign		0.55	0.59	0.62	0.48	0.56	0.48	0.08	0.47
Restrict intl. travel	0.55		0.80	0.68	0.66	0.35	0.33	0.10	0.59
Education lockdown	0.59	0.80		0.77	0.70	0.53	0.51	0.26	0.67
Cancel public events	0.62	0.68	0.77		0.83	0.63	0.57	0.29	0.64
Restrict gatherings >100 pers.	0.48	0.66	0.70	0.83		0.53	0.56	0.35	0.68
Close workplaces	0.56	0.35	0.53	0.63	0.53		0.74	0.35	0.50
Restrict internal movements	0.48	0.33	0.51	0.57	0.56	0.74		0.54	0.50
Close public transport	0.08	0.10	0.26	0.29	0.35	0.35	0.54		0.17
Home containment	0.47	0.59	0.67	0.64	0.68	0.50	0.50	0.17	

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Extended Data Figure 7. Pearson correlation between non-pharmaceutical interventions.

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Data derive from 14,829 sub-intervals, including 4,019 time-to-event sub-intervals and 10,810

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censored sub-intervals. Sub-intervals result from splitting phylogenetic branches (n = 8,210) in

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which a change of intervention (activation or release) occurs. Smaller absolute correlations

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(white) favor the identifiability of intervention effects in multivariable analysis while larger

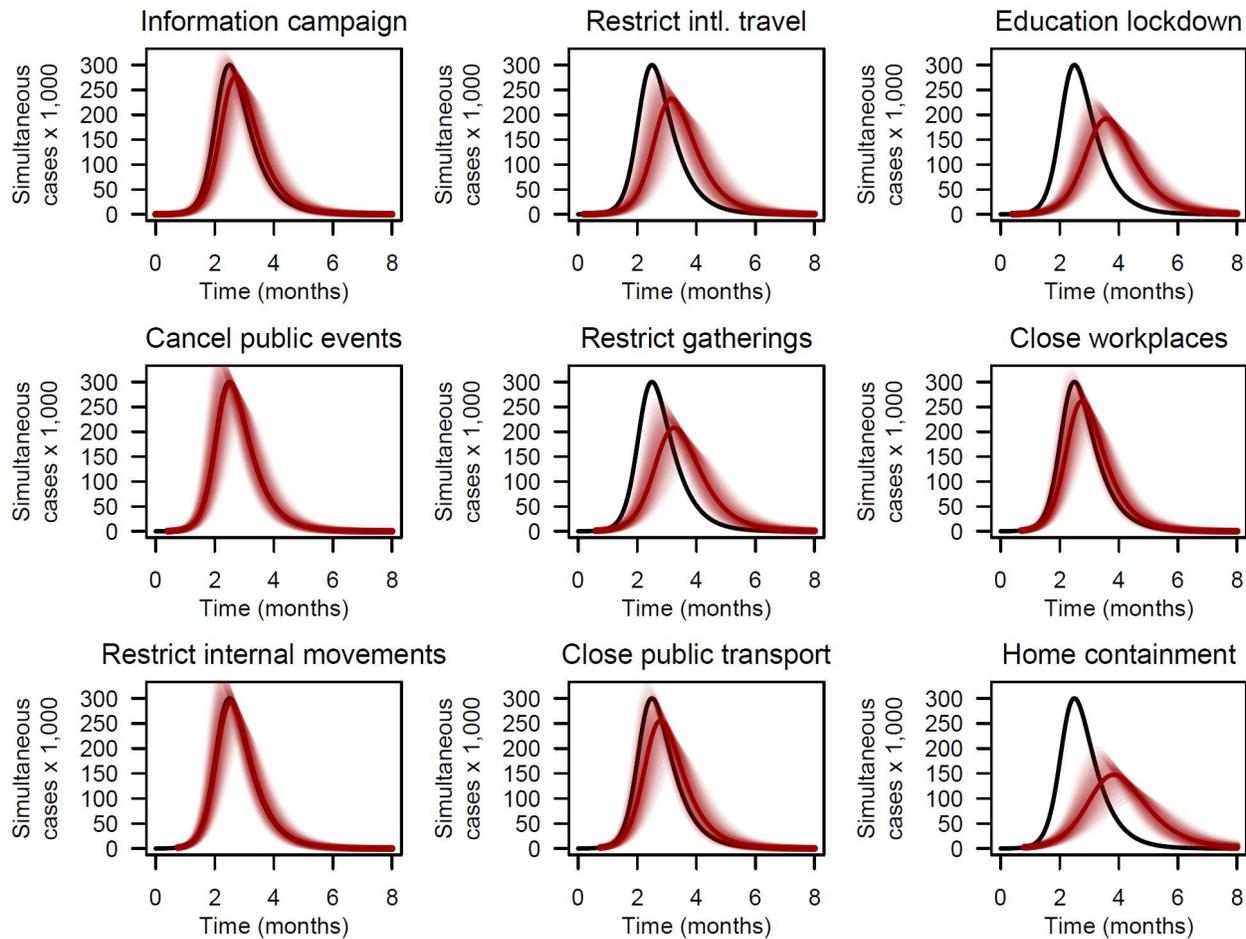
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absolute correlations (orange/red) can result into dependencies between model coefficients

