CORONAVIRUS UPDATE
80

LAST UPDATED:
29 SEP 2022

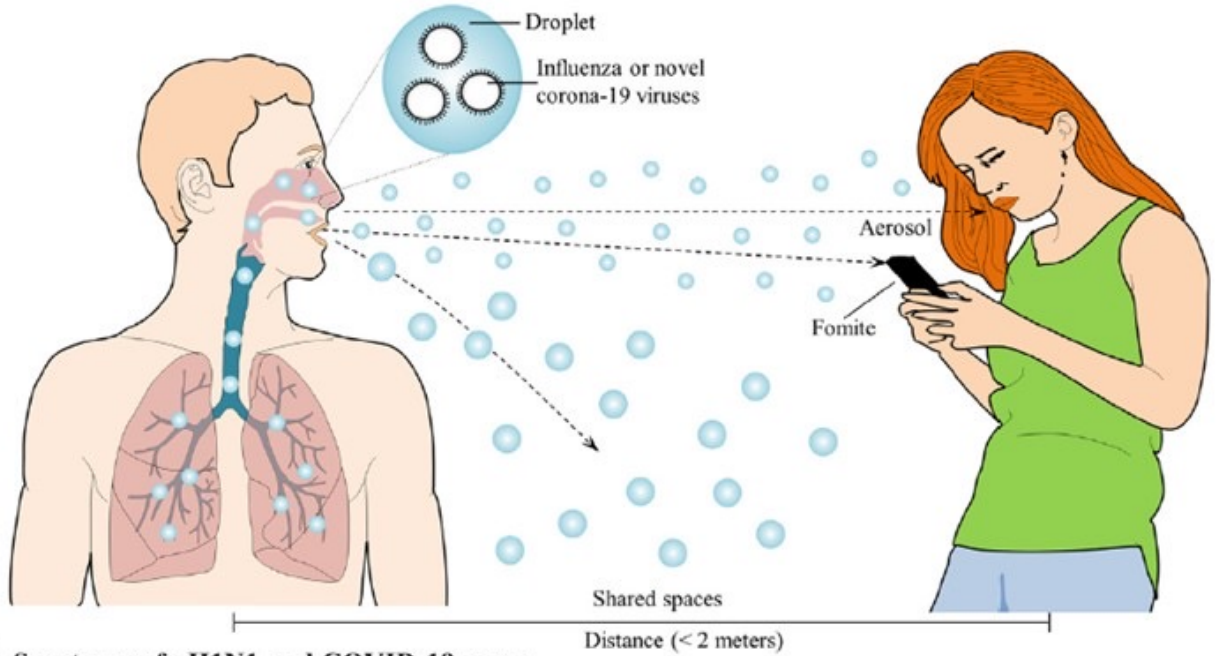
Managing influenza epidemics during a COVID-19 pandemic: the clinician's perspective

David SC Hui, MD
Stanley Ho Professor of Respiratory Medicine
Dept of Medicine & Therapeutics
The Chinese University of Hong Kong
Prince of Wales Hospital

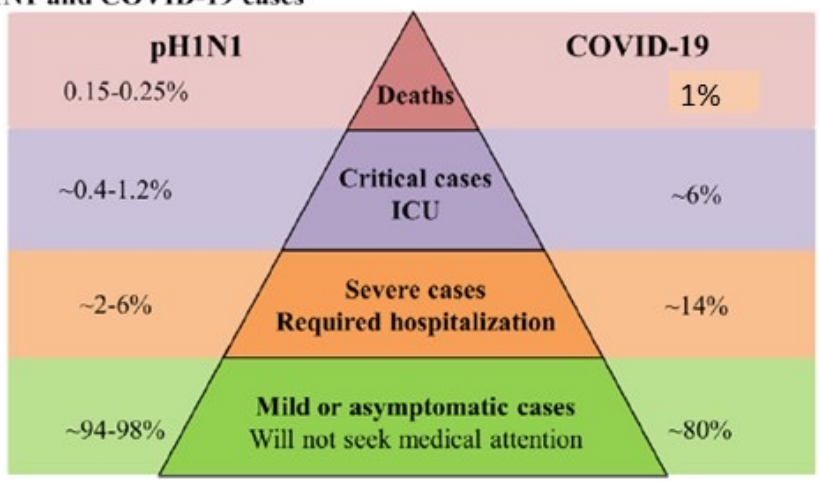
Managing flu epidemics during COVID-19 pandemic

- Clinical symptoms/signs/spectrum
- Viral kinetics & transmission
- Diagnostic tests
- Drug treatment
- Influenza vaccination

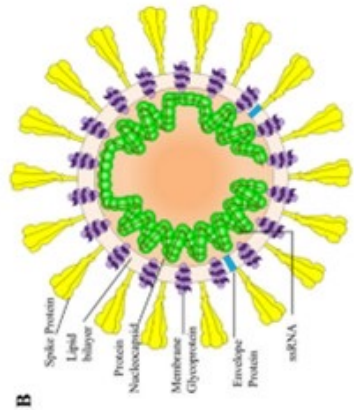
A Route of human-to-human transmission of the Influenza and SARS-CoV-2 viruses

