Safety and effectiveness of neuraminidase inhibitors in situations of pandemic and/or novel/variant influenza: a systematic review of the literature, 2009–15

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Objectives: To review systematically the published literature evaluating neuraminidase inhibitor (NI) safety and effectiveness in situations of pandemic and novel/variant influenza.

Methods: We searched six online databases using comprehensive search criteria for observational studies and randomized controlled trials investigating the effects of NI treatment, prophylaxis or outbreak control in patients of all ages.

Results: Overall, 165 studies were included (95% observational), which were generally of low methodological quality due to lack of adjustment for confounding variables. In studies reporting adjusted estimates in general populations, NI treatment appeared likely to be effective against mortality (primarily if administered within 48 h of symptom onset) and potentially effective in reducing pneumonia. NIs appeared effective in reducing secondary transmission when indicated for prophylaxis. Limited, low-quality data suggest NIs are likely safe in general populations and may be safe in pregnant women and children. Data are scarce regarding safety of NIs in adults and high-risk individuals.

Conclusions: Most included studies were observational, statistically underpowered and at high risk of reporting biased and/or confounded effect estimates. NI treatment appeared likely effective in reducing mortality (cause unspecified) and pneumonia in general populations, with increasing benefit when administered with 48 h of symptom onset. NI pre- or post-exposure prophylaxis is likely effective in reducing secondary transmission of influenza in a general population. Our evidence suggests NIs are likely safe to use in the general population; however, data for children and pregnant women are limited. Knowledge gaps persist in specific populations such as Aboriginals, high-risk individuals and the elderly.

Introduction

Influenza pandemics cause significant morbidity and mortality as populations possess little to no immunity against the emerging virus. Given the impacts and unpredictability of a pandemic, a sustainable and effective framework for pandemic preparedness should naturally be outlined prior to a pandemic’s onset. Influenza vaccines and antiviral medications are integral components of pandemic preparedness efforts. Although vaccination remains the optimal defence against influenza virus infection, using current technologies, it takes 4–6 months to develop and produce a reasonably effective pandemic vaccine. Thus, a vaccine is unlikely to be available by the time the first pandemic wave reaches a nation’s border. National stockpiles of antiviral drugs are needed to ensure equitable access to a secure, government-controlled supply of antivirals for pandemic influenza.

It has become increasingly challenging for policy-makers and other stakeholders to track and synthesize existing, high-quality evidence regarding both antiviral effectiveness and safety in a pandemic situation. Differences exist in the pharmacokinetics, cost, safety profile, resistance and availability of the two classes of influenza antiviral medications that are currently available: M2 inhibitors (amantadine and rimantadine) and neuraminidase inhibitors (NIs) oseltamivir, zanamivir, peramivir and laninamivir. Influenza A, the type that causes pandemics, has limited resistance to NIs. Several reviews have assessed the safety and/or effectiveness of NIs, however, the outcomes were evaluated in
the context of different patient subpopulations; the reviews have not included all NI types and have not focused solely on pandemic and/or novel influenza. As such, knowledge gaps exist regarding the safety and effectiveness of all available NIs against pandemic influenza in all patient populations and in the greater community. To address these gaps, we conducted a systematic review to assess and synthesize the literature from observational studies and randomized controlled trials (RCTs) regarding NI safety and effectiveness in situations of pandemic and novel/variant influenza.

**Methods**

**Protocol and search strategy**

A study protocol was developed in conjunction with the Public Health Agency of Canada and the Canadian Pandemic Influenza Preparedness Task Group. Post-hoc protocol amendments are listed in Part 1 of the Supplementary data (available at JAC Online). A glossary of all definitions and abbreviations used in this review is provided in Part 2 of the Supplementary data. Six databases were searched for published articles: BIOSIS Previews, CINAHL, EMBASE, MEDLINE, PubMed and Web of Science. The search criteria were initially developed for MEDLINE and were subsequently adapted for the other databases. Searches were limited to studies published from 1 April 2009–31 October 2015, in English or French that were not indexed as animal-only studies. 1 April 2009 was chosen as the start date for this review in consideration of the start date of the 2009 pandemic influenza outbreak. The search criteria were developed by a research librarian (G. G.) in consultation with team researchers and were peer-reviewed by a separate research librarian. Search results were subsequently cross-checked with a list of seminal pandemic/novel/variant influenza primary studies that are eligible for inclusion, identified a priori (see Supplementary data Part 3 for a Venn diagram describing the search strategy, inclusive with Boolean logic and Supplementary data Part 4 outlining the full search strategy of all databases). After execution of the database search, the reference lists of all included articles were also manually reviewed to identify any non-indexed or incorrectly indexed articles eligible for inclusion that were not initially identified.

**Study selection**

**Types of studies**

We included evidence from observational studies and RCTs evaluating the effects of NIs for treatment (defined as NI administration to an individual who has influenza at the time of administration), prophylaxis (defined as NI administration to a person without influenza at the time of administration prior to or following contact with a person infected with influenza), or outbreak control (defined as NI administration to a cohort or subpopulation for influenza treatment or prophylaxis). We excluded study types/designs that either did not answer the question of interest or lacked the methodological rigour that was deemed acceptable to answer our questions of interest adequately (see Supplementary data Part 5.1 for specific exclusion criteria).

**Types of interventions**

We included studies evaluating NIs, defined as the administration of any of the following generic name drugs, alone or in combination: oseltamivir, zanamivir, peramivir and/or laninamivir. For inclusion, studies of NIs must have been used in the context of pandemic influenza (defined as any influenza A/H1N1 strains circulating in 2008–2009 or 2009–2010 influenza seasons) or novel/variant influenza (defined as influenza strains endemic in avians or swine, not endemic in humans) treatment, prophylaxis and/or outbreak control. Studies with the following comparators alone or in combination were considered for inclusion: administration of another antiviral drug class, regimen or NI; standard of care at the time the study was conducted; placebo; or no treatment for influenza.

