New WHO guidelines for clinical management of patient with Influenza

Clinical Management Unit
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Prof Steve McGloughlin

World Health Organization

Influenza

Published 2021

The purpose of this document is to guide clinicians in the care of patients with or at risk of severe illness from influenza virus infection

Guidelines for the clinical management of severe illness from influenza virus infections

World Health Organization

Influenza

Published in 2024

The purpose of these updated guidelines is to assist clinicians in the care of persons with suspected or confirmed influenza virus infection.

This update includes recommendations on the management of ***both severe and non-severe influenza and also includes recommendations on the use of antiviral medications to prevent influenza virus infection in individuals exposed to the virus in the previous 48 hours.***

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Thank you to all the contributors

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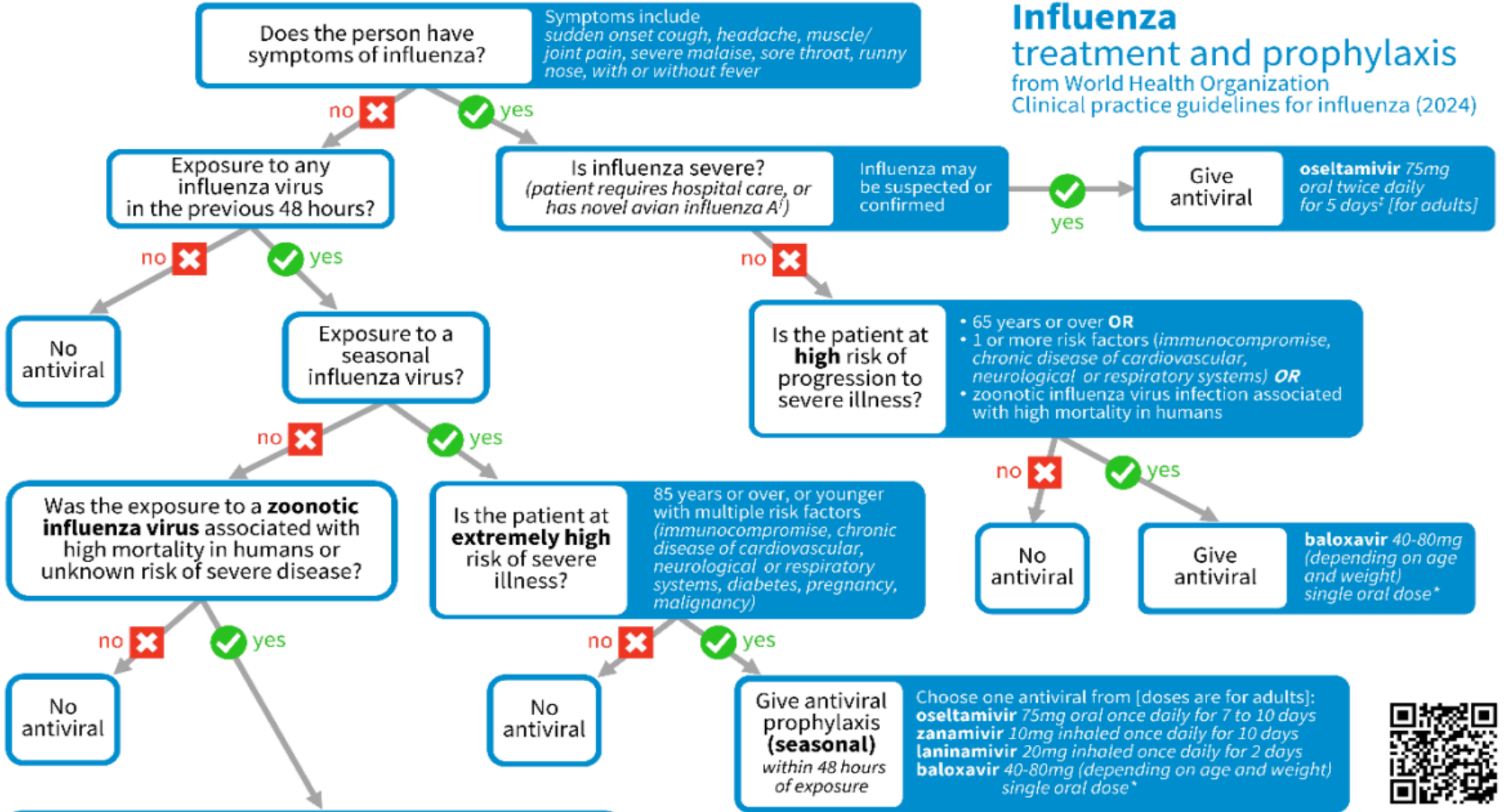
Influenza
treatment and prophylaxis
from World Health Organization
Clinical practice guidelines for influenza (2024)



