# Antiviral Use in Health Care Workers – A Systematic Review

# Appendix I. Methodology

## **Protocol, search strategy and study selection**

A study protocol was developed in conjunction with the Canadian Pandemic Influenza Preparedness Task Group (CPIP TG). A search strategy was developed in collaboration with a research librarian, using the following terms: “Antivirals” OR “Neuraminidase inhibitors”; “Influenza” OR “Seasonal influenza” OR “Pandemic”; “Healthcare workers” OR “Healthcare settings”. The strategy was initially developed on PubMed, then adapted for four other databases: EMBASE, Web of Science, CINAHL and ClinicalTrials.gov. The full search strategy is shown in *Supplementary I*. Key components of our research question were defined using a Population, Intervention, Comparator, Outcome(s), Time and Setting (PICOTS) format. The population (P) consisted of HCWs working in any healthcare setting. The intervention (I) of interest was NAI, given to HCWs in pre- or post-exposure to prevent infection with seasonal or pandemic influenza or as early treatment. NAI use was compared (C) to no NAI use, or to another strategy of NAI use (pre-exposure prophylaxis, post-exposure prophylaxis, early treatment). Outcomes (O) were the effectiveness of NAIs in preventing influenza and reducing influenza transmission between HCWs and between HCWs and their patients; reducing duration and severity of HCW influenza illness; and preventing disruption of healthcare services. They had to occur during influenza seasons or pandemics (T) and in healthcare settings (S).

We searched all databases and duplicates were removed. Unique citations were independently screened by title/abstract then at the full-text level by two reviewers (FT and ZL). A hand search was additionally performed by screening reference lists of previously published systematic reviews, meta-analyses and eligible studies.

## **Study eligibility**

Eligible studies were observational studies and experimental and quasi-experimental trials that were published in English or French from January 1st, 1995 to October 29th, 2019. Based on the CPIP definition, HCWs are “individuals who provide healthcare or support services in the healthcare setting, such as nurses, physicians, dentists, nurse practitioners, paramedics, medical laboratory workers, other health professionals, temporary workers from agencies, unregulated healthcare providers, students, volunteers and workers who provide support services (e.g., food, laundry, housekeeping). Concepts and advice for HCWs may also apply to other workers who are functioning in a healthcare capacity, for example police or fire personnel who are providing medical first response”. Similarly, according to the CPIP, we included all healthcare settings along the continuum of care, including – but not limited to – medical first responders, practitioners’ offices and other ambulatory care settings, acute care, long-term care and home care settings. The primary outcome of interest was the effectiveness of NAIs in reducing the incidence of confirmed influenza cases, influenza-like illness (ILI), influenza-related mortality and hospitalization in HCWs, and their effectiveness to prevent influenza transmission within healthcare settings. Secondary outcomes were the reduction of severity and duration of influenza symptoms after HCWs’ treatment with NAIs and the effect of NAIs in preventing the disruption of healthcare services due to influenza or ILI; the latter could be measured directly through appraising medical staff absenteeism/presenteeism, or indirectly, for example by assessing the workload in intensive care units as a result of reduction of personnel.

## **Data extraction and quality assessment**

An electronic form was specifically developed for this systematic review using DistillerSR (Evidence Partners, Ottawa, Canada). FT and ZL independently extracted relevant data from included studies. The risk of bias was then independently assessed for each study using Cochrane tools (ROBINS-I for observational studies and RoB2.0 for randomized trials)1,2. Studies were primarily assessed for the presence/absence of confounding (if not randomized), selection bias and measurement errors. In case of any discrepancies between the two reviewers, meetings were held to reach consensus. If a consensus could not be reached, a third reviewer (CQ) arbitrated.

## **Data analysis**

A descriptive analysis of included studies was performed. Major study characteristics and relevant findings were summarized and presented in evidence tables.