**Types of participants**

We did not restrict the types of participants eligible for inclusion and included studies that evaluated the intervention among any population. We defined the following a priori subpopulations of interest for stratified analyses: (i) infants and young children (0–59 months); (ii) healthy adults and children 5–64 years, with a robust immune system; (iii) people who are ≥65 years old; (iv) people living with chronic health conditions; (v) people who are immune-compromised; (vi) women who are pregnant or breastfeeding; and (vii) Aboriginal peoples. The following a priori subgroups of interest were identified for stratified analyses: (i) communities; (ii) hospitals; (iii) closed or semi-closed institutional settings (such as hospitals, prisons and long-term care facilities); (iv) residential community-based settings (including hostels, homeless shelters and non-healthcare residential settings); and (v) remote and isolated communities.

**Types of outcomes**

The primary outcome of interest for NI effectiveness in prophylaxis/outbreak control was secondary transmission. For NI effectiveness in treatment, outcomes included mortality (distinguishing between all-cause and influenza-related, if possible), pneumonia, ICU admission, hospitalization, secondary transmission, severe influenza infection (defined as either ICU admission or death), duration of fever (or time to afebrile), time to resolution of symptoms (duration of disease) and effectiveness of NIs in relation to timing of administration (either after symptom onset or presentation for medical care was also evaluated). For NI safety (for either treatment, prophylaxis or outbreak control) the primary outcomes of interest were all reported adverse events (AEs). Secondary outcomes included for NI effectiveness in treatment, prophylaxis or outbreak control were viral shedding, viral load and development of resistance.

**Types of outcome measures**

Studies meeting the inclusion criteria that reported at least one statistical comparison between the intervention and comparators were included. Statistical comparisons were defined as a P value or effect measure (EM), including OR, HR, risk/rate ratio (RR), risk/rate difference (RD) and reproductible number (R0).

**Data extraction**

Two reviewers (M. K. D. and C. B.) independently reviewed titles, titles and abstracts, and/or full text of all studies returned via the electronic search to determine study eligibility for inclusion. Articles were excluded by review of title alone or review of title and abstract, where exclusion consensus between reviewers was achieved based upon initial review only; all other articles were reviewed by full text. Following full-text review, the reviewers met to resolve any discrepancies regarding study eligibility decisions in consensus meetings. A third reviewer was available to resolve disagreements (C. Q.).

The data extraction tool was specifically developed for this review. Two reviewers (C. B. and M. K. D.) independently piloted the data collection form. Data were extracted independently by a team of four reviewers (C. B., C. C., M. D. and H. K.-M.). All reviewers met to discuss both the data extraction strategy and form to keep the type and quality of evidence extracted consistent among the four reviewers. Consensus meetings were also held to discuss any discrepancies among the reviewers and resolve conflicts. If needed, a third reviewer was available to resolve disagreements (M. K. D.).

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria for rating the quality of evidence were used to assess the quality of each study independently by each reviewer. We specifically evaluated the risk of bias (selection bias, measurement error...
and residual confounding) in RCTs and observational studies, and checked for any additional risk of bias in RCTs arising from random sequence generation, allocation concealment and blinding. Each study was assessed for the presence/absence of confounding, measurement error and selection bias (as determined by reviewers). We also evaluated the imprecision and indirectness of the outcomes of interest (see Supplementary data Part 5.2 for detailed criteria). Indirectness and imprecision were reported as a binary judgement (present/not present). Additional information regarding study quality that was relevant but not addressed by the GRADE tool was also extracted in the form of a text box left for open comments by the reviewers. Consensus meetings were held to discuss any discrepancies between the reviewers and resolve conflicts. If needed, a third reviewer was available to resolve disagreements (M. K. D.).

Hierarchy of evidence

Similar to the methodology employed in the systematic review of observational studies by Hsu et al., 10 we chose to include only adjusted outcomes for our quantitative description of the results for primary and secondary outcomes for the subsections of NIs indicated for treatment. If a study presented a P value or an unadjusted EM, we included only the latter. In situations where it was unclear whether an estimate was adjusted or not, we erred on the side of caution and assumed the EM was unadjusted. Both adjusted and unadjusted estimates were evaluated for the subsections of NIs indicated for prophylaxis and safety of NIs given the scarcity of the data within these sections.

Data synthesis

A descriptive analysis of the included studies was performed. Study results were evaluated by NI indication, outcome, type of NI used (where possible) and study population. Forest plots were created for the primary outcomes of interest; however, pooled effect estimates were not calculated, as a meta-analysis was not conducted (as specified in the study protocol). The results for safety of NIs are presented as a narrative given the heterogeneity of NIs used in the study populations, comparators evaluated and outcomes reported among these studies.

Results

Description of studies

Search results

We searched six electronic databases for observational and experimental studies. A flow diagram detailing the results of the literature search and review is provided in Figure 1. Initially, 17,633 articles were retrieved through the computer-assisted search. After the removal of duplicates, 8,492 articles were screened by title by two reviewers (M. K. D. and C. B.); 66% (5,599 of 8,492) of the articles were excluded on the basis of context, study design or type of influenza addressed. Roughly 61% (17,566 of 28,933) were excluded on the basis of incorrect study assessed by abstract. Therefore, the following mutually exclusive post-hoc subpopulations were created: (i) general population, defined as populations that overlap any subpopulation criteria (i.e. inclusive of multiple risk groups or strata); (ii) children, defined as people <18 years of age; (iii) adults, defined as people 18–65 years of age; (iv) elderly, defined as people ≥65 years old; (v) high risk (exact definition varies between studies but is inclusive of people living with chronic illness and/or people who are immunocompromised); and (vi) women who are pregnant or breastfeeding. These groups were considered in the results section of the a priori groups and the data from the literature retrieved.