For full guidance, including dosage in children and use in vulnerable populations, refer to the full guideline:
scan QR code or https://app.magicapp.org/#/guideline/jlPRdj

* Baloxavir may increase the risk of antiviral resistance emerging; use with caution in immunocompromised patients. Baloxavir is not recommended for use in pregnancy and postpartum period due to lack of safety and efficacy data.

† Patients with novel avian influenza A associated with high mortality, or with an unknown risk of severe disease, should be considered as "severe influenza"

‡ Longer durations can be considered for severe influenza, including zoonotic influenza

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Baseline risks for seasonal influenza

Outcome	Percentage (95% CI)	Baseline risk
Mortality – non-severe illness (seasonal)	0.10% (0.10 - 0.11)	1 per 1000
Mortality – severe disease (seasonal)	2.97% (2.93 - 3.01)	30 per 1000
Mortality – zoonotic disease (AH5N1, AH7N9, AH5N6)	38.30% (36.4 - 40.11)	383 per 1000
Hospitalization – non-severe (seasonal)	0.8% (0.79 - 0.80)	8 per 1000

Risk Factors for Severe Disease and Death

Major Risk Factors (OR > 2, mod certainty)

- influenza developing severe disease are:
- Immunocompromise
- cardiovascular disease
- neurological disease
- chronic respiratory disease.

A patient could be considered **high risk for severe disease** if they had one of the major risk factors OR were 65 years or older.

Additional risk factors (OR of 1.7 - 2, mod certainty)

- Malignancy
- Pregnancy
- Diabetes.

Risk Factors for Severe Disease and Death

Age:

Risk factor	Study results and measurements	Certainty of the evidence	Summary
Age (per 10 years increase)	**Odds ratio: 1.72** **(95% CI 1.02 - 2.89)** **Based on data from 1 study**	**Moderate** Due to serious imprecision	Age is probably associated with increased odds of hospitalization in non-severe patients.

Risk Factors for Severe Disease and Death

Extremely high risk was defined as patients above 85 years old with or without additional risk factors or patients at a younger age that have multiple major and additional risk factors that the clinician determines places the patient at extremely high risk of severe disease.

Non-severe influenza - Baloxavir

Conditional recommendation for

In patients with suspected or confirmed non-severe influenza virus infection and at high risk of progression to severe influenza, we **suggest administering baloxavir** (conditional recommendation, low-quality evidence).

Patients with non-severe influenza influenza and at high risk of developing severe disease include the following (see Sections 5.1 and 5.2):

- *Patients 65 years and older; or*
- *Patients with one or more major risk factors for severe influenza.*

Patients with zoonotic influenza virus infection associated with high mortality in humans, including HPAI A(H5N1), HPAI A(H5N6) virus; and HPAI and LPAI A(H7N9) , were not included in the clinical trials that informed this recommendation. The GDG agreed that evidence would indirectly apply to this population as well, in case they would present early to care with mild symptoms.

Treatment should be administered as early as possible, and within 2 days of symptom onset.

