Changing infectious disease incidence in China during the COVID-19 pandemic

Évolution de l'incidence des maladies infectieuses en Chine pendant la pandémie de COVID-19

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Summary

Background
In response to the pandemic of the Coronavirus disease 2019 (COVID-19), each country has implemented its own portfolio of public health interventions to mitigate the impact of the pandemic. During the first pandemic year, preventive interventions were mostly nonpharmaceutical (social distancing, mask-wearing, shelter-in-place, travel restrictions, school closure, etc), while vaccines were being developed.

Research question
How the nonpharmaceutical measures could act on a broad spectrum of infectious diseases, particularly the acute respiratory infections (ARIs).

Methodology
We obtained the etiologically diagnostic data from 142 559 cases with ARIs, who were tested for 8 viral pathogens, and to assess the changes in respiratory infections in China during the first COVID-19 pandemic year compared with pre-pandemic years. Daily case numbers of 31 notifiable infectious diseases at the province level during 2014–2020 were extracted from the China Information System for Disease Control and Prevention (CISDCP). The changes in the incidences of notifiable infectious diseases with different transmission modes before, during, and after the first wave of COVID-19 were quantified.

Results
Test-positive rates of all respiratory viruses decreased during 2020, compared to the average levels during 2012–2019, with changes ranging from −17.2% for respiratory syncytial virus (RSV) to −87.6% for influenza (IFV). Sharp decreases mostly occurred between February and August when massive NPIs remained active, although Human Rhinovirus (HRV) rebounded to the historical level during the summer. While Influenza (IFV) and human metapneumovirus (HMPV) were consistently suppressed year-round, The RSV, human parainfluenza virus (HPIV), human coronavirus (HCoV), human rhinovirus HRV), and human bocavirus (HBoV) resurged and went beyond historical levels during September 2020–January 2021, after NPIs were largely relaxed and schools reopened. Resurgence was more prominent among children <18 years and in northern China. These observations remain valid after accounting for seasonality and long-term trend of each virus. Incidence of 31 major notifiable infectious diseases in China in 2020 to the average level during 2014-2019, controlling for temporal phases defined by NPI intensity levels. Respiratory diseases and gastrointestinal or enteroviral diseases declined more than sexually transmitted or bloodborne diseases and vector-borne or zoonotic diseases. Early pandemic phases with more stringent NPIs were associated with greater reductions in disease incidence. Non-respiratory diseases, such as hand, foot and mouth disease, rebounded substantially towards the end of the year 2020 as the NPIs were relaxed.

Conclusions
Strong NPIs were associated with a broad mitigation effect on infectious diseases. Activities of respiratory viral infections were reduced substantially in the early phases of the COVID-19 pandemic. Lifting of NPIs can lead to resurgence of viral respiratory infections, particularly in children.

Keywords: COVID-19, acute respiratory infection, infectious diseases, nonpharmaceutical interventions, China

Résumé

Contexte
En réponse à la pandémie de coronavirus 2019 (COVID-19), chaque pays a mis en œuvre son propre éventail d'interventions de santé publique pour atténuer l'impact de la pandémie. Au cours de la première année de la pandémie, les interventions préventives étaient principalement non pharmaceutiques (INP) (distanciation sociale, port de masques, hébergement sur place, restrictions de voyage, fermeture des écoles, etc.), tandis que des vaccins étaient en cours de développement.

Question de recherche
Comment les mesures non pharmaceutiques pourraient-elles agir sur un large spectre de maladies infectieuses, en particulier les infections respiratoires aiguës (IRA) ?

Méthodologie
Nous avons obtenu les données de diagnostic étiologique provenant de 142 559 cas d'IRA, testés pour 8 agents pathogènes

viraux, et pour évaluer les changements dans les infections respiratoires en Chine pendant la première année de la pandémie COVID-19 par rapport aux années pré-pandémiques. Les nombres de cas quotidiens de 31 maladies infectieuses à déclaration obligatoire au niveau provincial au cours de la période 2014-2020 ont été extraits du Système d'information chinois pour le contrôle et la prévention des maladies. Les changements dans l'incidence des maladies infectieuses à déclaration obligatoire avec différents modes de transmission avant, pendant et après la première vague de COVID-19 ont été quantifiés.

Résultats

Les taux de tests positifs obtenus pour tous les virus respiratoires ont diminué en 2020 par rapport aux niveaux moyens enregistrés entre 2012 et 2019, avec des variations allant de -17,2 % pour le virus respiratoire syncytial (VRS) à -87,6 % pour le virus influenza (IFV). Les fortes baisses se sont surtout produites entre février et août, lorsque des INP massives sont restées actives, bien que le rhinovirus humain (HRV) ait rebondi à sa valeur historique au cours de l'été. Alors que l'influenza (IFV) et le métapneumovirus humain (HMPV) ont été endigués toute l'année, le VRS, le virus parainfluenza humain (HPIV), le coronavirus humain (HCoV), le rhinovirus humain (HRV) et le bocavirus humain (HBoV) sont réapparus et ont dépassé les niveaux historiques entre septembre 2020 et janvier 2021, après que les INP ont été largement allégées et que les écoles ont réouvert leurs portes. La résurgence était plus importante chez les enfants de moins de 18 ans et dans le nord de la Chine. Ces observations restent valables après prise en compte de la saisonnalité et de la tendance à long terme de chaque virus. Incidence des 31 principales maladies infectieuses à déclaration obligatoire en Chine en 2020 par rapport au niveau moyen de la période 2014-2019, en tenant compte des phases temporelles définies par les niveaux d'intensité des INP. Les maladies respiratoires et les maladies gastro-intestinales ou à entérovirus ont diminué davantage que les maladies sexuellement transmissibles ou à diffusion hématogène et les maladies à transmission vectorielle ou zoonotique. Les premières phases de la pandémie, caractérisées par des INP plus strictes, ont été associées à des réductions plus importantes de l'incidence des maladies. Les maladies non respiratoires, telles que la maladie des mains, des pieds et de la bouche, ont rebondi de manière substantielle vers la fin de l'année 2020, lorsque les INP ont été assouplies.