The majority of the included studies evaluated hospitalized participants (that are presumably also community-dwelling). Only one study, by Wada et al., 175 provided a statistical comparison in an elderly population (≥65 years old). Furthermore, a single study, by Lee et al., 35 evaluated a closed or semi-closed institutional setting (such as hospitals, prisons and long-term care facilities); the study evaluated the effectiveness of oseltamivir prophylaxis among the Singapore Armed Forces. An elaboration of the reported results of these studies can be found in the Results section. We also did not find many studies that evaluated the outcomes of interest particularly in situations of novel/variant influenza. No study provided statistical comparisons of interest in an Aboriginal population, in a residential community-based setting (includes hostels, homeless shelters, non-healthcare residential settings, such as university residences and group homes), nor among individuals residing in remote and isolated communities.

Included studies

Ninety-four per cent (155 of 165) of the included studies were observational and the remainder were experimental. 23,36,42,46,66,79,138,146,159,160 All included studies were written in English with the exception of one, 38 which was written in French. All but one study 36 identified all of the exact countries from which the data analysed were derived. The majority of studies were conducted in/used data from the USA (n = 26), Japan (n = 20) or Spain (n = 14). Five studies utilized Canadian data only 48,109,114,151,162 and four studies utilized data from multiple countries, which included Canada and (see Supplementary data Part 6 for a full list of countries in which the included studies were conducted/used data from).

At least one statistical comparison of interest was found in 63% (104 of 165) of the retrieved studies for the general population, in 20% (33 of 165) for children, in 9% (15 of 165) for pregnant women, in 8% (14 of 165) for high-risk individuals, in 7% (11 of 165) for adult populations and, as previously mentioned, in one study for the elderly population.

Pandemic influenza was evaluated in 154 (93%) studies, novel/variant influenza (H5N1, H7N7 and H7N9) 12,15,24,63,69,100,101,119,141 was evaluated in nine studies (5%), and both pandemic and novel influenza (H5N1 and novel H3N2) 138 were evaluated in two
studies (1%). Results from the studies evaluating novel influenza are subsequently presented (see Literature synthesis) with the exception of two studies where authors did not report any primary or secondary outcomes of interest. 15,100

Roughly 88% (145 of 165) of studies included participants with laboratory-confirmed influenza (most commonly by RT-PCR); however, the diagnostic methods that authors used varied widely by study (see Table S1 for specific laboratory methods used in each study). In the majority of studies, the study population exclusively received oseltamivir (107 of 165; 65%); in four studies 36,66,79,105 (2%) authors evaluated the effect of peramivir alone; and in the remaining 54 (33%) it was either unclear whether study participants received several NIs or one NI exclusively.

Risk of bias in included studies. We deemed selection bias to be unlikely in roughly half (77 of 165) of the included studies and likely/unclear in ~40% (61 of 165) (Figure 2). Selection bias was often attributed to lack of clear inclusion criteria and inappropriate reporting or handling of both losses to follow-up and missing data. Furthermore, measurement error was considered likely in 37% (61 of 165) of all included studies and unclear (or possible) in 35% (57 of 165) of studies. Measurement error was often attributed to recall bias in retrospective studies and unclear diagnostic measures used for influenza. Finally, confounding (or residual confounding in both studies where authors presented adjusted estimates or RCTs) was deemed likely in 95% (157 of 165) of studies. This was usually due to the presentation of unadjusted statistical comparisons (P values or estimates from univariable regression models) as well as confounding by indication in observational studies. Given that confounding was deemed the biggest threat to internal validity in the included studies, results were stratified by type of statistical comparison presented as mentioned previously in the section Hierarchy of evidence.

Furthermore, less than half of the included studies (69 of 165, 42%) reported direct evidence, i.e. the reported results were for a specific subgroup of interest and/or the effectiveness and/or safety of a specific NI drug was evaluated. In the remaining studies, authors reported indirect evidence, i.e. results that pertained to NIs in general (rather than one specific NI drug), and/or results were from a general study population (inclusive of many types of
subpopulations, settings, or both) or the composition of the study population was unclear (i.e. not addressed or described). Additionally, 38% (62 of 165) of studies were deemed to present precise evidence. The remaining studies presented imprecise evidence mainly due to small size of groups used in the comparisons of interest and the presentation of P values only. Other indications that results were imprecise included the presentation of EMs with very wide 95% CIs or credible intervals and/or a small number of events of interest (all of which relate to low statistical power to detect meaningful differences and effects).

Literature synthesis

NIs for treatment

Approximately 63% (104 of 165) of included studies were retained for the analysis of the effect of NI treatment (see the List of excluded studies for knowledge synthesis of NIs for treatment, Supplementary data Part 7).

Mortality

Importantly, in most studies a distinction between all-cause and influenza-related mortality was not provided. We deemed it inappropriate to try and discern or assume which type of mortality the included studies were reporting. As such, the results presented here are for mortality in general.

All statistical comparisons. Overall, 11 of 165 (7%) of included studies presented 13 comparisons that were statistically significant with respect to favouring NI treatment as compared with no treatment for the outcome of mortality (Figure 3). Of these, five studies evaluated novel/variant influenza. In 12 studies (7%), authors reported 12 comparisons that were not statistically significant at the \( \alpha = 0.05 \) level (i.e. an EM with a 95% CI that includes the null value of \( P \geq 0.05 \)). Only the observational study by Randolph et al. reported a statistically significant unadjusted increased risk of death with peramivir treatment in a general population \(<20\) years of age. Of note, this study also reported non-statistically significant protective effects of oseltamivir and zanamivir.

