The Effectiveness of Governmental Nonpharmaceutical Interventions Against COVID-19 On The Control of Seasonal Influenza Transmission: An Ecological Study

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Research Article

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Abstract

Background: A range of strict nonpharmaceutical interventions (NPIs) had been implemented in many countries to combat the COVID-19 pandemic. These NPIs might also be effective in controlling the seasonal influenza virus, which share the same transmission path with SARS-CoV-2. The aim of this study is to evaluate the effect of different NPIs for control of seasonal influenza.

Methods: Data on 14 NPIs implemented in 33 countries and corresponding data on influenza virologic surveillance were collected. The influenza suppression index was calculated as the difference between the influenza-positive rate during its decline period from 2019 to 2020 and that during influenza epidemic seasons in the previous 9 years. A machine learning model was developed by using extreme gradient boosting tree (XGBoost) regressor to fit NPI data and influenza suppression index. SHapley Additive exPlanations (SHAP) was used to characterize NPIs in suppressing influenza.

Results: Gathering limitation contributed the most (37.60%) among all NPIs in suppressing influenza transmission in the 2019-2020 influenza season. The top three effective NPIs were gathering limitation, international travel restriction, and school closure. Regarding the three NPIs, their intensity threshold to generate effect were restrictions on the size of gatherings less than 1000 people, travel bans on all regions or total border closure, and closing only some categories of schools, respectively. There was a strong positive interaction effect between mask wearing requirement and gathering limitation, whereas merely implementing mask wearing requirement but ignoring other NPIs would dilute mask wearing requirement's effectiveness in suppressing influenza.

Conclusions: Gathering limitation, travel bans on all regions or total border closure, and closing some levels of schools are the most effective NPIs to suppress influenza transmission. Mask wearing requirement is advised to be combined with gathering limitation and other NPIs. Our findings could facilitate the precise control of future influenza epidemics and potential pandemics.

Introduction

Influenza virus is highly infectious, which could cause seasonal epidemics around the world, leading to 3-5 million severe illness cases[1] and 290,000-650,000 deaths[2] annually worldwide. Some variants could even cause global pandemics, such as the 1918 Spanish flu and the 2009 swine flu.[3,4] The next influenza pandemic could occur anywhere and anytime around the world, which would not only cause huge disease burden but also result in enormous social and economic costs. Governments should also be well prepared for the rebound of seasonal influenza followed by the relief of control measures due to COVID-19 pandemic.

To curb the global pandemic of COVID-19 in 2020, government around the world has enforced a range of rigorous nonpharmaceutical interventions (NPIs) nationwide, such as closing schools and workplace, ordering mask wearing, and restricting non-essential travelling.[5] These NPIs control SARS-CoV-2 mainly by cutting off its air-borne transmission path, which is not specific to a single pathogen. Hence, it is

reasonable to theorize that these measures would also be effective in suppressing seasonal influenza, a virus sharing the same transmission path with SARS-CoV-2.[6]

Studies from mainland China[7,8], Hong Kong[6], Taiwan[9], and Singapore[10] found that the influenza activity in 2020 has decreased compared with previous influenza seasons, and estimated the effectiveness of NPIs in suppressing influenza transmission. However, the geographical scope investigated by these studies was only restricted to a specific region, limiting the type and intensity level of NPIs studied. Furthermore, these studies only evaluated the overall effect of a set of NPIs combined instead of disentangling the specific effect of individual NPIs. The effect of NPIs at different intensity levels also remains unstudied. However, policymakers need more detailed information for better decision-making in terms of designing more precise strategies for effective control of influenza.

The aim of this study is to quantify and compare the effectiveness of 14 NPIs in suppressing transmission of influenza in a total of 33 countries, so as to identify the optimal NPIs and their combination, and to provide detailed scientific evidence for the design of precise strategies to prevent and control spread of influenza.