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Non-severe influenza - Baloxavir

Mortality (low-risk)	Relative risk 0.83 (CI 95% 0.14 — 4.82) Based on data from 2144 participants in 2 studies	**0.2** per 1000 **0.17** per 1000 Difference: **0.03 fewer per 1000** (CI 95% 0.17 fewer — 0.76 more)	**High**	Baloxavir has little or no effect on mortality.
Mortality (high-risk)	Relative risk 0.83 (CI 95% 0.14 — 4.82) Based on data from 2144 participants in 2 studies	**2** per 1000 **1.66** per 1000 Difference: **0.34 fewer per 1000** (CI 95% 1.72 fewer — 7.64 more)	**High**	Baloxavir has little or no effect on mortality.
Admission to hospital (low-risk)	Relative risk 0.24 (CI 95% 0.05 — 1.19) Based on data from 1461 participants in 2 studies	**3** per 1000 **1** per 1000 Difference: **2 fewer per 1000** (CI 95% 3 fewer — 1 more)	**High**	Baloxavir has little or no effect on admission to hospital.
Admission to hospital (high-risk)	Relative risk 0.24 (CI 95% 0.05 — 1.19) Based on data from 1461 participants in 2 studies	**21** per 1000 **5** per 1000 Difference: **16 fewer per 1000** (CI 95% 20 fewer — 4 more)	**Low** Due to very serious imprecision	Baloxavir may reduce the risk of admission to hospital.
Time to alleviation of symptoms	Lower better Based on data from 1855 participants in 3 studies	**4.92** (Mean) **3.90** (Mean) Difference: **1.02 lower (MD)** (CI 95% 1.41 lower — 0.63 lower)	**Moderate** Due to serious imprecision	Baloxavir probably reduces time to alleviation of symptoms.

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Non-severe influenza - Baloxavir

Conditional recommendation against

In patients with suspected or confirmed non-severe influenza virus infection and at low risk of progression to severe influenza, we **suggest not administering baloxavir** (conditional recommendation, low-moderate quality evidence).

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Non-severe seasonal influenza - Oseltamivir

Strong recommendation against

In patients with suspected or confirmed non-severe seasonal influenza virus infection, we **recommend not administering oseltamivir** (strong recommendation, moderate quality evidence).

Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

In patients with non-severe influenza virus infection, oseltamivir treatment probably has no important effect on time to alleviation of symptoms and has little or no effect on admission to hospital or mortality in patients at high or low risk of progressing to severe disease, because of the low absolute risk of severe influenza. Oseltamivir treatment probably increases adverse events but probably has little or no effect on serious adverse events related to treatment. It is very uncertain whether oseltamivir increases emergence of resistance.

In clinical trials of oseltamivir versus placebo, oseltamivir was administered to participants within 36 to 48 hours of symptom onset of non-severe influenza virus infection.

Non-severe influenza - Oseltamivir

Mortality (Low-risk)	Relative risk 0.84 (CI 95% 0.34 — 2.07) Based on data from 12008 participants in 17 studies	**0.2** per 1000 **0.17** per 1000 Difference: **0.03 fewer per 1000** (CI 95% 0.13 fewer — 0.21 more)	**High**	Oseltamivir has little or no effect on mortality.
Mortality (High-risk)	Relative risk 0.84 (CI 95% 0.34 — 2.07) Based on data from 12008 participants in 17 studies	**2** per 1000 **1.68** per 1000 Difference: **0.32 fewer per 1000** (CI 95% 1.32 fewer — 2.14 more)	**High**	Oseltamivir has little or no effect on mortality.
Admission to hospital (Low-risk)	Relative risk 0.80 (CI 95% 0.54 — 1.18) Based on data from 12589 participants in 20 studies	**3** per 1000 **2** per 1000 Difference: **1 fewer per 1000** (CI 95% 1 fewer — 1 more)	**High**	Oseltamivir has little or no effect on admission to hospital.
Admission to hospital (High-risk)	Relative risk 0.80 (CI 95% 0.54 — 1.18) Based on data from 12589 participants in 20 studies	**21** per 1000 **17** per 1000 Difference: **4 fewer per 1000** (CI 95% 10 fewer — 4 more)	**High**	Oseltamivir has little or no effect on admission to hospital.
Time to alleviation of symptoms	Lower better Based on data from 9078 participants in 22 studies	**4.92** (Mean) **4.17** (Mean) Difference: **0.75 lower (MD)** (CI 95% 0.93 lower — 0.57 lower)	**Moderate** Due to serious risk of bias	Oseltamivir probably has no important effect on time to alleviation of symptoms.