Conclusions

Des INP fortes ont été associées à un large effet d'atténuation sur les maladies infectieuses. Les activités liées aux infections virales respiratoires ont été considérablement réduites au cours des premières phases de la pandémie de COVID-19. La levée des INP peut entraîner une résurgence des infections respiratoires virales, en particulier chez les enfants.

Mots-clés : COVID-19, infection respiratoire aiguë, maladies infectieuses, interventions non pharmaceutiques, Chine

Introduction

In response to the ongoing pandemic of the coronavirus disease 2019 (COVID-19), a variety of public health interventions have been implemented worldwide to mitigate the impact of the pandemic, including both nonpharmaceutical (social distancing, mask-wearing, shelter-in-place, travel restrictions, school closure, etc.) and pharmaceutical measures (ventilator, antibodies, vaccines, etc.). Studies have explored the impact of the COVID-19–related nonpharmaceutical interventions (NPIs) on respiratory infections[1-5], with most studies not including the time following the lifting of NPIs. To plan preventive programs for emerging and reemerging diseases in the post-pandemic era, it is necessary to understand the broad impact of the NPIs on common endemic infectious diseases other than COVID-19 during the pandemic. Although respiratory pathogens were likely affected the most by the nonpharmaceutical interventions, pathogens with other transmission modes, e.g., gastrointestinal, sexually transmitted, or even vector borne diseases, could have also been affected as the unprecedented changes in human movement and behavioral patterns might have changed exposure levels. For instance, incidence of norovirus was dramatically decreased in nine states in the United States due to NPIs[6]. In China, where COVID-19 was first reported, the trends of common infectious diseases during and after the first epidemic wave have not been systematically investigated at the national level, although studies on a particular disease or in a specific region have been reported[7,8]. In this study, we aim to quantify the changes in the incidences of respiratory infections, and notifiable infectious diseases with different transmission modes before, during, and after the first wave of COVID-19 in the mainland of China and to assess how these changes relate to the public health interventions, using the national surveillance data from 2014 to 2020.

Methods

The surveillance system.

Data from two surveillance systems were used in the current study. A nationwide surveillance for Etiology of Respiratory Infections (SERI) program that has been implemented by China CDC to test a spectrum of common Acute respiratory infection in 31 provinces since 2009. A total of 314 sentinel hospitals covering all 31 provinces across the mainland of China participated in the SERI project. During January 2012–January 2021, nasopharyngeal specimens from a random sample of inpatients and outpatients presenting ARIs at these hospitals were collected prior to any treatment. These samples were tested for the presence of 8 viral pathogens, including influenza virus (IFV), respiratory syncytial virus (RSV), human parainfluenza virus (HPIV), human adenovirus (HAdV), human metapneumovirus (HMPV), human coronavirus (HCoV), human bocavirus (HBoV), and human rhinovirus (HRV) [19]. Influenza virus, RSV, HPIV, HMPV, HCoV, and HRV were tested by reverse transcription– polymerase chain reaction (RT-PCR), and HAdV and HBoV were tested by PCR according to the standard operating protocol (SOP) of surveillance developed by China CDC. SARS-CoV-2–positive patients were excluded from the current analysis. China Information System for Disease Control and Prevention (CISDCP) is an Internet-based real-time disease-reporting system covering 40 notifiable diseases (COVID-19 was included since January 2020)[9]. First established in 2004, this system has evolved to cover 55 077 national health facilities in 397 cities of all 31 provinces in

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the mainland of China. All notifiable infectious diseases were diagnosed according to their standard diagnostic criteria[10]. Only patients with confirmed diagnosis were included in the analysis and the suspected cases were excluded.

Data collection.

Daily case numbers of 31 notifiable infectious diseases at the province level during 2014–2020 were extracted from the CISDCP. Diseases with less than 2000 reported cases during this period were excluded. The remaining 31 diseases were further grouped into four categories: respiratory diseases, gastrointestinal or enteroviral diseases, sexually transmitted or bloodborne diseases, and vector-borne or zoonotic diseases. For each reported case, we extracted age, sex, occupation, city of residence, date of symptom onset, severity of symptoms at diagnosis, type of diagnosis (clinical or laboratory), date of diagnosis, clinical outcome (recovery or death), and date of death if the outcome is death. Demographic statistics at the province level were collected from the National Bureau of Statistics of China (www.stats.gov.cn). Monthly outpatient-visit volumes were collected from the Center for Health Statistics and Information (http://www.nhc.gov.cn/ mohwsbwstjxxzx/s2906/new_list.shtml). It was determined by the National Health Commission of China that the collection of data on notifiable infectious diseases was part of continuing public health surveillance of infectious diseases and was exempt from Institutional Review Board assessment. All the data of cases used in this study were anonymized and personal identification information (e.g., name and street address) is not included in the data, and this study was approved by the Chinese Center for Disease Control and Prevention (202026).

Statistical analysis.

To demonstrate the impact of NPIs on the circulation patterns of the pathogens, we define 3 periods according to the timeline of major intervention events for containing the COVID-19 epidemic in China: 23 January to 7 April 2020 (phase I) when Wuhan city was placed under lockdown, 8 April to 31 August 2020 (phase II) when nationwide NPIs were relaxed while schools remained closed, and 1 September 2020 to 22 January 2021 (phase III) when schools were reopened in most provinces. To attain a controlled comparison with historical levels, the same periods were also defined based on corresponding calendar intervals for pre-pandemic years, starting from 23 January 2012 to 22 January 2020. Positive rates were then compared between the average of pre-pandemic years and the pandemic year for each period, using the percentage change calculated as follows: $[(PR_{t1}(k) - PR_{t0}(k)] / PR_{t0}(k) \times 100\ \%$ where $PR_{t1}(k)$ is the positive rate during phase k of the pandemic year, 23 January 2020 to 22 January 2021, and $PR_{t0}(k)$ is the average positive rate during phase k of the pre-pandemic years, 23 January 2012 to 22 January 2020. Both $PR_{t1}(k)$ and $PR_{t0}(k)$ were age-standardized positive rates based on population proportions of 3 age groups: children aged 0–17 years old, adults aged 18–59 years old, and senior adults aged 60 years and older.