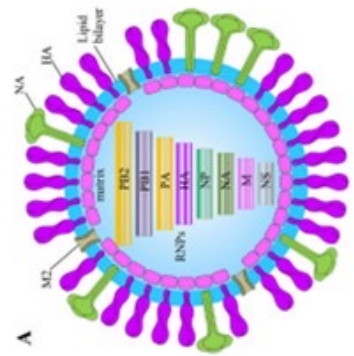


B Spectrum of pH1N1 and COVID-19 cases

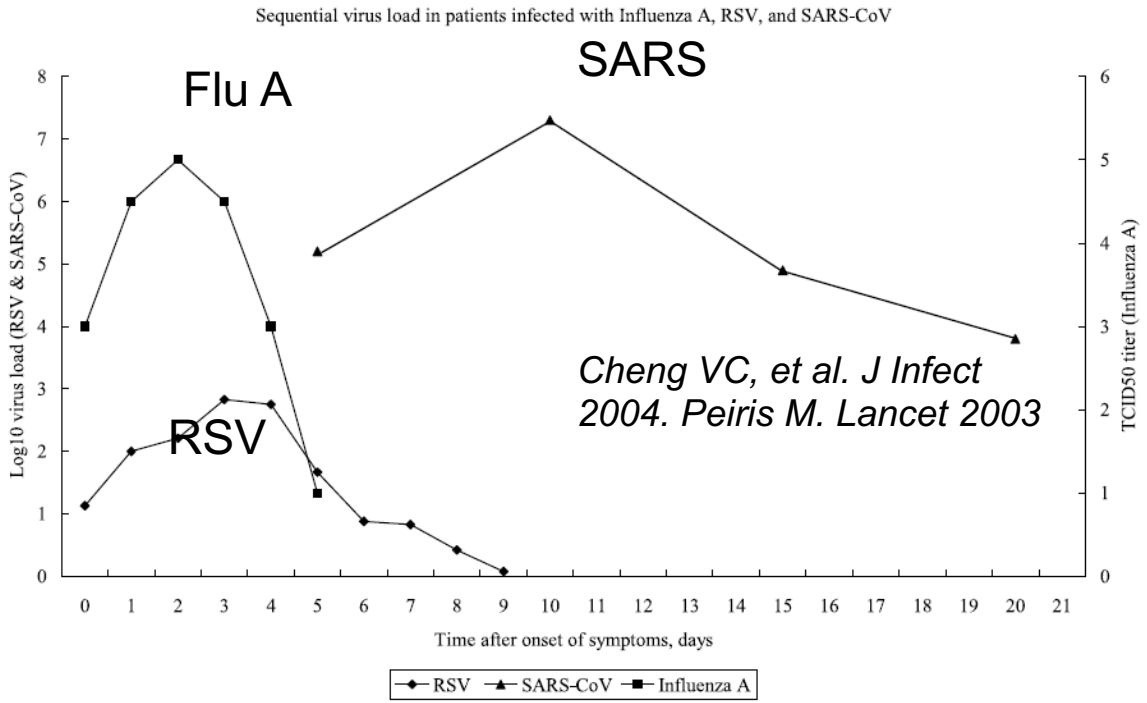


Journal of Infection and Public Health 13 (2020) 1797–1804

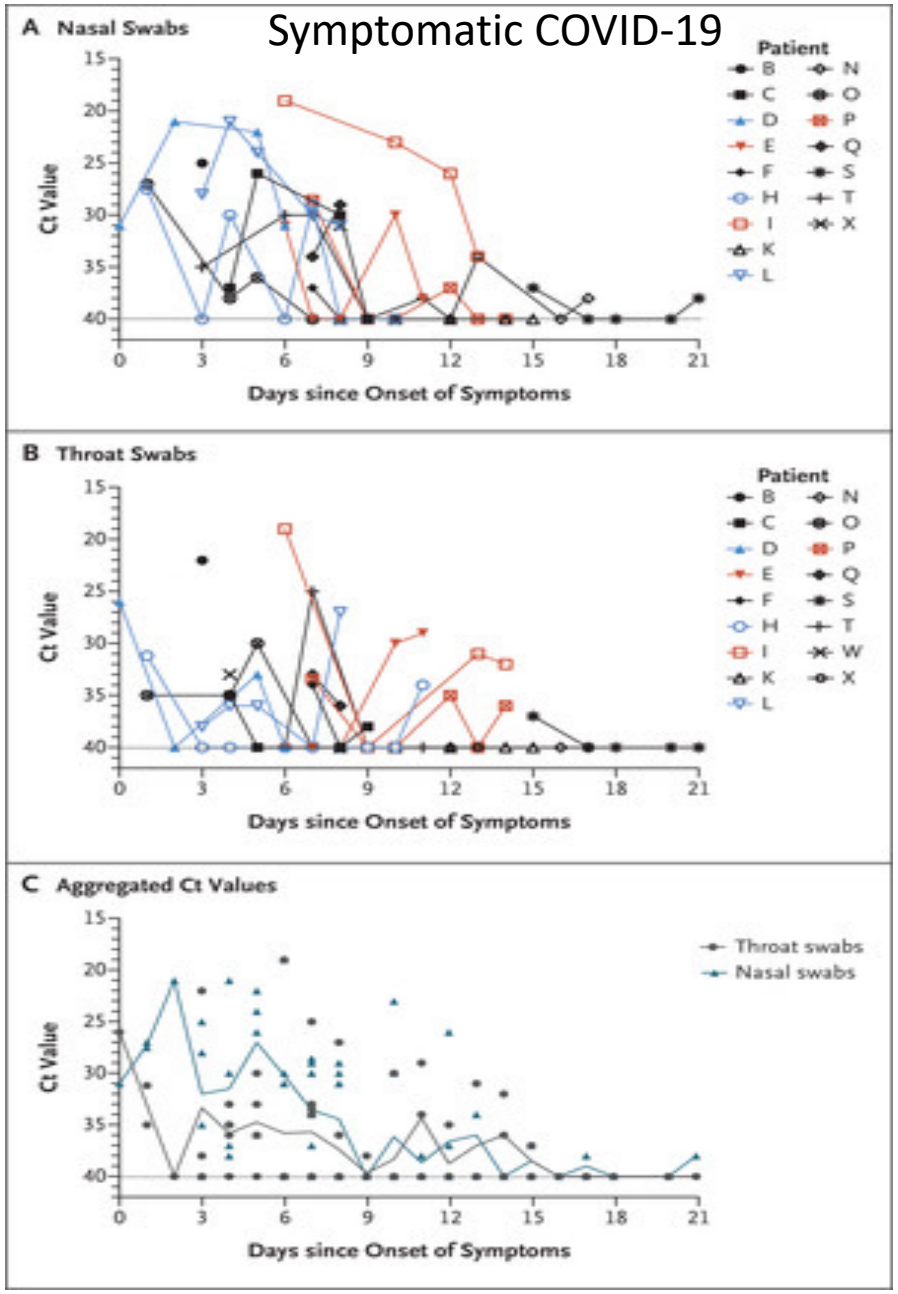




V.C. da Costa et al.



The viral nucleic acid shedding pattern of patients infected with SARS-CoV-2 resembles that of patients with influenza. *Zou L. NEJM 2020*



Supplementary Table 2. Characteristics of Seasonal Influenza A or B Virus Infections Compared with SARS-CoV-2 Infections

Parameter	Influenza Virus	SARS-CoV-2***
Asymptomatic proportion	Estimated 14% to >50%	Approximately 20%, higher estimates in some settings
Incubation period	Median 1.4 days for influenza A virus, range 1-4 days	Median - approximately 5 days for the original Wuhan strain (shorter for some variants; 3 days for Omicron; 4 days for Delta), range 2-14 days
Serial interval	2-3 days	Approximately 5 days for the original Wuhan strain (3-4 days for some variants)
Basic reproduction number (R_0)	Approximately 1.3	Approximately 2.7, but varies by time, country, setting, immunity among contacts, use of non-pharmaceutical interventions, and variants and sub variant viruses