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(see Fig. 3c).

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Extended Data Figure 8. Predicted individual impact of 9 non-pharmaceutical interventions (NPIs) on the number of simultaneous COVID-19 cases in an idealized population of 1 million susceptible individuals. Gray lines represent the case count predicted by an epidemiological SIR model with a basic reproduction number $R_0 = 3$, as estimated in the absence of NPIs, and a mean infectious period of 2 weeks. For each NPI, the simultaneous case count (red line) and 95% confidence band are derived from an SIR model in which the basic reproduction number is altered as predicted by the multivariate model coefficients shown in Fig. 3b. The delay between the 100th case and NPI implementation in SIR models coincides with the median delay between the 1st transmission event and the NPI implementation shown in Fig. 3a.

Extended Data Table 1. Predicted percent change of COVID-19 effective reproduction number in response to non-pharmaceutical interventions with and without adjustment for time. Data derive from multivariable mixed-effect Cox regression models including one random intercept per country and phylogenetic branch.

Factor	Relative R_t (% change)	
	Base model	Time-adjusted model
Elapsed time (per month)	-	-31.4 (-38.9 to -22.9)
Information campaign	-6.0 (-17.0 to 6.5)	3.2 (-9.6 to 17.8)
Restrict intl. travel	-16.9 (-27.5 to -4.8)	-11.0 (-22.8 to 2.7)
Education lockdown	-25.6 (-33.4 to -16.9)	-21.0 (-29.6 to -11.2)
Cancel public events	-1.0 (-14.7 to 15.0)	1.1 (-13.5 to 18.0)
Restrict gatherings >100 pers.	-22.3 (-33.4 to -9.3)	-17.3 (-29.5 to -2.9)
Close workplaces	-10.0 (-22.8 to 5.0)	-8.8 (-22.2 to 6.9)
Restrict internal movements	-2.2 (-16.8 to 15.0)	0.8 (-14.8 to 19.2)
Close public transport	-11.5 (-26.6 to 6.7)	-9.7 (-25.6 to 9.5)
Home containment	-34.6 (-43.2 to -24.7)	-35.4 (-44.0 to -25.4)

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Extended Data Table 2. Predicted reduction of the COVID-19 effective reproduction number by non-pharmaceutical interventions implemented alone.

Intervention	Probability that $R_t < 1$ if $R_0 = 1.5$
Information campaign	<0.01
Restrict intl. travel	<0.01
Education lockdown	0.03
Cancel public events	<0.01
Restrict gatherings >100 pers.	0.03
Close workplaces	<0.01
Restrict internal movements	<0.01
Close public transport	<0.01
Home containment	0.61

NOTE. The probability that $R_t < 1$ was less than 0.01 for all interventions if $R_0 \geq 2$.

