Influenza's plummeting and future dynamics: the roles of mask wearing, mobility change and SARS-CoV-2 interference

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Influenza's plummeting and future dynamics: the roles of mask wearing, mobility change and SARS-CoV-2 interference

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Abstract (150 words)

Untangling lessons from the influenza's plummeting during the COVID-19 pandemic is critical for mitigating seasonal and pandemic influenza. Here we explored a country-specific inference model to estimate the effects of mask-wearing, mobility changes (international and domestic) and SARS-CoV-2 interference in China, England and the United States. We found that mask wearing had a larger reduction than mobility changes in all the regions. Only in 2019-2020, SARS-CoV-2 interference had an observable effect, with values varying at the timing of the influenza season and the speed of SARS-CoV-2 community transmission. Compared to the epidemics in 2017–2019, longer and blunter rebounds could occur in the incoming 2021–2022 season, but the rebound would be smaller if less stringent mask mandates continued or the international mobility stayed low. Our results bear implications for understanding how influenza evolves under non-pharmaceutical interventions and other respiratory diseases, and will inform designing of tailored public health measures.

Words: 2878

Introduction

Seasonal influenza viruses circulate year-round throughout the world, typically peaking in winter of each hemisphere. However, since the first report of SARS-CoV-2 virus and the non-pharmaceutical interventions (NPIs) to mitigate the virus, influenza activity has remained unprecedently low, with laboratory-confirmed outbreak globally nonexistent during the influenza seasons[1–3]. In Northern Hemisphere countries, data from respiratory surveillance system in China, England and the United States (U.S.) indicated a 92·4%~99·9% decrease of past five year average in the 2020-2021 season[4–6]. In the Southern Hemisphere, where cold seasons are opposite of that in the Northern Hemisphere, influenza has also remained scarce for the two consecutive influenza seasons[7,8].

Influenza's global plummeting adds great uncertainty on preparedness for the incoming influenza circulations through targeted vaccination program[1–3], calling for a thorough investigation of the causes. Other than simulation findings from epidemic models[13], there has been little information to understand how influenza would rebound after the disruptions to seasonal patterns. Although the COVID-19 pandemic and interventions have been associated with the decline[7,9], how each individual NPI and SARS-CoV-2 interference contributes to the long-term influenza decline remains elusive. Data have shown that the transmission of influenza virus was interrupted by seasonal rhinovirus epidemic[10], but one virus's circulation may also be boosted by another virus[11,12], leading to the mechanism of SARS-CoV-2 interference being largely unclear.

Disentangling the roles of highly correlated NPIs and SARS-CoV-2 interference in the decline is the key. However, even without considering SARS-CoV-2 interference, the task is challenging in the context of seasonal influenza. The cross-country modelling [14] that is widely used for assessing the individual effects of NPIs in SARS-CoV-2 transmission is not

applicable to seasonal influenza, due to the high variation on the viral antigenic evolutions, climate conditions, socio-demographic features, influenza circulation strains and subtypes, as well as influenza vaccination coverages across countries[13,15]. Here we develop a country-specific inference model to estimate the individual effects of NPIs and SARS-CoV-2 interferences. Our approach relies on the long-term influenza surveillance data and mobility change, and identify the individual effects through a contrast of potential influenza activities under alternative hypothetical scenarios[16] (Methods). We assess the short-term effects of one-week increase of NPIs (denoted with percent reduction % in percent positivity) as well as the long-term effects of NPIs and SARS-CoV-2 interference in influenza seasons (denoted with absolute reduction in percent positivity). The estimated short-term effects are further used to forecast the influenza activity in the incoming 2021-2022 influenza season, under hypothetical scenarios without NPIs and with different assumptions on mask-wearing and mobility levels.

Results

We collect data on influenza, mobility (international and domestic) and mask-wearing intervention from public sources in China, England and the U.S.. We note that the changes on domestic mobility during the COVID-19 period may reflect several highly correlated mobility related NPIs including movement restriction and physical distancing (Methods; Extended Data Fig. 13 and Table S3). Since clinical influenza visits may be affected by NPIs[13], we use the percent positive tests reported from laboratory surveillance data as a measure of influenza activity. We consider Northern China and Southern China separately, due to the sharp difference in their patterns of seasonal influenza[9]. For Northern China, England and the U.S., the influenza season constitutes of 16~20 weeks (Northern China,

week 49–14; England, week 50–13; the U.S., week 48–15); while for Southern China, the influenza season is much longer (23 weeks, week 45–15).

Effect of the mask-wearing

One-week increase of mask-wearing intervention, under the realistic contexts of mask-wearing intervention, is capable of dramatically reducing the percent positivity tests in all the four regions, with the mean percent reduction varying from 11·3% to 35·2% (Table S1). The accumulated intervention time needed to achieve the maximal weekly reduction — i.e., the estimated lags of mask-wearing included, are 13 and 11 weeks in Northern China and Southern China, while in England and the U.S. they are much longer, 24 and 35 weeks respectively (Table S1). Considering the long-term impact of mask-wearing intervention, we estimate that, during the 2020-2021 season, the mask-wearing order alone could reduce 19·8 (with 95% confidence interval 15·8 to 24·8) percent positivity in Northern China, 16·6 (13·1 to 21·5) in Southern China, 13·3 (9·7 to 16·6) in England and 15·2 (11·9 to 18·5) in the U.S. (Fig. 1e-h; Table 1), compared to the scenario without NPIs. A larger variation is identified when the timings of mask-wearing orders differ. For example, in Northern China, the mask-wearing order starts before the end of the 2019–2020 season and the influenza positivity is estimated to decline by 12·3 (8·1 to 17·0) under the order alone; while in the U.S., the order starts at the end of the 2019–2020 season, no significant effect is found (Fig. 1a and 1d; Table 1).