Prevention:	***Primary:*** Annual influenza vaccination for persons aged ≥6 months: annual influenza vaccination (children aged 6 months through 8 years old not previously vaccinated need 2 vaccine doses 4 weeks apart) ***Secondary:*** Post-exposure prophylaxis with oseltamivir or baloxavir for institutional outbreaks, or high-risk individuals, depending upon age	***Primary:*** Age ≥6 months: approved or authorized COVID-19 vaccine primary series Age ≥5 years: booster dose after COVID-19 vaccine primary series if eligible ***Secondary:*** Pre-exposure prophylaxis with anti-SARS-CoV-2 monoclonal antibodies for adults with moderate or severe immunocompromise not expected to respond to COVID-19 vaccination Post-exposure prophylaxis with anti-SARS-CoV-2 monoclonal antibodies for persons at high risk for progression to severe disease
Symptoms of uncomplicated illness	Abrupt onset of upper respiratory symptoms (non-productive cough, rhinorrhea, sore throat), with or without fever and chills, often with myalgia, fatigue, headache, diarrhea in children	Cough, nasal congestion, rhinorrhea, fever and chills, fatigue or weakness, headache, myalgia, hyposmia or anosmia, nausea, vomiting, diarrhea, abdominal pain, sore throat, hypogeusia or ageusia, conjunctivitis, chilblain-like lesions of hands and toes