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Figures

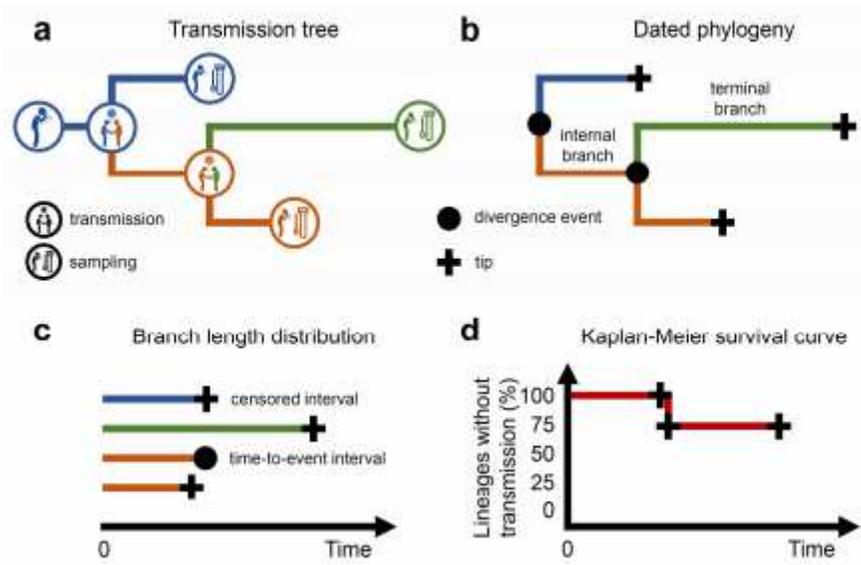


Figure 1

[Please see the manuscript file to view the figure caption.]

