Outline

I. Introduction

Influenza virus is an enveloped, segmented, negative-sense single-stranded RNA virus belonging to the family *Orthomyxoviridae*. There are 4 types of influenza viruses, i.e. A, B, C, D. Types A and B can cause human disease and epidemics, with Type A having the potential to cause severe disease and pandemics. Type C infection is typically mild in humans, and generally considered to be of limited clinical importance. Type D is known to primarily infect cattle.

WHO estimates that there are around a billion cases of seasonal influenza annually, including 3 to 5 million cases of severe illness, resulting in 290 000 to 650 000 respiratory deaths annually [1].

Influenza A and B viruses are detected all year-round in Singapore. Influenza incidence typically surges during two periods occurring from May to August and from December to March. These periods correspond broadly to the influenza seasons observed in temperate regions of the Southern Hemisphere (April–September) and the Northern Hemisphere (October–March) [2].

Influenza A viruses consist of several subtypes depending on the combination of two surface glycoproteins, i.e. hemagglutinin (H) and neuraminidase (N). There are 18 H subtypes and 11 N subtypes of Influenza A viruses (e.g. H1N1, H3N2). Influenza B can be classified into two main lineages, i.e. B/Victoria and B/Yamagata [3].

To differentiate from the older seasonal A(H1N1) viruses circulating before the 2019 pandemic, WHO uses the term "A(H1N1)pdm09" to describe the pandemic virus A(H1N1)2009 currently co-circulating with other seasonal viruses [4]. As of November 2025, the circulating strains in Singapore include Influenza A(pH1N1), Influenza A(H3N2), and Influenza B [5].

The virus can frequently acquire mutations in its surface glycoproteins over time (antigenic drift), allowing it to evade the host immune system. This mutability necessitates regular reviews and annual updates of influenza vaccine composition to match major circulating strains. The virus can also undergo major genetic reassortment (antigenic shift). Antigenic shift occurs when two or more different influenza A virus strains (e.g. of human or animal origin) infect the same host cell—often in an intermediate animal such as a pig—allowing their virus gene segments to mix and generate a completely new virus. Since this new strain possesses surface antigens that are novel to humans, antigenic shift is the mechanism most strongly associated with the emergence of influenza pandemics [6].

Influenza spreads via virus-containing droplets, aerosols, or contaminated surfaces typically during coughing, sneezing, or close interactions [7, 8]. Chow et al. (2023) have found that influenza virus in exhaled breath is predominantly found in

fine aerosols, with viable virus detected in approximately one-third of infected individuals [8]. This also highlights the importance of ventilation of shared spaces to prevent transmission.

Avian influenza ("bird flu") viruses may occasionally cause human infections in individuals exposed to infected animals (e.g. poultry, pigs, cattle) or contaminated environments. Certain highly pathogenic avian influenza (HPAI) strains (e.g. H5N1, H7N9) are more virulent and can cause more severe disease in humans with higher morbidity and mortality rates (e.g. exceeding 50%) [9].

II. Clinical Features and Disease Severity

WHO classifications of influenza severity [10]:

Non-Severe Influenza:

- Sudden onset of cough, headache, muscle/joint pains, severe malaise, sore throat, and rhinorrhea, with or without fever.
- Self-limiting; most recover within a week without medical care.
- Defined by the absence of any severe disease criteria.

Severe Influenza:

- Includes sepsis, septic shock, severe pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, exacerbation of chronic medical conditions, or death.
- Usually requires hospitalization; may need supplemental oxygen, mechanical ventilation, or vasopressors.
- Patients infected with novel influenza A strains with high mortality or unknown severity are automatically classified as severe, even if other criteria are not met.

	Uncomplicated	**Severe**
Constitutional	Sudden onset of malaise, fatigue, muscle and joint pains, with or without fever, anorexia	Persistent high fever, extreme lethargy
Cardiovascular	-	Myocarditis
Respiratory	Cough, sore throat, rhinorrhea	Severe pneumonia, ARDS, secondary bacterial pneumonia (most often *Streptococcus pneumoniae, Staphylococcus aureus*, or *Haemophilus influenzae*)
Neurological	Headache	Encephalitis, confusion (elderly patients), seizures, Guillain-Barré syndrome, Reye's syndrome
Gastrointestinal	Nausea, vomiting, or diarrhea, more common in children	Severe vomiting, dehydration, abdominal pain, liver dysfunction
Others	-	Sepsis, septic shock, multi-organ failure, exacerbation of chronic medical conditions, or death.

Table adapted from information in [2, 10, 11].