$$PR_{t1}(k) = PR_{t1}^{cr}(k) \times Prop_{0-17} + PR_{t1}^{cr}(k) \times Prop_{18-59} + PR_{t1}^{cr}(k) \times Prop_{\geq 60}$$

$$PR_{t0}(k) = PR_{t0}^{cr}(k) \times Prop_{0-17} + PR_{t0}^{cr}(k) \times Prop_{18-59} + PR_{t0}^{cr}(k) \times Prop_{\geq 60}$$

Specifically, $Prop_{0-17}$, $Prop_{18-59}$, and $Prop_{60}$ indicate the overall proportion of patients aged from 0 to 17, 18 to 59, and over 60 years old, respectively, during the whole pre-pandemic and pandemic years. The comparison was also conducted by age group, sex, geographic region.

Time series of monthly positive rates were plotted and fitted with generalized linear models (GLMs) to quantify the impact of the COVID-19–related NPIs in different periods for each virus, stratified by age groups (0–17 and ≥18 years) and geographic regions. The periods were redefined for the monthly data, with phases I–III corresponding to February–March, April–August, and September–January, respectively. We assumed the number of positive cases in each month followed a beta-binomial distribution. This assumption accounts for overdispersion and also considers the limited numbers of tested specimens when the data are stratified by region and age group. The effect of NPIs was coded by 3 dummy indicators for 4 phases, with phases I–IV corresponding to January 2012–January 2020, February 2020–March 2020, April 2020–August 2020, and September 2020–January 2021, respectively. Calendar year was included as a covariate to capture the long-term trend, and its functional format could be linear, quadratic, or discrete, depending on the Akaike's Information Criterion. When the discrete year effect was chosen—that is, each year had its own intercept—we assumed the years 2019 and 2020 share the same intercept, so that the effect of NPIs is estimable. We reported exponentiated regression coefficients as seasonality-adjusted odds ratios (ORs). Statistical significance was evaluated with 2-sided P values at the level of $\alpha = 5\%$. All statistical analyses were conducted in R software (version 4.0.3; R Development Core Team 2020).

Results

Overall Change Pattern of Positive Rates of respiratory viruses

We extracted diagnostic results and epidemiological data of 104 652 cases with ARIs who were tested for the 8 respiratory viruses over the period from 23 January 2012-31 January 2021. The annual number of tested ARI cases decreased from an average of 12 108 during the pre-pandemic years to 7783 during the pandemic year. The overall activity of the 8 tested viruses, measured by the percentage of specimens positive for any virus, decreased from prepandemic years to the pandemic year by 58.8% (from 37.9% to 15.6%) in phase I, 55.1% (from 30.6% to 13.7%) in phase II, and by 10.3% (from 30.1% to 27.0%) in phase III. Significant reductions in test-positive rate from pre-pandemic years to the pandemic year were noted for all tested viruses (Table 1). The largest drop in annual cumulative positive rate was observed for IFV, a reduction of 87.6% (from 9.94% to 1.23%), followed by 70.6% (1.63% to 0.48%) for HMPV, 47% (3.98% to 2.11%) for HAdV, and 32.3% (5.11% to 3.46%) for HPIV. The change patterns differed across the 3 phases (Table 1). Dramatic reductions in positive rates were seen for most pathogens in both phase I and phase II. Percentage changes above 70% were seen for HMPV (86.5%), IFV (76.8%), HRV (70.3%), and HPIV (70.1%) during phase I and for IFV (92.6%), HPIV (81.3%), HMPV (78%), and HBoV (77.1%) during phase II. Reductions in IFV, HPIV, HAdV, and HBoV were more substantial in phase II compared with phase I, despite partial relaxation of the mass NPIs in phase II. Influenza virus and HMPV were the only 2 with persistent decreases throughout all phases. Positive rates of RSV, HPIV, HCoV, and HBoV, however, rose significantly above historical levels during phase III, when NPIs were largely lifted. including reopening of schools. Human adenovirus returned to the pre-pandemic level (Table 1).

Table 1. Comparison of age-standardized test positive rate (%) of eight respiratory viruses between pre-pandemic years (2012–2019) and the COVID-19 pandemic year (2020) in the mainland of China.

	Overall				Phase I				Phase II				Phase III			
	2012–2019	2020	Relative change	Absolute change*	2012–2019	2020	Relative change	Absolute change*	2012–2019	2020	Relative change	Absolute change*	2012–2019	2020	Relative change	Absolute change*
IFV	9.94	1.23	-87.60%⋆	-8.71⋆	15.23	3.54	-76.80%⋆	-11.69⋆	7.17	0.53	-92.60%⋆	-6.64⋆	9.72	0.95	-90.20%⋆	-8.77⋆
HRV	6.54	5.39	-17.60%⋆	-1.15⋆	6.17	1.83	-70.30%⋆	-4.34⋆	6.86	7.88	14.90%	1.02	6.41	4.56	-28.90%⋆	-1.85. ⋆
RSV	5.57	4.61	-17.20%⋆	-0.96⋆	8.03	3.05	-62.00%⋆	-4.98⋆	3.69	1.84	-50.10%⋆	-1.85⋆	6.1	7.44	22.00%⋆	1.34⋆
HPIV	5.11	3.46	-32.30%⋆	-1.65%⋆	4.48	1.34	-70.10%⋆	-3.14⋆	6.69	1.25	-81.30%⋆	-5.44⋆	3.94	6.06	53.80%⋆	2.12⋆
HAdV	3.98	2.11	-47.00%⋆	-1.87⋆	3.67	1.49	-59.40%⋆	-2.18⋆	4.55	1.44	-68.40%⋆	-3.11⋆	3.61	3.17	-12.20%	-0.44
HCoV	2.31	1.9	-17.70%⋆	-0.41⋆	2.13	1.02	-52.10%⋆	-1.11⋆	3	1.76	-41.30%⋆	-1.24⋆	1.77	2.48	40.10%⋆	0.71⋆
HBoV	1.75	1.5	-14.30%⋆	-0.25⋆	1.05	0.84	-20.00%⋆	-0.21⋆	2.23	0.51	-77.10%⋆	-1.72⋆	1.63	2.46	50.90%⋆	0.83⋆
HMPV	1.63	0.48	-70.60%⋆	-1.15⋆	3.11	0.42	-86.50%⋆	-2.69⋆	1.32	0.29	-78.00%⋆	-1.03⋆	1.16	0.64	-44.80%⋆	-0.52⋆