Effect of the mobility change

Compared to the mask-wearing intervention, the effect due to mobility change is smaller. We estimate that, for one-week restriction of the international mobility during the influenza season, the influenza activity in the current week has an immediate percent reduction of 4·5% in Northern China. The effects in Southern China, England and the U.S. are similar, varying

from 1·7% to 6·5%. Domestic mobility mitigation measures have closer effects, varying slightly from 1·6% to 2·8% (Table S1). Further, despite the differentiation on timing and magnitude of mobility mitigation measures across regions (Extended Data Fig. 10), the international travel mitigation shows a larger effect than the domestic movement mitigation. In the 2020–2021 season, the mobility mitigation measures reduce 14·0 (8·0 to 18·9) percent positivity in Northern China, 5·2 (1·4 to 9·0) in Southern China, 10·4 (3·9 to 16·6) in England and 9·5 (2·8 to 18·0) in the U.S. (Fig. 2e-h, Table 1); about 79·8% to 98·2% of the reductions are attributable to the international mobility mitigation measure (Table S1). In the 2019–2020 season, only China implemented a short-period of mobility mitigation; we estimate that the reductions due to the mobility mitigation measures are 5·6 (2·0 to 9·9) in Northern China and 3·1 (-0·2 to 7·5) in Southern China respectively (Fig. 2a-b, Table 1).

Effect of SARS-CoV-2 interference

SARS-CoV-2 has an observable effect when it starts spreading during an influenza season. During the 2019-2020 season, we estimate that SARS-CoV-2 interference reduces 7·6 (2·4 to 14·4) and 10·2 (7·2 to 13·6) percent positivity in Norther China and England respectively, and 4·3 (-1·4 to 12·1) and 2·9 (-1·1 to 8·3) in Southern China and the U.S. respectively (Fig. 3; Table 1). The reductions are only significant in Northern China and England, where SARS-CoV-2 virus spreads starting at the peak of influenza season, and are followed by small rebounds (Fig. 3a and 3c). A large effect (mean 12·0, 95% CI 4·3 to 25·3) of SARS-CoV-2 interference is also identified in Hubei province in the 2019–2020 season (Extended Data Fig. 5). However, in all the four regions, no significant effects of SARS-CoV-2 interference are found in 2020-2021.

Influenza's rebound

129 For the incoming 2021–2022 season, we predict that influenza activity will rebound in all the
130 four regions, and the rebound will be longer and blunter compared to that in 2017–2019 (Fig.
131 4), if the mitigation measures discontinue starting from week 40 of 2021. In Southern China,
132 the rebound tends to continue until the summer with a secondary peak, a pattern more similar
133 to that in years before 2018 than in the recent years (Extended Data Fig. 1).

134 Further, these rebounds will vanish and influenza activity will stay at a low level with percent
135 positivity below 10 (Fig. 4), if the mask-wearing continues throughout the 2021–2022 season.
136 Late-season rebound is observed in Southern China after the mask intervention is relaxed.
137 For all the four regions, if the intervention is relaxed in the mid of influenza season, a sharper
138 rebound could occur (Extended Data Fig. 3). However, considering the potential lingering
139 effects of mask-wearing intervention — inclusion of estimated lags of mask-wearing
140 intervention, these rebounds will almost vanish and influenza activity will be kept at much
141 lower levels through the whole year (Extended Data Fig. 4).

142 Our projected estimates rely on the actual acceptance of mask-wearing measures during the
143 COVID-19 period. Should a mask-wearing measure with a magnitude 70% less than that in
144 COVID-19 period be implemented, the incoming winter would still have a modestly big
145 influenza outbreak in store (Extended Data Fig. 4e-h). Nevertheless, when coordinated with
146 an appropriate vaccination program, a much less stringent mask-wearing measure is capable
147 of keeping the influenza activity at low levels. For example, if an extra of 20% population
148 were vaccinated with influenza vaccines (considering 60% efficacy at all age groups[17])
149 before the influenza season starts, a winter mask-wearing intervention with only 30%
150 magnitude of that in the COVID-19 period for about two months, is be able to reduce
151 influenza activity into low levels (Extended Data Fig. 4i-l).

152

Finally, the rebound will also be smaller if international mobility mitigation measures continuous only, but the decline depends on the magnitude of the mitigation as well as the past seasonal patterns. Only in regions with the influenza profile exhibiting single winter-peak outbreak, e.g., Northern China, England and the U.S., and with mobility reduced by 50% or higher from normal levels, influenza activity will be deflected substantially (Fig. 4 and Extended Data Fig. 3). Domestic mobility mitigation is likely to have a smaller impact than international mobility except in Southern China, where reducing domestic mobility during the influenza season by half can maintain influenza activity at markedly lower levels (Fig. 4j and Extended Data Fig. 3j).

In sensitivity analysis, we find that the smoothing method and training window have little impact in the estimated effects, but exclusion of seasonal indicators may result in small negative effects for mobility change (Extended Data Fig. 6-9). We have also conducted a state-level analysis for the U.S.A and the results are in consistent with that for the U.S.A. (Extended Data Fig. 17-21).

Discussion

Although the international travel has been found playing an important role in spreading of influenza A (H1N1) virus in 2009 influenza pandemic[18], evidence on face mask from clinical trials, with limited sample size and low adherence, appears controversial to mechanism studies[19–22]. Our results suggest that, by a large population study for the four regions, mask-wearing alone can substantially reduce influenza activity, comparable to the combined NPIs. Mobility mitigation measures are mostly effective in flatting influenza activity in influenza seasons, with international mitigation making a larger contribution in regions where influenza profiles exhibit single winter-peak outbreak (e.g., Northern China, England and the U.S.) and domestic mitigation in regions having a secondary summer-peak outbreak (e.g., Southern China).

178 It is key to remark that the high effectiveness of mask intervention is obtained based on the
179 actual acceptance of mask-wearing measures during the COVID-19 period, with the
180 compliance to the order, the supply of mask and the lingering habit of mask use being
181 potentially higher than previous years[19]. The estimated weeks of mask-wearing intervention
182 needed to achieve the maximal weekly percent reduction are much shorter in China than that
183 in other regions, in consistent with literature[22] on the differentiation of populations' mask
184 behaviour. While the short-term effects of the mobility mitigations in the four regions are
185 similar, the long-term effects in the influenza seasons could vary substantially. The
186 differences could be due to the differential duration and long-term impact of the mobility
187 related NPIs. Notably, only domestic mobility in China gradually returned to almost normal
188 levels after a falloff in early 2020; the international mobility in all the four regions still stayed
189 in much low levels by week 28 of 2021(Extended Data Fig. 10).