III. Detection and Diagnostic Methods

The combination of sudden onset fever and cough (especially when influenza is circulating in the community) increases the likelihood of influenza. For example, cough and fever had a positive predictive value ~80% in one study [12]. Nevertheless, relying on symptoms alone is unreliable because many infections with other circulating respiratory viruses (such as SARS-CoV-2, respiratory syncytial virus, rhinoviruses, adenoviruses) and certain bacteria (such as *Streptococcus*

pneumoniae, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Legionella pneumophila*) may mimic similar clinical manifestations of influenza-like illness (ILI) [13].

For influenza testing in outpatients, nasopharyngeal specimens are preferred over other upper respiratory tract samples and should be collected as early as possible, ideally within four days of the onset of symptoms [14]. Combined nasal and throat swabs may also be useful [10]. Mid-turbinate swabs, although less invasive, yielded a 53% lower viral load versus nasopharyngeal swabs [15]. In another study, mid-turbinate swabs showed 98% sensitivity (versus nasopharyngeal swab reference), while nasal swabs showed lower sensitivity of 84% [16].

In critically ill patients with respiratory failure who have negative influenza test results from upper respiratory samples, lower respiratory tract specimens (such as endotracheal aspirate or bronchoalveolar lavage fluid samples) can be useful for testing [10].

- **Antigen rapid test kits**
  - Easy to perform and interpret
  - High specificity, but generally lower sensitivity (false negatives common), especially to influenza B [17-22]
  - 3-in-1 kits are also available for testing to detect Influenza A, Influenza B, or COVID-19 infection [23-25].
  - Ideally should be carried out early upon onset of symptoms (<4 days) when the viral load is higher (to reduce false negatives)
  - Some kits employ a digital analyzer to standardize interpretation of results
  - Negative result – especially when influenza is circulating, or if patient has severe illness, or at high risk for complications – should be followed up with RT-PCR or viral culture [17, 22]
- **RT-PCR**
  - Considered the gold-standard
  - High sensitivity and specificity
  - Requires specialized equipment, more expensive
- **Viral culture**
  - Also considered as another gold-standard
  - Less commonly used in routine clinical care due to long turnaround time (3-10 days), but valuable for surveillance and epidemiology. This will also help guide decisions by WHO on which strains to select in the updated annual vaccines.
  - Singapore conducts regular surveillance of influenza activity. This involves tracking weekly polyclinic visits for influenza-like illnesses, as well as laboratory reports of influenza-positive clinical specimens submitted to the Ministry of Health by Singapore General Hospital and other laboratories [11].