Uyeki T, et al. Lancet 2022

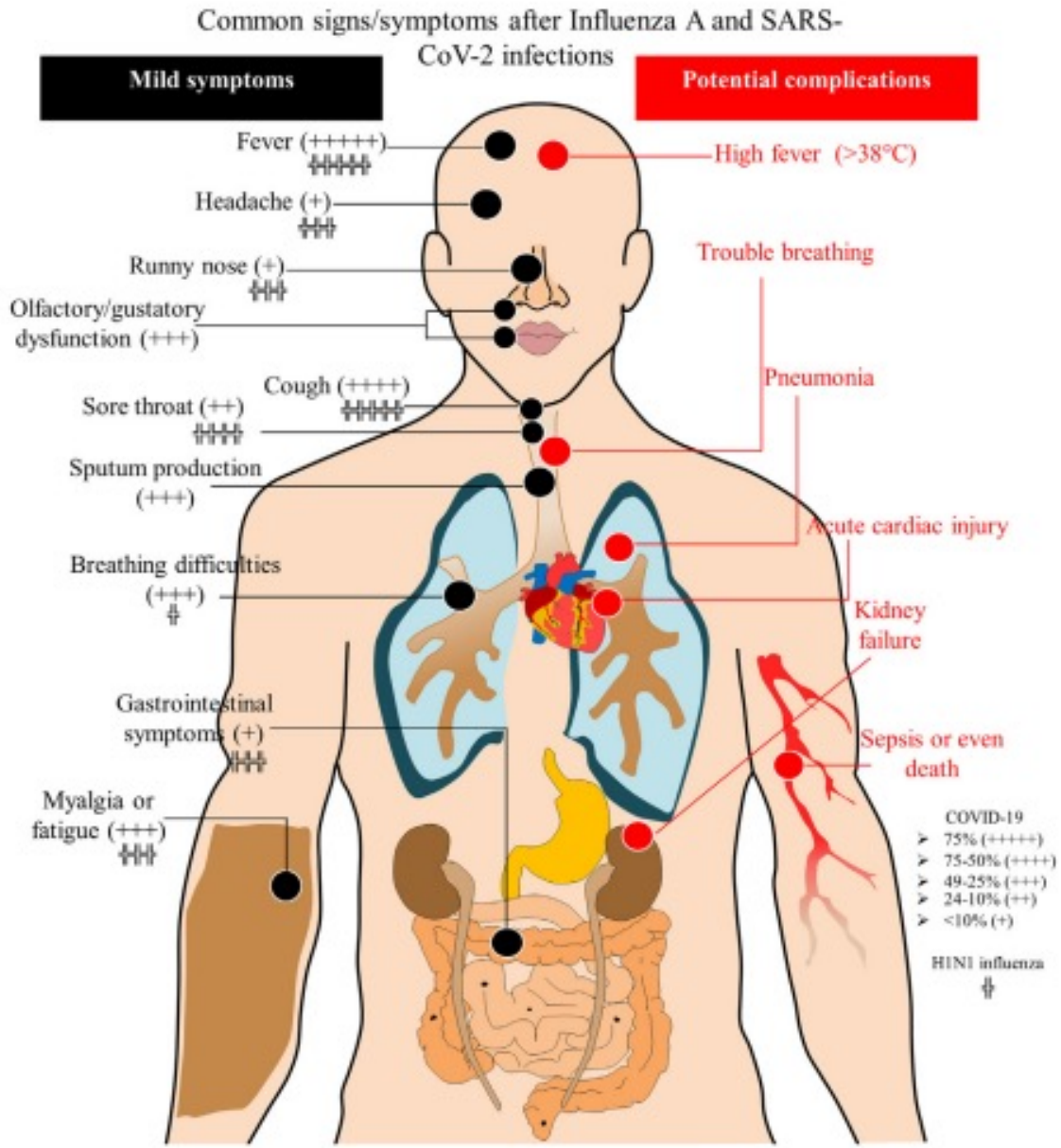


Fig. 4. Schematic image of the clinical picture of influenza A and COVID-19 [18,60,64,90–94].

Supplementary Table 2. Characteristics of Seasonal Influenza A or B Virus Infections Compared with SARS-CoV-2 Infections

Parameter	Influenza Virus	SARS-CoV-2***
Diagnostic testing (respiratory specimens)	Rapid antigen test, rapid molecular assay (including multiplex assays that detect influenza A/B/SARS-CoV-2), multiplex molecular assays can detect other viral pathogens *Respiratory specimens*: nasopharyngeal, nasal swabs preferred; lower respiratory specimens for molecular assays	Rapid antigen test, rapid molecular assay (including multiplex assays that detect influenza A/B/SARS-CoV-2), multiplex molecular assays (can detect other viral pathogens *Respiratory specimens:* nasopharyngeal, nasal swabs preferred, some assays use throat swabs or saliva specimens; lower respiratory specimens for molecular assays
Outpatient treatment	Early initiation of antiviral treatment (neuraminidase inhibitor or baloxavir) within 2 days of symptom onset; oseltamivir is recommended for pregnancy, high-risk persons and progressive disease even if >2 days from symptom onset; supportive care	High-risk patients within 10 days of symptom onset: treatment with anti-SARS-CoV-2 monoclonal antibody products High-risk patients within 5 days of symptom onset: treatment with oral antiviral (molnupiravir, PAXLOVID)
Time course to severe disease	Typically, within 3-7 days after onset	Often in the 2nd week of the clinical course after onset; multisystem inflammatory syndrome can present several weeks after recovery from initial COVID-19 illness or asymptomatic SARS-CoV-2 infection