Methods

Data Source

Our data on NPI were retrieved from the Oxford Covid-19 Government Response Tracker (OxCGRT).[11] This dataset provides the level and scope of daily NPIs implemented in almost all countries around the world. There were a total of 19 NPIs with three broad categories in the database (Supplementary Table 1): containment and closure policies (school and workplace closure, public events cancellation, gathering limitation, public transport suspension, stay at home requirement, and domestic and international travel restriction), economic policies (unemployment subsidy, debt/contract relief, fiscal measures, and international support), and health system policies (health education promotion, testing policy, contact tracing, emergency investment in healthcare, investment in vaccines, mask wearing requirement, and vaccination policy). Five NPIs with low variance (the frequency of no implementing was over 90%) were excluded, including fiscal measures, international support, emergency investment in healthcare, investment in vaccines, and vaccination policy. As a result, the remaining 14 NPIs were included in our analysis.

Given that some countries implemented a NPI nationwide, whereas others might only implement the NPI in a local area, the intensity value of each NPI was calculated to account for the geographic implementation scope of NPI. The intensity value of each NPI was calculated according to the formula provided by OxCGRT (sub-index),[11] by taking into account implementation level and implementation scope Details of the 14 NPIs at various intensity levels are shown in the Supplementary Table 1.

Global data on national influenza virological surveillance were obtained from the World Health Organization (https://www.who.int/influenza/gisrs_laboratory/flunet/en/). These data are mainly collected by the Global Influenza Surveillance and Response System (GISRS), which provides weekly updated information on specimens collected from the respiratory tract, including the collection time and source of specimens, the number of specimens received/collected, the number of specimens processed, the number of specimens with positive influenza, the number of influenza A/B viruses detected by subtypes, and the activity of influenza-like illness. The influenza positive rate was calculated by dividing the number of specimens with positive influenza by the number of specimens processed.

Given that the influenza epidemic in the southern hemisphere in 2020 was almost completely suppressed owing to the implementation of NPIs[12], only countries in the northern hemisphere were selected. Besides, the data quality of countries in northern hemisphere is uneven. To control data quality, countries without any influenza surveillance data during the presence of NPIs, and those countries in which influenza epidemic did not exhibit seasonal epidemic curve were excluded. Two researchers (ZQ and ZC) independently selected countries. Finally, A total of 33 countries were included (Figure S1).

For this study, the effectiveness of NPIs in suppressing influenza was evaluated based on the influenza season 2019-2020, where there was no NPI implemented at the early increasing stage and then enforced during the later declining stage. To compare the influenza epidemic level during periods with and without NPIs, the weekly influenza-positive rate during its declining stage at each year between 2011 and 2019 was obtained, when NPIs could be considered absent.

The length of the declining interval was fixed as that observed in influenza season 2019-2020, which started from the epidemic peak and ended at the trough. Next, the average values of the influenza-positive rate at each time point during its declining stage between 2011 and 2019 were calculated as reference. Given that the influenza prevalence in each country might be different, the influenza-positive rate for season 2019-2020 as well as the reference were normalized to 0 to 1. Finally, the effectiveness of NPIs on controlling influenza (i.e., Influenza suppression index) was quantified as the difference between the two sets of influenza-positive rates for season 2019-2020 and the reference from 2019 to 2020, respectively.

Data Analysis

In general, NPIs usually do not have an immediate impact after they are implemented (i.e., lag effect[5,13]). In this study, the time needed for each NPI to reach its maximal level of effect was assumed to vary from one to 14 days. To determine the minimal time that each NPI needed to generate its maximal effect, lags of one to 14 days for each NPI were examined and the spearman rank correlation coefficient between influenza suppression index and the intensity of each NPI at each lagged day was calculated. For each NPI, the lagged day with the largest correlation coefficient was selected.

A machine learning model, extreme gradient boosting tree (XGBoost)[14], was used to estimate the individual effectiveness of each NPI in suppressing the transmission of influenza. Specifically, the

dataset was randomly split into a training set and another separate testing set, at a ratio of 8:2. The hyperparameters of XGBoost were tuned by using Bayes optimization with ten-fold cross-validation in the training set to overfit the model. Subsequently, regularization terms of XGBoost were tuned to reduce the model overfitting, which was evaluated in the testing set. At last, the final model was refitted using the whole dataset.

Explainable artificial intelligence algorithm could facilitate the interpretation of the machine learning model on the prediction of the outcome (i.e., influenza suppression index) based on features (i.e., NPI). SHapley Additive exPlanations (SHAP)[15] was used in this study, which is based on solid mathematical theory (cooperative game theory).