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Non-severe influenza - antibiotics

7.2.1 Antibiotics

Strong recommendation against

In patients with suspected or confirmed non-severe influenza virus infection and low probability of bacterial co-infection we **recommend not administering antibiotics** (strong recommendation, low-quality evidence).

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Severe Influenza

8.1.1 Oseltamivir

Conditional recommendation for

In patients with suspected or confirmed severe influenza virus infection, we **suggest administering oseltamivir** (conditional recommendation, very low quality evidence).

- Treatment should be administered as early as possible, and within 2 days of symptom onset.
- This recommendation applies to patients with novel influenza A virus infection associated with high mortality, or with an unknown risk of severe disease, even where they do not otherwise fulfil criteria for severe influenza.

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Severe Influenza - Oseltamivir

Data from clinical trials are very limited for oseltamivir in patients with severe influenza virus infection. The GDG inferred that for severe seasonal influenza virus infection, the threshold for use of oseltamivir treatment would be a reduction in mortality of 3 in 1000.

For both seasonal influenza and zoonotic influenza (novel influenza Aviruses associated with high mortality) it is very uncertain if oseltamivir increases or reduces mortality or ICU admission.

The GDG inferred that the threshold for use of oseltamivir treatment of severe influenza virus infection would be a reduction in duration of hospitalization by 1 day for seasonal influenza, and the low certainty evidence suggests that oseltamivir decreases the duration of hospitalization.

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Severe Influenza - Oseltamivir

Antivirals for treatment of severe influenza: a systematic review and network meta-analysis of randomised controlled trials

Ya Gao, Gordon Guyatt, Timothy M Uyeki, Ming Liu, Yamin Chen, Yunli Zhao, Yanjiao Shen, Jianguo Xu, Qingyong Zheng, Zhifan Li, Wanyu Zhao, Shuyue Luo, Xiaoyan Chen, Jinhui Tian, Qiukui Hao

Interpretation In hospitalised patients with severe influenza, oseltamivir and peramivir might reduce duration of hospitalisation compared with standard care or placebo, although the certainty of evidence is low. The effects of all antivirals on mortality and other important patient outcomes are very uncertain due to scarce data from randomised controlled trials.

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Severe Influenza – Adjunctive Therapies

8.2.1 Corticosteroids

Conditional recommendation against

In patients with suspected or confirmed severe influenza virus infection, we **suggest not administering corticosteroids** (conditional recommendation, very low quality evidence).

- *There is a possibility of important benefit from corticosteroid treatment, especially where the clinical diagnosis overlaps with ARDS.*

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Outcome Timeframe	**Study results and measurements**	**Comparator** No systemic corticosteroids	**Intervention** Systemic corticosteroids	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality (observational, unadjusted) [1] 30 days 9 Critical	Odds ratio 4.79 (CI 95% 2.35 — 9.79) Based on data from 1,006 participants in 10 studies. [2] (Observational (non-randomized))	70 per 1000 Difference:	209 per 1000 **139 more per 1000** (CI 95% 90 more — 197 more)	Very low Due to very serious risk of indication bias, and serious inconsistency (unadjusted odds ratios and varying definition of mortality). [3]	We are uncertain whether systemic corticosteroids increases or decreases mortality
Mortality (observational, adjusted) 30 days 9 Critical	Odds ratio 2.23 (CI 95% 1.54 — 3.24) Based on data from 1,206 participants in 5 studies. [4] (Observational (non-randomized))	70 per 1000 Difference:	144 per 1000 **74 more per 1000** (CI 95% 34 more — 126 more)	Very low Due to very serious risk of indication bias, and serious inconsistency (varying definition of mortality) [5]	We are uncertain whether systemic corticosteroids increases or decreases mortality
Mortality (ARDS, RCT, indirect)	Relative risk 0.82 (CI 95% 0.72 — 0.95) Based on data from 2,740 participants in 16 studies. [6] (Randomized controlled)	446 per 1000 Difference:	366 per 1000 **80 fewer per 1000** (CI 95% 125 fewer — 22 fewer)	Low Due to serious indirectness, and indirect evidence from COVID-19 and non-COVID-19 ARDS applied to populations with influenza [7]	Corticosteroids possibly decrease mortality.