⋆ Statistically significant changes were found (p-value<0.05 based on chi-square test).

*The absolute change was calculated as positive rate in 2012–2019 minus that in 2020.

†Period I: 23rd Jan to 7th Apr; Period II: 8th Apr to 31st Aug; Period III: 1st Sep to 22nd Jan of the following year. The p-values were based on chi-square test. Blue (red) color indicates statistically significant decrease (increase) of test positive rate during the first pandemic year compared to pre-pandemic year

Overall trend of notifiable diseases by disease category.

The highest average annual incidence during 2014–2019 was seen for gastrointestinal or enteroviral diseases, followed by respiratory diseases, sexually transmitted or bloodborne diseases, and vector-borne or zoonotic diseases (Table 2). The annual incidence of the 31 infectious diseases combined decreased from 573.28 per 100,000 people during 2014–2019 to 428.88 in 2020, with the largest drop in the gastrointestinal or enteroviral diseases from 261.92 to 142.16 per 100,000, a 45.7% reduction, followed by the vector-borne or zoonotic diseases, a 32.5% reduction (Table 2). In Phase I, the nationwide annual incidence of seasonal influenza rose sharply from 8.99 during 2014–2019 to 57.81 per 100,000 in 2020, which drove the increase of the overall respiratory-disease incidence

Table 2. Comparison of crude average annual incidence (/100 000) of 31 notifiable infectious diseases between 2014–2019 and 2020 in the mainland of China.

Disease	Overall		Phase I†		Phase II†		Phase III†		Phase IV†	
	2014–2019	2020	2014–2019	2020	2014–2019	2020	2014–2019	2020	2014–2019	2020
Respiratory diseases	156.24	145.12	15.44	62.99	36.07	25.45	51.89	30.51	52.84	26.17
Seasonal influenza	66.69	82.29	8.99	57.81	17.98	13.49	13.94	4.96	25.79	6.04
Tuberculosis	64.27	51.42	5.06	3.70	14.18	10.29	25.70	21.78	19.33	15.65
Mumps	16.83	9.60	0.93	0.94	2.40	1.39	8.18	3.42	5.32	3.85
Scarlet fever	5.12	1.25	0.34	0.40	0.63	0.11	2.23	0.24	1.91	0.49
Measles	1.59	0.06	0.07	0.01	0.54	0.01	0.85	0.02	0.13	0.02
Pertussis	0.97	0.34	0.03	0.06	0.16	0.14	0.52	0.06	0.25	0.08
Rubella	0.76	0.16	0.02	0.07	0.17	0.03	0.47	0.02	0.10	0.03
Gastrointestinal or enteroviral diseases	261.92	142.16	10.53	8.72	29.44	11.62	143.41	46.19	78.56	75.64
Hand, foot and mouth disease	164.71	56.42	3.56	1.66	11.09	0.71	103.33	7.45	46.74	46.60
Infectious diarrhea	81.49	76.36	6.30	6.57	15.92	9.54	32.22	34.19	27.04	26.07
Bacterial dysentery	8.43	4.19	0.27	0.17	1.04	0.47	4.68	2.29	2.44	1.25
Acute hemorrhagic conjunctivitis	2.79	2.16	0.12	0.12	0.43	0.35	1.31	0.96	0.94	0.73
Hepatitis E	2.04	1.37	0.15	0.10	0.51	0.24	0.79	0.58	0.59	0.45
Hepatitis A	1.51	1.08	0.09	0.07	0.31	0.23	0.61	0.43	0.50	0.34
Typhoid and paratyphoid	0.87	0.56	0.04	0.03	0.13	0.08	0.43	0.27	0.28	0.18
Amoebic dysentery	0.08	0.05	0.004	0.003	0.01	0.01	0.04	0.02	0.02	0.02
Sexually transmitted or bloodborne diseases	148.48	137.08	10.15	10.27	30.30	22.09	60.77	58.57	47.25	46.14
Hepatitis B	75.19	67.57	5.64	5.52	16.23	11.43	30.23	28.60	23.08	22.03
Syphilis	35.11	34.95	2.08	2.35	6.69	5.56	14.78	15.21	11.56	11.83
Hepatitis C	15.85	13.94	1.14	1.05	3.36	2.23	6.42	5.95	4.94	4.70
HIV/AIDS	13.74	12.97	0.75	0.87	2.55	2.09	5.80	5.61	4.65	4.41
Gonorrhea	8.58	7.64	0.53	0.49	1.48	0.78	3.54	3.20	3.03	3.16
Vector-borne or zoonotic diseases	6.64	4.48	0.30	0.23	1.09	0.71	2.79	2.17	2.46	1.39
Dengue	1.08	0.06	0.002	0.004	0.01	0.003	0.16	0.01	0.91	0.04
Schistosomiasis	0.56	0.003	0.01	0.0001	0.09	0.0005	0.19	0.001	0.27	0.001
Malaria	0.22	0.08	0.01	0.02	0.04	0.02	0.10	0.02	0.06	0.02
Typhus	0.09	0.09	0.0032	0.003	0.01	0.01	0.04	0.04	0.04	0.03
Japanese encephalitis	0.08	0.02	0.00006	0	0.0003	0.00007	0.06	0.01	0.02	0.01
Brucellosis	3.41	3.36	0.19	0.16	0.73	0.57	1.79	1.77	0.70	0.87
Hemorrhagic fever with renal syndrome	0.78	0.59	0.05	0.04	0.13	0.07	0.27	0.19	0.32	0.29
Hydatid diseases.	0.32	0.24	0.03	0.02	0.07	0.03	0.12	0.10	0.11	0.09
Rabies	0.04	0.02	0.003	0.001	0.01	0.002	0.02	0.01	0.02	0.01
Anthrax	0.03	0.02	0.0007	0.0009	0.003	0.002	0.02	0.01	0.01	0.01
Leptospirosis	0.02	0.03	0.0002	0.0002	0.0009	0.0003	0.01	0.01	0.01	0.02