190 We found that the impact of SARS-CoV-2 interference differed in the four regions, with the
191 effects in Southern China and the U.S. particularly small. This is probably due to the low
192 transmission of SARS-CoV-2 virus in the two regions in early 2020, since the extent of viral
193 interference highly relies on the spread of the intervening virus[12,23]. Of note is the large effect
194 of SARS-CoV-2 interference in Hubei province in the 2019–2020 season, where SARS-CoV-
195 2 community transmission was widespread in most parts of the province. It is, however, also
196 possible that the interference depends on the particular cocirculating strains[24,25].

197 Our study adds to the literature in several ways. First, despite the wide association of the
198 NPIs to mitigate SARS-CoV-2 transmission, to the best of our knowledge, this is the first
199 investigation of their individual effects and SARS-Cov-2 inference in seasonal influenza and
200 in a long-term as COVID-19 pandemic evolves over one year. Unlike the early detection for
201 the novel SARS-CoV-2 virus, influenza's virological surveillance system has been long
202 established in many countries and can provide high quality influenza epidemiologic and

203 laboratory data for monitoring and evaluating influenza transmission. We rely on the long-
204 term surveillance data to estimate the individual effects for each region independently.
205 Second, we find that mask-wearing is more effective than mobility mitigation in all the four
206 regions, although the relative advantage depends on the timing and duration of the NPIs.
207 Given the relatively small cost on society[26,27], wearing mask for a short period could be
208 considered as an accompanying method to influenza vaccination in preparedness for
209 influenza pandemics or severe seasonal epidemics, in populations at higher risk for
210 developing severe complications or having lower vaccine efficacy[17,28]. Finally, the insight
211 from our study could offer a head start on understanding SARS-CoV-2 interference in
212 influenza transmission. The results on SARS-CoV-2 interference suggest that the effect
213 varies at the timing of the influenza season and the speed of SARS-CoV-2 community
214 transmission, providing a valuable knowledge for facilitating a deeper understanding of the
215 viral ecology.

216 Our findings on sharp rebound after lifting the mask-wearing intervention in the mid of
217 influenza season (Extended Data Fig. 3a-d) supports the relevance of immunity debt where
218 low viral exposure may spur a growing proportions of susceptible people due to a lack of
219 immune stimulation[29]. Similar rebounds have been found in SARS-CoV-2 circulation when
220 the NPIs are lifted[30]. However, we also found that the long period of low exposure to
221 influenza virus — i.e., the plummeting of influenza throughout the year 2020, instead could
222 induce a blunter 2021–2022 season as in comparison to the recent epidemics in 2017–2019,
223 in all the four regions (Fig. 4 versus Extended Data Fig. 1). The difference could be due to
224 the short duration of protective immunity against influenza virus[17,31] or the naturally small
225 susceptible population in interannual seasons, where in either case the size of susceptible
226 population in a long term is only loosely related to the infection history. Further work is

227 needed to better understand how the immunity debt varies at the timing and period of low
228 exposure to influenza virus.

229 There are several caveats of these results. First, we used the percent positivity reported by
230 laboratory and clinical surveillance system, but the total influenza specimens collected also
231 dropped following the start of NPIs. Nevertheless, the decline coincided with the end of
232 2019–2020 season when the influenza surveillance naturally decreases; the sampling
233 specimens collected during the 2020–2021 season have returned to normal[8]. Second,
234 although in all the four regions no substantial differences in the influenza vaccination
235 behaviour between the 2019–2021 seasons and other recent seasons were found [32–34], in
236 England and the U.S., the yearly influenza vaccination uptake increases steadily with small
237 values, which may result in slightly overestimated effects for these two regions. Third, we
238 have leveraged the COVID-19 vaccine data to account for the time-varying change of the
239 mask-wearing as the COVID-19 pandemic evolves, the effectiveness of the order may also
240 depend on the type of mask in use[19], the presence of other personal protection behaviour
241 (e.g., hand hygiene and respiratory etiquette). Finally, our domestic mobility data are
242 collected from mobile phone users and public transport statistics, which may only provide an
243 incomplete picture of human movement change. Although this surely represents a limitation,
244 in all the four regions, the change of domestic mobility pattern during the COVID-19 period
245 closely coincide with the mobility related NPIs in each region (Extended Data Fig. 13 and
246 Table S3). Our results on domestic mobility thus support the findings on school-closing in an
247 earlier study[35].

248 Influenza's global plummeting provides a great opportunity to understand the individual
249 effects of mask-wearing and mobility mitigation at policy level and offer a head start on
250 fighting future influenza and other respiratory infectious diseases. Vaccination is one of most
251 effective measures in influenza control but provides protection only against the strains and

252 subtypes they have been matched to. Our result is thus highly timely in this context where
253 there is a high uncertain on the upcoming strains, due to the long period of low-exposure to
254 influenza viruses; and with respect to the high interannual variation in circulating strains and
255 subtypes as well as the complication of antigenic immunity changes in response to
256 vaccines[25,36], our findings could also have a far-reaching impact for preventing influenza
257 pandemics. Given the relatively low negative impact of wearing mask in relative to the
258 burden of influenza[37,38], our results suggest that wearing mask for a short period could be
259 considered as a coordinated measure to influenza vaccination in preparedness and response
260 for seasonal and pandemic influenza in populations with low vaccination coverage, especially
261 when the matched vaccines are not available, calling a revisit the role of mask-wearing in the
262 WHO's pandemic influenza intervention guidance[39].

263 # Methods

264 ## Method summary

265 The model consists of two self-correcting regularized multiple regression models, both of
266 which are dynamically trained and regularized with LASSO methods, and are fitted for each
267 of the four regions separately. Modelling parameters capture the short-term effects of one-
268 week interventions. We estimate the effects in influenza seasons due to an intervention
269 through a contrast of the imputed influenza activities under the scenario without NPIs and
270 that under that intervention alone. The delay between the start of NPIs and the first report of
271 SARS-CoV-2 virus enables identification of the effect of SARS-CoV-2 interreference, which
272 is estimated by comparing the influenza activity using the data from 2011 to the first report of
273 SARS-CoV-2, with the activity using the data from 2011 to the start of NPIs. We assume that
274 there is no substantial difference in climate conditions, socio-demographic features, influenza
275 transmissibility as well as influenza vaccination coverages in 2020–2021 compared with the
276 previous years. We also assume that the impacts of these external factors in influenza are
277 consistent and can be captured by past influenza activity. All data are obtained from public
278 source and summarized in Table S2.