Severe Influenza – Adjunctive Therapies

Conditional Recommendations Against:

- Macrolide Antibiotics
- mTOR inhibitors
- NSAIDS
- Passive Immune Therapy

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Severe Influenza – Testing

Conditional recommendation for

In patients with suspected severe influenza virus infection, we **suggest using high sensitivity and high specificity tests (NAAT or PCR)** for the diagnosis of influenza and treating all patients who are positive with a WHO recommended antiviral agent.

If high sensitivity and specificity tests are available but results will be delayed for more than 24 hours then we recommend starting treatment with a WHO-recommended antiviral agent, and ceasing the treatment if the test is negative (conditional recommendation, low-quality evidence).

- *If NAAT testing is available and results are rapidly available then this is the preferred approach.*
- *If PCR testing is available and results are available within 24 hours then "PCR-Wait" is a reasonable approach.*
- *If PCR testing is available and results are not available within 24 hours then "PCR-Treat" may be a reasonable approach, provided that that treatment is stopped if the test is negative.*

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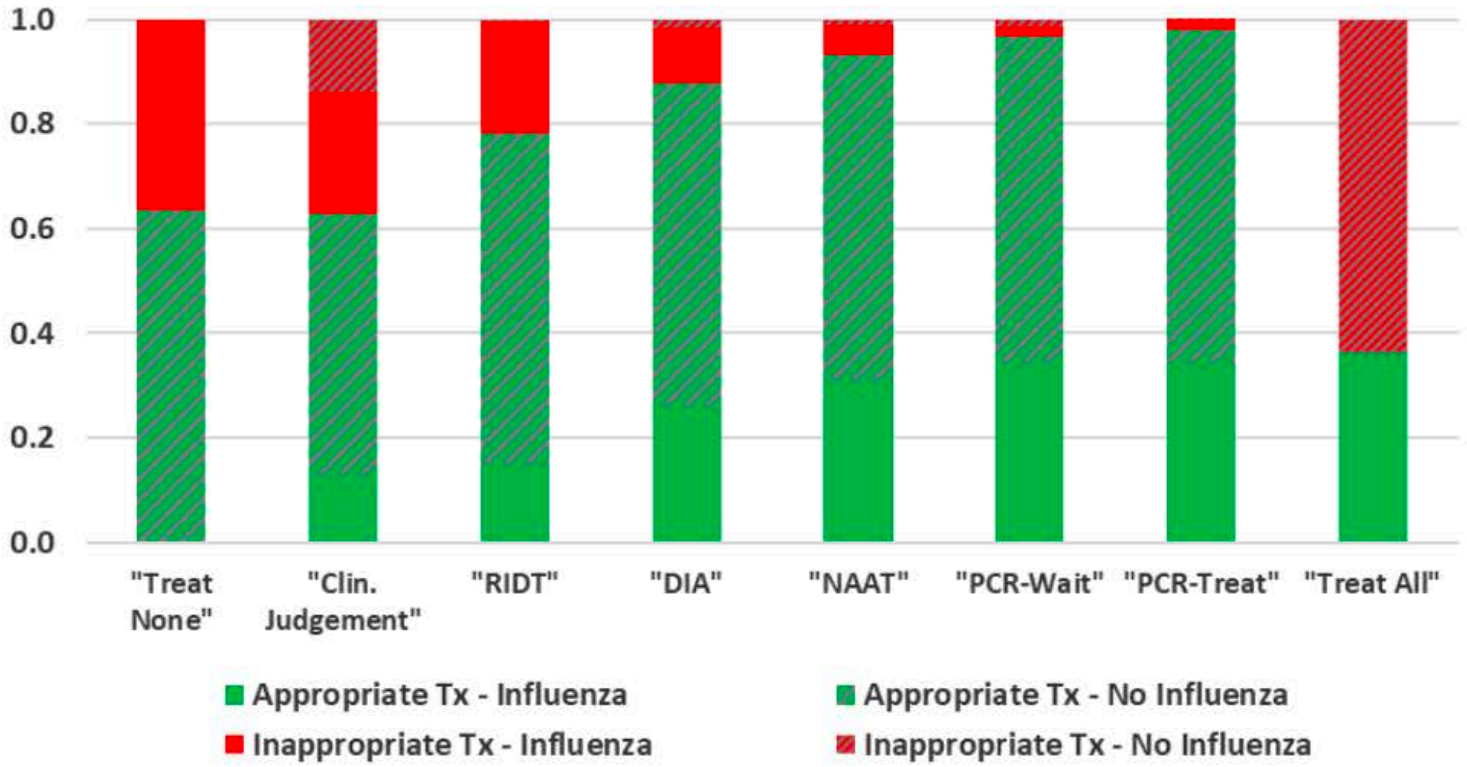
Severe Influenza – Testing