Uyeki T, et al. Lancet 2022

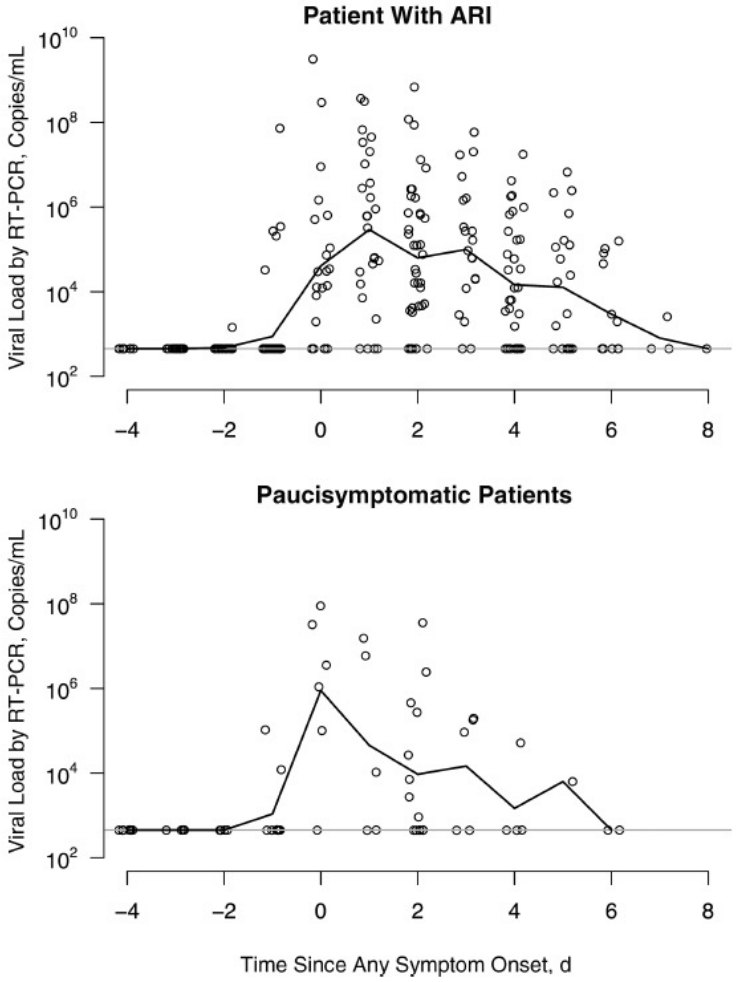


Figure 2. Patterns of viral shedding in naturally acquired influenza virus infections by day since first symptom onset (day 0) in patients with acute respiratory illness (ARI) (*upper panel*) and paucisymptomatic patients (*lower panel*). RT-PCR, reverse-transcription polymerase chain reaction.

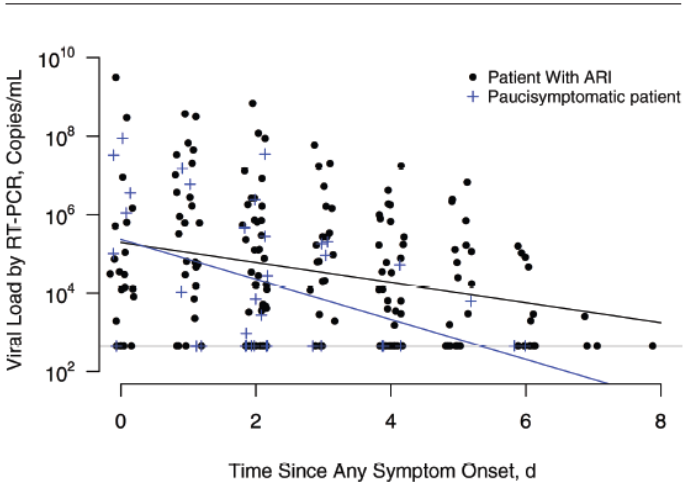
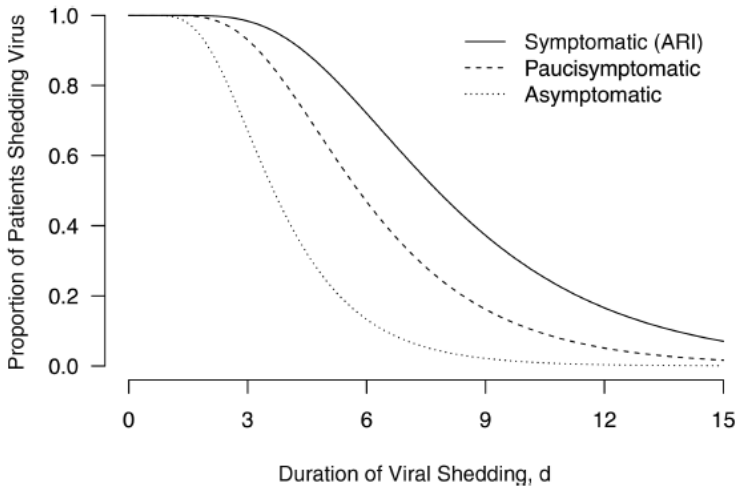


Figure 3. Rate of viral load decline as measured by reverse-transcription polymerase chain reaction (RT-PCR) in paucisymptomatic patients (*blue line*) and patients with acute respiratory illness (ARI) (*black line*).



Viral Shedding and Transmission Potential of Asymptomatic and Paucisymptomatic Influenza Virus Infections in the Community CID 2017

Dennis K. M. Ip,[1] Lincoln L. H. Lau,[4] Nancy H. L. Leung,[1] Vicky J. Fang,[1] Kwok-Hung Chan,[2] Daniel K. W. Chu,[1,3] Gabriel M. Leung,[1] J. S. Malik Peiris,[1,3] Timothy M. Uyeki,[5] and Benjamin J. Cowling[1]

The duration of viral RNA shedding was shorter & declined more rapidly in paucisymptomatic and asymptomatic than in symptomatic cases.

The mean levels of influenza viral RNA shedding in asymptomatic and paucisymptomatic cases were about 1–2 log10 copies lower than in symptomatic cases.

The presence of influenza viral shedding in patients with influenza who have very few or no symptoms reflects their potential for transmitting the virus to close contacts.

WHO 2022

Table 1.1. People at greater risk for severe illness or complications

People with certain medical conditions *(6–8)*:

- chronic cardiac disease (such as coronary artery disease, congenital heart disease, congestive heart failure);
- asthma and chronic pulmonary disease (such as chronic obstructive pulmonary disease [COPD], cystic fibrosis);
- chronic renal disease;
- metabolic disorders;
- endocrine disorders (such as diabetes);
- neurologic and neurodevelopmental disorders;
- liver disease;
- haematologic diseases (such as sickle cell disease);
- individuals with immunosuppressive conditions (such as HIV/AIDS, receiving chemotherapy or systemic corticosteroids or malignancy).

Other persons at greater risk for severe disease include:

- pregnant women and women up to 2 weeks postpartum;
- children under 59 months, particularly younger than 2 years old;
- persons 65 years and older;
- people younger than 19 years of age on long-term aspirin- or salicylate-containing medications;
- people with a body mass index (BMI) of 40 or higher.

Health care workers are at high risk of acquiring influenza virus infection due to increased exposures during patient care and risk further spread, particularly when caring for vulnerable patients.

