Coronavirus disease 2019 (COVID-19)
Situation Report – 77

World Health Organization

Data as reported by national authorities by 10:00 CET 6 April 2020

HIGHLIGHTS

- One new country/territory/area reported cases of COVID-19 in the past 24 hours: South Sudan.
- At a joint press conference and in a co-authored opinion piece, the WHO Director-General and IMF Managing Director reiterated the importance of saving lives and saving livelihoods and made it clear that the trade-off between saving lives or jobs is a false dilemma. The press conference remarks are here, and the op-ed here.
- Almost 90 per cent of the world's students are now affected by nationwide school closures – that's more than 1.5 billion children and young people. Together with UNICEF and the International Publishers Association, the World Health Organization has launched the 'Read the World' children's reading initiative. More information on this initiative can be found here. WHO has also published advice for parenting during the COVID-19 pandemic, available here.

SITUATION IN NUMBERS
total (new) cases in last 24 hours

Globally
1 210 956 confirmed (77 200)
67 594 deaths (4810)

Western Pacific Region
112 522 confirmed (1126)
3861 deaths (23)

European Region
655 339 confirmed (33 932)
49 479 deaths (3063)

South-East Asia Region
8828 confirmed (1012)
344 deaths (42)

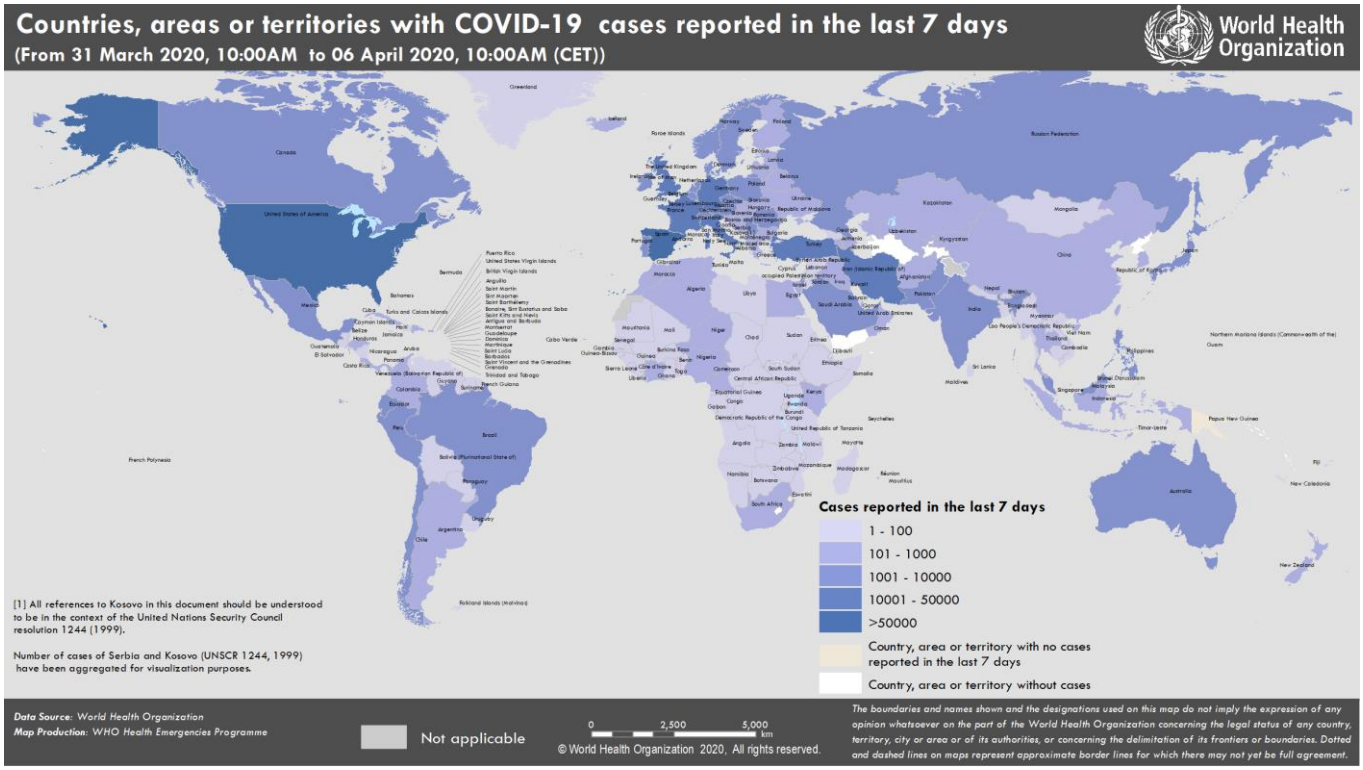
Eastern Mediterranean Region
74 347 confirmed (4054)
3976 deaths (182)

Region of the Americas
352 592 confirmed (36 878)
9680 deaths (1493)

African Region
6616 confirmed (198)
243 deaths (7)

WHO RISK ASSESSMENT
Global Level Very High

Figure 1. Countries, territories or areas with reported confirmed cases of COVID-19, 6 April 2020



SURVEILLANCE

Table 1. Countries, territories or areas with reported laboratory-confirmed COVID-19 cases and deaths. Data as of 6 April 2020*

Reporting Country/ Territory/Area†	Total confirmed ‡ cases	Total confirmed new cases	Total deaths	Total new deaths	Transmission classification§	Days since last reported case
Western Pacific Region						
China	83005	75	3340	2	Local transmission	0
Republic of Korea	10284	47	186	3	Local transmission	0
Australia	5744	109	36	2	Local transmission	0
Malaysia	3662	179	61	4	Local transmission	0
Japan	3654	383	73	3	Local transmission	0
Philippines	3246	152	152	8	Local transmission	0
Singapore	1309	120	6	1	Local transmission	0
New Zealand	911	39	1	0	Local transmission	0
Viet Nam	241	1	0	0	Local transmission	0
Brunei Darussalam	135	0	1	0	Local transmission	1
Cambodia	114	0	0	0	Local transmission	2
Mongolia	14	0	0	0	Imported cases only	4
Fiji	12	0	0	0	Local transmission	1
Lao People's Democratic Republic	11	1	0	0	Local transmission	0
Papua New Guinea	1	0	0	0	Imported cases only	16
Territories**						
Guam	112	19	4	0	Local transmission	0
French Polynesia	41	1	0	0	Local transmission	0
New Caledonia	18	0	0	0	Local transmission	3
Northern Mariana Islands (Commonwealth of the)	8	0	1	0	Local transmission	3
European Region						
Spain	130759	6023	12418	674	Local transmission	0
Italy	128948	4316	15889	527	Local transmission	0
Germany	95391	3677	1434	92	Local transmission	0
France	69607	1850	8064	518	Local transmission	0
The United Kingdom	47810	5903	4934	621	Local transmission	0
Turkey	27069	3135	574	73	Local transmission	0
Switzerland	21065	576	715	49	Local transmission	0
Belgium	19691	1260	1447	164	Local transmission	0
Netherlands	17851	1224	1766	115	Local transmission	0
Austria	11983	217	204	18	Local transmission	0
Portugal	11278	754	295	29	Local transmission	0
Israel	8018	429	46	4	Local transmission	0
Sweden	6830	387	401	28	Local transmission	0
Norway	5640	130	58	8	Local transmission	0
Russian Federation	5389	658	45	2	Local transmission	0
Ireland	5111	507	158	21	Local transmission	0

Czechia	4587	115	67	8	Local transmission	0
Denmark	4369	292	179	18	Local transmission	0
Poland	4102	475	94	15	Local transmission	0
Romania	3864	251	148	7	Local transmission	0
Luxembourg	2804	75	36	5	Local transmission	0
Finland	1927	45	28	3	Local transmission	0
Serbia	1908	284	51	12	Local transmission	0
Greece	1735	62	73	5	Local transmission	0
Iceland	1486	69	4	0	Local transmission	0
Ukraine	1319	68	38	6	Local transmission	0
Croatia	1182	56	15	3	Local transmission	0
Estonia	1097	79	15	2	Local transmission	0
Slovenia	997	20	28	6	Local transmission	0
Republic of Moldova	864	112	15	3	Local transmission	0
Lithuania	811	40	13	4	Local transmission	0
Armenia	746	0	7	0	Local transmission	1
Hungary	744	11	38	4	Local transmission	0
Bosnia and Herzegovina	662	30	21	0	Local transmission	0
Kazakhstan	604	73	5	0	Local transmission	0
Azerbaijan	584	72	5	0	Local transmission	0
Belarus	562	122	8	4	Local transmission	0
North Macedonia	555	72	18	1	Local transmission	0
Latvia	533	24	1	0	Local transmission	0
Bulgaria	531	28	20	3	Local transmission	0
Andorra	523	57	17	0	Local transmission	0
Slovakia	485	14	0	0	Local transmission	0
Cyprus	446	20	14	3	Local transmission	0
Uzbekistan	390	92	2	0	Local transmission	0
Albania	377	44	21	3	Local transmission	0
San Marino	266	7	32	0	Local transmission	0
Malta	234	21	0	0	Local transmission	0
Kyrgyzstan	216	69	4	3	Local transmission	0
Montenegro	203	6	2	0	Local transmission	0
Georgia	188	18	2	1	Local transmission	0
Liechtenstein	78	1	1	0	Under investigation	0
Monaco	37	0	0	0	Local transmission	5
Holy See	7	0	0	0	Under investigation	3
Territories**						
Faroe Islands	181	0	0	0	Local transmission	1
Jersey	155	32	3	0	Local transmission	0
Guernsey	154	18	3	1	Local transmission	0
Kosovo[1]	145	5	1	0	Local transmission	0
Isle of Man	127	1	1	0	Local transmission	0
Gibraltar	103	5	1	0	Local transmission	0
Greenland	11	1	0	0	Under investigation	0
South-East Asia Region						
India	4067	693	109	32	Local transmission	0
Indonesia	2273	181	198	7	Local transmission	0

Thailand	2169	102	23	3	Local transmission	0
Sri Lanka	176	17	5	0	Local transmission	0
Bangladesh	88	18	8	0	Local transmission	0
Myanmar	21	1	1	0	Local transmission	0
Maldives	19	0	0	0	Local transmission	3
Nepal	9	0	0	0	Local transmission	1
Bhutan	5	0	0	0	Imported cases only	3
Timor-Leste	1	0	0	0	Imported cases only	16
Eastern Mediterranean Region						
Iran (Islamic Republic of)	58226	2483	3603	151	Local transmission	0
Pakistan	3277	397	50	5	Local transmission	0
Saudi Arabia	2463	93	34	5	Local transmission	0
United Arab Emirates	1799	294	10	0	Local transmission	0
Qatar	1604	279	4	1	Local transmission	0
Egypt	1173	103	78	7	Local transmission	0
Morocco	1113	153	71	5	Local transmission	0
Iraq	961	83	61	5	Local transmission	0
Bahrain	700	12	4	0	Local transmission	0
Tunisia	574	21	22	3	Local transmission	0
Kuwait	556	0	1	0	Local transmission	1
Lebanon	527	0	18	0	Local transmission	1
Jordan	345	22	5	0	Local transmission	0
Afghanistan	337	38	7	0	Local transmission	0
Oman	331	33	2	0	Local transmission	0
Djibouti	59	8	0	0	Local transmission	0
Syrian Arab Republic	19	3	2	0	Local transmission	0
Libya	18	1	1	0	Local transmission	0
Sudan	12	2	2	0	Local transmission	0
Somalia	7	0	0	0	Local transmission	2
Territories**						
occupied Palestinian territory	246	29	1	0	Local transmission	0
Region of the Americas						
United States of America	307318	33510	8358	1338	Local transmission	0
Canada	13904	966	231	17	Local transmission	0
Brazil	10278	1222	432	73	Local transmission	0
Chile	4471	310	34	7	Local transmission	0
Ecuador	3465	0	172	0	Local transmission	1
Mexico	1890	202	79	19	Local transmission	0
Panama	1801	128	46	5	Local transmission	0
Peru	1746	151	73	12	Local transmission	0
Dominican Republic	1488	0	68	0	Local transmission	2
Argentina	1451	98	44	2	Local transmission	0
Colombia	1406	139	32	7	Local transmission	0
Costa Rica	435	19	2	0	Local transmission	0
Uruguay	400	14	5	1	Local transmission	0
Cuba	320	32	8	2	Local transmission	0
Honduras	268	4	22	7	Local transmission	0