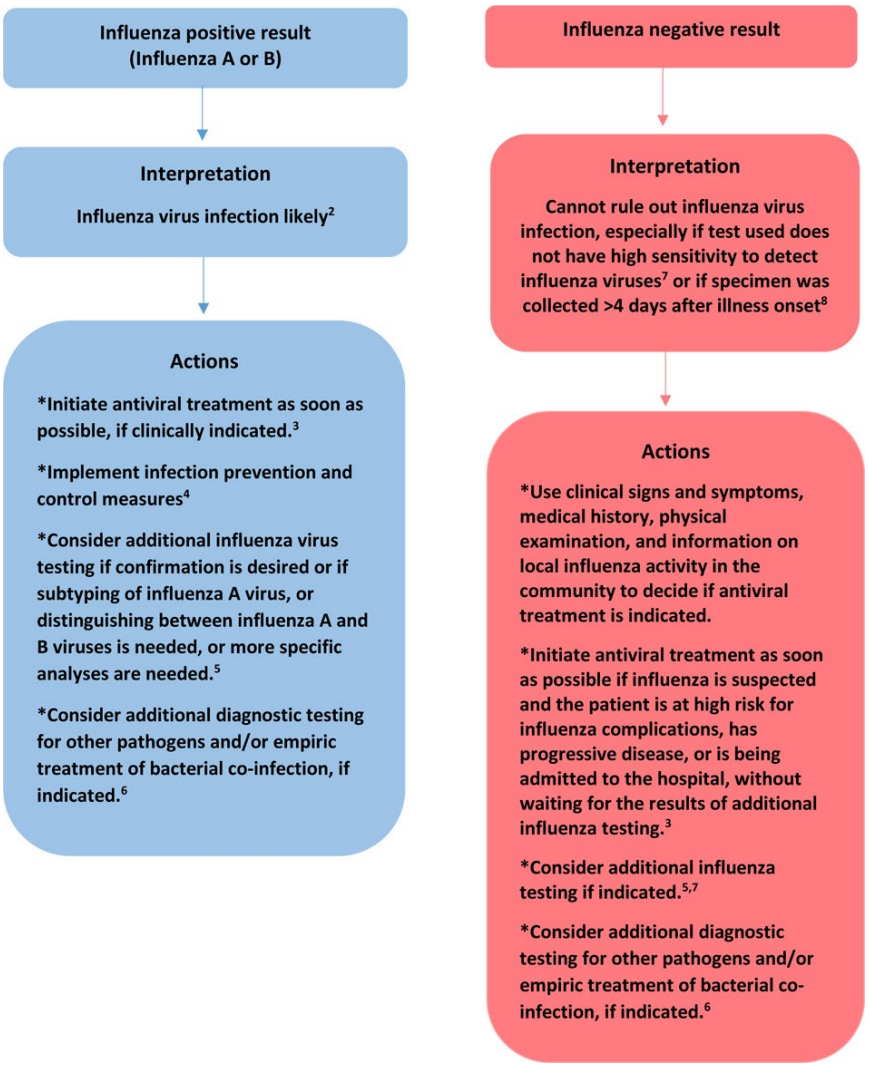

Figure 1: Influenza testing algorithm to help interpret results when influenza viruses are circulating in the community. Source from [26]. This material is in the public domain and may be freely used or reproduced without obtaining copyright permission.

IV. Prevention and Control Strategies

- **Vaccination**
  - Considered the safest and most effective method to prevent influenza disease.
  - The composition of seasonal influenza vaccines is updated twice annually, based on information on currently circulating strains gathered through the WHO Global Influenza Surveillance and Response System or GISRS [27].
  - Vaccination is recommended annually or per season for high-risk groups [28, 29]. For example:
    - ➔ Children aged 6 months to under 5 years.
    - ➔ Elderly aged 65 years and above.
    - ➔ Those with chronic disorders or co-morbidities, immunocompromised, living in communal settings (nursing homes, hospice), on long-term aspirin therapy (persons aged 6 months to 18 years who are at higher risk for Reye's syndrome)

- ➔ Pregnant women
- ➔ Healthcare workers

- Inactivated vaccines: Influenza trivalent vaccines (2 strains of Influenza A, 1 strain of Influenza B) and quadrivalent cell-based or egg-based vaccines (2 strains of Influenza A, 2 strains of Influenza B) are available in Singapore.
- These vaccines are produced either in embryonated eggs (traditional method) or in mammalian cell cultures. Cell-based vaccines employ mammalian cell culture instead of eggs, which avoids egg-adaptation mutations and may better match circulating viruses, potentially improving effectiveness [30].
- New live attenuated influenza vaccine (LAIV) - FluMist Trivalent (first and only intranasal influenza vaccine introduced in Singapore) for individuals aged from 2 to 49 years [31].

- **Infection control and personal hygiene**
  - Public educational campaigns to promote hygiene practices such as frequent hand-washing, covering nose/mouth when sneezing/coughing, using a mask (especially by influenza patients)
  - Social distancing
  - Well-ventilated areas and surface disinfection of frequently touched surfaces
  - Encouraging influenza vaccination (e.g. for travelers)
- **Chemoprophylaxis [11]**

Drug	Age/Weight group	Dose and frequency
Oseltamivir	Adults	75 mg once daily
	<40kg	Weight-based dosing
Zanamivir	≥5 years	1 puff (5 mg) twice daily

V. Treatment Options

Category	Details	Notes
Symptomatic treatment	Antipyretics, antihistamines, adequate bed rest and fluids	Avoid salicylates in children (due to risk of Reye's syndrome)
Neuraminidase inhibitors	Reduce duration of symptoms for both influenza A and B by one day if administered within 48 hours of illness onset. Especially for severe disease.	Oseltamivir: 75 mg orally twice daily for 5 days, age ≥1 year; weight-based dosing for <40 kg Zanamivir: Inhaled, 2 puffs (10 mg) twice daily for 5 days, age ≥5 years Zanamivir: Intravenous, limited to life-threatening cases, provided on a compassionate use basis. Requires approval from Health Science Authority and hospital committees [32, 33]. Peramivir: Intravenous, single-dose infusion, in patients aged ≥6 months; 12 mg/kg (max 600 mg) for children, 600 mg for ≥13 years old patients, infused over ≥15 minutes.
M2 proton channel inhibitors	Can shorten the duration and severity of influenza A illness if used within 48 hours of onset.	Amantadine: No longer recommended due to drug resistance. Rimantadine: No longer recommended due to drug resistance.
RNA-dependent RNA polymerase inhibitors	Inhibits influenza A and B viral transcription and replication,	Baloxavir marboxil: Oral single-dose therapy for otherwise healthy children age ≥5 years; 2 mg/kg (<20

	should be taken within 48 hours of onset.	kg), 40 mg (20–<80 kg), 80 mg (≥80 kg). Adults: 40 mg (20–<80 kg), 80 mg (≥80 kg).
Complications	Other complications managed supportively	Only use antibiotics if bacterial infection is confirmed

Table summarized from [11, 34, 35].

WHO recommends using antiviral treatments for those patients at high risk for severe disease and hospitalization. Additionally, individuals infected with novel influenza A strains that have unknown severity or are associated with high mortality are considered high-risk and should also receive antiviral therapy [10].

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