Supplementary Table 2. Characteristics of Seasonal Influenza A or B Virus Infections Compared with SARS-CoV-2 Infections

Parameter	Influenza Virus	SARS-CoV-2***
Complications (rare complications not included)	Exacerbation of chronic disease; respiratory (otitis media, sinusitis, laryngotracheobronchitis, bronchiolitis, reactive airway disease, pneumonia, respiratory failure, acute respiratory distress syndrome); cardiac (myocardial infarction, myocarditis, pericarditis, heart failure); gastrointestinal (hepatic inflammation); musculoskeletal (myositis, rhabdomyolysis); neurologic (encephalopathy, encephalitis, meningoencephalitis, febrile seizures); acute kidney injury	Respiratory (pneumonia, respiratory failure, acute respiratory distress syndrome, pulmonary embolism); cardiac (acute cardiac injury, myocarditis, acute coronary syndrome, heart failure, arrhythmias, thromboembolic events, sudden cardiac death); gastrointestinal (hepatic inflammation); musculoskeletal (myositis, myopathy, rhabdomyolysis); neurologic (encephalopathy, meningoencephalitis, impaired consciousness, syncope, seizures, ischemic stroke, cardioembolic stroke, intracerebral hemorrhage, cranial nerve impairment, visual deficits, and oculomotor impairment, neuroinflammatory disorders, peripheral neuropathies; coagulopathy (venous thromboembolism – pulmonary embolism, deep venous thrombosis, arterial thrombi; cerebral venous sinus thrombosis); multisystem inflammatory syndrome in children and adults; Post-COVID conditions
Co-infections	Community-acquired bacterial pneumonia can be common in hospitalized patients; invasive fungal infection is generally uncommon, but frequency varies widely, more common in immunocompromised and with corticosteroid treatment	Community-acquired invasive bacterial or fungal co-infections are generally uncommon in hospitalized patients, but frequency varies widely
Outpatient treatment**	Early initiation of antiviral treatment (neuraminidase inhibitor or baloxavir) within 2 days of symptom onset; oseltamivir is recommended for high-risk patients and progressive disease even if >2 days from symptom onset; supportive care	High-risk patients within 10 days of symptom onset: treatment with anti-SARS-CoV-2 monoclonal antibody products for susceptible variant/sub variant infections High-risk patients within 5 days of symptom onset: treatment with oral antiviral (nirmatrelvir-ritonavir, molnupiravir) High-risk patients within 7 days of symptom onset: treatment with intravenous antiviral (remdesivir)
In-patient treatment**	Antiviral treatment (oseltamivir); antimicrobial therapy for community-acquired secondary co-infections and healthcare-associated co-infections, including ventilator-associated pneumonia; supportive care, advanced organ support for organ failure	Antiviral treatment (remdesivir); immunomodulators (dexamethasone, IL-6 receptor inhibitor, Janus Kinase Inhibitor); antimicrobial therapy for uncommon community-acquired secondary co-infections and healthcare-associated infections, including ventilator-associated pneumonia; supportive care including anticoagulation if indicated, advanced organ support for organ failure

Uyeki T, et al. Lancet 2022

Corticosteroids as adjunctive therapy in the treatment of influenza (Review)

Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS

Cochrane Database of Systematic Reviews 2016, Issue 3. Art. No.: CD010406.

On meta-analysis, corticosteroid Rx was associated with ↑ in mortality (OR 3.06, 95%CI 1.58 to 5.92). Pooled subgroup analysis of adjusted estimates of mortality from 4 studies found OR 2.82, 95% CI 1.61 to 4.92.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Corticosteroid therapy			
Mortality	141 per 1000	334 per 1000 (206 to 493)	OR 3.06 (1.58 to 5.92)	1915 (13 studies)	⊕◯◯◯ very low[a]
Hospital-acquired infection	See comment	See comment	Not estimable	619 (3 studies)	⊕◯◯◯ very low[b]
Critical illness (composite outcome including death and intensive care unit admission)	See comment	See comment	Not estimable	322 (2 studies)	⊕◯◯◯ very low[c]
Mechanical ventilation	See comment	See comment	Not estimable	377 (2 studies)	⊕◯◯◯ very low[d]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

High-dose corticosteroids associated with increased mortality & longer viral shedding in pts with influenza A (H7N9) viral pneumonia.

TABLE 5. Outcomes From 65 Propensity Score–Matched Patient Pairs

Outcome	All			Low-to-Moderate Corticosteroid Dose			High Corticosteroid Dose		
	Corticosteroid, *n* = 65	Control, *n* = 65	*p*	Corticosteroid, *n* = 39	Control, *n* = 39	*p*	Corticosteroid, *n* = 26	Control, *n* = 26	*p*
Mortality,[a] *n* (%)				(25–150mg/d methylpred)			(> 150 mg/d methylpred eqv)		
30-d mortality	19 (29.2)	8 (12.3)	0.019	9 (23.1)	6 (15.4)	0.508	10 (38.5)	2 (7.7)	0.021
60-d mortality	27 (41.5)	10 (15.3)	0.002	14 (35.9)	6 (15.4)	0.057	13 (50.0)	4 (15.4)	0.022
Nosocomial infections,[a] *n* (%)									
HAP	17 (26.2)	18 (27.7)	1.000	10 (25.6)	12 (30.8)	0.804	7 (26.9)	6 (23.1)	1.000
HAP complicated by bacteremia, *n* (%)	7 (10.8)	3 (4.6)	0.289	3 (7.7)	1 (2.6)	0.625	4 (15.4)	2 (7.7)	0.625
Nosocomial bacteremia or candidemia, *n* (%)	4 (6.2)	2 (3.1)	0.625	0 (0.0)	1 (2.6)	1.000	4 (15.4)	1 (3.8)	0.250
Invasive pulmonary aspergillosis or mucormycosis, *n* (%)	4 (6.2)	4 (6.2)	1.000	2 (5.1)	1 (2.6)	1.000	2 (7.7)	3 (11.5)	1.000
Viral shedding (d)[b]	14 (12–17)	12 (11–15)	0.027	13 (10.3–16)	12 (10.5–15)	0.252	15 (13.5–20)	13 (10.8–15.3)	0.039