Bolivia (Plurinational State of)	157	18	10	0	Local transmission	0
Venezuela (Bolivarian Republic of)	144	0	3	0	Local transmission	3
Paraguay	104	8	3	0	Local transmission	0
Trinidad and Tobago	103	3	6	0	Local transmission	0
El Salvador	62	6	3	0	Local transmission	0
Guatemala	61	11	2	1	Local transmission	0
Jamaica	55	2	3	0	Local transmission	0
Barbados	51	0	0	0	Local transmission	1
Bahamas	28	4	4	1	Local transmission	0
Guyana	24	1	4	0	Local transmission	0
Haiti	21	3	0	0	Imported cases only	0
Saint Lucia	14	1	0	0	Local transmission	0
Grenada	12	0	0	0	Local transmission	1
Dominica	11	0	0	0	Local transmission	10
Suriname	10	0	0	0	Local transmission	2
Saint Kitts and Nevis	9	0	0	0	Imported cases only	1
Antigua and Barbuda	7	0	0	0	Local transmission	9
Belize	5	1	0	0	Local transmission	0
Nicaragua	5	0	1	0	Imported cases only	4
Saint Vincent and the Grenadines	3	0	0	0	Imported cases only	2
Territories**						
Puerto Rico	452	0	18	0	Local transmission	1
Martinique	145	0	3	0	Local transmission	1
Guadeloupe	134	4	7	0	Local transmission	0
French Guiana	66	4	0	0	Local transmission	0
Aruba	64	0	0	0	Local transmission	1
United States Virgin Islands	42	2	0	0	Local transmission	0
Bermuda	37	2	0	0	Local transmission	0
Cayman Islands	35	7	1	0	Local transmission	0
Saint Martin	29	5	2	0	Under investigation	0
Sint Maarten	23	0	2	0	Imported cases only	2
Curaçao	11	0	1	0	Imported cases only	6
Montserrat	6	0	0	0	Imported cases only	1
Saint Barthélemy	6	0	0	0	Under investigation	6
Turks and Caicos Islands	5	0	1	1	Local transmission	6
Anguilla	3	0	0	0	Local transmission	2
British Virgin Islands	3	0	0	0	Imported cases only	5
Bonaire, Sint Eustatius and Saba	2	0	0	0	Imported cases only	2
Falkland Islands (Malvinas)	2	1	0	0	Under investigation	0
African Region						
South Africa	1655	70	11	2	Local transmission	0
Algeria	1251	0	130	0	Local transmission	1
Cameroon	555	0	9	0	Local transmission	1

Burkina Faso	302	0	15	0	Local transmission	1
Côte d'Ivoire	245	0	2	0	Local transmission	1
Mauritius	227	31	7	0	Local transmission	0
Senegal	222	3	2	0	Local transmission	0
Nigeria	208	0	4	0	Local transmission	1
Ghana	205	0	5	0	Local transmission	1
Democratic Republic of the Congo	161	13	18	2	Local transmission	0
Niger	144	0	8	0	Local transmission	1
Kenya	142	20	4	0	Local transmission	0
Guinea	111	0	0	0	Local transmission	1
Rwanda	102	0	0	0	Local transmission	1
Madagascar	77	7	0	0	Local transmission	0
Uganda	48	0	0	0	Local transmission	1
Congo	45	0	5	0	Local transmission	1
Togo	44	4	3	0	Local transmission	0
Ethiopia	43	5	1	1	Local transmission	0
Mali	39	0	4	0	Local transmission	1
Zambia	39	0	1	0	Local transmission	3
Eritrea	29	9	0	0	Local transmission	0
Benin	22	9	0	0	Local transmission	0
United Republic of Tanzania	22	2	1	0	Local transmission	0
Gabon	21	0	1	0	Imported cases only	2
Guinea-Bissau	18	0	0	0	Imported cases only	1
Equatorial Guinea	16	0	0	0	Local transmission	1
Namibia	16	2	0	0	Local transmission	0
Angola	14	4	2	0	Imported cases only	0
Liberia	13	3	3	2	Local transmission	0
Mozambique	10	0	0	0	Local transmission	4
Seychelles	10	0	0	0	Imported cases only	4
Central African Republic	9	0	0	0	Local transmission	1
Chad	9	2	0	0	Imported cases only	0
Eswatini	9	0	0	0	Imported cases only	9
Zimbabwe	9	0	1	0	Local transmission	2
Mauritania	6	0	1	0	Imported cases only	2
Sierra Leone	6	2	0	0	Imported cases only	0
Cabo Verde	5	0	1	0	Imported cases only	9
Botswana	4	0	1	0	Imported cases only	3
Gambia	4	0	1	0	Imported cases only	3
Malawi	4	1	0	0	Local transmission	0
Burundi	3	0	0	0	Local transmission	2
South Sudan	1	1	0	0	Under investigation	0
Territories**						
Réunion	344	10	0	0	Local transmission	0
Mayotte	147	0	2	0	Local transmission	1
Subtotal for all regions	**1 210244**	**77 200**	**67 583**	**4810**		
International	712	0	11	0	Local transmission	21

conveyance (Diamond Princess)						
Grand total	**1 210956**	**77 200**	**67 594**	**4810**		

*Numbers include both domestic and repatriated cases

†The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

‡Case classifications are based on WHO case definitions for COVID-19.

§Transmission classification is based on WHO analysis of available official data and may be subject to reclassification as additional data become available. Countries/territories/areas experiencing multiple types of transmission are classified in the highest category for which there is evidence; they may be removed from a given category if interruption of transmission can be demonstrated. It should be noted that even within categories, different countries/territories/areas may have differing degrees of transmission as indicated by the differing numbers of cases and other factors. Not all locations within a given country/territory/area are equally affected.

Terms:

- **Community transmission** is evidenced by the inability to relate confirmed cases through chains of transmission for a large number of cases, or by increasing positive tests through sentinel samples (routine systematic testing of respiratory samples from established laboratories).
- **Local transmission** indicates locations where the source of infection is within the reporting location.
- **Imported cases only** indicates locations where all cases have been acquired outside the location of reporting.
- **Under investigation** indicates locations where type of transmission has not been determined for any cases.
- **Interrupted transmission** indicates locations where interruption of transmission has been demonstrated (details to be determined)

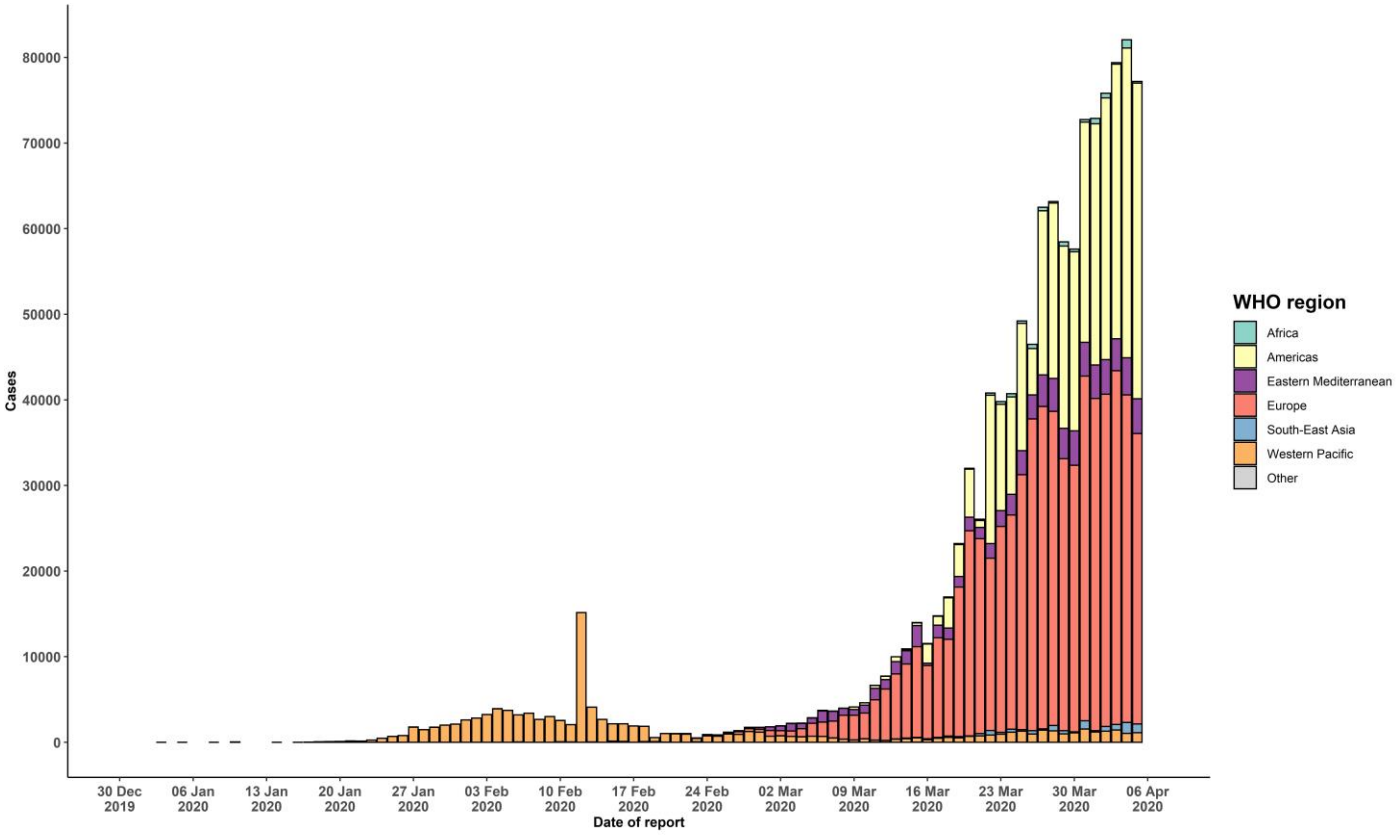
** "Territories" include territories, areas, overseas dependencies and other jurisdictions of similar status

[1] All references to Kosovo should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

Due to differences in reporting methods, retrospective data consolidation, and reporting delays, the number of new cases may not always reflect the exact difference between yesterday's and today's totals. WHO COVID-19 Situation Reports present official counts of confirmed COVID-19 cases, thus differences between WHO reports and other sources of COVID-19 data using different inclusion criteria and different data cutoff times are to be expected.

New countries/territories/areas are shown in red.

Figure 1. Epidemic curve of confirmed COVID-19, by date of report and WHO region through 6 April 2020



STRATEGIC OBJECTIVES

WHO's strategic objectives for this response are to:

- Interrupt human-to-human transmission including reducing secondary infections among close contacts and health care workers, preventing transmission amplification events, and preventing further international spread*;
- Identify, isolate and care for patients early, including providing optimized care for infected patients;
- Identify and reduce transmission from the animal source;
- Address crucial unknowns regarding clinical severity, extent of transmission and infection, treatment options, and accelerate the development of diagnostics, therapeutics and vaccines;
- Communicate critical risk and event information to all communities and counter misinformation;
- Minimize social and economic impact through multisectoral partnerships.

*This can be achieved through a combination of public health measures, such as rapid identification, diagnosis and management of the cases, identification and follow up of the contacts, infection prevention and control in health care settings, implementation of health measures for travelers, awareness-raising in the population and risk communication.