279 ## Influenza surveillance data

280 The virological data in 2011–2021 are obtained from the corresponding government website,
281 National Influenza Surveillance Network in China[4], Respiratory DataMart System in Public
282 Health England[6] and U.S. Centers for Disease Control and Prevention (CDC)[5]. The National
283 Influenza Surveillance Network system monitories influenza viruses circulating in China and
284 consists of 554 sentinel hospitals and 407 network laboratories located in over 300 cities in
285 mainland China. The Respiratory DataMart System serves for systematically monitoring
286 influenza and other respiratory viruses circulating in England, with weekly viral test results

287 reported from 14 laboratories representing all nine regions of England. Surveillance of
288 influenza virus in the U.S. is monitored through the U.S. influenza surveillance system and
289 collated by CDC and over 400 public health and clinical laboratories located throughout all
290 50 states, Puerto Rico, Guam, and the District of Columbia. Weekly virological data, the
291 percentage of respiratory specimens tested that are positive for influenza, are released on the
292 respective government influenza surveillance website. The weekly percent positivity are
293 shown in Extended Data Fig. 1.

294 As in literature[9], the start of an influenza epidemic period is defined as the first week starting
295 from which percent positive stays above 10 for at least two weeks and the end is defined as
296 the last week after which percent positive drops below 10 for at least three consecutive
297 weeks. Influenza activity typically peaks in winter season for Northern China, England and
298 the U.S., while for Southern China, it may active in summer as well. The influenza season
299 represents the common period over the nine influenza epidemics in 2011–2020. The start and
300 end of the influenza season are defined as the medians of the starts and ends of the nine
301 influenza epidemics respectively.

302 **Mobility data**

303 We use the normalized international inbound travel volume to measure the international
304 mobility in the four regions. Inbound travel in the U.K. are obtained from Department for
305 Transport[40] in 2011–2021 and are used to represent the inbound travel in England. Inbound
306 travel in Northern China and Southern China in 2011–2021 are represented by the monthly
307 inbound travel in Shanghai released by Shanghai Bureau of Statistics[41]. Inbound travel in the
308 U.S. is collected from U.S. Department of Transportation[42] in 2011–2021. Weekly mobility
309 are estimated using the moving average over the past M weeks, to account for the delaying
310 between mobility changes and laboratory testing and reporting[43]. In baseline, we assume that
311 $M = 2$ in England and the U.S., and $M = 4$ in Northern China and Southern China to account

for a longer delay in China. We have conducted an extensive sensitivity analysis on the delay M. In normalization, since mobility increases with a steady yearly trend while influenza activity evolves with a highly irregular interannual pattern — due to differences in circulating strains[44], we scale down the weekly mobility using the average value in the first month for each year separately.

We collect the domestic mobility data in Northern China and Southern China through Gaode Map API[45] in 2019–2021, which provides daily relative inflow of smartphone users for each of the city covered by National Influenza Surveillance Network in China. The daily inflow is aggregated into the week level using the moving average method as described above. Inflow in 2019–2020 is directly projected into the year 2011–2018 without adjustment, because the yearly trend is removed in the analysis. Domestic mobility in England and the U.S. are estimated by relying on the transportation data in the U.K. and the U.S. respectively. We collect the monthly released domestic transportation data in the U.K. from Office for National Statistics[46] and in the U.S. from U.S. Department of Transportation[42,47]. If monthly data is not available, we estimate the monthly mobility flow by equally allocating the quarterly flow data into each month. In England, since monthly pedal data is only available in 2020, we estimate the domestic mobility in 2020 as the average of vehicle and pedal flows. We estimate the weekly domestic mobility in England and the U.S. using the same moving average and normalization methods. International mobility and domestic mobility are presented in Extended Data Fig. 10.

Mask-wearing index data

We collect data on mask-wearing interventions from the start of the SARS-CoV-2 transmission until week 28 of 2021. In China, the mask-wearing order was imposed starting from week 4 of 2020 (Jan 23) until the end week, week 28 of 2021[48]; for England, the mask-

336 wearing regulation was made from week 30 of 2020 (Jul 23) until week 28 of 2021(Jul 19)[49].
337 We denote the mask-wearing index with 1 during the implementation period and 0 otherwise.
338 U.S. CDC imposed the mask-wearing order from week 14 of 2020 until the end week, with a
339 short-term lift during week 22 of 2021 to week 29 of 2021 for fully COVID-19 vaccinated
340 people in non-healthcare settings[50]. Since state governments did not simultaneously comply
341 with the order imposed by CDC, we estimate the degree of mask-wearing as the proportion of
342 the number of states that imposed the mask-wearing order during the period of CDC mask-
343 wearing recommendation. We refer the data here as Mask Index. The mask-wearing indexes
344 are displayed in Extended Data Fig. 11.

345 **Domestic mobility related NPIs**

346 The change on domestic mobility during the COVID-19 period represents several mobility
347 related NPIs. We estimated the Pearson's correlation between our real-time domestic
348 mobility data with the domestic movement restriction (denoted with categorical levels) as
349 well as the Pearson's correlation between mobility related NPIs, using the data from the
350 Oxford COVID-19 Government Response Tracker[51]. The levels of domestic movement
351 restriction and other mobility related NPIs in each region are estimated using the averages
352 over the local places. The results are shown in Extended Data Fig. 13 and Table S3.

353 **Multiple regression models**

354 We explore two self-correcting regularized multiple regression models to forecast the weekly
355 influenza activity. Both two regression models are dynamically trained and regularized with
356 LASSO methods; and, unlike autoregressive integrated moving average models[52,53] , they
357 allow self-selection of multiple lags (up to 52) of influenza activities as model inputs. The
358 regression models are described below in turn.

First, we use a multiple regression model with a linear combination of N lags of influenza activity as well as the current domestic mobility (denoted with V_t) and international mobility (denoted with W_t) to fit the percent positivity under the mobility change only (denoted with Y_t^{mob}). The international mobility is included during the influenza season only; a sensitivity analysis considering the international mobility throughout the year is conducted and compared to the baseline analysis. S_t indicates the influenza season.