# Appendix II. Search documentation

PubMed (2371)

((zanamivir[MeSH Terms]) OR (oseltamivir[MeSH Terms]) OR ("r 125489"[Supplementary Concept]) OR ("peramivir"[Supplementary Concept]) OR (antiviral agents[MeSH:NoExp]) OR ("neuraminidase/antagonists and inhibitors"[MeSH Terms]) OR (zanamivir[Text Word]) OR (oseltamivir[Text Word]) OR (laninamivir[Text Word]) OR (peramivir[Text Word]) OR (neuraminidase inhibitor\*[Text Word]) OR (NA inhibitor\*[Text Word]) OR (antiviral\*[Text Word]) OR (anti viral\*[Text Word]) OR (sialidase inhibitor\*[Text Word]) OR (tamiflu[Text Word]) OR (relenza[Text Word]) OR (rapivab[Text Word])) **AND** ((influenza, human[MeSH Terms]) OR (influenza, avian[MeSH Terms]) OR (influenzavirus a[MeSH Terms]) OR (influenzavirus b[MeSH Terms]) OR (influenzavirus c[MeSH Terms]) OR (flu[Title/Abstract]) OR (influenza[Title/Abstract]) OR (grippe[Title/Abstract]) OR (respiratory tract infections[MeSH:NoExp]) OR (pandemics[MeSH Terms]) OR ("ILI" [Text Word]) OR (pandemi\*[Text Word]) OR (seasonal\* [Text Word])) **AND** ((health personnel[MeSH Terms]) OR (allied health personnel[MeSH Terms]) OR (Cross Infection[Mesh:NoExp])OR (infectious disease transmission, patient to professional[MeSH Terms]) OR (infectious disease transmission, professional to patient[MeSH Terms]) OR (Disease Transmission, Infectious[MeSH:NoExp]) OR (caregivers[MeSH Terms]) OR (physicians[MeSH Terms]) OR (medical staff[MeSH Terms]) OR (nurses[MeSH Terms]) OR (aide, nurses[MeSH Terms]) OR (nurse practitioners[MeSH Terms]) OR (students, medical[MeSH Terms]) OR (healthcare[Text word]) OR (health care[Text word]) OR (health care worker\*[Text word]) OR (HCW\*[Title/Abstract]) OR (HCP\*[Text word]) OR (medical staff[Text Word]) OR (nurs\* staff[Text word]) OR (health personnel[Text word]) OR (doctor\*[Text word]) OR (physician\*[Text word]) OR (practitioner\*[Text word]) OR (ambulatory care[Text word]) OR (long term care[Text word]) OR (home care[Text Word]) OR (medical care[Text Word]) OR (medical setting[Text word]) OR (hospital\*[Text Word]) OR (primary care[Text Word]) OR (paramedic\*[Text word]) OR (“ambulance worker\*”[Text Word]))

Filters: **Publication date from 1995/01/01; English; French**

Embase (2731)

1. exp influenza/

2. exp Influenza B virus/

3. exp seasonal influenza/

4. exp swine influenza virus/

5. exp pandemic influenza/

6. exp Influenza A virus/

7. exp swine influenza/

8. (influenza\* or flu or ili or grippe).mp.

9. respiratory tract infection/

10. avian influenza/

11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

12. antivirus agent/

13. (antiviral\* or anti viral\*).mp.

14. exp sialidase inhibitor/

15. neuraminidase inhibitor\*.mp.

16. NA inhibitor\*.mp.

17. sialidase inhibitor\*.mp.

18. oseltamivir/

19. oseltamivir.mp.

20. Zanamivir/

21. zanamivir.mp.

22. peramivir.mp.

23. Laninamivir/

24. laninamivir octanoate/

25. Laninamivir.mp.

26. CS-8958.mp.

27. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28. 11 and 27

29. exp health care personnel/

30. ((healthcare or 'health care' or health or medical or ambulance or paramedic\*) adj2 (worker\* or personnel or staff or professional\* or facilit\* or setting\*)).mp.