Adjusted EMs. Seven studies reported at least one adjusted measure (an EM reported from an RCT or adjusted for at least one confounder) of the effect of NIs versus no treatment on mortality in the context of pandemic/novel influenza (Figure 4).

In a general population, four of seven studies reported a statistically significant protective effect of NIs against mortality. Of note, only the observational study by Oner et al. reported an increased odds of death in those with NI treatment compared to no treatment; however, the estimate was not statistically significant at the \( \alpha = 0.05 \) level; it was not clear whether the comparator in the study was no treatment. In children, only the study by Yang et al. presented an adjusted EM that favoured the use of NI treatment for the outcome of mortality in this population; however, this was not statistically significant. No other populations of interest were represented in the studies presenting adjusted EMs for this outcome.

Mortality and timing of NI treatment

All statistical comparisons. Twenty-five studies (16%) provided 28 statistically significant comparisons in one or more populations of interest in favour of NI treatment earlier versus later (relative to both symptom onset and presentation for medical care). Of these, four studies evaluated novel/variant influenza. Twelve studies (7%) reported 15 non-statistically significant results and no studies reported statistically significant results that did not favour earlier antiviral treatment. Of these, only one study provided a statistical comparison in an elderly population \((\geq 65\) years old); this study found that the timing of antiviral administration did not appear to affect significantly the clinical course (i.e. the risk of death) among either those with influenza-associated encephalopathy or in critically ill cases.

Adjusted EMs. When restricting to studies that evaluated time-to-administration of NI treatment and presented an adjusted EM (either including one covariate in a multivariable regression model or had an experimental study design), 4 of 165 (2%) studies reported adjusted EMs evaluating the effect of NI treatment on mortality. In a general population, three studies presented adjusted EMs for this outcome.
all reported increasing odds of mortality for each day of delay from illness onset to treatment with oseltamivir (data not shown). In adults, Viasus et al.\textsuperscript{157} presented a similar EM. No other populations of interest were represented by the studies presenting adjusted EMs for this outcome.

**Hospitalization**

**All statistical comparisons.** Two studies (1%) reported comparisons that were statistically significant in favour of NI treatment with regard to hospitalization\textsuperscript{109,140} and two studies (1%) reported two comparisons that were not statistically significant (Figure 3).\textsuperscript{97,142}

**Adjusted EMs.** Three studies (2%) presented an adjusted effect estimate evaluating NI treatment on hospitalization (Figure 5).\textsuperscript{97,109,140} In children, the studies by Lera et al.\textsuperscript{97} and Shi et al.\textsuperscript{140} both reported an EM favouring NI treatment for the outcome of hospitalization. In a general population, the study by Marra et al.\textsuperscript{109} reported a similar result. No other populations of interest were represented by the studies presenting adjusted EMs for this outcome.

**Hospitalization and timing of NI treatment**

**All statistical comparisons.** Five studies (3%) presented non-statistically significant comparisons for the effect of earlier NI treatment on hospitalization (Figure 3).\textsuperscript{97,111,130,142,151} Three studies (2%) reported statistically significant comparisons favouring earlier NI treatment for the outcome of hospitalization.\textsuperscript{64,83,140}

**Adjusted EMs.** Only one study\textsuperscript{140} presented an adjusted EM evaluating the timing of antiviral administration for the outcome of hospitalization. Among children, Shi et al.\textsuperscript{140} reported an adjusted effect estimate that favoured NI treatment (specific NI not evaluated) within 2 days of presentation for medical care (compared to later) for the outcome of hospitalization (Figure 5). No other populations of interest were represented by the studies presenting adjusted EMs for this outcome.

**ICU admission**

**All statistical comparisons.** In four studies (2.5%), authors presented at least one statistically significant comparison in favour of NI treatment for the outcome of ICU admission.\textsuperscript{57,124,127,171} In two studies (1%), authors presented non-statistically significant comparisons for the effect of NI treatment on ICU admission (Figure 3).\textsuperscript{57,174}

**Adjusted EMs.** Two studies\textsuperscript{57,124} reported adjusted EMs evaluating NI treatment for the outcome of ICU admission. In children, Hagerman et al.\textsuperscript{57} presented adjusted effect estimates in favour of oseltamivir use for the outcome of ICU admission. In a general population, Poepl et al.\textsuperscript{124} presented adjusted effect estimates in favour of oseltamivir use for the outcome of ICU admission. No other populations of interest were represented by the studies presenting adjusted EMs for this outcome.
ICU admission and timing of NI treatment

All statistical comparisons. Only one study, by Reid et al.,\textsuperscript{130} presented an unadjusted, non-statistically significant estimate evaluating earlier NI treatment (comparator unclear) for the outcome of ICU admission (Figure 3). Six studies (~4%) presented statistically significant comparisons in favour of earlier NI treatment for the outcome of ICU admission. Moreover, the observational study by Zheng et al.\textsuperscript{171} presented statistically significant results against earlier administration of NIs in a hospitalized cohort of paediatric patients; however, the estimate was not adjusted for confounders.\textsuperscript{40,54,83,142,154,165}

Adjusted EMs. In three studies, authors reported adjusted EMs for the timing of NI treatment on the outcome of ICU admission. In a study having a high-risk population of solid organ transplant recipients, Kumar et al.\textsuperscript{83} reported a statistically significant benefit of NI treatment within 48 h of symptom onset. In pregnant women, Yates et al.\textsuperscript{165} and Varner et al.\textsuperscript{154} also reported a statistically significant benefit of NI treatment administered within 48 h of symptom onset (Figure 5). No other populations of interest were represented in the studies where adjusted EMs were reported for this outcome.