The model is represented by

$$Y_t^{mob} = \alpha + \sum_{n=1}^{N} \beta_n \cdot Y_{t-n}^{mob} + \gamma \cdot V_t + \theta \cdot W_t S_t + \varepsilon_t, \qquad (1)$$

where α, β_n, γ and θ are the parameters, and ε_t represents the error term, with $\varepsilon_t \sim^{iid} \mathrm{Norm}(0, \sigma)$. Parameters γ and θ capture the association relationship of influenza activity with domestic mobility and international mobility during the influenza season respectively. Model (1) is used to predict the influenza activity under varying scenarios with different assumptions on mobility mitigation as well as SARS-CoV-2 transmission. Influenza activity under the scenario with no SARS-CoV-2 transmission is predicted from the first week when the first few COVID 19 cases are reported worldwide (i.e. week 1 of 2020)[54].

Second, we consider a time-varying mask-wearing intervention and denote by D_t^{mas} the mask-wearing intervention at time t. The mask-wearing intervention and the NPIs related to mobility change are the focus of the study and are referred to as two major NPIs; other NPIs that may affect the influenza activity are referred to as minor NPIs. We use Y_t^{npi} to represent the influenza percent positivity under all NPIs. Since Y_t^{mob} is capable of accounting for the NPIs associated with mobility change, the difference between Y_t^{npi} and Y_t^{mob} is attributed to the effect of the mask-wearing intervention and the minor NPIs. Note that the effects of mask-wearing intervention can be isolated if the mask-wearing intervention vary over time.

We include L lags of mask-wearing intervention, to account for the lingering effect of mask use as well as the delay in the compliance[19]. Best value of L is selected according to R^2 criteria and reflects the accumulated intervention time needed to achieve the maximal weekly reduction.

The influenza activity under all NPIs is modelled as

$$Y_t^{npi} = Y_t^{mob} \cdot e^{\mu \cdot I + \tau \cdot (\sum_{l=0}^{L} D_{t-l}^{mas}) + \epsilon_t}, \quad (2)$$

where ϵ_t represents the error term, with $\epsilon_t \sim^{iid} \mathrm{Norm}(0, \zeta)$ and I is an indicator, with $I = 1$ if there exists at least one minor NPI during the week and 0 otherwise. Parameter τ represents the effect of one-week increase of mask-wearing intervention. Parameter μ captures the effect due to the minor NPIs. Here, Y_t^{mob} is obtained from the forecast values from the first regression Model (1) under the mitigated mobility as observed. Under the mobility mitigation measure alone — i.e., there exists no minor NPIs ($I = 0$) or mask-interventions ($\sum_{l=0}^{L} D_{t-l}^{mas} = 0$), Y_t^{npi} is equivalent to Y_t^{mob}. Finally, we explore Model (2) to forecast influenza activity under the mask-wearing intervention alone, where the values of Y_t^{mob} are estimated based on the normal mobility under a hypothetical scenario without mobility mitigation measures.

Mask-wearing intervention estimation

To account for the influence of COVID-19 vaccination on the mask-wearing intervention[55,56], we assume that the values of D_t^{mas} decrease with the vaccination coverage rate r_t, which is estimated according to the percentage of daily administered doses in the total population[57–59] (Extended Data Fig. 12). We consider a linear decreasing pattern and adjust Mask Index accordingly,

$$D_t^{mas} = \text{Mask Index} \times \max\{\delta, 1 - \mu \cdot r_t\}. \quad (3)$$

The adjust term represents that the mask-wearing intervention relaxes with a rate μ as the vaccination campaign continuous and it decreases until a value of δ. Their best fitted values are selected according to the R^2 criteria from the sets $\{0.0, 0.01, 0.05, 0.1, 0.5\}$ and $\{0.0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0\}$. The mask-wearing intervention D_t^{mas} is equivalent to the mask-wearing index before COVID-19 vaccination campaigns start — i.e., $r_t = 0$.

Normal mobility estimation

In England and the U.S., the normal mobility in 2020–2022 under no movement mitigation measures are projected by a regression model using the normal mobility in 2011–2019 before NPIs start. A separate regression model is fitted for each month to keep the inter-month variation the same as in history. In Northern China and Southern China, since the 2019 mobility data is the only available data before NPIs start, we leverage the observed mobility data in 2020 and 2021 to impute the normal mobility. For months from January to June, we impute using the yearly difference estimated from the 2019 and 2021 data; and for months from July to December, we use the yearly difference from the 2019 and 2020 data.

Baseline analysis

We use a look-back window of 52 week (i.e., N = 52) to capture the within-year seasonality in influenza percent positivity and the mobility data to account for the variations due to the changes in human mobility. To avoid the overfitting with the large number of input variables, we use LASSO regression and impose L1-regularization for parameter estimation[52]. Mobility data are normalized to the same scale as the percent positivity for regularization. For simplicity, the regularization strength parameter is set at the same level and the best model is selected through bootstrap validation from the set $\{10^{-5}, 10^{-4}, 10^{-3}, 10^{-2}, 10^{-1}\}$. Separate autoregressive models are fit for Northern China, Southern China, England and the U.S.. A

429 rolling window of over 400 weeks is used to dynamically train all parameters in Model (1).
430 When investigating the impact of mobility mitigations, the window covers the period from
431 week 40 of 2011 to the week before the start of any NPIs; for investigating the impact of
432 SARS-COV-2 interference, it corresponds to the period from week 40 of 2011 to the week
433 before the arrival of SARS-COV-2 transmission. In England, since the mask-wearing law
434 was implemented starting from week 30 of 2020, much later than the start of mobility
435 mitigation (week 11 of 2020), we have tested an alternative analysis where the training
436 window ends at week 29 of 2020.

437 We estimate the effect of mask-wearing intervention using a lag of up to 52 observations of
438 mask-wearing interventions. The best fitted values of L are selected according to the R^2
439 criteria. Parameters in Model (2) are dynamically trained every week rolling over from the
440 start of the NPIs until the end of NPIs and are further used to forecast the influenza activity
441 under the mask intervention alone.

442 To explore the possible implications of relaxing NPIs for the 2021–2022 season, we
443 investigate three scenarios under different NPIs, (i) mask-wearing intervention is imposed
444 during the full influenza season; (ii) international mobility is reduced by 50%; and (iii)
445 domestic mobility is reduced by 50%. The model is implemented in scikit-learn 0.24.2 with
446 Python 3.6.13 (Python Software Foundation).

447 **Sensitivity analysis**

448 Validation

449 We conduct a cross validation analysis through the forward chaining approach, using a) the
450 2011–2016 data for training and the 2017 data for test; b) the 2011–2017 data for training and
451 the 2018 data for test; c) the 2011–2018 data for training and the 2019 data for test. The
452 results are displayed in Extended Data Fig. 14-16.