† Phase I: Jan 1 to Jan 22; Phase II: Jan 23 to Apr 7; Phase III: Apr 8 to Aug 31; Phase IV: Sep 1 to Dec 31.

All the incidences in the table were crude incidence rate without age adjustment.

The denominator to calculate the incidence of 2014–2019 was 1383.7 million and the denominator to calculate the incidence of 2020 was 1403.9 million.

Table 3. GLM-estimated odds ratios (OR) for the odds of a positive test between the pandemic year 2020 and pre-pandemic years 2012–2019 within each of the three period and for each of the eight respiratory viruses. Statistically significant increases (decreases) were colored in red (blue).

Virus		Phase I†		Phase II†		Phase III†	
		OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Region							
South	HAdV	0.05 (0.01–0.34)	0.002	0.23 (0.14–0.37)	<0.001	0.51 (0.34–0.76)	<0.001
	HBoV	1.73 (0.61–4.87)	0.302	0.21 (0.09–0.48)	<0.001	0.94 (0.54–1.63)	0.828
	HCoV	0.22 (0.05–0.92)	0.038	0.49 (0.26–0.92)	0.027	1.48 (0.89–2.48)	0.134
	HMPV	0‡		0.4 (0.17–0.94)	0.036	0.91 (0.42–1.98)	0.820
	IFV	0.09 (0.03–0.23)	<0.001	0.19 (0.10–0.36)	<0.001	0.23 (0.12–0.44)	<0.001
	HPIV	0.38 (0.16–0.93)	0.035	0.28 (0.17–0.47)	<0.001	1.14 (0.77–1.69)	0.517
	HRV	0.46 (0.22–0.98)	0.043	1.40 (1.02–1.94)	0.040	0.59 (0.39–0.89)	0.012
	RSV	0.50 (0.22–1.11)	0.089	0.66 (0.38–1.15)	0.14	1.54 (1.04–2.28)	0.031
North	HAdV	0.58 (0.26–1.30)	0.187	0.21 (0.09–0.50)	<0.001	1.09 (0.61–1.96)	0.763
	HBoV	0.49 (0.06–3.65)	0.482	0.77 (0.29–2.03)	0.593	3.74 (1.95–7.19)	<0.001
	HCoV	1.26 (0.54–2.90)	0.594	1.46 (0.82–2.58)	0.199	3.62 (1.97–6.64)	<0.001
	HMPV	0.17 (0.04–0.70)	0.014	0.16 (0.04–0.68)	0.013	0.52 (0.16–1.63)	0.259
	IFV	0.28 (0.12–0.68)	0.004	0.10 (0.02–0.42)	0.002	0.08 (0.02–0.32)	<0.001
	HPIV	0.69 (0.28–1.70)	0.420	0.10 (0.03–0.32)	<0.001	2.73 (1.67–4.48)	<0.001
	HRV	0.14 (0.02–0.99)	0.049	1.11 (0.65–1.91)	0.707	2.48 (1.49–4.12)	<0.001
	RSV	0.26 (0.08–0.84)	0.024	0.11 (0.01–0.79)	0.029	1.71 (1.04–2.81)	0.033
Age groups							
0–17 years	HAdV	0.31 (0.11–0.87)	0.027	0.22 (0.12–0.40)	<0.001	0.64 (0.41–0.99)	0.046
	HBoV	1.56 (0.55–4.46)	0.407	0.26 (0.13–0.52)	<0.001	1.66 (1.08–2.55)	0.021
	HCoV	0.71 (0.22–2.34)	0.578	0.93 (0.53–1.64)	0.805	2.09 (1.26–3.46)	0.004
	HMPV	0.10 (0.01–0.75)	0.025	0.23 (0.08–0.62)	0.004	0.75 (0.39–1.47)	0.405
	IFV	0.17 (0.05–0.54)	0.003	0.14 (0.05–0.38)	<0.001	0.17 (0.08–0.39)	<0.001
	HPIV	0.27 (0.08–0.85)	0.026	0.12 (0.05–0.27)	<0.001	2.08 (1.49–2.90)	<0.001
	HRV	0.62 (0.25–1.57)	0.316	1.91 (1.39–2.62)	<0.001	1.38 (0.96–1.97)	0.078
	RSV	0.37 (0.15–0.91)	0.030	0.64 (0.34–1.20)	0.168	1.93 (1.34–2.78)	<0.001
≥ 18 years	HAdV	0.21 (0.07–0.63)	0.005	0.29 (0.14–0.62)	0.001	0.77 (0.37–1.58)	0.469
	HBoV	0.47 (0.06–3.75)	0.478	0.85 (0.24–3.05)	0.802	0‡	
	HCoV	0.61 (0.24–1.51)	0.283	0.76 (0.43–1.34)	0.338	2.23 (1.22–4.07)	0.009
	HMPV	0.08 (0.01–0.58)	0.012	0.47 (0.16–1.37)	0.168	0.43 (0.06–2.92)	0.384
	IFV	0.16 (0.06–0.42)	<0.001	0.20 (0.08–0.46)	<0.001	0.14 (0.05–0.40)	<0.001
	HRV	0.24 (0.09–0.68)	0.007	0.73 (0.45–1.19)	0.207	0.48 (0.26–0.87)	0.016
	RSV	0.38 (0.14–1.05)	0.062	0.21 (0.05–0.88)	0.033	0.81 (0.35–1.87)	0.623

* Phase I: Feb–Mar, 2020; Phase II: Apr–Aug, 2020; Phase III: Sep, 2020 – Jan, 2021
† IFV, influenza virus; HRV, human rhinovirus; RSV, respiratory syncytial virus; HPIV, human parainfluenza virus; HAdV, human adenovirus; HCoV, human coronavirus; HBoV, human bocavirus; HMPV, human metapneumovirus.
‡ When OR=0, the 95% CI and p-value were not calculated.