SHAP could provide SHAP value, SHAP main effect value, and SHAP interaction value. Contribution of NPIs in suppressing influenza transmission was derived from SHAP value; effectiveness of each NPI's intensity level and threshold intensity of NPIs to generate effect were derived from SHAP main effect value; interaction of each pair of NPIs was derived from SHAP interaction value. Additionally, the effectiveness of each NPI's intensity level were grouped into "strong", "moderate", or "weak" by using K-means clustering. Detailed information was provided in the supplementary material.

A range of sensitivity analyses was performed to test the robustness of our contribution results: 1) each country was removed one at a time and the analysis was repeated; 2) four countries (i.e., Canada, China, Russia, and United States) with a large territory and therefore high regional heterogeneity were removed from the dataset; 3) the unnormalized influenza positive rate was used; 4) whether NPIs were implemented nationwide or only within a local area was disregarded by only using implementation level 5) different methods were used to select features, including least absolute shrinkage and selection operator (Lasso) with 10-fold cross-validation, random forest algorithm with a hybrid SHAP feature contribution ranking, random forest algorithm wrapped with sequential feature selection, and support vector machine wrapped with sequential feature selection.

Results

1. Ranking of the contribution and effectiveness of NPI

Four NPIs with negligible effect were excluded by the model regularization. Among the remaining 10 NPIs, those with a contribution greater than 10% to suppress influenza were gathering limitation (37.60%), school closure (15.24%), contact tracing (12.33%), and health education promotion (11.47%), respectively, resulting in a total contribution of 76.64% (Figure 1A). A series of sensitivity analyses consistently confirm that the 4 NPIs making the greatest contribution are robust (Table S2).

Three groups of NPIs were obtained based on clustering algorithm and assigned as strong, moderate and weak according to their effectiveness (Figure 1B). For gathering limitation, all its selected intensity levels were classified as strong. The following NPIs were categorized as moderate: banning on all foreign regions or total border closure, requiring closing some or all schools, limited or comprehensive contact

tracing, requiring closing some or all-but essential workplaces, and coordinated public information campaign. And the remaining NPI intensity levels were classified as weak (Figure 1B).

2. The intensity threshold and lag effect for NPI to take effect

The intensity thresholds of NPIs with their effectiveness classified as strong or moderate are as follows (Figure 2, and check Figure S2 for all the 10 NPIs). In terms of the NPI of restrictions on gatherings, enforcing restriction on very large gatherings (> 1000 people) started to take effect in suppressing influenza transmission, and expanding this order nationwide could reach maximal effect. Regarding the NPI of international travel restriction, enforcing travel bans on all regions or total border closure started taking effect. For the NPI of school closing, the intensities for starting to take effect and reach maximum effect were requiring closing some levels or categories of schools in a specific geographical region and expanding this order nationwide, respectively. Regarding the NPI of contact tracing, enforcing tracing on limited contact, no done for all cases, started to take effect and also reached maximum effect in suppressing transmission of influenza. As for the NPI of workplace closure, requiring closing for some sectors or categories of workers (or working from home) started to take effect and also reached maximal effect. Regarding the NPI of health education promotion, enforcing coordinated public information campaigns (e.g., across traditional and social media) targeted to a specific geographical region not only started to take effect but also reached maximal effect. Further tightening these above-mentioned NPIs beyond the level generating maximal effect did not exhibit obvious improvement (saturation point).

The effects of introduced NPIs were not immediate. The time needed for each NPI to reach its maximal levels of effect was different but all under one week (Figure S3). Health education promotion needed the longest time to take effect (7 days), followed by school closure and public events cancellation (5 days, respectively). The following NPIs had a lag time of less than three days: domestic travel restriction, international travel restriction, stay at home requirement, public transport suspension, unemployment subsidy, debt/contract relief, and testing policy.

3. The interaction between pair of NPIs

Results of significant interaction effect between pair of NPIs are extracted (Figure S4 and Figure S5). Among them, the top 2 pairs of NPIs with the largest overall interaction effect were contact tracing paired with international travel restriction, and mask wearing requirement paired with gathering limitation, respectively (Figure 3). Decreasing the intensity of contact tracing had a positive interaction effect with increasing the intensity of international travel restriction (Figure 3A). While increasing the intensity of contact tracing had a negative interaction effect with tightening international travel restriction.