31. health care facility/

32. exp medical profession/

33. exp virus transmission/

34. exp caregiver/

35. exp physician/

36. exp nurse/

37. exp medical staff/

38. exp rescue personnel/ or exp paramedical personnel/

39. (((healthcare or 'health care' or health or medical or paramedic\* or ambulance) adj2 (worker\* or personnel or staff or professional\* or facilit\* or setting\*)).mp. or HCW\*.ti,ab. or HCP\*.ti,ab. or physician.mp. or practioner\*.mp. or nurse\*.mp. or ambulatory care.mp. or long term care.mp. or home care.mp. or hospital\*.mp. or primary care.mp.) adj4 (transmission\* or transmit\* or contagion\*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

40. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 39

41. 28 and 40

42. 41 not ((exp animal/ or nonhuman/) not exp human/)

43. limit 42 to (yr="1995 -Current" and (english or french))

CINAHL (798)

TX ( zanamivir OR oseltamivir OR laninamivir OR peramivir OR neuraminidase inhibitor\* OR NA inhibitor\* OR antiviral\* OR anti viral\* OR sialidase inhibitor\* OR tamiflu OR relenza OR rapivab ) AND TX ( flu OR influenza OR grippe OR "ILI" OR pandemi\* OR seasonal\* ) AND TX ( healthcare professionals or healthcare workers or healthcare providers OR health care workers OR health care provider\* OR health care professional\* OR hospital\* OR caregiver\* or physician\* or nurse\* or medical staff OR practitioner\* OR primary care OR paramedic\* OR ambulance worker\*)

Opérateurs de restriction - Date de publication: 19950101-; Humain; Langue: English, French

Modes de recherche - Booléen/Phrase

Web of Science (1595) – WoS Core Collection

|  |  |  |  |
| --- | --- | --- | --- |
| # 4 | 1,595 | (#3 AND #2 AND #1) *AND* **LANGUAGE:** (English OR French) *AND* **DOCUMENT TYPES:** (Article OR Review)  Indexes=SCI-EXPANDED, CPCI-S Timespan=1995-2019 | |
| # 3 | 1,658,300 | | TS=(healthcare professionals or healthcare workers or healthcare providers OR health care workers OR health care provider\* OR health care professional\* OR healthcare personnel OR hospital\* OR caregiver\* or paramedic\* physician\* or nurse\* or medical staff OR practitioner\* OR primary care OR ambulance worker\*)  Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years |
| # 2 | 152,513 | | TS=(zanamivir OR oseltamivir OR laninamivir OR peramivir OR neuraminidase inhibitor\* OR NA inhibitor\* OR antiviral\* OR anti viral\* OR sialidase inhibitor\* OR tamiflu OR relenza OR rapivab)  Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years |
| # 1 | 389,096 | | TS=(flu OR influenza OR grippe OR "ILI" OR pandemi\* OR seasonal\* )  Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years |

ClinicalTrials.gov (46 studies, PDF)

zanamivir OR oseltamivir OR peramivir OR laninamivir OR neuraminidase inhibitor OR sialidase inhibitor OR tamiflu OR relenza OE rapivab | Studies With Results (46 records)

# Appendix III. Results

## **Search findings**

We searched five electronic databases for observational and experimental studies. Overall, 7541 citations were retrieved, of which 2285 duplicates were removed leaving 5256 unique records that were screened by title/abstract. Altogether, 5126 were excluded based on the intervention used, study design, population and outcomes assessed. Subsequently, the remaining 130 articles were screened at the full-text level. Finally, eight studies were included in the systematic review. Hand searching did not reveal any additional records. (Appendix IV)