PREPAREDNESS AND RESPONSE

- To view all technical guidance documents regarding COVID-19, please go to this webpage.
- WHO has developed interim guidance for laboratory diagnosis, advice on the use of masks during home care and in health care settings in the context of the novel coronavirus (2019-nCoV) outbreak, clinical management, infection prevention and control in health care settings, home care for patients with suspected novel coronavirus, risk communication and community engagement and Global Surveillance for human infection with novel coronavirus (2019-nCoV).
- WHO is working closely with International Air Transport Association (IATA) and have jointly developed a guidance document to provide advice to cabin crew and airport workers, based on country queries. The guidance can be found on the IATA webpage.
- WHO has been in regular and direct contact with Member States where cases have been reported. WHO is also informing other countries about the situation and providing support as requested.
- WHO is working with its networks of researchers and other experts to coordinate global work on surveillance, epidemiology, mathematical modelling, diagnostics and virology, clinical care and treatment, infection prevention and control, and risk communication. WHO has issued interim guidance for countries, which are updated regularly.
- WHO has prepared a disease commodity package that includes an essential list of biomedical equipment, medicines and supplies necessary to care for patients with 2019-nCoV.
- WHO has provided recommendations to reduce risk of transmission from animals to humans.
- WHO has published an updated advice for international traffic in relation to the outbreak of the novel coronavirus 2019-nCoV.
- WHO has activated the R&D blueprint to accelerate diagnostics, vaccines, and therapeutics.
- OpenWHO is an interactive, web-based, knowledge-transfer platform offering online courses to improve the response to health emergencies. COVID-19 courses can be found here and courses in additional national languages here. Specifically, WHO has developed online courses on the following topics:
    - A general introduction to emerging respiratory viruses, including novel coronaviruses (available in Arabic, Chinese, English, French, Russian, Spanish, Hindi, Indian Sign Language, Persian, Portuguese, Serbian and Turkish);
    - Clinical care for Severe Acute Respiratory Infections (available in English, French, Russian, Indonesian and Vietnamese);
    - Health and safety briefing for respiratory diseases - ePROTECT (available in Chinese, English, French, Russian, Spanish, Indonesian and Portuguese);
    - Infection Prevention and Control for Novel Coronavirus (COVID-19) (available in Chinese, English, French, Russian, Spanish, Indonesian, Italian, Japanese, Portuguese and Serbian); and
    - COVID-19 Operational Planning Guidelines and COVID-19 Partners Platform to support country preparedness and response (available in English and coming soon in additional languages).
- WHO is providing guidance on early investigations, which are critical in an outbreak of a new virus. The data collected from the protocols can be used to refine recommendations for surveillance and case definitions, to characterize the key epidemiological transmission features of COVID-19, help understand spread, severity, spectrum of disease, impact on the community and to inform operational models for implementation of countermeasures such as case isolation, contact tracing and isolation. Several protocols are available here. One such protocol is for the investigation of early COVID-19 cases and contacts (the "First Few X (FFX) Cases and contact investigation protocol for 2019-novel coronavirus (2019-nCoV) infection"). The protocol is designed to gain an early understanding of the key clinical, epidemiological and virological characteristics of the first cases of COVID-19 infection detected in any individual country, to inform the development and updating of public health guidance to manage cases and reduce the potential spread and impact of infection.

RECOMMENDATIONS AND ADVICE FOR THE PUBLIC

If you are not in an area where COVID-19 is spreading or have not travelled from an area where COVID-19 is spreading or have not been in contact with an infected patient, your risk of infection is low. It is understandable that you may feel anxious about the outbreak. Get the facts from reliable sources to help you accurately determine your risks so that you can take reasonable precautions (see Frequently Asked Questions). Seek guidance from WHO, your healthcare provider, your national public health authority or your employer for accurate information on COVID-19 and whether COVID-19 is circulating where you live. It is important to be informed of the situation and take appropriate measures to protect yourself and your family (see Protection measures for everyone).

If you are in an area where there are cases of COVID-19 you need to take the risk of infection seriously. Follow the advice of WHO and guidance issued by national and local health authorities. For most people, COVID-19 infection will cause mild illness however, it can make some people very ill and, in some people, it can be fatal. Older people, and those with pre-existing medical conditions (such as cardiovascular disease, chronic respiratory disease or diabetes) are at risk for severe disease (See Protection measures for persons who are in or have recently visited (past 14 days) areas where COVID-19 is spreading).

CASE DEFINITIONS

WHO periodically updates the Global Surveillance for human infection with coronavirus disease (COVID-19) document which includes case definitions.

For easy reference, case definitions are included below.

Suspect case

A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset.

OR

B. A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to symptom onset;

OR

C. A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

Probable case

A. A suspect case for whom testing for the COVID-19 virus is inconclusive.
    a. Inconclusive being the result of the test reported by the laboratory.

OR

B. A suspect case for whom testing could not be performed for any reason.

Confirmed case

A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

- Technical guidance for laboratory testing can be found here.

Definition of contact

A contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days

after the onset of symptoms of a probable or confirmed case:

1. Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 minutes;
2. Direct physical contact with a probable or confirmed case;
3. Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment[1]; OR
4. Other situations as indicated by local risk assessments.

Note: for confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days *after the date on which the sample was taken* which led to confirmation.

[1] World Health Organization. Infection prevention and control during health care when COVID-19 is suspected https://www.who.int/publications-detail/infection-prevention-and-control-during-health-care-when-novel-coronavirus-(ncov)-infection-is-suspected-20200125

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REVIEW

Use of non-pharmaceutical interventions to reduce the transmission of influenza in adults: A systematic review

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ABSTRACT

During seasonal influenza epidemics and pandemics, virus transmission causes significant public health concern. Reduction of viral transmission by non-pharmaceutical interventions (NPI) has a significant appeal and is often recommended. However, the efficacy of such interventions is unclear. A systematic literature review was undertaken to identify and evaluate the published literature on NPI efficacy to prevent human transmission of influenza virus in adults. Reviewers assessed the quality of eligible studies utilizing the Critical Appraisal Skills Programme for bias and the Scottish Intercollegiate Guidelines Network for methodological quality. Studies were assessed for risk of bias domains of random sequence generation, allocation concealment, attribution bias, selective reporting and blinding. Relevant citations of 2247 were reduced to 100 for full-text evaluation. Only seven met all selection criteria and pooled analysis was not feasible. Of the seven studies, two were randomized controlled trials (RCT) and five were cluster RCT. The main NPI studied were disinfection and hygiene; barriers; and combined NPI. However, these seven RCT had significant design flaws. Only two studies used laboratory confirmed influenza and poor statistical power was a major problem. Positive significant interventions included professional oral hygiene intervention in the elderly and hand washing. Despite the potential for NPI in preventing influenza transmission, there is very limited data available. Hand washing and dental hygiene may be useful, but other interventions have not been fully assessed. Properly designed studies evaluating large populations including 'at risk' patients and in a variety of communities are needed.

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Key words: epidemic, influenza, non-pharmaceutical, pandemic, seasonal.

Abbreviations: CI, confidence interval; ILI, influenza-like-illness; NPI, non-pharmaceutical intervention; PCR, polymerase chain reaction; RCT, randomized control trials.

INTRODUCTION

Influenza spreads between people in seasonal influenza outbreaks, epidemics and pandemics, and is of public health significance.[1] Reduction in person to person virus transmission may potentially reduce infection rates and decrease the morbidity and mortality associated with influenza. Three modes of influenza virus transmission have been identified[2] and comprise droplet transmission, contact with influenza virus surviving on hard non-porous surfaces and airborne transmission.[3,4] One public health strategy for the reduction in transmission relies on the implementation of non-pharmaceutical interventions (NPI). These were reported as a public health measure as early as during the 1918–1919 influenza pandemic. During this pandemic, a number of US cities implemented home quarantine for infected persons, social distancing and a reduction in public gatherings such as church meetings and closure of schools.[5]

NPI, currently recommended by the Centers for Disease Control and Prevention, have been categorized as either personal or community based.[6,7] Personal interventions[7] comprise encouraging people to cover their mouth and nose during coughing and sneezing, frequent hand washing and self-quarantine when a person feels unwell, whereas community-based actions[6] include public education through a variety of communication strategies, social distancing and restriction on public gatherings. Evidence-based simple activities such as washing surfaces and hands with detergent have previously proven successful in reducing transmission as the virus is killed by soap,

and so disinfectants *per se* are not necessary.[8–10] The use of masks and personal protective equipment may not be appropriate for non-clinical areas unless there is a medical reason to do so such as when an individual is immunocompromised.[10,11] Importantly, research into NPI from the recent 2009 pandemic has provided good evidence that home quarantine is feasible and acceptable; however, support for mandatory social distancing appears limited.[10,12,13]

Analysis and assessment of NPI has been very limited and have focussed on single specific interventions such as face masks.[8] Other influenza reviews[14] have restricted themselves to observations on a specific epidemic/pandemic or simply make suggestions of how to limit transmission based upon reviewing selected articles and appear to have merged expert opinion with what can be inferred from the literature or a selection of publications. Only one previous review[10] has utilized a well-designed systematic process to review the literature on physical barriers to limit the spread of respiratory viruses. Despite the limitations of these previous reviews, all agreed our knowledge base and evidence for effective interventions is poor. As such, it seemed important to undertake a detailed systematic review on the evidence for NPI that help reduce person-to-person transmission of the influenza virus. As part of this review, we sought to include evidence of NPI associated with both seasonal influenza and influenza pandemics.

METHODS

The objective of this systematic review was to identify and evaluate the published medical literature on the efficacy of NPI to prevent human-to-human transmission of influenza virus in adults.

Search strategy

A protocol was devised, and a systematic search of peer-reviewed literature was performed in accordance with the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[15] From July 2013 to February 2014, we searched the following electronic databases: Cochrane, Medline, Pubmed, CINAHL, Embase, Sciencedirect, Google Scholar and Scopus. References of publications retrieved in the search were scanned for any relevant additional citations. As well as scanning listed inclusion articles in related review papers, the *American Journal of Infection Control*, *Infection Control* and *Hospital Epidemiology*, *Journal of Hospital Infection and Emerging Infectious Disease* journals were also hand-searched for possible inclusion articles. Influenza and NPI search terms were combined, the search strategy adapted for the Medline database is provided in the Supplementary Table S1. Search limits applied were the English language, abstracts and humans. No restrictions were placed on publication date. Supplementary Table S2 presents the topically relevant but excluded publications in this study.

Eligibility criteria

Articles were eligible for inclusion if they were randomized controlled trials (RCT) reporting on the efficacy of an NPI against influenza infection. The participants of interest were adults (male and female 18 years and over) who had serologically or virologically confirmed influenza, or had clinical features of influenza, influenza-like-illness (ILI) or acute respiratory infection or were asymptomatic but at risk of contracting influenza due to health-care or community exposure. Interventions comprised any NPI, device or behaviour that was used to contain or mitigate the spread of influenza infection. Simulation models and studies conducted in controlled laboratory settings were excluded. Comparative groups included no intervention, inactive alternative intervention or standard care. Utilizing the categories of NPI outlined by Aledort *et al.*,[14] intervention types included contact management, index-patient management, community restrictions and surveillance. We included interventions that were either self-administered or administered by a clinician and conducted in health care, home or community settings. Studies that described purely pharmacological or vaccine-based interventions were excluded. Bundled NPI consisting of a combination of measures were considered if the interventions were composed primarily of NPI. The primary outcome of interest was evidence of decreased transmission of the influenza virus. This outcome was evaluated by the level of reduction in influenza or ILI attack rates, secondary infection ratios, viral illness severity, mortality rates and health-care utilization. Secondary outcome measures were increased awareness and education in NPI.

Study selection and data extraction

After conducting the database searches and removing duplicates, the inclusion criteria were applied using a standardized form to assess the eligibility of the retrieved articles. This was performed by two independent reviewers (SMS, SS) by scanning titles and abstracts for relevance. Full-text articles were obtained for studies that were identified as meeting the inclusion criteria. Disagreements over inclusion articles were settled through discussion until consensus was reached, or resolved by an independent arbitrator (NM). Extraction of data was performed by the two reviewers (SMS, SS) working independently, using a pre-designed data extraction spreadsheet with categories for capturing data items such as study design, sampling, setting, participant, intervention, comparison and outcome data.