Tightening the mask wearing requirement had a positive interaction effect with strengthening the following NPIs: gatherings limitation (Figure 3B), workplace closure, health education promotion, contact tracing, and domestic travel restriction (Figure S5). However, only strengthening mask wearing requirement without increasing the intensity of other NPIs demonstrated a negative interaction effect.

Discussion

Compared with COVID-19, the influenza epidemics is a persistent public health challenge that had occurred many times in human history, but there has been a lack of guidance on formulating NPI strategies to cope with influenza epidemics. To the best of our knowledge, the current study is the first to use a machine learning algorithm combined with explainable artificial intelligence tool to quantify the effectiveness of 14 NPIs targeted to COVID-19 in suppressing influenza transmission in 33 countries. We found that the gathering limitation made the biggest contribution in suppressing influenza transmission. Additionally, we also estimated the effectiveness of each level of NPIs, the intensity and time threshold for each NPI to take effect, and the interaction between each pair of NPIs.

We found that gathering limitation, school closure, contact tracing, and health education promotion contributed the most in suppressing influenza transmission. These results partially agree with previous studies on estimating the effectiveness of NPIs against COVID-19.[16,17] We found that school closure was more effective than workplace closure. The reason might be that the transmission of the influenza virus mainly occurs in children rather than adults. Previous studies also found that closing school played an important role in the 2009 H1N1 pandemic.[18–20]

We found that contact tracing generated effects on suppressing influenza transmission even though this NPI was specific to the contact of COVID-19 patients. It might be because the disease symptoms of the two viruses are very similar (e.g., fever, cough), and both viruses are airborne transmitted. Therefore, patients with COVID-19 exposure history might also be previously or currently exposed to the influenza virus, and those patients with suspected COVID-19 symptoms under close tracing and monitoring might actually be infected with the influenza virus. Another reason might be the high co-infection rate of SARS-CoV-2 and influenza virus. A single-centered retrospective study conducted in Wuhan, China reported that among 307 COVID-19 patients, 57.3% of them were also positive for influenza viruses.[21] A recent experimental study found that influenza A virus pre-infection could significantly enhance the infectivity of SARS-CoV-2.[22] Similarly, other NPIs such as workplace closure and health education promotion were also effective in suppressing influenza transmission regardless of whether the NPI was restricted to regions suspected of COVID-19 outbreak or implemented nationwide. These results could partly be explained by the same transmission route of the two pathogens and further indicate that there exist interactions between influenza virus and SARS-CoV-2. Although our results show that the main effect of health education promotion was moderate and the lag time was the longest one among the 14 NPIs, this NPI's contribution in suppressing influenza in 2020 was sizeable (11.47%). This might be because health education promotion is easy to use and therefore frequently implemented by many governments worldwide.

We for the first time quantify the intensity for each NPI to start to generate effect and that to reach maximum effect. As for the NPI of the international travel restriction, we found that only banning arrivals from some foreign regions rather than all regions or total border closure could not produce the effect in suppressing influenza transmission. The reason for this might be that for viruses that could cause global

pandemic, such as influenza virus and SARS-CoV-2, it is crucial to strictly restrict their transmission across country borders. For example, at the early age of COVID-19, the US only banned traveling from China[23] even if there were some emerging cases in Europe. But this incomplete restriction of international movement resulted in a surge in COVID-19 cases in the US due to the imported COVID-19 cases also from Europe.[24] We found that for school and workplace closure, the recommendation alone was not sufficient to generate a significant effect in suppressing the influenza transmission. This is might because leaders of schools and factories have inadequate knowledge about the threat of infectious diseases, thereby continue the normal operation of organizations. This means that the government needs to enforce the requirement of closing schools and workplace. In terms of the NPI of health education promotion, our results show that official notice alone was not sufficient to generate a significant effect in suppressing the transmission of influenza, unless it was combined with social media. Therefore, the key role of social media in public health education and disease prevention should be recognized and deployed by policymakers. However, false information and rumors can easily spread via the social media[25], so the authority of official notification is indispensable.