(Table 2). Small increases were also seen for scarlet fever, pertussis, and rubella in Phase I. In contrast, disease-specific incidences all decreased during phases II-IV in 2020. The largest decreases were associated with seasonal influenza during Phase III (13.94 vs. 4.96 per 100,000) and Phase IV (25.79 vs. 6.04 per 100,000) (Table 2).

Change Pattern of Positive Rates of respiratory viruses by demographic

Positive rates of IFV, HPIV, and HMPV decreased significantly from pre-pandemic years to the pandemic year in all 3 age groups (Figure 1). For HRV, RSV, and HBoV, positive rates were significantly reduced in adults (≥18 years) but not in children (<18 years). The declines in positive rates during the first 2 phases were similar in all 3 age groups, except for the increased activity of HRV among children during phase II. During phase III, the activities of RSV, HPIV, HCoV, and HBoV among children resurged to be substantially above historical levels, and the circulation of HRV, HAdV, and HMPV also nearly reached historical levels. In particular, the higher than historical levels of RSV, HPIV, HCoV, and HBoV in phase III observed for the whole population were mostly attributed to their resurgence in children (Figure 1A). Among adults aged 18 years and older, activities of HPIV, HAdV, and HCoV also returned to their historical levels during period III (Figure 1B, C). The change patterns were largely consistent between the 2 sexes (Figure 2A); however, they did differ to some extent between northern China and southern China, especially during phase III. Positive rates of HRV and HAdV increased significantly in the north but decreased significantly in the south during phase III (Figure 2B). In addition, more increases in RSV, HPIV, HCoV, and HBoV were seen in the north than in the south during phase III. No regional difference was seen for IFV and HMPV.

Effects of NPIs on Seasonality and Activity of Respiratory Viruses

We fitted GLMs to temporal trajectories of monthly positive rates of the viruses by age group. As the change patterns of virus-positive rate were similar between adults (18-59 years) and older adults (≥60 years) in all phases (Figure 1B and C). We therefore combined the 2 adult age groups to model the specific impact of NPIs during the COVID-19 pandemic on a finer time scale (monthly data), which also helps to ensure adequate sample sizes. For viruses peaking in late winter, spring, or early summer, their expected peaks in the first half of 2020 were either suppressed or delayed, consistent with the massive strict NPIs during phase I. The peaks of IFV, HAdV, HMPV, and RSV were suppressed or flattened. The peaks of HPIV and HBoV were delayed to phase III among children. The only exception was for HRV, for which the actual activity during the summer and autumn of 2020 exceeded model-projected levels among children for the hypothetical scenario. During the second half of 2020, most viruses went back to or beyond historical levels, except for IFV.

The pattern of the phase-specific ORs (Table 3) was further revealed to be largely