Pneumonia

All statistical comparisons. In one study, Di Giambenedetto et al.\textsuperscript{39} reported a statistically significant (unadjusted) comparison favouring no treatment compared with NI treatment for the outcome of pneumonia (Figure 3). Furthermore, two studies (1%) reported non-statistically significant comparisons favouring NI treatment\textsuperscript{112,139} and Yu et al.\textsuperscript{168} reported a statistically significant comparison of NI treatment compared to no treatment for pneumonia in their study.

Adjusted EMs. One study\textsuperscript{168} reported an adjusted EM evaluating NI treatment on the outcome of pneumonia. In a general population, Yu et al.\textsuperscript{168} reported an EM that favoured NI treatment compared with no treatment for the outcome of pneumonia (Figure 5). No other populations of interest were represented in the studies that presented adjusted EMs for this outcome.

Pneumonia and timing of NI treatment

All statistical comparisons. Two studies (1%) reported non-significant comparisons for earlier NI treatment\textsuperscript{108,151} and seven studies (4%) reported statistically significant results
favouring earlier NI treatment for the outcome of pneumonia (Figure 3).  

**Adjusted EMs.** In two studies, authors presented adjusted EMs evaluating the effect of NI treatment on pneumonia. In adults, Viasus et al.\(^\text{156}\) reported a favourable adjusted EM for the effect of NI treatment within 48 h of symptom onset compared with >48 h for the outcome of pneumonia. Yu et al.\(^\text{168}\) reported similar results in a study conducted in a general population (Figure 5). No other populations of interest were reported by authors in the studies where adjusted EMs were presented for this outcome.

**Severe influenza**

**All statistical comparisons.** One study\(^\text{157}\) presented a non-statistically significant comparison for the outcome of severe influenza and one study\(^\text{37}\) presented a statistically significant comparison in favour of NI treatment versus no treatment for the outcome of severe influenza (Figure 3).

**Adjusted EMs.** In one study, Delgado-Rodriguez et al.\(^\text{37}\) presented an adjusted effect measure favouring zanamivir treatment versus no treatment for the outcome of severe influenza (Figure 5). No other populations of interest were represented by the studies presenting adjusted EMs for this outcome.

**Severe influenza and timing of NI treatment**

**All statistical comparisons.** Three studies (~2%) presented four statistical comparisons for early NI treatment that were not statistically significant.\(^\text{31,113,170}\) Four studies (2%) presented statistically significant results in favour of earlier NI treatment (Figure 3).\(^\text{31,34,37,157}\)

**Adjusted EMs.** In two studies, adjusted EMs were presented which evaluated the effect of NI treatment timing and severity of influenza (Figure 5). In a general population, Delgado-Rodriguez et al.\(^\text{37}\) reported an adjusted EM that favoured NI administration within 48 h (compared with no treatment). However, Yu et al.\(^\text{167}\) reported no effect of NI administration within 48 h of symptom onset for the outcome of influenza severity for both a general...
population and in pregnant women. No other populations of interest were represented in the studies where adjusted EMs were presented for this outcome.

**Duration of fever**

**All statistical comparisons.** Five studies (3%) presented non-statistically significant results38,76,80,160,165 and nine studies (5%) presented statistically significant results favouring NI treatment for the outcome duration of fever (Figure 3).47,73,79,95,124,135,146,153,159 Of the studies presenting statistically significant results favouring NI treatment, the study by Sugaya et al.146 evaluated novel/variant influenza (P value reported).

**Adjusted EMs.** One study, Saito et al.135 presented two adjusted EMs (for oseltamivir and zanamivir respectively) evaluating the effect of NI treatment on duration of fever in children. Both EMs favoured NI treatment compared with no treatment, but only the adjusted EM for oseltamivir treatment was statistically significant (Figure 5). No other populations of interest were represented in the studies where adjusted EMs were reported for this outcome.

**Duration of fever and timing of NI treatment**

**All statistical comparisons.** One study (~1%) presented a comparison that was not statistically significant102 and three studies (~2%) presented comparisons that were statistically significantly in favour of early NI administration versus late (Figure 3).144,157,168

**Adjusted EMs.** In one study,157 an adjusted EM was reported that evaluated the effect of NI treatment timing on duration of fever. In adults, Viasus et al.157 reported an adjusted EM that favoured the administration of NIs within 48 h of symptom onset, compared with no treatment (Figure 5). No other populations of interest were represented in the studies where adjusted EMs were reported for this outcome.

**Time to resolution of influenza symptoms**

**All statistical comparisons.** Four studies (2%) presented at least one comparison that was not statistically significant156,191,153,160 and eight studies (~5%) presented comparisons that were statistically significantly in favour of NI treatment compared with no treatment for the outcome of resolution of influenza symptoms (Figure 3).32,47,79,125,127,129,146,159

**Adjusted EMs.** In one study,125 authors reported an adjusted effect estimate evaluating the effect of NI treatment of the time to resolution of influenza symptoms. In adults, Pop-Vicas et al.125 found that days to antiviral initiation was independently associated with prolonged influenza, defined as an influenza-like illness (ILI) lasting beyond 7 days (data not shown in Pop-Vicas et al. article; adjusted in a multivariable regression model). No other populations of interest were represented in the studies where adjusted EMs were reported for this outcome.

**Time to resolution of influenza symptoms and timing of NI treatment**

**All statistical comparisons.** One study136 (~1%) reported non-statistically significant results for NI treatment within 48 h versus later and three studies presented four statistically significant comparisons favouring the administration of NI treatment within 48 h of symptom onset (two studies111,125 comparing with treatment >48 h and one study129 comparing with no treatment) (Figure 3).

**Adjusted EMs.** There were no studies where an adjusted EM was reported evaluating the effect of NI treatment timing on the duration of influenza symptoms.