We found that there existed saturation points of NPIs. Finding the saturation points indicates that maximize suppressing effect could be achieved while minimizing the social and economic costs of their interventions. The reasons behind this phenomenon might because enforcing NPIs at a certain level could reach saturation. However, we lacked data regarding the public's actual behaviors in reaction to NPIs, which is more closely relevant to the influenza transmission. Therefore, another possible reason could be the deterrent effect of a certain level of NPIs. For example, restricting 1000 gatherings might make people think twice before attending social activities with less than 1000 participants. However, our analysis was restricted to the earlier stage of the pandemic, while the deterrent effect might decline with the prolonging of the pandemic period because of the growing pandemic-policy fatigue[26] among the public.

We took into consideration and calculated the lag time of each NPI. Results show that the lag time of health education is the longest. It is reasonable given that it takes a longer time for the public to receive and internalize public health information compared with other NPIs. We also found that the lag time of some NPIs (e.g., domestic movement restriction, testing policy) was less than three days, which is not reasonable in theory because the series interval (i.e., the time between two successive cases) of influenza is around three days.[27] This might be mainly because the fact that the impact of these NPIs might be too negligible to calculate a reasonable lag time. This could also be supported by the low contribution rank of these NPIs.

We found a positive interaction effect when the intensity of mask wearing requirement and other NPIs (e.g., gathering limitation) are both strong, whereas merely implementing mask wearing requirement at high intensity shows a negative effect. This could be explained by risk compensation.[28] In other words, the public might assume that only wearing masks could fully protect them from respiratory infection, thereby increasing the frequency and time of contacting with others. However, influenza virus is not only

transmitted by air, but also by contact transmission (e.g., a person touches the surface accumulated with droplets from infected patients and then touches his/her face).[1] Therefore, influenza cases could rise in those people who have close contact with others despite wearing masks.

A negative interaction was shown when both the intensity of international travel restriction and the intensity of contact tracing were strong, while a positive interaction effect was shown when the intensity of contact tracing was weak. This might be because when the intensity of international travel restriction is strong enough to suppress influenza transmission, contact tracing might no longer be necessary with the reduction of cases. Additionally, during the early decline period of influenza epidemic, we observed a positive interaction effect when both the intensity of contact tracing and that of testing policy were strong (Figure S4C), which may indicate other NPI factors may be involved.

Our study has some strengths. First, compared with previous studies that simply used the time of introducing NPIs as a surrogate for the effect of NPIs, we used a more reliable, detailed, and comprehensive NPI database, which allowed us to quantify different levels of each NPI. Second, most previous studies[6,8–10] simply investigated one country or region, whereas we for the first time included and compared the impact of various NPIs on influenza transmission across a total of 33 countries in the northern hemisphere. Third, the previous studies[5,16,17] evaluating the effectiveness of NPIs in suppressing COVID-19 lack accurate case data, because COVID-19 is an emerging infectious disease that lacks detection kits of high sensitivity and specificity, and the testing rate is very likely to be influenced by the intensity of testing policies vary by country. In comparison, the well-established influenza surveillance system used in this study (i.e., GISRS) has consistently and reliably monitored influenza activity since 1952.[29] Lastly, from the perspective of methodology, we used the machine learning model and explainable machine learning method to capture the complex relationship between the intensity of NPIs and influenza suppression index. Hence, we could obtain a range of more detailed and informative results.

Nevertheless, our study has several limitations. First, due to the lack of influenza incidence in our dataset, we only used the influenza-positive rate to approximate actual influenza activity. Although previous studies[30,31] used influenza positive rate multiple influenza-like illness rate to approximate the incidence, the majority of countries (20/33, 60.6%) in our dataset did not report influenza-like illness rate. Second, the influenza positive rate might be underestimated because under the impact of COVID-19 pandemic, the health seeking behavior of influenza patients might be reduced and medical resources tend to be inadequate. Nevertheless, the number of specimens tested in 2020 was comparable with that in previous year (1,701,758 vs 1,675,945).[32] Lastly, we used an ecological study design, so the effectiveness of NPIs might be impacted by a range of uncontrolled confounding factors specific to the country in which NPIs were implemented, such as country demographic structure, climate, and the presence of other NPIs. Due to the same reason, we were unable to adjust for specific implementation details of each NPI which may vary by country. And the interpretation for interaction between NPIs should be careful.