Fig. 11.4 Treatment appropriateness (proportion of patients with severe influenza-like illness appropriately treated and proportion of patients without influenza inappropriately treated) under the strategies examined



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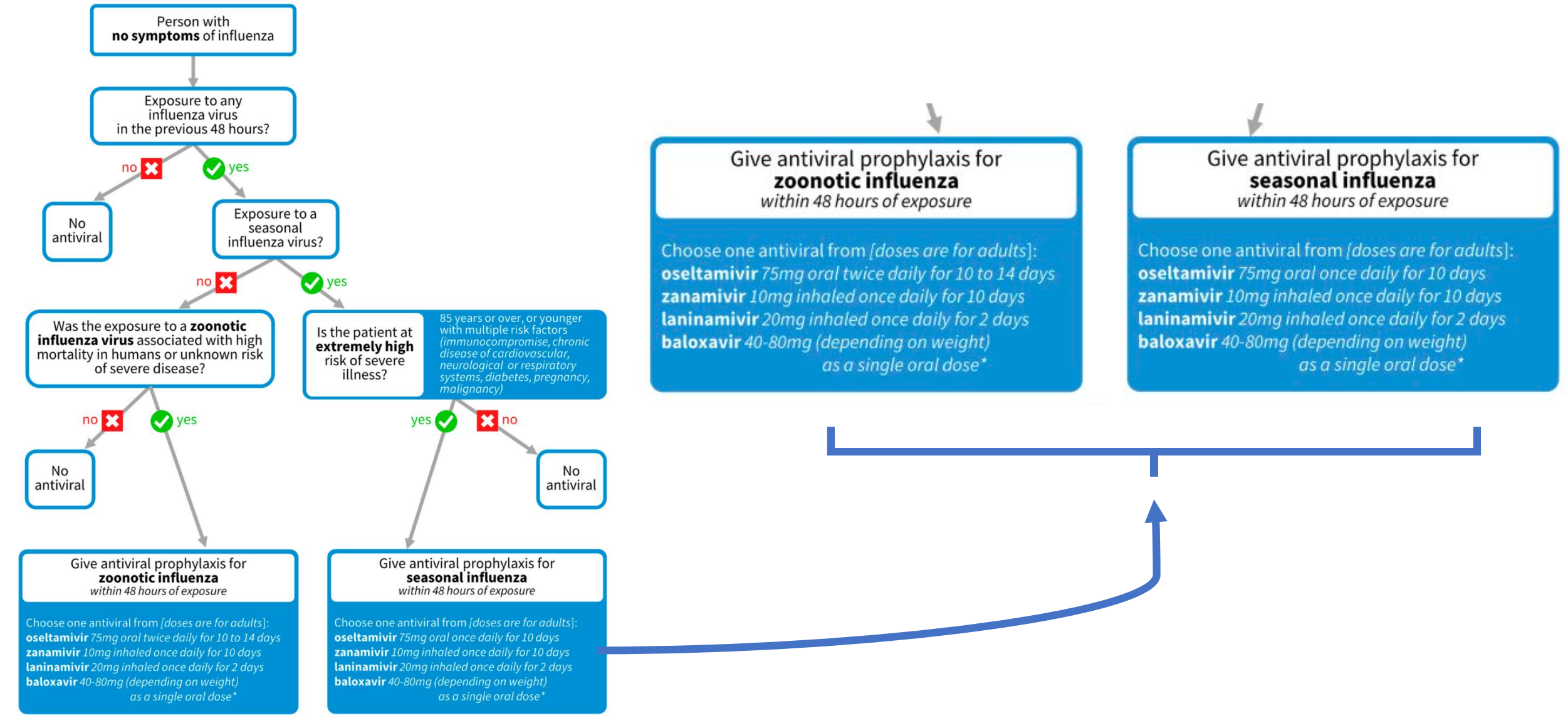
Persons Exposed to Influenza