## **Study characteristics**

Overall, eight studies met our pre-established inclusion criteria and were included in the systematic review.3-10 Four were randomized trials,5,6,8,10 three were cohort studies4,7,9 and one was a quasi-experimental trial.3 All comprised HCWs and were conducted in healthcare settings: seven in tertiary care settings and outpatient centres3-5,7-10 and one in aged care facilities (ACFs)6. Studies were carried out in Asia (50%)3,7-9, Canada (25%),5,10 Argentina (12.5%)4 and Australia (12.5%)6, between 2006 – 2010. HCWs were predominantly healthy or with stable medical conditions. Oseltamivir and Zanamivir were the main NAIs assessed. Overall, seven studies assessed the effectiveness of NAI prophylaxis in preventing influenza in HCWs,3-5,7-10 whereas Booy et al. compared the effectiveness of two different NAI use strategies: treatment & prophylaxis vs. treatment alone.6 No study assessed the effect of NAIs in preventing healthcare service disruption. (Table I)

## **Summary of findings**

### ***NAI use for prophylaxis***

#### Influenza-like illness and laboratory confirmed influenza

Efficacy and effectiveness of NAIs in preventing influenza were assessed in four RCTs5,6,8,10 and three non-randomized studies,3,4,7 respectively. Two pilot trials conducted by Coleman et al. assessed the relative efficacy of NAIs compared to trivalent influenza vaccine (TIV) in HCWs.5,10 The incidence of symptomatic laboratory-confirmed influenza was 24% (95% CI 12.8, 38.3) in the Oseltamivir group vs. 17% (95% CI 2.4, 48.4) in the TIV group. The difference in incidence between both groups was not significant and 50% of influenza cases (i.e. 5 out of 10 reported cases) in the Oseltamivir group occurred before prophylaxis was initiated.5 The authors concluded that both interventions were similarly effective in preventing influenza in HCWs. In their second pilot trial, HCWs were randomized to receive either Zanamivir prophylaxis or TIV.10 The authors reported an adjusted OR of 1.30 (95% CI 0.84, 2.01), showing that there was no difference in the number of acute respiratory illness (ARI) episodes for people receiving Zanamivir prophylaxis compared to those receiving TIV, and the antiviral seemed to be effective in preventing influenza infections in HCWs. However, these two studies included a small number of HCWs, which could have limited their power to detect any difference between groups. In another trial that assessed the safety and tolerability of Zanamivir and Oseltamivir prophylaxis, Anekthananon et al. randomized HCWs to four groups: Active Zanamivir, active Oseltamivir and two placebos. The authors reported ILI in 6 HCWs as follows: 2 (3.07%) in the Oseltamivir placebo, 3 (2.29%) in active Zanamivir and 1 (1.53%) in Zanamivir placebo. No ILI events were reported in the active Oseltamivir arm and none of the reported ILI episodes in any of the groups was laboratory confirmed for influenza A or B.8 Non-randomized studies assessed the effectiveness of NAI prophylaxis compared to no prophylaxis in HCWs.3,4,7 During the 2009 influenza pandemic, Cheng et al. conducted a quasi-experimental study to assess the effectiveness of implementing an infection control bundle in a tertiary care hospital, to minimize nosocomial transmission.3 Data on Oseltamivir post-exposure prophylaxis in HCWs and patients with unprotected exposure were collected and no influenza confirmed cases were reported in HCWs who received Oseltamivir prophylaxis, whereas a secondary attack rate of 0.46% was reported in HCWs who did not receive prophylaxis. In a prospective cohort, Querci et al. followed up 1519 HCWs in two university hospitals and 6 outpatient centres.4Among all HCWs, 96 presented with ILI. Logistic regression analysis comparing influenza H1N1-positive and negative cases found Oseltamivir pre-exposure prophylaxis was deemed protective against confirmed H1N1 with an adjusted OR = 0.08 (95% CI 0.01, 0.43), whereas Samra and Pawar reported no significant reduction in ILI for the pre-exposure prophylaxis group compared to the no prophylaxis group with a crude OR = 1.994 (95% CI 0.803 - 4.950).7 Finally, two strategies of NAI use were compared in a cluster-randomized trial conducted in ACFs over three consecutive influenza seasons.6 Patients and staff members in participating ACFs – with reported outbreaks during the study period, were cluster-randomized for a treatment and prophylaxis (T&P) strategy or treatment only strategy (T). In this trial, Booy et al. reported a non-statistically significant reduction in confirmed, probable and possible influenza cases attack rates in staff in T&P facilities (13.4%) compared to those in T facilities (21.3%).24 (Table II)