Quality assessment

Two reviewers assessed the quality of eligible studies utilizing the Critical Appraisal Skills Programme[16] tools for reporting bias and the Scottish Intercollegiate Guidelines Network[17] checklists for methodological quality. Studies were assessed using the standard risk of bias domains; random sequence generation, allocation concealment, attribution bias, selective reporting and blinding. All studies were assigned a risk of bias grading of low, medium or high, based on the number of methodological problems identified

Table 1 Assessment of quality rating

Quality of evidence rating	
Low	Studies with up to one methodological issue or limitation
Medium	Studies with two to three methodological issues or limitations
High	Studies with more than 3 methodological issues or limitations
Methodological quality items assessed	
Clearly focussed research question	
Description of participant recruitment	
Randomization methods	
Blinding	
Allocation concealment	
Attrition	
Data collection and inclusion/exclusion criteria	
Statistical analysis methods and provision of confidence intervals	
Clearly defined outcomes	
Appropriate outcome assessment instruments	
Adequate controls	
Reporting of study limitations	
Measures taken to control for confounders	

Adapted from the National Health and Medical Research Council levels of evidence guidelines.[18]

with low risk representing one or no items, medium risk two to three items and high risk being more than three items. In Table 1, an overview of the rating scale items employed for the quality of evidence is provided.[16–18]

RESULTS

There were 2247 potentially relevant citations retrieved from the searches of electronic databases, journal hand searching and secondary references. After removal of duplicates, preliminary relevance screening of titles identified 790 articles for further evaluation. Abstracts of these articles were reviewed, resulting in the exclusion of 690 publications on the basis of not meeting the required inclusion criteria. The full-text publications were retrieved for the remaining 100 articles. Of these, 93 failed to meet eligibility criteria, leaving seven articles to be included in the review.[9,11,19–23] Figure 1 shows an overview of the article selection review process. Due to the significant variation in interventions, outcome measures and settings, the seven included studies did not allow for a pooled analysis. A narrative approach to the search findings was undertaken instead and a qualitative synthesis of the data is presented here.

Overview of included studies

Table 2 provides a summary of the included studies. Included study types consisted of two RCT[19,20] and five cluster RCT.[8,11,22–24] Three main categories of NPI were identified among the included studies: (i) disinfection

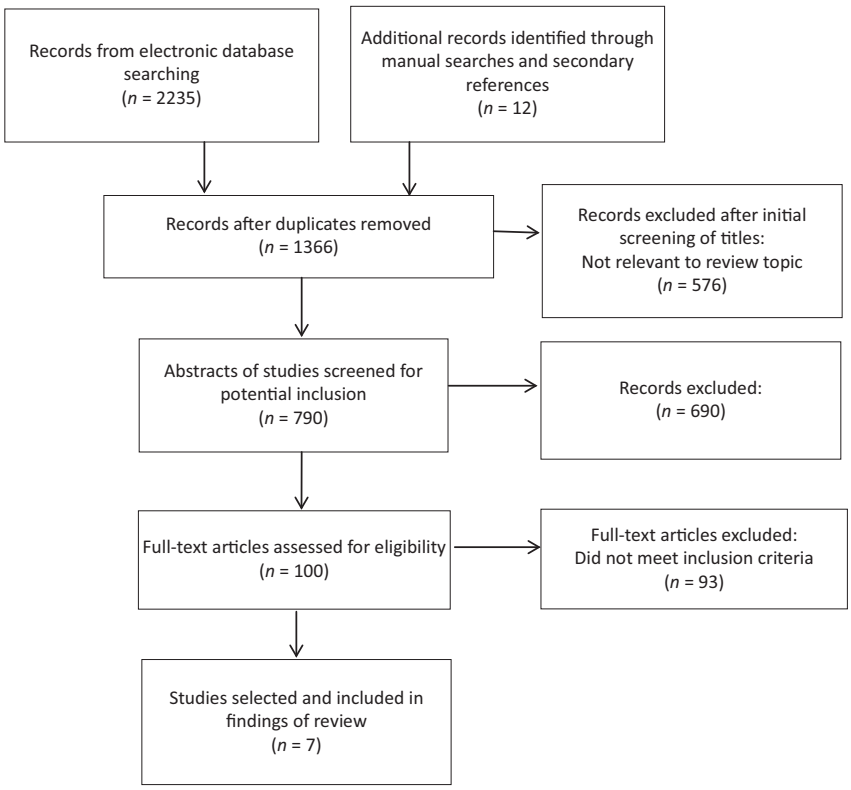

Figure 1 Overview of the article selection review process.

Table 2 Summary of included studies

Study (first author, year, location)	Study type	Sampling	Setting	NPI evaluated	Intervention description	Control	Intervention duration and frequency	Summary of findings on effectiveness	Pandemic or seasonal
Disinfection and hygiene:									
Abe 2006, Japan[19]	RCT	190 elderly patients visiting day care service	Community	Oral care	Professional oral care consisting of cleaning of teeth and gingivae by dental hygienist in addition to guidance on oral care. ($n = 98$)	Personal oral care as usual. ($n = 92$)	Once weekly for a period of 6 months	Study suggested weekly professional oral care and oral health advice reduced the risk of infection from influenza by reducing the number of oral bacteria and neuraminidase and trypsin-like protease activities in saliva.	Seasonal
Satomura, 2005 & supplement: Kitamura 2007, Japan[20,21]	RCT	380 healthy participants at 18 sites across Japan during 2002–2003 winter season.	Community	Gargling	Water gargling group ($n = 122$) and povidone-iodine gargling group ($n = 132$).	Usual personal care ($n = 130$).	60 days. Gargling conducted 3 times a day.	No significant preventive effects were found for gargling and ILI infection. No significant differences were observed between effectiveness of water gargling and povidone-iodine gargling in prevention of ILI.	Seasonal
Barriers:									
Canini, 2010, France[11]	Cluster RCT	Households from 3 French regions during 2008–2009 influenza season. Index patients selected by GPs. $n = 105$ households (306 contacts).	Community	Surgical masks	Index patient was required to wear a surgical masks in the household for a period of 5 days from medical visit when in a shared or confined space. Masks were changed every 3 h and not required to be worn at night, however were encouraged to sleep alone. ($n = 52$ households/index patients).	Control arm had no intervention applied. ($n = 53$ households/index patients)	7 days	No significant differences were found between surgical mask use and non-mask use. Low effectiveness is suggested for surgical masks in the prevention of influenza transmission. Fomites and contaminated surfaces are indicated to be a greater proportion of influenza transmission routes than large droplet.	Seasonal
Combined NPIs: disinfection, barriers									
Aiello, 2010, USA[22]	Cluster RCT	Students from University residence halls recruited during 2006–2007 influenza season ($n = 1437$).	Community	Hand hygiene, face masks and education	Mask and hand sanitizer group ($n = 367$), Face mask-only group ($n = 378$). Both treatment groups received basic hand hygiene education.	Control group received basic hand hygiene education-only ($n = 552$).	6 weeks duration. Baseline, followed by weekly web-based survey.	Findings suggest that face masks and hand hygiene may reduce spread of respiratory illness in shared living settings and may mitigate pandemic influenza transmission.	Seasonal
Aiello, 2012, USA[23]	Cluster RCT	Students from University residence halls recruited during 2007–2008 influenza season were recruited ($n = 1178$)	Community	Hand hygiene, face masks and education	Face mask and hand hygiene group ($n = 349$) and face mask-only group ($n = 392$). All participants received basic hand hygiene education.	Control group received basic hand hygiene education-only ($n = 370$).	6 weeks duration. Baseline, followed by weekly web-based surveys.	Face mask and hand hygiene combined were associated with reduced ILI rates and may reduce the spread of influenza in community settings.	Seasonal
Cowling, 2009, China[8]	Cluster RCT	Households in Hong Kong. Index subjects were recruited from 45 outpatient clinics with confirmed influenza. Total of 259 households (794 contacts).	Community	Hand hygiene, face masks and education	Hand hygiene treatment group ($n = 85$ households) Face mask + hand hygiene treatment group ($n = 83$ households). Both treatment groups also received education on lifestyle measures.	Control arm received education regarding lifestyle measures ($n = 91$ households).	6 days duration. Households were visited on days 1, 3 and 6.	No significant difference was found between the face mask plus hand hygiene group and the hand hygiene group in RT-PCR-confirmed influenza virus infections in household contacts.	Seasonal
Larson, 2010, USA[24]	Cluster RCT	Households were recruited from the upper Manhattan neighbourhood with a high population of immigrant Latinos. $n = 2788$ (509 households).	Community	Hand hygiene, face masks and education	Intervention groups were education and hand sanitizer group ($n = 169$ households) and education, hand sanitizer and face mask group ($n = 166$ households).	Education only group ($n = 174$ households)	Study protocol duration was 19 months. Mean duration was 55.5 weeks.	The wearing of face masks was associated with reduced secondary transmission in households. It is also suggested that alcohol-based hand hygiene may confer protection against influenza transmission in communities. Compliance with face masks was poor.	Seasonal

ILI, influenza-like-illness; RCT, randomized control trials.

and hygiene; (ii) barriers; and (iii) combined NPI: disinfection, hygiene and barriers. The studies were classified into these groups based on the nature of the NPI used or described. All studies involved seasonal influenza in community settings. Study participants were healthy or influenza-infected volunteers and patients from a variety of community sources including aged-care facilities, university residences and households. Frequency and duration of the interventions varied among the studies. Sample sizes ranged from 190 to 2788 and originated from five different countries.

Types of interventions

Disinfection and hygiene interventions focussed on personal hygienic practices, these including oral care[19] and gargling.[20,21] Barrier interventions included studies on the effectiveness of surgical masks.[11] Combined NPI involved multiple interventions used concurrently with the most common combination being hand hygiene, face masks and education, which was evaluated in four different studies.[8,22–24]

Quality assessment and evidence level summary

The quality of the influenza NPI studies included in this review was assessed and has been tabulated in Table 3. Of the seven RCT, one study did not report random sequence generation technique.[19] Allocation concealment was not described in four trials.[19,22–24] None of the trials was double blinded. No blinding methods were reported in three trials,[19,20,24] while four trials reported blinding methods for investigators or acknowledged the impossibility of blinding participants and investigators due to the nature of the intervention (face mask use).[8,11,22,23] Appropriate analysis was used for the five cluster RCT with all studies reporting cluster coefficients.[8,11,22–24] In terms of reliability and assessment of the primary outcome, only one study used laboratory confirmation by reverse-transcription polymerase chain reaction (RT-PCR) as their primary analysis.[8] One study used rapid antigen detection kits,[19] three studies used ILI case definitions as their primary analysis and laboratory confirmed RT-PCR for a fraction of the study groups.[22–24] Two trials used ILI case definitions only.[11,20] Other problems identified were lack of statistical power,[11,19] early termination of the trial[11] and possible confounding in the non-intervention control groups in which an increased awareness of influenza could have led to increased protective measures against influenza infection.[8,11,19,22–24] Furthermore, in cases where interventions were tested in shared living environments such as university dormitory halls, the risk of detection and contamination between study groups was particularly high.[22,23]

Effectiveness of NPI in preventing and reducing influenza transmission

Disinfection and hygiene

Two studies from Japan investigated gargling and oral hygiene as interventions to interrupt transmission. One RCT indicated gargling was effective at decreasing the overall upper respiratory tract infection rates (water gargling incidence rate ratio 0.64, 95%

Table 3 Quality assessment of included studies

NPI category	Intervention	Total no. studies	Study ID	Risk of bias	Summary of evidence
Disinfection and hygiene	Oral care	1	Abe, 2006[19]	Med	Suggested effectiveness in prevention of influenza in the elderly.
	Gargling	1	Satomura, 2005 & Kitamura, 2007[20,21]	Med	No significant protective effects against ILI.
Barriers	Surgical mask	1	Canini 2010[11]	Low	Low effectiveness against influenza transmission.
Combined NPI	Hand hygiene, face masks and education	4	Aiello, 2010[22]	Low	Face masks and hand hygiene may reduce spread of influenza in shared living areas.
			Aiello, 2012[23]	Low	Face masks and hand hygiene appear to reduce rate of influenza in the community.
			Cowling, 2009[8]	Low	Hand hygiene and face masks seem to prevent household transmission of influenza
			Larson, 2010[24]	Med	No detectable additional benefit of hand hygiene or face masks in reducing rates of URIs. Mask wearing may reduce secondary transmission.