Modelling assumptions

We performed three sensitivity analyses on modelling assumptions. First, we analyzed the scenario where the seasonal indicator is excluded in Model (1) , and a scenario where the seasonal indicators are included for both international mobility and domestic mobility. Second, we have conducted an extensive sensitivity analysis on the lags of mobility data used in the smoothing average (M = 2, 3, 4) in all the four regions. Finally, since in England the mask-wearing law was implemented starting from week 30 of 2020, we have tested an alternative analysis for England where the training window in Model (1) continuous until week 29 of 2020.

Alternative analysis for the incoming 2021-2022 season

a) Timing of mask-wearing: We explore two alternative assumptions on the timing of the mask-wearing order: (i) imposed only in the first half of the 2021–2022 season and (ii) imposed only in the second half of the 2021–2022 season.
b) Magnitude of mobility mitigation: We explore two alternative reductions, 30% and 70%, of the mobility, for international mitigation and domestic mitigation respectively.
c) Intensity of mask-wearing: We explore three alternative intensities of the mask-wearing interventions, with values equal to 30%, 50% and 70% less than that during the COVID-19 pandemic.
d) Lingering effect of mask-wearing intervention: We consider three timings of mask-wearing interventions, (i) imposed only in the first half of the 2021–2022 season, (ii) imposed only in the second half of the 2021–2022 season, and (iii) imposed in the full 2021–2022 season, and include the estimated number of lags of mask-intervention L into the analysis.

e) Coordination of mask-wearing with vaccination: We assume an extra of 20% population are vaccinated before the start of the influenza season and consider a mask-wearing intervention with intensity 70% less than that during the COVID-19 pandemic.

Analysis for U.S. states

We also conduct a state-level analysis for the U.S.A., using the influenza data reported by states[5]. As an illustration, we consider four U.S. states: Colorado, Indiana, Minnesota, and Washington. We estimate their domestic mobility in 2020–2021 using the state-level data from Google Mobility Reports[60] and the Mask Index using the state-level mask-wearing order. The full analysis conducted for the U.S.A. is repeated for the four states.

Data availability

All the data used in the study were detailed in Methods and provided in Supplementary Information.

Code availability

Codes will be made available on GitHub upon manuscript acceptance.

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634

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643 Author contributions

644 X.-H.Z., and L.F. supervised the work. S.H. designed the study. S.H., T.Z., Y.L., and P.D.
645 collected data. S.H. ,T.Z., and Y.L. finalized the analysis. S.H., T.Z., Y.L., S.L., X.-H.Z., and
646 L.F. interpreted the findings. S.H. and T.Z. wrote the manuscript. S.L., J.Z., W.Y, X.-H.Z., and
647 L.F. commented on and revised the manuscript. All authors approved the final manuscript as
648 submitted.

649 Competing interests

650 The authors declare no competing interests.

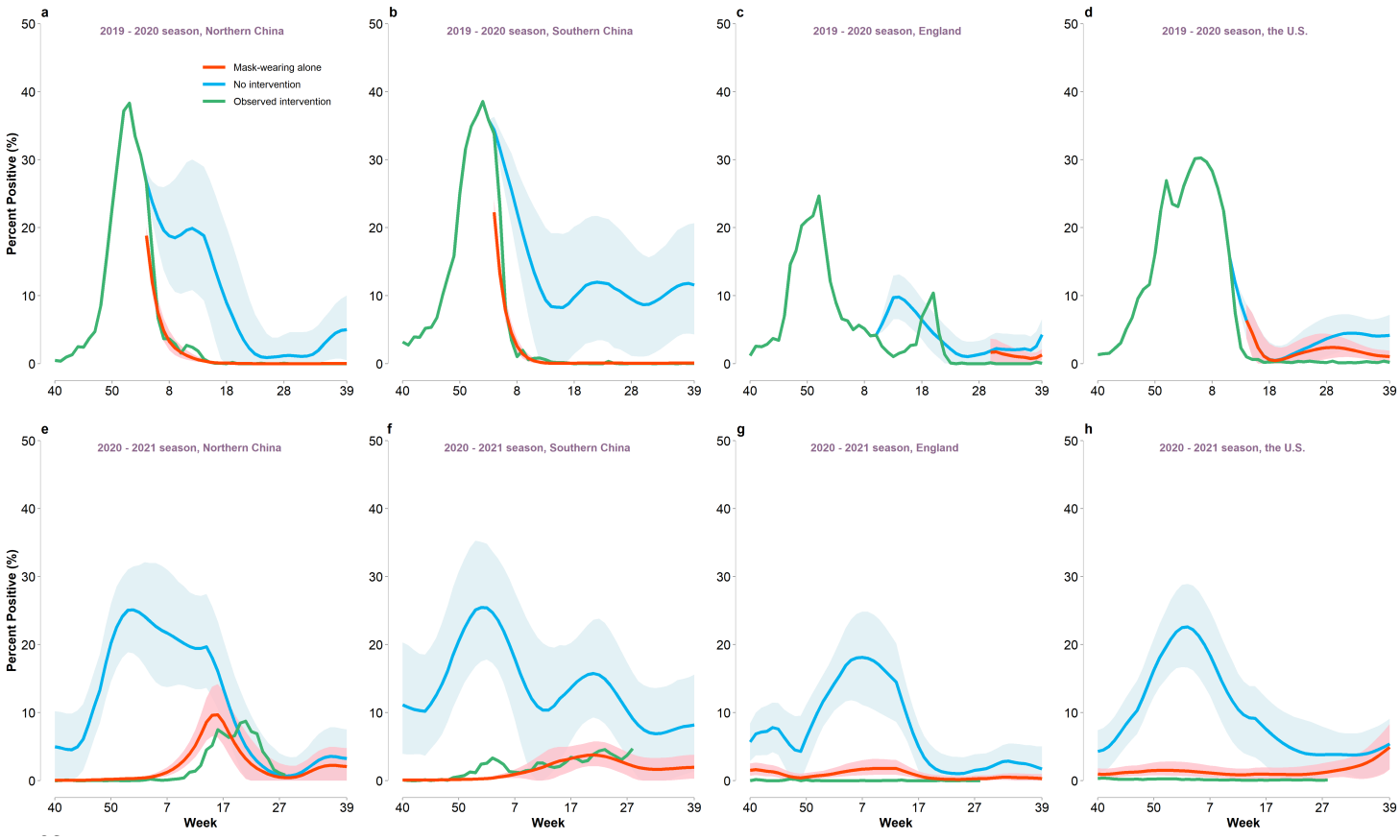

Fig. 1 Estimated influenza activities under the mask-wearing order alone and no intervention as well as the observed activity. **a** Weekly percent positivity in 2019-2020 season for Northern China. **b** As **a**, but for Southern China. **c** As **a**, but for England. **d** As **a**, but for the U.S.. **e** As **a**, but in 2020-2021. **f** As **e**, but for Southern China. **g** As **e**, but for England. **h** As **e**, but for the U.S.. Shaded area refer to 95% CI.