**Secondary transmission**

**All statistical comparisons.** Two studies (1%) presented non-statistically significant results22,81 and one study presented two statistically significant results149 (1%) favouring NI treatment in index cases of influenza compared to no treatment for secondary transmission (Figure 3).

**Adjusted EMs.** In no study was an adjusted EM reported that evaluated the effect of NI treatment (compared with no treatment) on secondary transmission of influenza.

**Secondary transmission and timing of NI treatment**

**All statistical comparisons.** Two studies65,117 (1%) presented statistically significant results favouring earlier NI treatment for the outcome of secondary transmission while one study presented non-statistically significant results56 (Figure 3).

**Adjusted EMs.** In two studies, adjusted estimates were reported evaluating the effect of NI treatment timing on secondary transmission (Figure 5). In a general population, Hirotsu et al.45 and Goldstein et al.56 both reported adjusted estimates that favoured the administration of NI within 48 h of illness onset in index cases for the prevention of secondary transmission of influenza. No other populations of interest were represented in the studies where adjusted EMs were reported for this outcome.

**Virological outcomes**

Virological outcomes including antiviral resistance, viral shedding and viral load were evaluated in 29 studies (18%) reviewed19,21,23,26,36,42,46,51,55,59,66,76,86,93,99,102,106,110,112,115,125,134,135,138,145,146,160,168,169 Among the 28 studies reporting on antivirals as treatment, six reported on antiviral resistance.42,59,76,86,110,135 Nine studies reported on viral load among the general population123,125,133,135,137,164,168 and among adults.125 Viral shedding was reported in 19 studies conducted in children66,146 the general population21,36,42,55,66,99,102,112,115,134,138,145,168,169 high-risk individuals108 and adults.125 All of the included studies that evaluated virological outcomes assessed antivirals as treatment, rather than prophylaxis or outbreak control, with the exception of a single case-control study that evaluated the
predictors and outcomes of patients with antiviral resistance, within which the indication was unclear. The abovementioned case–control study compared cases with oseltamivir-resistant pandemic (H1N1) 2009 strains with controls with oseltamivir-susceptible pandemic (H1N1) 2009 strains and observed a statistically significant (adjusted) OR for immunosuppressive condition and a significant higher risk for complications, particularly for respiratory complications (see the full description of virological outcomes, Supplementary data Part 8).

NIs indicated for prophylaxis/outbreak control
Secondary transmission
In 10% of studies (17 of 165), authors evaluated the effectiveness of NIs when indicated for prophylaxis or outbreak control. (16 observational studies and one experimental study). Of these studies, only three were used to evaluate the effectiveness of NIs generally and the remainder specifically evaluated the effectiveness of oseltamivir for prophylaxis/outbreak control. Studies that presented effect estimates comparing NI prophylaxis with no prophylaxis (both adjusted and unadjusted) were conducted either in a general population or in a study population composed of adults; no other populations of interest were represented by the studies reporting EMs for this outcome. Notably, it was unclear whether prophylaxis was pre-exposure or post-exposure in two of the included studies (Figure 6).

All studies showed either a statistically significant decreased risk or odds of influenza, or a lower $R_0$ in individuals who received NIs as prophylaxis compared to those that did not (in a general population and in adults), with the exception of an observational study conducted in healthcare personnel workers by Samra and Pawar (Figure 6). That study, conducted in a population of adults, found no statistically significant difference (unadjusted OR) in the incidence of flu-like illness between healthcare personnel working in areas of high aerosol generation (such as an ICU, where alternative infection control measures are adopted) receiving chemoprophylaxis with oseltamivir and those that did not receive the drug.

Moreover, in an RCT, Carrat et al. compared the effectiveness of different NIs indicated for prophylaxis and included patients ≥18 years who sought medical advice within 36 h of the onset of influenza symptoms and who had tested positive with a rapid influenza test. The study randomized participants to one of three treatment arms: oseltamivir/zanamivir combination therapy, oseltamivir monotherapy and zanamivir monotherapy. No statistically significant difference in secondary transmission of pandemic influenza between the three treatment arms was found. However, multivariable logistic regression modelling suggested greater odds of secondary transmission of influenza in both the oseltamivir and zanamivir monotherapy arms versus the combination therapy arm. Finally, one study evaluated the effectiveness of oseltamivir prophylaxis among the Singapore Armed Forces and found that after intervention the infection rate and $R_0$ were reduced. This result was also observed when the analysis was restricted to
both confirmed cases and unconfirmed cases of influenza, respectively.

Virological outcomes
As previously mentioned, in no study did authors evaluate virological outcomes in patients receiving oseltamivir for prophylaxis.

Safety of NIs
AEs related to NIs were evaluated in 13 included studies (8%): 11 observational studies\(^{13,35,41,47,50,85,94,121,153,162,163}\) and two experimental studies.\(^{56,79}\) Results are presented below stratified by subpopulation.

Adults
A multicentre, uncontrolled, randomized, double-blind study by Kohno et al.\(^{79}\) evaluated the efficacy of intravenous peramivir treatment administered at 300 or 600 mg/day for 1–5 days, as needed, in 37 adult patients (300 mg, \(n = 18\) patients; 600 mg, \(n = 19\) patients). Included participants were influenza virus-infected patients >20 years old who were influenza rapid antigen test positive and had >1 risk factor, had experienced onset of influenza symptoms within the previous 48 h and showed >2 of 7 influenza symptoms of moderate or greater severity. Overall, there were no statistically significant differences in adverse drug reactions and adverse drug events between the two treatment arms: 44 AEs were reported in 15 of 21 (71.4%) patients in the 300 mg/day group, compared with 38 AEs reported in 16 of 21 patients (76.2%) in the 600 mg/day group (\(P = 1.0000\) for 300 mg peramivir, unknown test). Furthermore, among those in the 300 mg group: 11 adverse drug reactions were reported in 6 of 21 (28.6%) compared with 10 adverse drug reactions that were reported in 8 of 21 (38.1%) of patients in the 600 mg group (\(P = 0.7442\) for 300 mg peramivir, unknown test).