Cao B, et al. Crit Care Med 2016

WHO 2022

Recommendations on antivirals – neuraminidase inhibitors	
1	**We suggest administering oseltamivir as soon as possible (vs not administering oseltamivir).** Conditional recommendation, low-quality evidence. Implementation: when the decision to use oseltamivir is made, it should be administered as soon as possible.
2	**We suggest not administering inhaled zanamivir (vs administering inhaled zanamivir).** Conditional recommendation, very low-quality evidence.
3	**We suggest not administering inhaled laninamivir (vs administering inhaled laninamivir).** Conditional recommendation, very low-quality evidence.
4	**We suggest not administering intravenous peramivir (vs administering intravenous peramivir).** Conditional recommendation, very low-quality evidence.

Recommendations on adjunctive therapies	
5	**We suggest not administering corticosteroids (vs administering corticosteroids).** Conditional recommendation, very low-quality evidence.
6	**We suggest not administering passive immune therapy (vs administering passive immune therapy).** Conditional recommendation, very low-quality evidence.
7	**We suggest not administering a macrolide antibiotic for treatment of influenza (vs administering a macrolide).** Conditional recommendation, very low-quality evidence.

During the COVID-19 pandemic, WHO recommends below priority groups for seasonal influenza vaccination:

- Highest priority:
  - Health workers
  - Older adults
- Priority (in no particular order):
  - Pregnant women
  - Individuals with specific chronic medical conditions
  - Children aged 6-59 months

The WHO recommends that quadrivalent vaccines for use in the 2022-2023 influenza season in the northern hemisphere contain the following:

Egg-based vaccines

- an A/Victoria/2570/2019 (H1N1)pdm09-like virus;
- an A/Darwin/9/2021 (H3N2)-like virus;
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus; and
- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

Cell culture- or recombinant-based vaccines

- an A/Wisconsin/588/2019 (H1N1)pdm09-like virus;
- an A/Darwin/6/2021 (H3N2)-like virus;
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus; and
- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

WHO recommends that **quadrivalent vaccines** for use in the 2023 southern hemisphere influenza season contain the following:

Egg-based vaccines

- an A/Sydney/5/2021 (H1N1)pdm09-like virus;
- an A/Darwin/9/2021 (H3N2)-like virus;
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus; and
- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

Cell culture- or recombinant-based vaccines

- an A/Sydney/5/2021 (H1N1)pdm09-like virus;
- an A/Darwin/6/2021 (H3N2)-like virus;
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus; and
- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

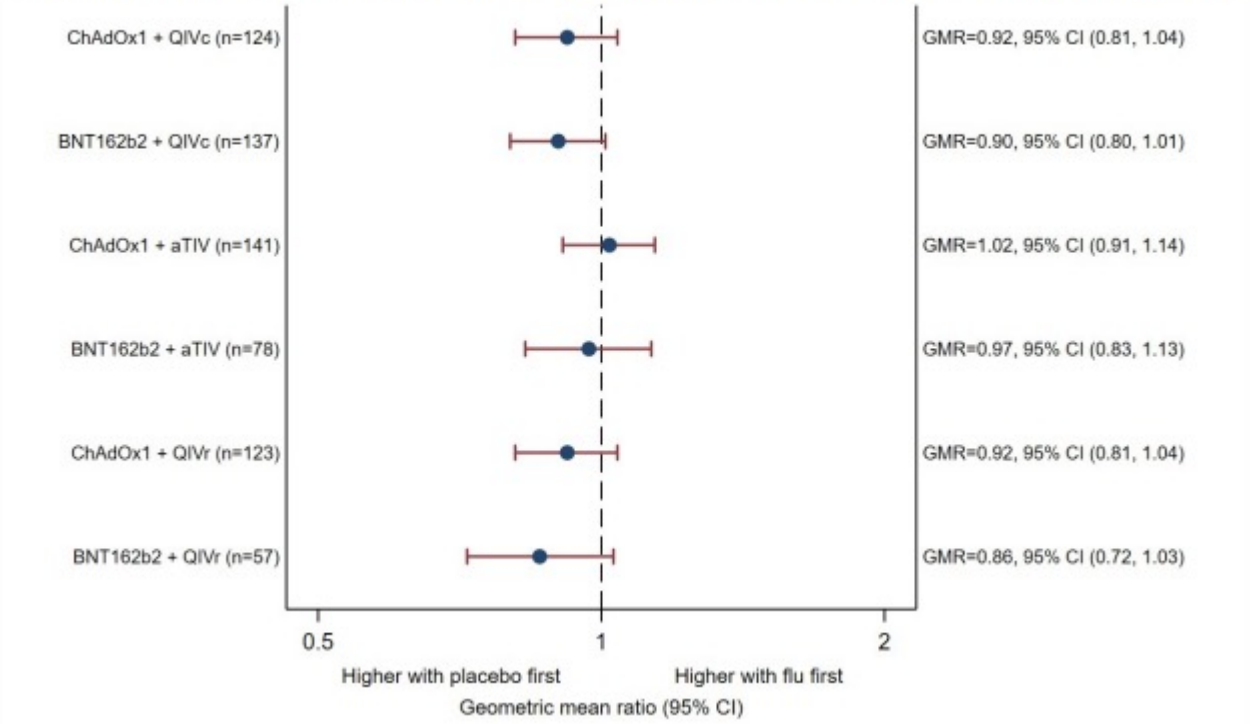
Interim guidance

21 October 2021

Coadministration of seasonal inactivated influenza and COVID-19 vaccines

World Health Organization

Figure 2. Anti-S IgG GMT ratios between participants given COVID-19 vaccine with or without influenza vaccine.