NPI, non-pharmaceutical intervention.

confidence interval (CI): 0.41–0.99; povidone-iodine incidence rate ratio 0.89, 95% CI: 0.60–1.33); however, there were no benefits found specifically against seasonal ILI infection rates for either intervention.[20,21] The other Japanese RCT investigated the effects of professional oral care by dentists versus standard oral care among elderly participants visiting community day care services. The relative risk of influenza infection for professional compared to standard oral care was 0.1 (95% CI: 0.01–0.81, $P = 0.008$), suggesting professional oral care may confer some protective benefit in the elderly through reduction of bacterial and enzymatic activities in saliva.[19]

Barriers

In a French cluster-RCT assessing the effectiveness of surgical face masks alone against influenza transmission in community households, no significant differences were noted in the rate of secondary ILI (difference between control and intervention group of 0.40% (95% CI: −10% to 11%, $P = 1.00$)).[11]

Combined NPI

Four cluster RCT tested combinations of education, face masks and hand hygiene, and were assessed within community settings. Two US studies by Aiello *et al*.[22,23] were carried out in university halls during two consecutive influenza seasons (2006–2007 and 2007–2008). Results for one of these trials found cumulative reductions in influenza rates for both face mask with hand hygiene group (43%, adjusted relative risk (RR) = 0.57 (95% CI: 0.26 to 1.24)) and face mask-only group (8%, adjusted RR = 0.92 (95% CI: 0.59 to 1.42)) compared to the control; however, statistical significance was not attained.[23] Similarly, the other trial observed a ~ 10% reduction in cumulative ILI incidence for both face mask with hand hygiene and face mask alone compared to the control group yet did not reach statistical significance.[22] A study by Cowling *et al*.[8] conducted in Hong Kong households involved laboratory-confirmed influenza index patients. This study found that hand hygiene (with or without face masks) appeared to reduce influenza infection, although differences were again not statistically significant compared to control. Comparably, the trial by Larson *et al*.[24] conducted in USA households showed that the hand hygiene-only group had a higher protective effect against developing influenza symptoms (57.6%, $P < 0.01$), compared to the hand hygiene with face mask group (38.7%) and control group (49.4%); however, no significant differences were found in infection rates by intervention groups,[24] suggesting hand hygiene may have some general protective effect. Common issues in all studies were that the protective effects of each individual intervention were difficult to discern, with adherence of face mask use in particular being poorly described indicating an inability to demonstrate significant change due to small numbers in studies or a lot of noise in measurements or both.

Awareness and education on NPI

Five studies included some form of educational component related to either the appropriate use of NPI or influenza viral transmission as part of the intervention or control group.[8,11,22–24] These studies utilized education, guidance or advice as part of a comprehensive layered NPI approach, and were associated in each case with increased influenza awareness and contributed to the overall intervention effect.

Excluded studies

Among the excluded articles, 19 were identified as not being RCT, however met other inclusion criteria.[5,25–42] The level of evidence types consisted of seven level III-2 studies (prospective/retrospective cohort, case control and quasi-experimental) with the remaining studies being level III-3 (retrospective cross-sectional, cross-sectional, historical observational). The overall quality of these excluded studies was poor, with only a small number representing a low risk of bias. Of the 19 studies, 11 were quarantine, surveillance or social distancing interventions; three were disinfection and hygiene studies, three assessed combined NPI, and two studies evaluated barrier interventions. Twelve of the 19 studies were conducted during pandemic conditions, six during seasonal influenza and one study during both seasonal and pandemic influenza conditions. Settings comprised community (eight studies), health care (nine studies) and international airports (two studies).

Of the few excluded studies that were evidence level III-2 and had the least methodological issues, there were promising results in one study assessing the use of hand hygiene and education.[26] In this study, a higher frequency of hand washing after contact with contaminated surfaces was found to be a protective factor against influenza hospitalization. Also, and importantly, receiving less information on influenza pandemic precautions was associated with likelihood of influenza infection.[26] Among the evidence level III-3 excluded studies with low risk of bias, five studies reported effectiveness for NPI. These interventions included protective sequestration measures for at-risk populations,[5] school closure,[35,39] entry screening[37] and open-air treatment.[40]

DISCUSSION

The evidence for NPI reducing influenza viral transmission during seasonal and pandemic outbreaks was lacking with most studies being significantly flawed. There were only a few studies with acceptable methodological quality, and of these very few showed statistically significant differences. The key NPI reported in the well-designed studies were related to disinfection, physical barriers such as face masks, multifaceted interventions that combined disinfection, hygiene and barriers and studies associated with population based barriers such as quarantine and social distancing and surveillance.[8,19,22–24] In the acute care clinical setting, a comparison of N95 respirator and surgical masks found neither mask to be superior in protecting health professionals against influenza.[43]

Simple and yet potentially effective measures for disinfection included oral hygiene and hand washing

to reduce transmission. These low-cost infection control methods were likely to be effective given that influenza virus has been found to survive for up to 30 min on unwashed hands.[44] There is evidence for hand washing with water alone being as effective in removing colony forming units and viruses compared to disinfectant.[45] The effectiveness of oral hygiene may be due to reducing the oral load of influenza virus and thereby minimizing systemic influenza infection especially in the elderly.[19]

Health professionals are at risk of becoming infected when delivering clinical care to influenza infected patients and physical barriers such as surgical masks and N95 respirators[11] have been proven to be effective in acute settings. Using these personal physical barriers in the community is without evidence and does not seem to reduce influenza symptoms or rates of influenza. The combination of disinfection and barrier methods has been purported to reduce secondary influenza infection in people who live in university residential accommodation.[22,23] However, it is not known if the students' behaviour changed including reduced socialization due to the reporting of influenza deaths in the media. Despite several complex interventions being studied, hand hygiene is likely to be the most effective in reducing rates of influenza transmission, but this is based on very limited data.

Quarantine measures have been considered standard practice as part of infection control in human and animal migration.[46] Quarantine measures for influenza usually consist of infected individuals remaining at home until they are no longer infectious. However, there is data to suggest that this measure is acceptable to people with influenza[47] while home-based quarantine raises a number of other issues relating to safety, education and information[48] and the availability of sick leave and other financial support mechanisms.[49] Nevertheless, compliance with home quarantine has been reported as being high. Our findings build considerably on a previous review[10] which was limited to assessing physical barriers and provides the additional finding of the potential for oral care in reducing transmission of the influenza virus while confirming the ongoing need for methodologically sound and well-designed studies.

In conclusion, this review found a small number of NPI appeared to be useful in reducing the transmission of influenza, with oral hygiene and hand washing showing efficacy. The implementation of home quarantine may be useful but requires further assessment. Overwhelmingly evident was the need for well-developed and carefully planned large-scale studies to assess the efficacy of NPI and to address the important question of whether we can limit influenza spread using NPI methods.

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Supplementary Information

Additional Supplementary Information can be accessed via the *html* version of this article at the publisher's web-site.

Table S1 Search strategy for Medline OvidSP.

Table S2 Topically relevant excluded studies.

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Article

Assessing the Role of Voluntary Self-Isolation in the Control of Pandemic Influenza Using a Household Epidemic Model

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Abstract: In the absence of effective vaccines, antiviral drugs and personal protective measures, such as voluntary self-isolation, have been a part of preparedness plans for the next influenza pandemic. We used a household model to assess the effect of voluntary self-isolation on outbreak control when antiviral drugs are not provided sufficiently early. We found that the early initiation of voluntary self-isolation can overcome the negative effects caused by a delay in antiviral drug distribution when enough symptomatic individuals comply with home confinement at symptom onset. For example, for the baseline household reproduction number $R_{H0} = 2.5$, if delays of one or two days occur between clinical symptom development and the start of antiviral prophylaxis, then compliance rates of $q \geq 0.41$ and $q \geq 0.6$, respectively, are required to achieve the same level of effectiveness as starting antiviral prophylaxis at symptom onset. When the time to beginning voluntary self-isolation after symptom onset increases from zero to two days, this strategy has a limited effect on reducing the transmission of influenza; therefore, this strategy should be implemented as soon as possible. In addition, the effect of voluntary self-isolation decreases substantially with the proportion of asymptomatic infections increasing.

Keywords: mathematical modeling; pandemic influenza; voluntary self-isolation; antiviral prophylaxis; household reproduction number

1. Introduction

Influenza viruses are associated with high morbidity and mortality in humans and continue to be a major threat to public health [1]. For example, Dawood *et al.* estimated that the emergence of pandemic H1N1 in 2009 resulted in 200,000 respiratory deaths and 83,000 cardiovascular deaths worldwide [2].

Because influenza is an important global public health concern, the methods by which pandemic influenza could be contained are of widespread interest, and a variety of control measures have been implemented to contain the spread of influenza strains. Vaccination is the most widely available form of disease control, and vaccination is most effective at the start of an epidemic [3]; however, several months would be required to produce a vaccine against a novel influenza strain [4–6]. Before effective vaccines would become available, prevention measures would be limited to antiviral medications and to personal and societal hygienic measures.

Previous research has indicated that antiviral drugs can reduce the risk of becoming infected with currently-circulating influenza strains and can inhibit infectivity [7–9]. The effective use of antiviral drugs is a critical problem for influenza control. The measure of providing antiviral prophylaxis to the close contacts of influenza patients has been recommended by the World Health Organization as a principle of early aggressive measures to prevent pandemic influenza [10,11]. The United Kingdom specifically implemented the policy of dispensing antiviral drugs to infected persons and their close contacts between May and July 2009, and Pebody *et al.* suggested that this strategy was highly effective in reducing the incidence of secondary cases [12]. Using stochastic epidemic simulations, Longini *et al.* showed that targeted antiviral prophylaxis (*i.e.*, offering antiviral prophylaxis to the close contacts of suspected index influenza patients) was an effective control measure to contain pandemic influenza until vaccines became available [1]. In addition, the combination of targeted antiviral prophylaxis and other interventions has been successfully used to combat the spread of pandemic influenza [13–18]. Thus, in the present study, household-based antiviral prophylaxis is considered as a control measure. As performed by Becker and Wang [8], household-based antiviral prophylaxis was carried out by dispensing antiviral drugs to household members immediately after the first household case showed clinical symptoms.

Unfortunately, logistical constraints, such as a limited distribution capacity and an insufficient stockpile, might limit the effect of antiviral drugs [4]. Because influenza is a highly contagious disease that can be transmitted via close contact with an infected individual, minimizing contact with infected people helps reduce transmission [19]. Intervention measures aimed at reducing the contact rates between infected and susceptible individuals should be considered. Voluntary home confinement of infected individuals (*i.e.*, voluntary self-isolation) can reduce contact between ill people and other community members; thus, voluntary self-isolation is usually considered as an intervention capable of limiting the transmission of pandemic influenza. The European Centre for Disease Prevention and Control (ECDC) also recommends this measure [20]. Because self-isolation restricts the activity of ill people, it is controversial [21]. The public's doubts regarding the effectiveness of this intervention might also make it a difficult strategy to implement [21]. To ease these doubts, it is important to investigate

the efficacy of voluntary self-isolation in the control of pandemic influenza. Mathematical models are powerful tools with which to study the dynamics of infectious diseases and to evaluate the effects of various control measures [22,23]. Moreover, because transmission within a household is the dominant mode of transmission of infections, household epidemic models have recently received widespread attention [7,13,24–27].

Moreover, certain studies have suggested that asymptomatic cases and asymptomatic infections indeed occur during influenza transmission. Based on active clinical follow-up and laboratory-confirmed outcomes, Papenburg *et al.* estimated that approximately 10% of A(H1N1) 2009 infections were completely asymptomatic [28]. Additionally, one recent study by Hayward *et al.* suggested that for the 2009 H1N1 pandemic, the proportion of asymptomatic individuals was as high as 70% to 80% [29]. Several earlier studies confirmed that asymptomatic infections also occurred in H5N1 pandemic influenza [30,31]. Note that the presence of asymptomatic infections likely affects the epidemic outbreak and the effectiveness of certain control measures. Hence, asymptomatic infection is a critical factor when considering the transmission dynamics of infectious diseases and pandemic control strategies. Many researchers have thus investigated the impact of asymptomatic cases and asymptomatic infections [1,15,32,33].

Given these considerations, we used a household epidemic model to investigate how household-based control measures, including household-based antiviral prophylaxis and voluntary self-isolation of symptomatic individuals within households, contribute to the containment of influenza outbreaks. We examined the effects of voluntary self-isolation alone and in combination with antiviral prophylaxis on the control of pandemic influenza. We also explored the impacts of a delay in implementing voluntary self-isolation and of asymptomatic infections on the effectiveness of voluntary self-isolation. "Self-isolation" means that symptomatic individuals stay and confine themselves at home [34]. In practice, it would be difficult for a government to offer antiviral drugs for prophylaxis, but not for treating patients. Therefore, as in [35,36], an antiviral prophylaxis strategy of treating symptomatic initial cases and offering prophylaxis to those who had close contact with these initial cases is considered. Hence, the term "antiviral prophylaxis" in this paper refers to the use of antiviral drugs in the treatment of the symptomatic index cases of influenza in a household and in the prophylaxis of those who have had close contact with these index individuals.