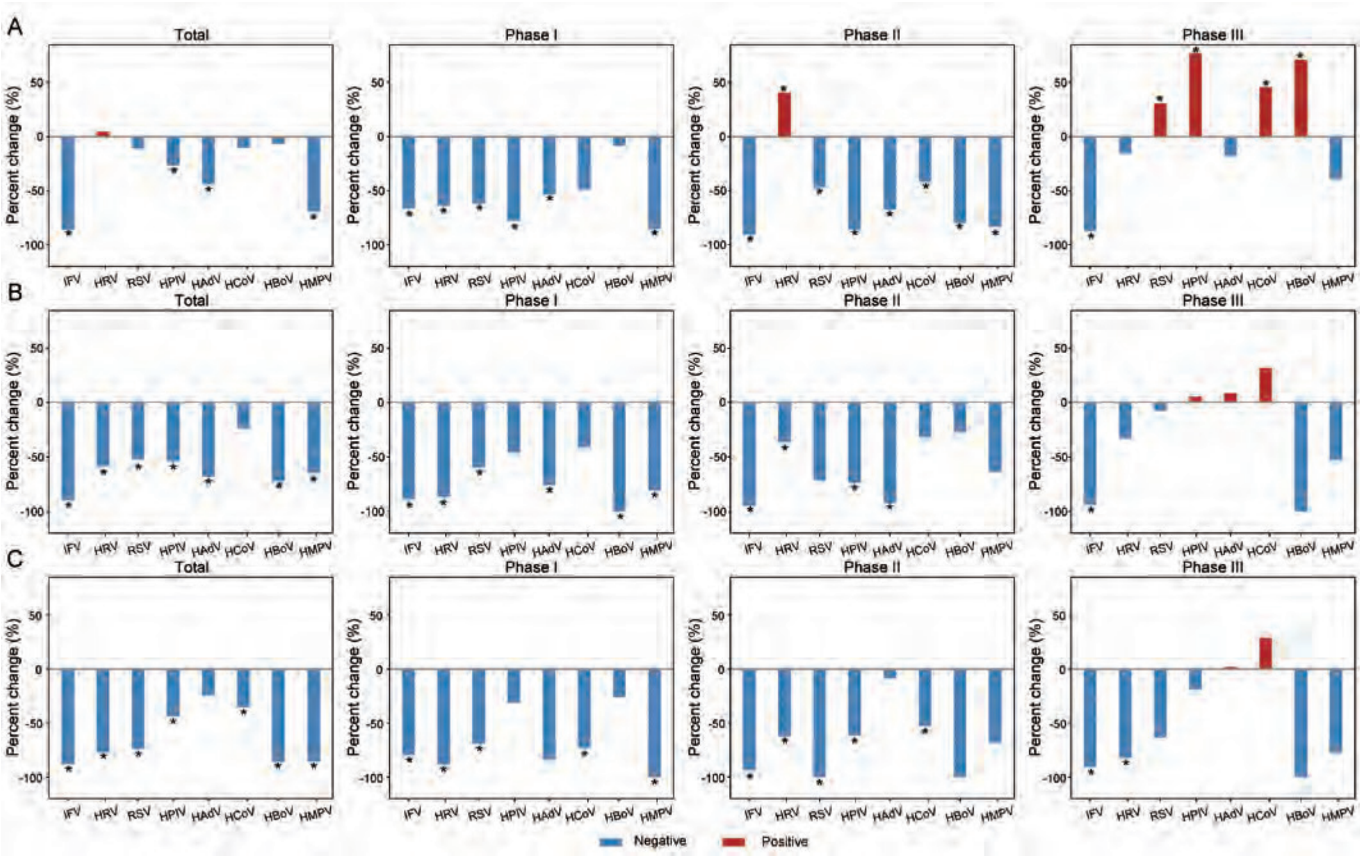

Figure 1. Percent change of test positive rate during the COVID-19 pandemic year 2020 compared to the average incidences during pre-pandemic years 2012-2019 for each of three predefined periods and stratified by age group. (A) Children <18 years old; (B) Younger adults 18-59 years old; (C) Older adults ≥60 years old. Eight respiratory pathogens were investigated: influenza virus (IFV), human rhinovirus (HRV), respiratory syncytial virus (RSV), human parainfluenza virus (HPIV), human adenovirus (HAdV), human coronavirus (HCoV), human bocavirus (HBoV), and human metapneumovirus (HMPV). Red and blue bars indicate positive and negative percent changes, respectively. Statistically significant changes were marked with asterisks.

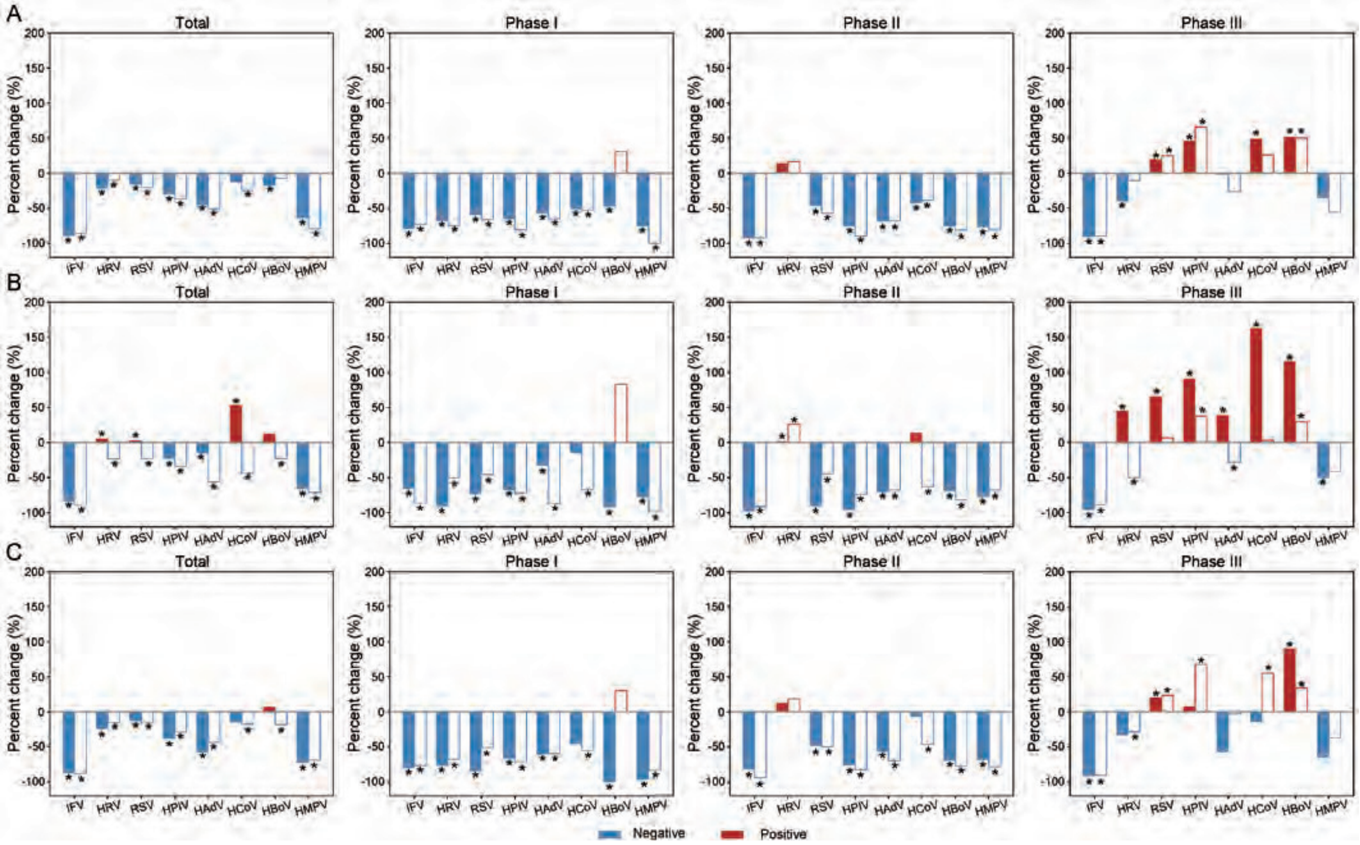

Figure 2. Percent change of test positive rate during the COVID-19 pandemic year 2020 compared to the average incidences during pre-pandemic years 2012-2019 for each of three predefined periods and stratified by sex, region and clinical type. (A) Males (solid) vs. females (unfilled); (B) North (solid) vs. South (unfilled); (C) Pneumonia cases (solid) vs. Non-pneumonia cases (unfilled). Eight respiratory pathogens were investigated: influenza virus (IFV), human rhinovirus (HRV), respiratory syncytial virus (RSV), human parainfluenza virus (HPIV), human adenovirus (HAdV), human coronavirus (HCoV), human bocavirus (HBoV), and human metapneumovirus (HMPV). Red and blue bars indicate positive and negative percent changes, respectively. Statistically significant changes were marked with asterisks.