In conclusion, our results estimated the effectiveness of various NPIs in suppressing influenza transmission and provided detailed scientific evidence from different aspects. These results could provide reference to policymakers to deal with potential influenza pandemics in the future. Nevertheless, more detailed information from other aspects such as other unincluded NPIs in our analysis and the cost effectiveness of implementing NPIs could be further explored.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The policy datasets generated and analyzed during the current study are available in the Oxford COVID-19 Government Response Tracker repository, https://covidtracker.bsg.ox.ac.uk/.[11] The Influenza virological datasets generated and analyzed during the current study are available in Global Influenza Surveillance and Response System (GISRS) at https://www.who.int/influenza/gisrs_laboratory/flunet/en/. The data and code are available at https://github.com/qqqqqzk/NPI-against-influenza.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XD and ZQ designed the study. ZQ, ZC, KT, CZ, JT, JZ, QS, and DW collected the data, ZQ and ZC analysed the data. XD, ZQ, and ZC interpreted the data. XD and ZQ prepared the manuscript. XD, ZQ, and MZ edited the paper. All authors reviewed and approved the submitted manuscript.

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Figures

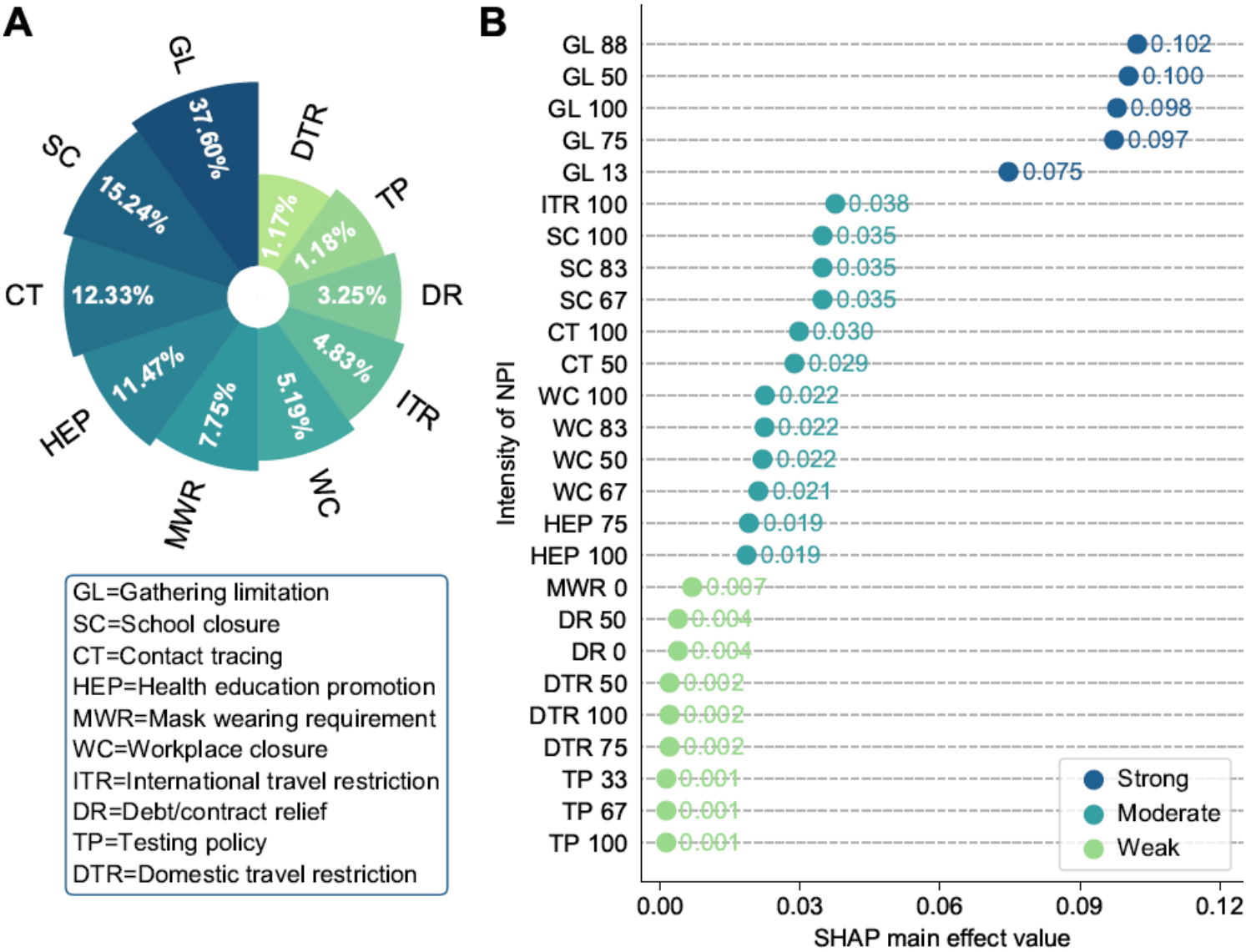

Figure 1

Ranking of the contribution and effectiveness of each NPI.

(A) Percentages of NPIs' contribution in suppressing influenza transmission during the declining phase of 2019-2020 influenza season. (B) The effectiveness of each NPI at different intensity levels. The number after the name of each NPI on the y-axis represents intensity levels.