Persons Exposed to Seasonal Influenza

9.1.1 Baloxavir

Conditional recommendation for

For asymptomatic persons, who are at extremely high risk of severe illness if they develop influenza and who are exposed to **seasonal influenza viruses** in the prior 2 days, we **suggest administering baloxavir** (conditional recommendation, moderate quality evidence).

- *Antiviral post-exposure prophylaxis does not replace influenza vaccination.*
- *Extremely high-risk patients are considered those patients over 85 years old with or without risk factors for severe disease or younger patients with multiple risk factors.*

Conditional recommendation against

For asymptomatic persons, who are NOT at extremely high risk of severe illness if they develop influenza and who are exposed to **seasonal influenza viruses** in the prior 2 days, we **suggest not administering baloxavir** (conditional recommendation, moderate quality evidence).

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Persons Exposed to Zoonotic Influenza

9.2.3 Oseltamivir

Conditional recommendation for

For asymptomatic persons exposed to **zoonotic influenza viruses associated with high mortality in humans or with an unknown risk of causing severe disease** in the prior 2 days, we **suggest administering oseltamivir** (conditional recommendation, low-quality evidence).

- *Avian influenza A viruses that have been associated with high mortality in humans when they become infected, include HPAI A(H5N1), HPAI A(H5N6) virus; and HPAI and LPAI A(H7N9).*
- *It is likely there will be uncertainty with any novel influenza A virus as to the potential clinical consequences or virulence.*
- *It is likely that there is variable susceptibility of antiviral medications to novel influenza A viruses so in vitro and clinical studies will remain necessary.*

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Research Questions : Seasonal Influenza

- **Accurate clinical tools** for seasonal influenza, especially to predict hospitalization and mortality
- High certainty efficacy data for new and existing **antiviral therapies** in patients with non-severe disease and high risk for progression
- High certainty efficacy data for new and existing **antiviral therapies** in patients with severe disease (to reduce severe outcomes including mortality). **The optimal dose of antivirals** in severe disease also requires further urgent investigation.
- High certainty efficacy data for **adjuvant therapies** in patients with severe disease

- **An urgent need for large, adaptive randomised controlled trials that investigate the impact of combination therapy with antivirals and immunomodulatory therapy in severe disease.**

- Understanding of longer-term outcomes of influenza, including functional status for patients with non-severe and severe disease.
- High certainty efficacy data for new and existing antiviral therapies in patients exposed to influenza (post-exposure prophylaxis).

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Research Questions : Novel Influenza A

- Understanding of hospitalization and mortality (establishing the relative and absolute risks associated with patient and viral factors).
- High certainty efficacy data for new and existing antiviral therapies in patients with novel influenza A.
- High certainty efficacy data for new and existing antiviral therapies in patients exposed to novel influenza A(post-exposure prophylaxis), including those at high risk of occupational transmission.

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Questions

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