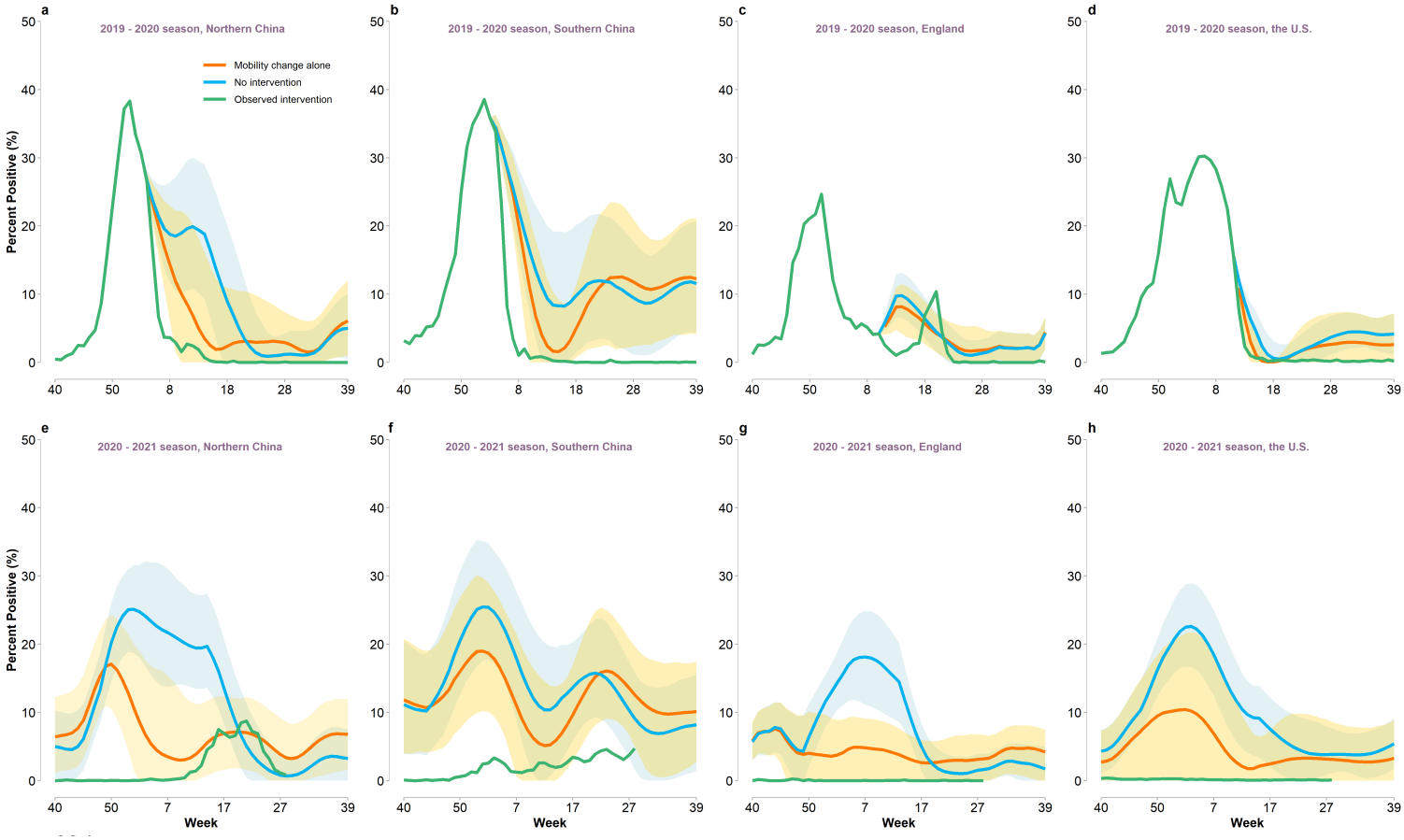

Fig. 2 Estimated influenza activities under the mobility change alone and no intervention as well as the observed activity. a Weekly percent positivity in 2019-2020 season for Northern China. **b** As **a**, but for Southern China. **c** As **a**, but for England. **d** As **a**, but for the U.S.. **e** As **a**, but in 2020-2021. **f** As **e**, but for Southern China. **g** As **e**, but for England. **h** As **e**, but for the U.S.. Shaded area refer to 95% CI.