2. Methods

We considered the spread of an influenza strain within a community of households. A household refers to a group of people who share the same living facilities under a single shelter structure [37]. In general, people more often have contact with their household members than with other persons outside their households [21]. Suppose that the community consists of a large number of households of various sizes. Let h_n denote the proportion of households of size n ($n = 1, 2, \cdots$) in the community, and let $g_j = \dfrac{jh_j}{\sum_{n=1}^{\infty} nh_n}$ ($j = 1, 2, \cdots$) denote the probability that a randomly-selected community member resides in a household of size j.

Based on certain literature on epidemic modeling [37,38], we assume that after the disease is introduced into a household, the chance that a household member will be infected by infectious people outside the household is negligible relative to the chance that he or she will be infected by an infectious household member. In other words, outbreaks within affected households evolve independently of each other [8,37]. The assumption of independence between household outbreaks is likely questionable, but fortunately, this problem has been resolved by Ball *et al.* [39]. These researchers considered a model that explicitly allows disease transmission between households and showed that given a major outbreak, household outbreaks are actually approximately (*i.e.*, asymptotically) independent if the number of households is large [40]. The chain of infection in a household outbreak is denoted by $C = (c_1, c_2, c_3, \cdots)$, where c_j represents the number of infected individuals in the j-th generation. In this study, the primary household case is considered to be the first generation. Suppose only one introductory case lives in every infected household; hence, c_1 equals one, and c_2 is the number of individuals infected by the primary case in the same household. For any $j \geq 2$, c_j represents the number of infected individuals infected by the previous generation. For example, considering a household of size 5, the members are called "a", "b", "c", "d" and "e". Suppose that this household consists of four susceptible individuals and one introductory case and that "a" is the introductory case and infects "b", "c" and "d", after which "b" infects "e". Here, the chain is denoted by $1 \to 3 \to 1$, i.e., $c_1 = 1, c_2 = 3, c_3 = 1$, $c_i = 0$ $(i \geq 4)$. The probability that an epidemic chain C occurs in a household of size j is denoted by $P(C|j)$; v_H denotes the average size of an outbreak within a household that is selected randomly from the community.

It is inevitable that infectious individuals infect susceptible persons outside their households. We assume that one k-th generation household case infects other susceptible persons outside his or her household according to a Poisson process with a rate of μ_k [41], which is the average number of infected persons generated by a single k-th generation infected individual. Additionally, the probability that one k-th generation case in a household outbreak infects i members outside his or her household is denoted by $\phi_{i,k}$ $(i = 0, 1, 2, \cdots;\ k = 1, 2, \cdots)$. According to Ball *et al.* [39], under the condition that the number of households is large and the number of infected households is relatively small, the probability that a given infected household member will infect an individual outside his or her household who is residing in a previously-infected household is negligible compared to the probability that a given infected household member will infect an individual outside his or her household who is residing in a previously-uninfected household. That is, each individual infected by one k-th generation infective outside the latter's household resides in an otherwise previously-uninfected household.

Let q denote the fraction of symptomatic individuals who comply with voluntary self-isolation. We assume that the voluntary home confinement of patients begins on the l day after symptom onset. As in [38], we assume that the infected individual's symptoms appear T_I days after infection. As infected persons can transmit the infection prior to the onset of their symptoms, even self-isolated individuals may transmit the infection outside their households. As above, we assume that a k-th generation infected individual creates other infected individuals outside his or her household according to a Poisson process with a rate of μ'_k, where μ'_k is the mean number of cases that one k-th generation household patient infects outside of his or her household prior to voluntary self-isolation. Then, let

$\phi'_{i,k}$ $(i = 0, 1, 2, \cdots;\ k = 1, 2, \cdots)$ represent the probability that one k-th generation household case infects i individuals outside his or her household before voluntary self-isolation.

During the voluntary self-isolation period of patients, we assume that the behavior of their household members is unconstrained. It is unrealistic to segregate infected individuals from their household members [42]; thus, we further assume that self-isolation does not have any impact on the contacts between the isolated individuals and their household members. That is, the transmission chain within a household is not affected by the voluntary self-isolation strategy.

In addition to symptomatic cases, infected individuals who do not develop clinical symptoms also play a major part in the transmission of influenza [43]. We therefore consider asymptomatic infections in our model. We assume that infected people with influenza develop clinical symptoms with a probability of α. We also assume that one k-th generation asymptomatic household case infects other susceptible persons outside his or her household according to a Poisson process with a rate of $\epsilon_k \mu_k$. The parameter ϵ_k $(k = 1, 2, \cdots)$ is the reduction in the infectiousness of the k-th generation individuals with asymptomatic infection to other community members, where $0 \leq \epsilon_k \leq 1$. The case $\epsilon_k = 0$ represents the scenario in which asymptomatic infected people are not contagious, and $\epsilon_k = 1$ corresponds to the scenario in which asymptomatic cases and symptomatic cases have the same infectiousness. The probability that one k-th generation asymptomatic case in a household outbreak infects i members outside his or her household is denoted by $\phi''_{i,k}$ $(i = 0, 1, 2, \cdots;\ k = 1, 2, \cdots)$.

We assume that the epidemic is seeded by a single infected individual who arrives from another location. Here, Y denotes the total number of cases in which antiviral prophylaxis and voluntary self-isolation are implemented. The derivation method for the eventual mean number of infected individuals is based on the premise that each newly-infected individual in the community will start an independent epidemic process with the same eventual average number of patients. This method of determining the eventual mean number of infected individuals was used by Becker and Wang [8]. The eventual mean number of infected individuals, EY, can be obtained by:

$$EY = \frac{v_H}{1 - R_H}, \tag{1}$$

where:

$$\begin{aligned} R_H &= \alpha \sum_{j=1}^{\infty} g_j \sum_{C} P_1(C|j) \sum_{k=1}^{j} c_k \left(q\mu'_k + (1-q)\mu_k\right) \\ &\quad + (1-\alpha) \sum_{j=1}^{\infty} g_j \sum_{C} P_2(C|j) \sum_{k=1}^{j} c_k \epsilon_k \mu_k \end{aligned} \tag{2}$$

which is the mean number of primary cases generated in the community by all of the infected individuals of an affected household that is selected randomly from the community [8]. This is also the mean number of households with infections that are generated by all infected individuals within a random household outbreak [8,14,44], where $P_1(C|j)$ corresponds to the probability of an infection chain within a household receiving antiviral drugs and $P_2(C|j)$ corresponds to the probability of an infection chain within a household not receiving antiviral drugs. We briefly outline the derivation and interpretation of Equation (1) in the Appendix. Obviously, the household reproduction number must be $R_H < 1$ for Equation (1) to be valid.

To describe the effects of the control measures on the household reproductive number, R_H, as in [8], we adopt the approach of Glass and Becker [38] to describe within-household transmission. We outline the method of [38] as follows. Transmission within the household is based on the Reed–Frost model [37,45], but the probability of escaping being infected by a household case varies with the generation [8]. The level of infectiousness of infected individuals is measured by the size of the virus population carried by the individual. The size of the virus population follows a deterministic birth-death process, with birth rate λ and death rate d. In the absence of control measures, the virus population dynamics at first follow a deterministic birth process with a constant rate λ. T_I days after infection, influenza virus particles are cleared at a rate d because the body's immune system is activated. After antiviral drugs are dispensed to infected individuals, the effectiveness of these drugs is represented by an additional death rate, δ, in the virus population. When antiviral drugs are dispensed to susceptible individuals, the protective effects of these drugs are reflected in the reduction of the per contact probability of transmission by a factor of σ [8]. In other words, the effects of antiviral drugs on susceptibility change the parameter θ to θ^σ, where θ is the probability that a susceptible individual escapes infection by a single household member in the absence of antiviral drugs. For a full description of this change, please refer to [37]. According to [37], the parameter θ can be expressed by $\theta = \exp(-\int_0^\infty \lambda_x dx)$, where λ_x represents the infectiousness function.

As mentioned above, because generations differ in the amounts of time between being infected and taking antiviral drugs, the probability that a susceptible individual escapes infection by an infected household member is related to that infected household member's generation. We let θ_i $(i = 1, 2, \cdots)$ denote the probability that a susceptible household member avoids being infected by a single i-th generation case.

3. Results

The containment of the spread of a disease in a community consisting of households is indicated by a reduction in the household reproduction number, R_H, to below one. For the purpose of containing an outbreak, we show the effectiveness of various interventions strategies in reducing the household reproduction number, R_H. As in [8], we show the change in the household reproduction number, R_H, with respect to the parameters μ, which is the average number of cases that an infected individual generates outside his or her household, and θ, which is the probability that an individual escapes infection by an infectious household member during the latter's entire infectious period, with the goal of describing the effects of interventions on transmission. These definitions of parameters μ and θ apply to an entirely susceptible community in the absence of any control measures. Because the parameter μ quantifies between-household transmission and the parameter θ quantifies within-household transmission, they are two important factors for determining the values of R_{H0}. With the coordinates of μ and θ, we can display the results with a wide range of values of R_{H0}. The distribution of household sizes was simulated to be consistent with Australian census data from 2001. For simplicity, households with only one person and those with more than six persons were not considered, and the percentages of households with $2, 3, 4, 5$, and 6 people were $44\%, 21\%, 21\%, 10\%$, and 4%, respectively [8,38]. The values of the model parameters are given in Table 1. These values are consistent with experimental data, as in [8,38].

Table 1. Values of the model parameters.

Parameter	Value	Description
λ	4	Birth rate of the virus population.
d	5	Death rate of the virus population due to the immune response.
δ	0.5	Additional death rate of the virus population due to antiviral drugs.
σ	0.5	The factor by which the probability of infection during a single contact is reduced for an individual who is taking antiviral drugs.
T_I	2	The number of days after infection after which clinical symptoms appear.

3.1. Antiviral Prophylaxis and Voluntary Self-Isolation

The effects of prophylaxis with antiviral drugs have been studied previously [8]; the authors noted that timely distribution of antiviral drugs can reduce the household reproduction number, R_H, significantly. However, because the distribution capacity is limited in practice [4], it would be difficult to dispense antiviral drugs to affected households immediately after primary cases develop symptoms. Therefore, we considered the combination of antiviral prophylaxis and voluntary self-isolation as the interventions that would contain the transmission of influenza. We primarily focused on the role of voluntary self-isolation when antiviral drugs cannot be dispensed in a timely manner. The delays of one or two days were considered between symptom development and antiviral drug distribution. Home confinement of symptomatic individuals began at clinical symptom onset. T_A is the time at which antiviral drugs are dispensed to all household members relative to the onset of the primary case's symptoms. To evaluate the effect of voluntary self-isolation, the following six scenarios were considered:

- Strategy 1: antiviral prophylaxis (antiviral drugs were distributed to all household members at the introductory case's symptom onset; *i.e.*, $T_A = 0, q = 0$);
- Strategy 2: antiviral prophylaxis (antiviral drugs were distributed to all household members one day after the introductory case's symptom onset; *i.e.*, $T_A = 1, q = 0$);
- Strategy 3: antiviral prophylaxis (antiviral drugs were distributed to all household members two days after the introductory case's symptom onset; *i.e.*, $T_A = 2, q = 0$);
- Strategy 4: antiviral prophylaxis and voluntary self-isolation (antiviral drugs were distributed to all household members one day after the introductory case's symptom onset, where the rate of self-isolation compliance was $q = 0.5$; *i.e.*, $T_A = 1, q = 0.5, l = 0$);
- Strategy 5: antiviral prophylaxis and voluntary self-isolation (antiviral drugs were distributed to all household members two days after the introductory case's symptom onset, where the rate of self-isolation compliance was $q = 0.5$; *i.e.*, $T_A = 2, q = 0.5, l = 0$);
- Strategy 6: antiviral prophylaxis and voluntary self-isolation (antiviral drugs were distributed to all household members two days after the introductory case's symptom onset, where the rate of self-isolation compliance was $q = 0.7$; *i.e.*, $T_A = 2, q = 0.7, l = 0$).