General population
Results similar to the Kohno et al.\(^{79}\) experimental study were obtained in the open-label, randomized study by Ison et al.,\(^{56}\) whereby participants were randomized to intravenous peramivir treatment 300 mg twice daily or 600 mg once daily (laboratory confirmed influenza: \(n = 127\)); the proportion of subjects who reported AEs during the study was similar between treatment groups. Among those with AEs, 61% reported mild or moderate events and 20% each reported severe or life-threatening events. The subjects who remained clinically unstable on day 5 and therefore received >5 days of treatment with peramivir were more likely (86%) to report AEs than those receiving treatment ≤5 days (56%). Approximately half of the serious AEs reported were respiratory related (e.g., acute respiratory distress syndrome, respiratory failure, COPD), followed by infections (e.g., septic shock, sepsis, pneumonia), renal failure and cardiovascular disorders.

In an observational study by Tuna et al.,\(^{153}\) evaluating the safety of NI treatment, no serious AEs were reported, no patients died due to AEs, no drug discontinuation was required due to AEs (with the exception of one patient in the zanamivir group) and respiratory distress was not observed in patients using oseltamivir. However, one of the patients on zanamivir discontinued therapy due to the onset of respiratory distress, while development of respiratory distress was observed in five (12.5%) patients using zanamivir (\(P < 0.05\)). In a prospective cross-sectional study, Dashti-Khavidaki et al. reported that the dose of prescribed oseltamivir for treatment had the strongest correlation to the incidence of adverse reactions in a univariable model (OR 3.843, 95% CI 1.093–13.509, \(P = 0.04\)) in hospitalized patients.\(^{35}\) In an observational study by Anovadiya et al., the authors compared adverse drug reactions between patients on a therapeutic regimen and their close contacts on a prophylactic regimen of oseltamivir.\(^{13}\) Adverse drug reactions reported in the therapeutic group were statistically significantly higher as compared with the prophylactic group (\(P = 0.029\)). Severity assessment showed 76% mild and 24% moderate reactions in the therapeutic group, 89% mild and 11% moderate reactions in the prophylactic group. Severity of adverse drug reactions was significantly higher in the therapeutic group.\(^{13}\) Similarly, in a retrospective study by Fallo et al., mild AEs from oseltamivir treatment were reported in 8 of 64 (12%) school-aged patients (vomiting and diarrhoea were the most frequently reported symptoms in this group) while 15 of 266 (5.6%) household contacts with oseltamivir prophylaxis reported AEs, with abdominal pain the most frequently described symptom (\(P < 0.05\)).\(^{57}\)

Children
Two observational studies evaluated safety of NIs in a paediatric population. One observational study by L’Huillier et al.,\(^{85}\) evaluated the association between influenza genotype and neuropsychiatric events in children with a median age of 7.02 years (IQR 6.99). Of all oseltamivir-treated children who were genotyped for ABCB1 3435C>T and 2677G>T/A variants, 36% presented with an event. Furthermore, no statistical association was found between the development of a neuropsychiatric AE (NPAE) and age or gender (\(P = 0.756\) and \(P = 0.621\), respectively), and the findings suggest a potential influence of ABCB1 polymorphisms in oseltamivir-related NPAE. Furthermore, Leick-Courtois et al.\(^{94}\) found no evidence of statistically significant adverse digestive effects associated with oseltamivir treatment (\(n = 4\)) and prophylaxis (\(n = 13\)) in a high-risk population of preterm infants. The volume fed increased slightly as postnatal age increased for the periods before, during and after treatment. Despite an increased number of stools during treatment, there was no negative effect of oseltamivir on weight or short-term growth.

High risk
In one study, Pannaraj et al.\(^{21}\) found no association between occurrence of an AE and the received dose-by-weight of oseltamivir for prophylaxis (\(n = 21\)) or treatment (\(n = 11\)) in neonates in the NICU (\(P = 0.24\), t-test). See Supplementary data Part 9 (Summary of results in high-risk group) for a specific description of all results in the population of pregnant women.

Pregnant women
Four observational studies evaluated the safety of NIs in pregnant women. Yamada et al. found no association between the use of either oseltamivir or zanamivir for treatment (\(n = 229\)) and for
prophylaxis (n = 353) during the first trimester and malformations. Similarly, Xie et al. found no statistical association between maternal treatment with oseltamivir and fetal outcomes (including small for gestational age <3rd percentile, preterm birth <37 weeks, very preterm birth <32 weeks and Apgar score <7) adjusted for potential confounding factors (results from models with or without influenza vaccination were similar). The risk of being born small for gestational age <10th percentile was significantly lower among women who used oseltamivir at some time during pregnancy compared with those who did not (6.9% versus 9.2%; adjusted RR 0.77; 95% CI 0.60–0.98). Dunstan et al. also determined that the incidence of major malformations in live-born infants exposed to NIs (either for treatment or prophylaxis) in the first trimester of pregnancy was not significantly higher than that in the reference group. Preterm delivery (<37 gestational weeks) occurred in 14 (8.3%) of the zanamivir-exposed infants, three (15.0%) of the oseltamivir-exposed infants and 46 (10.3%) of the infants in the unexposed group; however, no significant differences were reported between the groups [zanamivir adjusted OR (aOR) 0.95, 95% CI 0.45–1.89; oseltamivir aOR 1.68, 95% CI 0.38–5.38]. Similarly, there were no differences between the zanamivir- and oseltamivir-treated groups versus the reference group for the association between NI treatment and low birth weight <2500 g (zanamivir aOR 0.94, 95% CI 0.25–2.90; oseltamivir aOR 4.12, 95% CI 0.59–17.99). Finally, Figueiro-Filho et al. found no association between the occurrence of adverse perinatal outcomes (spontaneous abortion, preterm delivery, stillbirth or neonatal death) and early initiation (within the first trimester) of oseltamivir treatment (OR 1.41; 95% CI, 0.08–24.96; P > 0.99). See Supplementary data Part 10 (Summary of results in pregnant women) for a specific description of all results in the population of pregnant women.