Anti-S IgG geometric mean titres (GMTs), measured 21 days after receipt of either ChAdOx1 or BNT162b2, were similar in those who received concomitant vaccination or COVID-19 vaccine alone in all cohorts (Figure 2)

Only limited evidence on COVID-19 vaccine coadministration with influenza vaccine exist, but available evidence does not show increased adverse events. Therefore, WHO considers that coadministration of an inactivated seasonal influenza vaccine and any dose of a COVID-19 vaccine is acceptable, given that the known risk of serious illness for adults infected with influenza virus or SARS-CoV-2 is substantial.

WHO recommends using the contralateral limb for injection, when the two vaccines are administered during the same visit, to minimize any perceived risk.

Reactogenicity of Simultaneous COVID-19 mRNA Booster and Influenza Vaccination in the US

Table 4. Reactions and Health Impacts Reported in v-safe Respondents

Reaction	Simultaneous influenza and COVID-19 mRNA booster vaccine received, aOR (95% CI)[a,b] (N = 92 023)	
	Pfizer-BioNTech (n = 61 390)	Moderna (n = 30 633)
Any injection site reaction	1.10 (1.08-1.12)	1.05 (1.02-1.08)
Any systemic reaction fatigue, headache, and muscle ache	1.08 (1.06-1.10)	1.11 (1.08-1.14)
Any health impact[c]	0.99 (0.97-1.02)	1.05 (1.02-1.08)
Unable to perform normal daily activities	0.99 (0.97-1.01)	1.04 (1.01-1.07)
Unable to work or attend school	1.04 (1.01- 1.07)	1.08 (1.04-1.12)
Needed medical care	0.92 (0.84-1.01)	0.94 (0.83-1.07)

Hause AM, et al. JAMA Network Open 2022

Key Points

Question Are systemic reactions more common after simultaneous administration of COVID-19 mRNA booster and seasonal influenza vaccines than after COVID-19 mRNA booster alone?

Findings In this cohort study of self-reported data from 981 099 persons aged 12 years or older, simultaneous administration of a COVID-19 mRNA booster dose and an influenza vaccine was associated with 8% to 11% increases, respectively, in systemic reaction compared with COVID-19 mRNA booster alone. These differences were statistically significant.

Meaning Findings from this study suggest that simultaneous administration of COVID-19 mRNA booster and influenza vaccines may be associated with increased likelihood of systemic reactions.

Coadministration of seasonal influenza and COVID-19 vaccines: A systematic review of clinical studies

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2022, VOL. 18, NO. 6, e2131166 (12 pages)

Janssen C, et al

3 randomized trials, <1500 subjects

No safety concerns or immune interferences were found whatever the vaccines (Moderna, BNT, Astra, Novavex) or the age of vaccinated subjects (65- or 65+).

No efficacy/effectiveness data were available.

Avian Influenza Report

衞生防護中心
Centre for Health Protection
保障市民健康
Protecting Hong Kong's health

Avian Influenza Report *is a weekly report produced by the Surveillance Division of the Communicable Disease Branch of the Centre for Health Protection. This report highlights global avian influenza activity in humans and birds.*

VOLUME 19, NUMBER 02

Reporting period: Jan 8, 2023 – Jan 14, 2023 (Week 02)

(Published on January 17, 2023)

Summary

1. Since the previous issue of Avian Influenza Report (AIR), there were no new human cases of avian influenza A(H7N9). Since March 2013 (as of January 14, 2023), there were a total of 1568 human cases of avian influenza A(H7N9) reported globally (all were reported in the seven waves between 2013 and September 2019). The latest case was reported on April 5, 2019.

2. Since the previous issue of AIR, there were no new human cases of avian influenza A(H5N6). Since 2014 (as of January 14, 2023), there were 83 human cases of avian influenza A(H5N6) reported globally and 82 of them occurred in Mainland China. The latest case was reported on January 6, 2023.

3. Since the previous issue of AIR, there were no new human cases of avian influenza A(H5N1). From 2013 to 2022, 0 to 145 confirmed human cases of avian influenza A(H5N1) were reported to the World Health Organization (WHO) annually (according to onset date).* The latest case was reported on November 30, 2022.

Summary

- Increased flu activity expected in countries/cities without universal masking/ tight social distancing measures.
- Viral kinetics of SARS-CoV2 resembles that of flu. Asymptomatic/pre-symptomatic transmission occurs. Similar URT and systemic symptoms. More rapid progression to severe disease vs COVID-19.
- Unique to COVID: longer taste/smell disturbances, skin manifestations, higher risk of thrombotic events, multi-system inflammatory disease, Long COVID.
- Multiplex PCR useful for early diagnosis
- Early treatment of flu with NAI or Baloxavir
- Co-adminstration of flu vaccine & COVID-19 vaccine more practical

Mobile vaccination teams