consistent with that of the percentage changes in Figures 1 and 2, with some subtle differences. During phase I or phase II, the ORs of NPIs on most viruses were observed to be less than 1. Only HRV showed a strong early resurgence in phase II, especially in the south (OR: 1.40; 95% CI: 1.02–1.94) and among children (OR: 1.91; 95% CI: 1.39–2.62). During phase III, most viruses renewed their activities, especially in the north, with the odds of positive samples more than doubled for HBoV (OR: 3.74), HCoV (OR: 3.62), HPIV (OR: 2.73), and HRV (OR: 2.48). Respiratory syncytial virus significantly increased its activity in both the south and the north, but age-standardized percentage changes shown in Figure 2B failed to capture the increase in the south. During phase III, HCoV resurged sharply in both age groups, and children additionally experienced a substantial resurgence of HBoV, HPIV, and RSV. Influenza virus was consistently suppressed in all periods, regardless of region or age, and suppression of HAdV also persisted in the south and among children.

Discussion

By exploring the national surveillance data of ARIs and notifiable diseases in China during the process of NPI against COVID-19, we found that the spread and seasonality of most of these pathogens were interrupted during 2020, particularly during weeks 5–15 (phases I–II) when massive stringent NPIs were active. Transmission activities of HMPV, IFV, and HPIV were more suppressed than other tested respiratory viruses. However, during phase III when most NPIs were lifted and schools were reopened, HRV, RSV, HPIV, HCoV, and HBoV resurged quickly, especially in children. The buildup of susceptibility during the control periods might have contributed to the resurgence[11]. These observations verified the critical role of school-aged children in spreading respiratory infections. In contrast to most other respiratory pathogens, the activity of influenza viruses remained lower than historical levels consistently throughout the pandemic year, regardless of region and age group. Similar situations were found in other countries in both northern and southern hemispheres [12]. A possible reason is the greatly reduced regional and international travel during the pandemic. It has long been recognized that domestic and international air travel likely plays an important role in the spread of IFV from the tropical zones towards subtropical and temperate zones in winters [13-15]. Towards the end of 2020, international travel had far from recovered. Although domestic travel essentially returned to normal in many countries, some NPIs such as mask wearing and social distancing were still in place in transportation hubs, which could be highly effective against influenza, which is mainly transmitted via droplets and fomites. For example, a study found that wearing masks could effectively block the transmission of IFV and HCoV but might be less effective in blocking HRV[16]. In addition to travel restrictions and NPIs, interactions among respiratory viruses might have also played a role. For example, infection with HRV was shown to reduce the risk of infection with IFV [17,18]. These results may shed light on future immunization campaigns in the post–COVID-19 era.

COVID-19-related NPIs likely affected the transmission of other infectious diseases mainly through reducing human-to-human contact (affecting respiratory diseases, gastrointestinal or enteroviral diseases, and sexually transmitted or bloodborne diseases) and environmental exposure (affecting gastrointestinal or enteroviral diseases and vector-borne or zoonotic diseases). Soon after Wuhan's lockdown was lifted in April, NPIs were gradually relaxed and socioeconomic activities resumed nationwide, leading to resurgence of some diseases, with the most typical example as HFMD. The rebound of HFMD in Phase IV was likely a result of reopening of schools and daycares in September.

Less variation of sexually transmitted or bloodborne diseases was observed in comparison with respiratory diseases and gastrointestinal or enteroviral diseases, possibly due to the difference in their transmission modes. However, the incidences of most sexually transmitted or blood-borne diseases did decline, particularly in Phase II when human movement was strictly restricted. historical levels in phases III and IV in southern China. The rebound might be related to the lifting of travel restrictions and renewal of socioeconomic activities. NPIs likely modulated the incidences of vector-borne or zoonotic diseases in at least two more ways in addition to altering healthcare-seeking behavior. The restrictions on human mobility inevitably reduced people's outdoor activities and hence lowered their exposure to vectors and animal hosts of vector-borne or zoonotic diseases. Meanwhile, restrictions and screening of international travelers dramatically reduced the number of imported cases. Dengue fever and malaria, two mosquito-borne diseases, are examples of the latter mechanism. The two diseases are currently not endemic in China but mainly imported by international travelers in winter seasons. Low incidences persisted though the end of the year as border control remained tight. The resurgence of zoonotic diseases such as brucellosis and typhus could be a result of the recovering work activity of herdsmen and farmers. Educational programs and personal-protection equipment are needed to reduce their exposure. Our study highlights the broad-spectrum correlations of NPIs with the spread of infectious diseases. However, strongly disruptive NPIs such as travel and gathering bans are generally not affordable as a long-term solution for their negative impact on economic and social activities. A combination of less disruptive NPIs, such as social distancing and mask-wearing for large indoor gathering and mass-transportation vehicles, with efficacious vaccines and therapies, is likely a better solution than relying on either one alone. For the diseases insensitive to less-disruptive NPIs such as HFMD, development and evaluation of new NPIs should be encouraged. Finally, the variation of reported incidences of chronic infectious diseases such as HIV/AIDS and TB could be more related to underreporting than to the NPIs, and potential future increase in disease progression and mortality due to delayed diagnosis and treatment during the pandemic needs to be closely monitored.

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