#### Secondary transmission

Nosocomial transmission was assessed by Higa et al. in a retrospective cohort study carried out over three consecutive influenza seasons, in an acute hospital setting.9 Patients and HCWs who had a close contact with index cases were given NAI for post-exposure prophylaxis (primarily Oseltamivir, which was replaced by Zanamivir in some participants). The authors observed that whether index cases were patients or HCWs, the incidence of influenza did not significantly decrease in HCWs who received post-exposure prophylaxis compared to those who did not. Indeed, unadjusted OR were 0.30 (95% CI 0.03–2.68) and 0.95 (95% CI 0.17–5.29), respectively. (Table II)

### ***NAI used as treatment***

Except for Booy and colleagues’ trial detailed above, the literature search did not reveal any study evaluating NAI treatment in HCWs.

## **Quality assessment**

Included studies were deemed at low (25%), moderate (37.5%) and high risk of bias (37.5%) according to the Cochrane tools criteria. (Table II) Most observational studies were at high risk of confounding bias as no statistical adjustment was performed in the analysis. Information bias was also present in many studies as influenza related events assessment was based on self-reports and outcome measurement errors could occur.

# Appendix IV. PRISMA flowchart



Figure 1 Study selection flowchart

**References**

**1.** Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.

**2.** Higgins JPT, Sterne, J.A.C., Savović, J., Page, M.J., Hróbjartsson, A., Boutron, I., Reeves, B., Eldridge, S. A revised tool for assessing risk of bias in randomized trials In: Chandler J, McKenzie J, Boutron I, Welch V (editors). *Cochrane Methods. Cochrane Database of Systematic Reviews 2016* 2016.

**3.** Cheng VC, Tai JW, Wong LM, et al. Prevention of nosocomial transmission of swine-origin pandemic influenza virus A/H1N1 by infection control bundle. *J Hosp Infect* 2010;74:271-277.

**4.** Querci M, Stryjewski ME, Herrera F, et al. Healthcare personnel infected with novel influenza A H1N1 virus in university hospitals in Buenos Aires, Argentina. *Scand J Infect Dis* 2011;43:70-74.

**5.** Coleman BL, Boggild AK, Drews SJ, Li Y, Low DE, McGeer AJ. Respiratory illnesses in Canadian health care workers: a pilot study of influenza vaccine and oseltamivir prophylaxis during the 2007/2008 influenza season. *Influenza Other Respir Viruses* 2011;5:404-408.

**6.** Booy R, Lindley RI, Dwyer DE, et al. Treating and preventing influenza in aged care facilities: a cluster randomised controlled trial. *PLoS One* 2012;7:e46509-e46509.

**7.** Samra T, Pawar M. Health care personnel and risk of H1N1-chemoprophylaxis with oseltamivir. *Indian Journal of Pharmacology* 2012;44:754-758.

**8.** Anekthananon T, Pukritayakamee S, Ratanasuwan W, et al. Oseltamivir and inhaled zanamivir as influenza prophylaxis in Thai health workers: a randomized, double-blind, placebo-controlled safety trial over 16 weeks. *Journal of Antimicrobial Chemotherapy* 2012;68:697-707.

**9.** Higa F, Tateyama M, Tomishima M, et al. Role of neuraminidase inhibitor chemoprophylaxis in controlling nosocomial influenza: an observational study. *Influenza Other Respir Viruses* 2012;6:299-303.

**10.** Coleman BL, Fadel SA, Drews SJ, Hatchette TF, McGeer AJ. Zanamivir versus trivalent split virus influenza vaccine: a pilot randomized trial. *Influenza Other Respir Viruses* 2015;9:78-84.