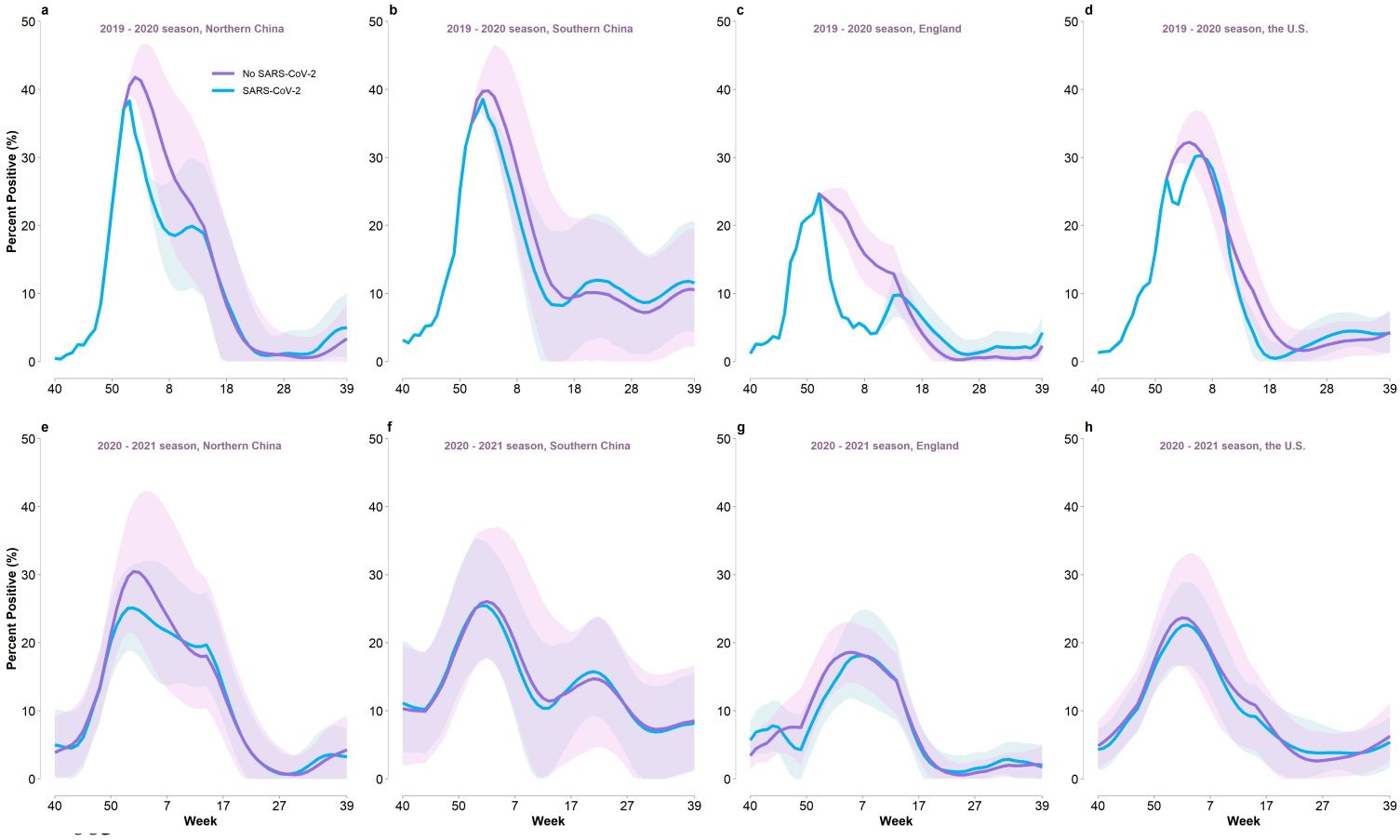

Fig. 3 Estimated influenza activities under the scenarios with no SARS-COV-2 transmission and with SARS-COV-2 transmission, both without COVID-19 NPIs. a Weekly percent positivity in 2019-2020 season for Northern China. **b** As **a**, but for Southern China. **c** As **a**, but for England. **d** As **a**, but for the U.S. **e** As **a**, but in 2020-2021. **f** As **e**, but for southern China. **g** As **e**, but for England. **h** As **e**, but for the U.S.. Shaded area refer to 95% CI.

Fig. 4 Predicted influenza activities in 2021–2022 season under no NPI and varying NPIs. a Weekly percent positivity under mask-wearing intervention for the full season in Northern China. **b** As **a**, but for Southern China. **c** As **a**, but for England. **d** As **a**, but for the U.S.. **e** As **a**, but under international mobility mitigation reduced by 50%. **f** As **e**, but for Southern China. **g** As **e**, but for England. **h** As **e**, but for the U.S.. **i** As **a**, but under domestic mobility mitigation reduced by 50%. **j** As **i**, but for Southern China. **k** As **a**, but for England. **l** As **a**, but for the U.S.. Shaded area refer to 95% CI.

Table 1 Estimated effects of mask-wearing and mobility mitigation and SARS-CoV-2 interference in the influenza seasons.

	Northern China		Southern China		England		The U.S.	
	Mean	**95%CI**	**Mean**	**95%CI**	**Mean**	**95%CI**	**Mean**	**95%CI**
In 2019-2020								
Relative to no NPIs								
Mask-wearing alone	12·3	(8·1, 17·0]	11·7	(6·8, 16·8)	——[a]	——[a]	0·0	(0·0, 0·0)
Mobility change alone	5·6	(2·0, 9·9)	3·1	(-0·2, 7·5)	0·2	(0·1, 0·6)	0·7	(0·2, 1·5)
Observed NPIs	11·2	(6·4, 16·4)	10·2	(5·0, 15·6)	1·4	(0·9, 1·9)	1·3	(0·8, 1·9)
Relative to no SARS-CoV-2								
SARS-CoV-2	7·6	(2·4, 14·4)	4·3	(-1·4, 12·1)	10·2	(7·2, 13·6)	2·9	(-1·1, 8·3)
In 2020-2021								
Relative to no NPIs								
Mask-wearing alone	19·8	(15·8, 24·8)	16·6	(13·1, 21·5)	13·3	(9·7, 16·6)	15·2	(11·9, 18·5)
Mobility change alone	14·0	(8·0, 18·9)	5·2	(1·4, 9·0)	10·4	(3·9, 16·6)	9·5	(2·8, 18·0)
Observed NPIs	21·2	(16·7, 26·8)	16·0	(12·2, 21·1)	14·6	(10·6, 18·2)	16·2	(12·8, 19·8)
Relative to no SARS-CoV-2								
SARS-CoV-2	2·1	(-1·5, 8·9)	0·7	(-1·6, 4·8)	1·5	(-2·0, 5·4)	1·2	(-2·2, 6·1)
In 2021–2022								
Relative to no NPIs								
Mask-wearing alone	16·8	(11·5, 22·2)	15·9	(11·8, 20·6)	7·0	(4·2, 9·5)	9·3	(6·2, 12·4)
International mobility alone (reduced by 50%)	7·2	(3·8, 10·7)	3·2	(1·0, 5·4)	3·7	(1·5, 5·7)	4·6	(1·9, 7·3)
Domestic mobility alone (reduced by 50%)	3·0	(-2·6, 11·9)	4·7	(-4·2, 12·9)	1·2	(0·0, 8·9)	3·3	(0·0, 14·1]

Notes: a. In England, the mask-wearing order started after the end of the 2019-2020 influenza season.

Supplementary Files

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