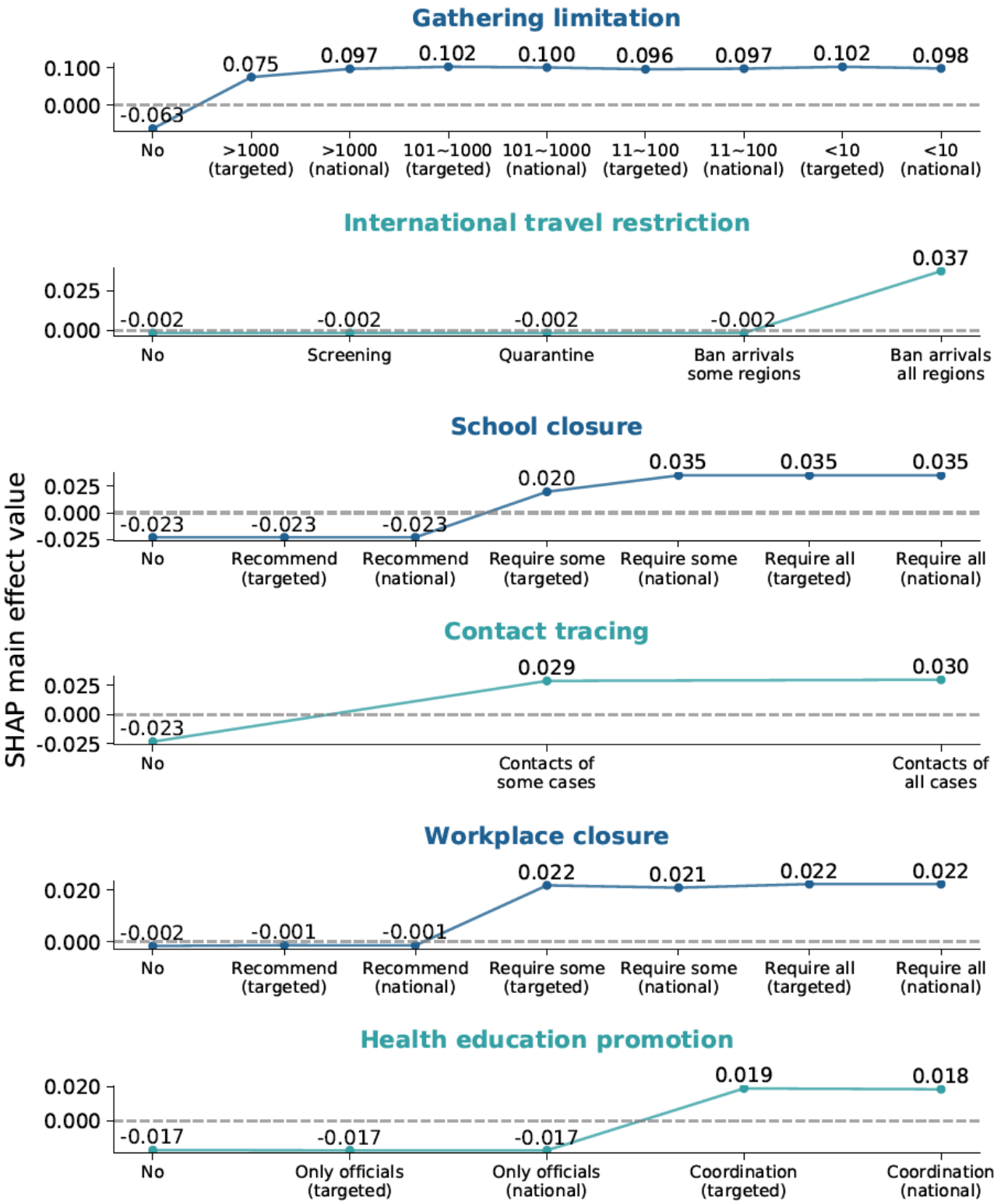

Figure 2

SHAP main effect value of each NPI at different intensity levels.

For each NPI, the first time when its SHAP main effect value exceeded zero represents that the NPI with the corresponding intensity level started to suppress influenza transmission, and the intensity below this level means that the NPI did not produce effects. The inflection point