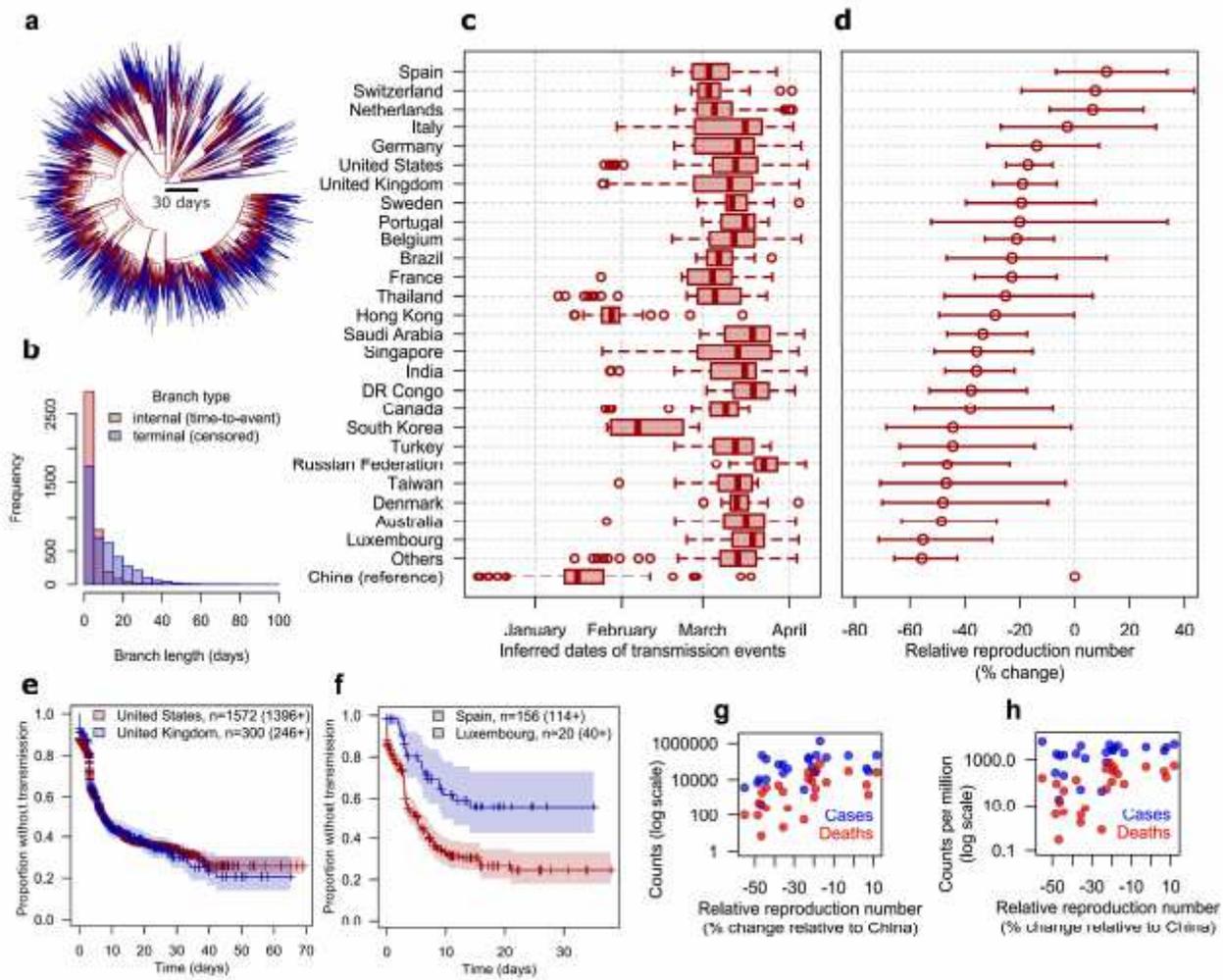


Figure 2

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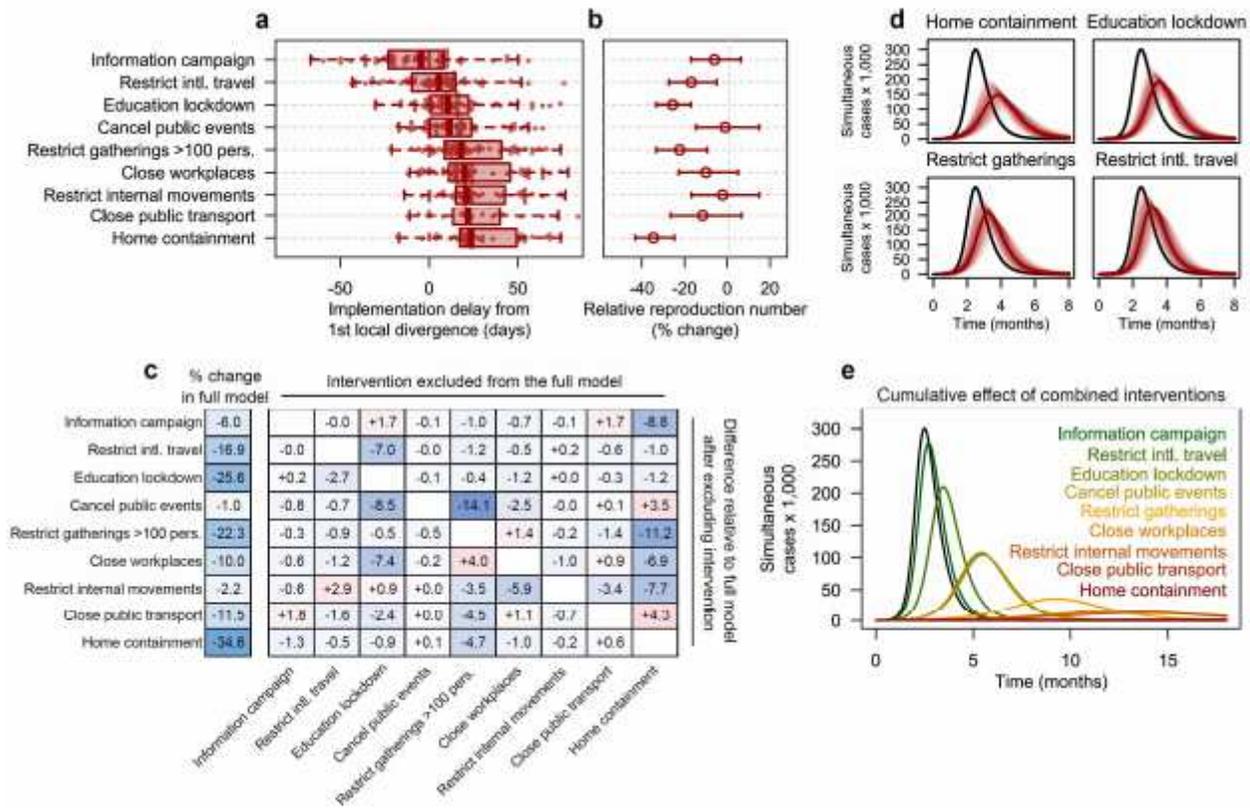


Figure 3

[Please see the manuscript file to view the figure caption.]

Supplementary Files

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- [ExtendedDataTable3.xlsx](#)
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