Figure 1 shows the effects of the above six strategies on reducing the household reproduction number, R_H, where $\alpha = 1$ and other parameters assume the values in Table 1. The curves in Figure 1 show the values of the parameter pairs (μ, θ) when R_H equals one in the above six scenarios. For each curve in Figure 1, the parameter pairs (μ, θ) that satisfy $R_H > 1$ lie above the $R_H = 1$ curve, and those that satisfy $R_H < 1$ lie below the $R_H = 1$ curve.

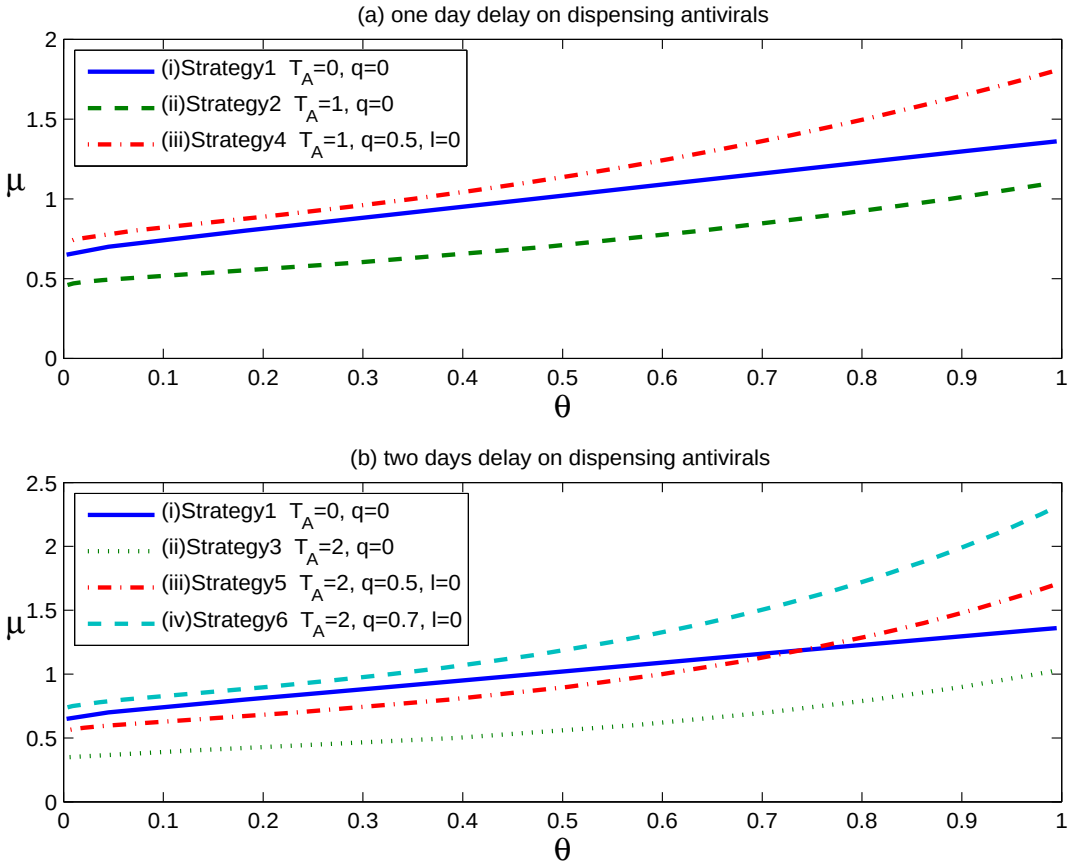

Figure 1. The effects of antiviral prophylaxis and voluntary self-isolation are displayed in two scenarios: (**a**) one day delay on dispensing antiviral drugs; (**b**) two days delay on dispensing antiviral drugs.

As shown in Figure 1a, Curve (iii) lies above Curve (ii), implying that the strategy of confining patients at home expands the set of parameter values (μ, θ) for which $R_H < 1$. In other words, the implementation of voluntary self-isolation expands the set of scenarios for which containment is achievable. In addition, Curve (iii) also lies slightly above Curve (i), denoting that Strategy 4 is nearly as effective as Strategy 1 with regard to reducing the household reproduction number, $R_H < 1$. Thus, assuming that 50% of symptomatic individuals complied with home confinement at symptom onset, the voluntary self-isolation would overcome the negative effect caused by an antiviral drug distribution delay of one day.

Figure 1b shows that the implementation of voluntary self-isolation was also effective when a two-day delay occurred between symptom development and the start of antiviral prophylaxis. Importantly, however, a high-enough compliance rate is required to achieve the same level of effectiveness as the strategy of dispensing antiviral drugs to affected households at symptom onset. Table 2 specifically

lists the needed compliance rates to achieve the same level of effectiveness as Strategy 1 or $R_H < 1$, corresponding to delays of one or two days from the start of antiviral prophylaxis after clinical symptom onset. These calculations assumed the baseline household reproduction numbers of $R_{H0} = 2.5$ and $\theta = 0.5$.

Table 2. The needed compliance rates to achieve the same level of effectiveness as Strategy 1 or $R_H < 1$.

Delay in start of antiviral prophylaxis	The compliance rate	The effectiveness of interventions
1 day ($T_A = 1$)	$q = 0.41$	same as the effectiveness of Strategy 1
2 days ($T_A = 2$)	$q = 0.6$	same as the effectiveness of Strategy 1
1 day ($T_A = 1$)	$q \geq 0.23$	$R_H < 1$
2 days ($T_A = 2$)	$q \geq 0.47$	$R_H < 1$

3.2. Voluntary Self-Isolation

We evaluated the effectiveness of voluntary self-isolation (as a single intervention) and explored how the household reproduction number, R_H, varied with the changes to the compliance rate, q.

The curves in Figure 2 show the values of parameters μ and θ when $R_H = 1$ for scenarios in which (i) no interventions were implemented, (ii) the fraction of voluntary self-isolation was 0.3, (iii) the fraction of voluntary self-isolation was 0.5 or (iv) the fraction of voluntary self-isolation was 0.7. The last three scenarios assumed that infected individuals confined themselves to home at symptom onset (*i.e.*, $l = 0$). The parameters $\alpha = 1, \delta = 0, \sigma = 1$ and other parameters assume the values in Table 1. For each curve in Figure 2, the parameter pairs (μ, θ) that satisfy $R_H > 1$ lie above the $R_H = 1$ curve, and those that satisfy $R_H < 1$ lie below the $R_H = 1$ curve.

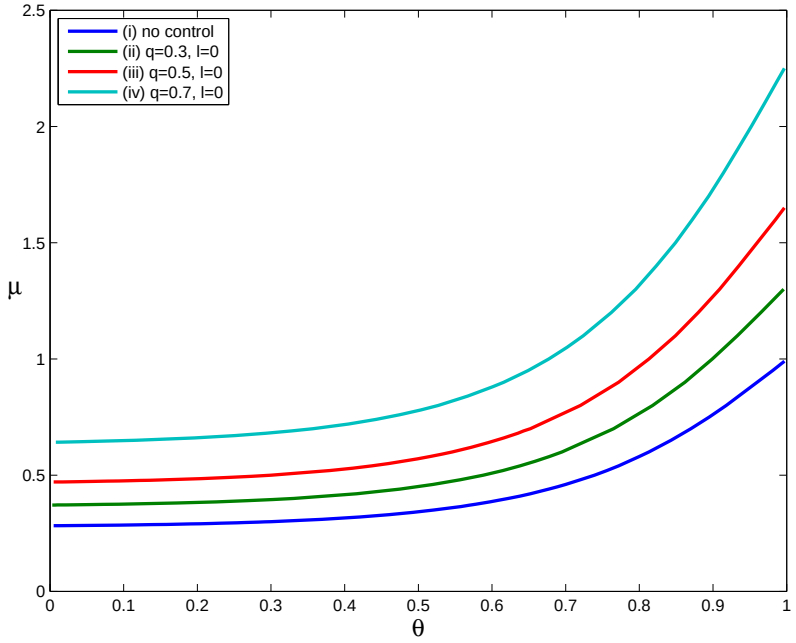

Figure 2. The effect of voluntary self-isolation.

As Figure 2 shows, Curves (ii) through (iv) lie above Curve (i), implying that the implementation of voluntary self-isolation expands the set of parameter pairs (μ, θ) for which $R_H < 1$. That is, the implementation of voluntary self-isolation effectively reduces the household reproduction number. Moreover, comparing the three Curves (ii), (iii) and (iv), we can see that the increase in the compliance rate q makes the $R_H = 1$ curve shift upward and significantly expands the set of parameter points for which $R_H < 1$. When we calculate values of R_H using the parameter points (μ, θ) that lie on Curves (ii), (iii) and (iv), but suppose that no interventions are implemented, we obtain the values of R_H in the intervals [1.3127, 1.3159], [1.6627, 1.6668] and [2.2673, 2.2729] corresponding to $q = 0.3$, $q = 0.5$ and $q = 0.7$, respectively. As shown here, an intervention strategy based only on voluntary self-isolation can reduce values of R_H from well above one to a value of one if a large proportion of infected individuals follow a public health department's voluntary self-isolation guidelines. Clearly, as the compliance rate falls, the effectiveness of this strategy would be greatly reduced. However, if even 30% of cases are persuaded to stay at home at the onset of their symptoms, transmission can be reduced to some extent.

3.3. The Impact of Delay in Voluntary Self-Isolation

The above results were obtained under the assumption that infected individuals voluntary self-isolate at the onset of their symptoms. However, in practice, delays often occur between the onset of symptoms and the implementation of voluntary self-isolation. Therefore, we considered how a delay in the implementation of voluntary self-isolation affects the effect of the voluntary self-isolation strategy. Considering a situation in which the compliance rate is 0.5 ($q = 0.5$) as an example, we examined the influence of a delay in the implementation of voluntary self-isolation on the household reproduction number, R_H.

Four scenarios were used to evaluate the effect of delayed voluntary self-isolation (Figure 3): (i) no interventions, (ii) voluntary self-isolation beginning two days after symptom onset, (iii) voluntary self-isolation beginning one day after symptom onset and (iv) voluntary self-isolation beginning at symptom onset. The parameters $\alpha = 1, \delta = 0, \sigma = 1$ and other parameters assume the values in Table 1. For each curve in Figure 3, $R_H < 1$ when the parameter points (μ, θ) lie below the $R_H = 1$ curve and $R_H > 1$ when the parameter pairs (μ, θ) lie above the $R_H = 1$ curve.

Comparing Curves (iv) and (i) in Figure 3, we can find that the implementation of voluntary self-isolation beginning at symptom onset significantly expands the set of parameter values (μ, θ) for which $R_H < 1$. This suggests that implementing the voluntary self-isolation strategy as soon as symptoms appear leads to a significant expansion in the set of scenarios in which containment is achievable (relative to the scenario in which no control measures were implemented). However, as the time between symptom onset and the start of voluntary self-isolation increases, the set of scenarios in which containment is achievable becomes smaller. Therefore, the effectiveness of voluntary self-isolation in reducing transmission decreases when voluntary self-isolation is delayed. For example, Curve (ii) lies slightly above Curve (i), which implies that home confinement of symptomatic individuals beginning two days after the onset of symptoms results in a slight expansion in the set of scenarios in which containment is possible. In other words, voluntary self-isolation had little effect on mitigating the transmission of influenza when voluntary confinement of cases occurred two days after the onset of

symptoms. Patients infected with influenza are infectious before their symptoms appear and are most infectious in the two to three days after symptom onset [8]. Therefore, voluntary self-isolation strategies are much more effective if implemented as soon as possible.

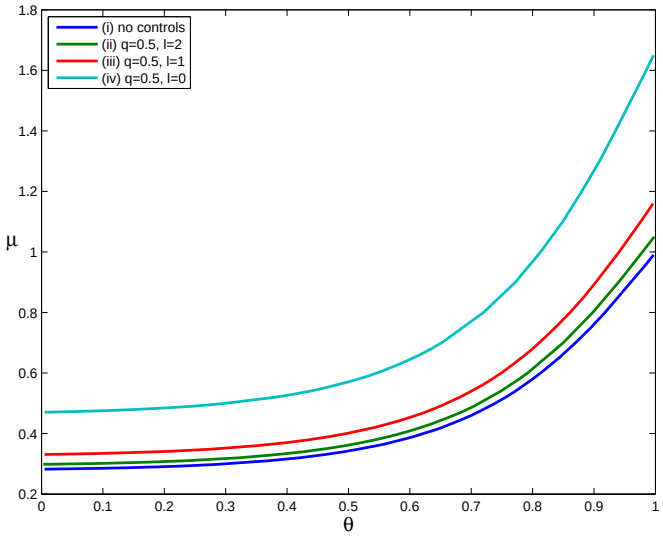

Figure 3. The impact of delay in voluntary self-isolation.