in the plot corresponds to the intensity of the NPI that could approximately reach the maximal effect.

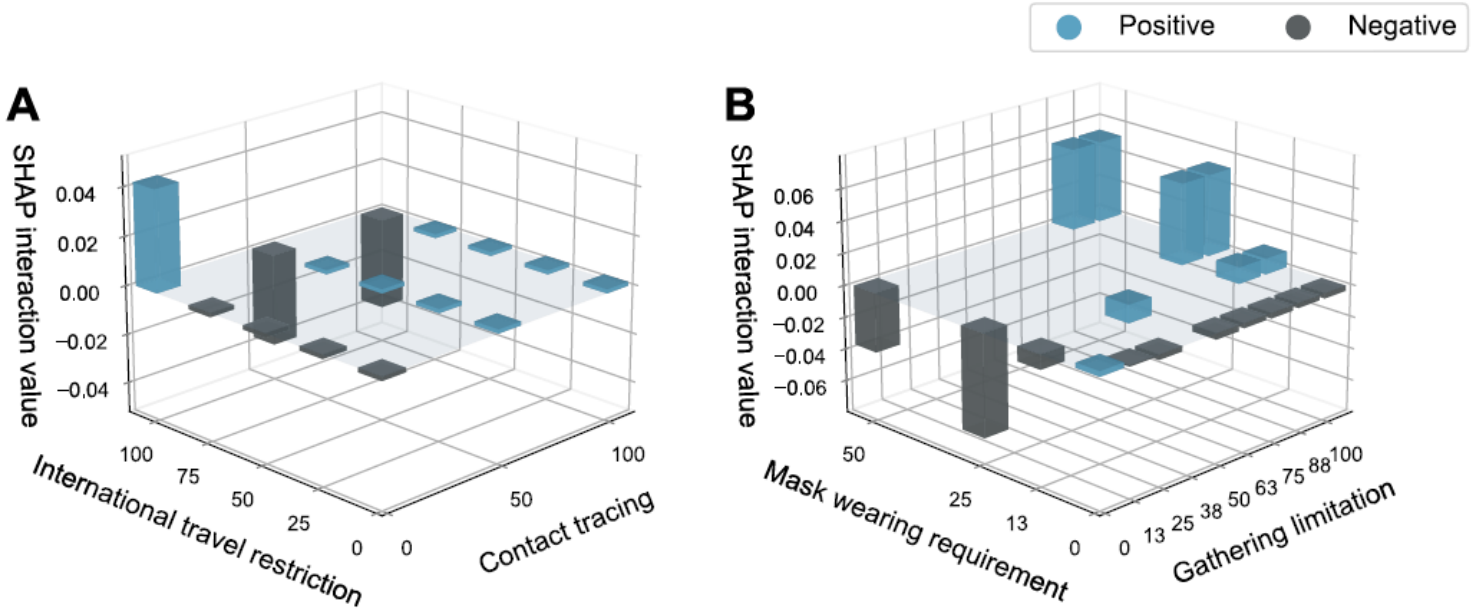

Figure 3

SHAP interaction value of NPIs.

The absence of cubes at the intersection of the X and Y axes was due to a lack of data, which does not mean that there was no interaction effect.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterial.docx