3.4. The Impact of Asymptomatic Infections

It is widely accepted that asymptomatic infection is an important route of influenza transmission [46]. Although asymptomatic cases can still shed the influenza virus, they are often excluded from the control objects, because they do not show apparent clinical symptoms. Therefore, the existence of asymptomatic infections will likely reduce the effectiveness of traditional control strategies. We examined the extent to which asymptomatic infections influence the effectiveness of voluntary self-isolation.

Due to their features, asymptomatic cases are difficult to diagnose, so clinical evidence of asymptomatic infection is extremely scarce [32]. The frequency of asymptomatic infections and the infectivity of asymptomatic individuals are thus hard to ascertain. Although there are a considerable variety of asymptomatic transmission scenarios, we assume that asymptomatic people have the same infectiousness as those with obvious clinical symptoms (*i.e.*, $\epsilon_k = 1, k = 1, 2, \cdots$).

We assume that infected individuals would only consider placing themselves in self-isolation after showing symptoms; consequently, asymptomatic cases and those individuals who develop clinical symptoms, but are not willing to stay home, would infect the same number of people as they would in the complete absence of voluntary self-isolation measures.

Based on the assumptions above, considering only voluntary self-isolation, the household reproduction number, R_H, can be expressed by:

$$\begin{aligned} R_H &= \alpha \sum_{j=1}^{\infty} g_j \sum_{C} P_1(C|j) \sum_{k=1}^{j} c_k \left(q\mu_k' + (1-q)\mu_k\right) \\ &\quad + (1-\alpha) \sum_{j=1}^{\infty} g_j \sum_{C} P_2(C|j) \sum_{k=1}^{j} c_k \mu_k \end{aligned} \tag{3}$$

where α is the probability that an infected individual will develop symptoms.

As noted by Carrat *et al.* [47], the frequency with which infected individuals develop symptoms is a key consideration in intervention strategies. Some studies have suggested that about two-thirds of individuals infected with influenza exhibit clinical symptoms, and the remainder are asymptomatic [46,47]. According to Hayward *et al.* [29], asymptomatic individuals infected with seasonal and pandemic influenza comprise approximately three-fourths of all infected individuals; only one-fourth of infected individuals are symptomatic. Numerical simulations use three different values of α ($\alpha = 1/4,\ 2/3,\ 1$).

Figure 4 illustrates how asymptomatic infections influence the effectiveness of voluntary self-isolation. Four scenarios were considered: (i) no intervention, (ii) $q = 0.5$ and $\alpha = 1$, (iii) $q = 0.5$ and $\alpha = 2/3$ and (iv) $q = 0.5$ and $\alpha = 1/4$. For each curve in Figure 4, $R_H < 1$ when the parameters (μ, θ) lie below the $R_H = 1$ curve and $R_H > 1$ when the parameters (μ, θ) lie above the $R_H = 1$ curve. From Figure 4, we can see that as the value of the parameter α decreases, the $R_H = 1$ curve moves down. This phenomenon implies that the decrease in the probability that an infected individual develops symptoms shrinks the set of scenarios in which containment is possible. In short, the effectiveness of voluntary self-isolation decreases as the probability of developing symptoms after infection decreases. For example, if an individual only has a one in four chance of developing symptoms after infection, voluntary self-isolation of symptomatic individuals with a compliance rate of $q = 0.5$ did not substantially reduce disease transmission. Assuming no voluntary self-isolation, when the values of R_H are calculated for the parameter pairs (μ, θ) on Curve (iv), R_H values are approximately 1.11. From this, we can see that voluntary self-isolation has only a limited effect on reducing the values of R_H if a high proportion of asymptomatic infections does indeed exist and if asymptomatic infected people have the same infectiousness as those with obvious clinical symptoms.

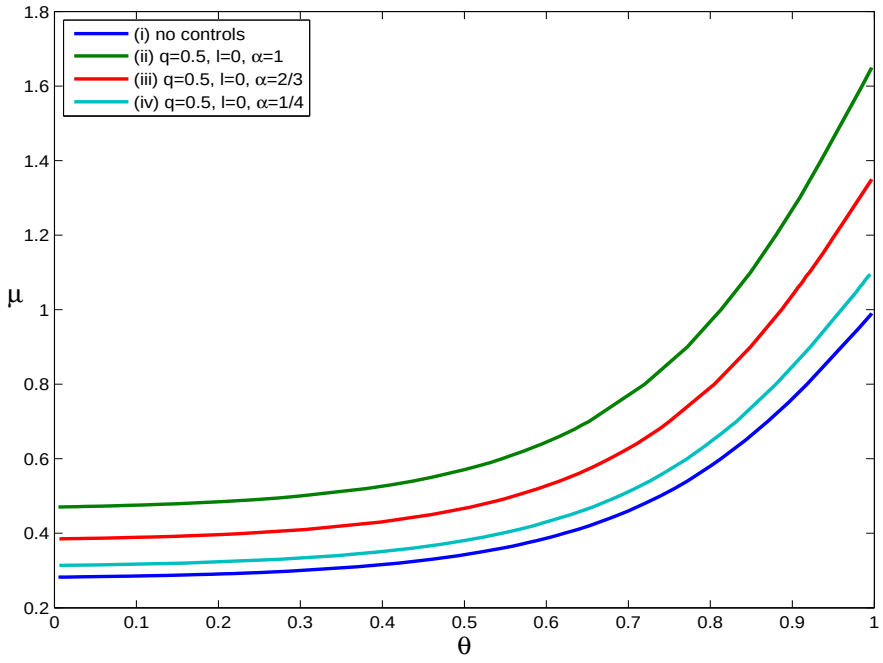

Figure 4. The impact of asymptomatic infected individuals.

4. Discussion and Conclusions

In the absence of a sufficient quantity of vaccines, antiviral drugs are often considered an important countermeasure against the influenza virus.

The effects of targeted prophylactic use of antiviral drugs have been studied previously [8]; the authors of that study noted that administering antiviral drugs to affected households immediately after symptom onset in the initial case reduced transmission significantly; furthermore, the effectiveness of this strategy decreases as antiviral drug distribution time increases. However, a delay between distribution of antiviral drugs and onset of symptoms is usually inevitable in practice because of a limited capacity to quickly distribute drugs [4]. In this case, measures aimed at reducing the contact rates between ill and susceptible people should be considered. Therefore, voluntary self-isolation should be applied as an intervention to reduce the transmission of pandemic influenza when antiviral drugs cannot be dispensed in a timely manner.

Our results indicate that the implementation of a voluntary self-isolation strategy would improve transmission containment or, in other words, that the household reproduction number, R_H, would be reduced to less than one if a large proportion of symptomatic infected individuals complied with public health departments' instructions to isolate themselves from other community members as soon as symptoms appeared. Naturally, if fewer infected individuals complied with this recommendation, this strategy would be less effective. However, if even a relatively small fraction of infected individuals were to comply with voluntary self-isolation, transmission could be reduced to some extent, and voluntary self-isolation is extremely critical when antiviral drugs are not immediately available. Importantly, the home confinement of infected individuals only succeeds when ill people are willing to comply with this containment measure. The effectiveness of voluntary self-isolation largely depends on public adherence to this intervention measure. With further understanding of pandemic influenza, the compliance with public health containment measures increased significantly [48]. Therefore, before possible intervention measures can be implemented against pandemic influenza, it might be necessary to disseminate knowledge of its clinical symptoms and associated containment measures to the public [34].

In addition, the efficacy of voluntary self-isolation is reduced if the implementation of voluntary self-isolation is delayed. Simulation results suggest that voluntary self-isolation has little impact on reducing the values of R_H if voluntary self-isolation is implemented two days after the onset of symptoms. Therefore, one prerequisite for the voluntary self-isolation policy is the timeliness of its execution.

It is widely believed that asymptomatic infections are one of the major sources of influenza transmission. Here, we evaluated the impact of asymptomatic cases on the spread of influenza using the assumption that asymptomatic infected individuals were as infectious as symptomatic individuals [38]. We found that as the probability of infected individuals exhibiting symptoms decreases, the effectiveness of voluntary self-isolation likewise decreases. If the frequency of asymptomatic infections exceeds a given value, the effectiveness of voluntary self-isolation becomes very limited.

There are several requirements for the implementation of antiviral prophylaxis. (1) The stockpile of antiviral drugs must be adequate. (2) Infected individuals must develop clinically-recognizable symptoms and have access to healthcare. (3) Lastly, antiviral drugs must be dispensed rapidly to

affected families. Some obstacles to the implementation of antiviral prophylaxis strategies may be found in practice because of the level of logistical support that would be required. Therefore, voluntary self-isolation should be implemented especially when antiviral drugs cannot be provided immediately. Unfortunately, voluntary self-isolation strategies may inconvenience individuals, lead to economic losses or even contribute to moral conflicts; thus, voluntary self-isolation remains a controversial strategy [21]. However, our results suggest that voluntary self-isolation is a feasible way to contain an influenza pandemic. It is worthwhile to note that voluntary self-isolation should be implemented as early as possible after symptoms develop and that, if an especially high proportion of cases are asymptomatic, other control measures should be considered, because the effectiveness of voluntary self-isolation will be reduced. These topics will be explored further in future studies.

Appendix

Outline of the Derivation of Equation (1)

During the containment phase of the pandemic, as [8], we assume that each newly-infected person who is selected at random from the community gives rise to a new independent transmission process with the same eventual mean number of cases. Then, the eventual mean number of cases, EY, satisfies the following equation:

$$\begin{aligned} EY = \; & \alpha \sum_{j=1}^{\infty} g_j \sum_{C} P_1(C|j) \sum_{k=1}^{j} c_k \left(q \sum_{m=0}^{\infty} \phi'_{m,k}(1+mEY) + (1-q) \sum_{m=0}^{\infty} \phi_{m,k}(1+mEY) \right) \\ & + (1-\alpha) \sum_{j=1}^{\infty} g_j \sum_{C} P_2(C|j) \sum_{k=1}^{j} c_k \sum_{m=0}^{\infty} \phi''_{m,k}(1+mEY). \end{aligned}$$

By simply computation, we obtain:

$$\begin{aligned} EY = \; & \alpha \sum_{j=1}^{\infty} g_j \sum_{C} P_1(C|j) \sum_{k=1}^{j} c_k + (1-\alpha) \sum_{j=1}^{\infty} g_j \sum_{C} P_2(C|j) \sum_{k=1}^{j} c_k \\ & + EY \left(\alpha \sum_{j=1}^{\infty} g_j \sum_{C} P_1(C|j) \sum_{k=1}^{j} c_k \left(q\mu'_k + (1-q)\mu_k \right) + (1-\alpha) \sum_{j=1}^{\infty} g_j \sum_{C} P_2(C|j) \sum_{k=1}^{j} c_k \epsilon_k \mu_k \right). \end{aligned}$$

Denote:

$$v_H = \alpha \sum_{j=1}^{\infty} g_j \sum_{C} P_1(C|j) \sum_{k=1}^{j} c_k + (1-\alpha) \sum_{j=1}^{\infty} g_j \sum_{C} P_2(C|j) \sum_{k=1}^{j} c_k,$$

which is the average size of an outbreak within a household that is selected randomly from the community, and:

$$R_H = \alpha \sum_{j=1}^{\infty} g_j \sum_{C} P_1(C|j) \sum_{k=1}^{j} c_k \left(q\mu'_k + (1-q)\mu_k \right) + (1-\alpha) \sum_{j=1}^{\infty} g_j \sum_{C} P_2(C|j) \sum_{k=1}^{j} c_k \epsilon_k \mu_k,$$

which is the mean number of primary cases generated in the community by all of the infected individuals of an affected household that is selected randomly from the community. Then, the eventual mean number of cases, EY, can be expressed as:

$$EY = \frac{v_H}{1 - R_H}. \tag{1}$$

Obviously, the household reproduction number must be $R_H < 1$ for Equation (1) to be valid.

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Conflicts of Interest

The authors declare no conflicts of interest.

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