Discussion

NI effectiveness for treatment

Overall, approximately half (34 of 62, 55%) of all statistical analyses comparing NI treatment with no treatment were statistically significant, favouring the use of NIs for all outcomes with limited significant evidence opposing their use. Evaluating adjusted estimates only, NIs are likely effective in reducing mortality and may be effective in reducing pneumonia, in the general population. These benefits of NI treatment for pneumonia and mortality outcomes were more pronounced when the association between timing of NI administration was also considered. As such, our findings (albeit weakly due to the small number of studies per subpopulation as well as the low quality of studies) support the findings from a previously published systematic review of observational studies. In that study, Hsu et al. concluded that therapy with oral oseltamivir and inhaled zanamivir may provide a net benefit over no treatment of influenza. However, the authors also reported very low confidence in the estimates of the effects for decision making due to methodological flaws of the included studies. Our findings are in agreement with the meta-analysis of individual patient data from observational studies conducted by Muthuri et al., which also found a beneficial effect of NIs for the outcome of mortality in adults admitted to hospital with suspected or proven influenza infection. Likewise, these results are consistent with the findings of the systematic review and meta-analysis of observational studies conducted by Muthuri et al., which found that early initiation of NI treatment reduced the likelihood of severe outcomes compared with late (or no) treatment.

Furthermore, there was a trend in the evidence supporting NI treatment for the reduction of severe influenza, hospitalization, ICU admission and fever duration (in a general population, children and adults). No statistically significant evidence was presented against the use of NIs in the first 48 h of symptom onset (compared with later or no treatment) for these outcomes. However, the number of studies within each outcome and subpopulation was very small (one to three studies per outcome) and no adjusted EMs were presented regarding the effectiveness of NI treatment (compared to no treatment) for duration of illness. As such, we conclude that the evidence presented from the included studies is insufficient to make conclusive judgements on the effectiveness of NI treatment for the outcomes of hospitalization, severe influenza, ICU admission, secondary transmission, time to resolution of symptoms and fever duration.

NI effectiveness for prophylaxis/outbreak control

In all studies, a statistically significantly decreased risk, odds or lower R_{0} were reported in individuals who received NIs as prophylaxis (both pre- and post-exposure) compared with those that did not (in a general population and in adults) with the exception of one observational study conducted in adult healthcare personnel workers. In their study, Samra and Pawar found no statistically significant difference in the incidence of influenza-like illness between healthcare personnel working in areas of high aerosol generation, such as an ICU (where alternative infection control measures are adopted), receiving chemoprophylaxis with oseltamivir and those that did not receive the drug. As such, we conclude that NIs are likely to be effective for the outcome of secondary transmission when indicated for prophylaxis in a general population.

NI safety

The exposure–outcome associations were not homogeneous across included studies and for all study populations, precluding a quantitative description of this outcome. The limited, low quality data suggest that NIs are likely safe to use in a general population. Moreover, our findings suggest that NIs may possibly be safe to use in children and pregnant women. While no authors in any study presented data explicitly against the use of NIs, it should once again be highlighted that we have low confidence in the amount (and quality) of evidence regarding the safety of NIs in all populations. This is particularly evident in adult populations, the elderly and high-risk individuals (i.e. individuals living with chronic diseases). Our data does not justify a conclusion as to the safety of NIs in these populations.

Limitations of the review

The results of this review should be interpreted in light of several limitations. First, we judged that the included studies were generally of low quality based upon presence of confounding, measurement error and/or selection bias. Although we did not use a traditional assessment scale to determine quality, the presence of any of these factors is likely to bias the effect measures reported in the included studies. Based on these criteria, the most important
quality issue was confounding (specifically confounding by indication) as most studies presented only unadjusted effect estimates. Confounding (mainly by indication for NIs) was a main concern regarding the quality of the included studies. Future RCTs evaluating the effectiveness, efficacy and/or safety of NIs should be statistically powered such that the randomization process adequately distributes both known and unknown confounders. Similarly, future observational studies evaluating the effects of NIs should attempt to adjust (e.g. by using propensity score methods to minimize confounding by indication) for variables that could confound the effect estimate, to produce data of higher quality, with a specific focus on confounding by indication. The choice of confounders should be explicitly stated and justified (either chosen based on biological plausibility, subject matter expert or from previous literature). All studies should present both crude and adjusted effect estimates. Furthermore, future observational studies should also address imperfect sensitivities and specificities of the influenza diagnostics and attempt to use the same diagnostic tests for all groups being compared.

Second, the search strategy was designed to identify studies that included both the pandemic/novel concept and NIs. As a corollary, if studies did not discuss both of those concepts in their title, abstract or key words they would not have been identified from the database search. However, we conducted a manual search of the reference lists of 100% of the included articles (which returned only three additional articles), mitigating the possibility that pertinent studies were not captured by the original database search. Third, the definition of influenza was based on calendar time (2008–09 and 2009–10 influenza seasons), which may have led to the capture of studies that were conducted during the 2008–09 season that did not include the pandemic influenza strain. However, to avoid including studies irrelevant to our objective, we particularly excluded studies conducted during the 2008–09 season that did not explicitly include pandemic influenza. Furthermore, the WHO declared the pandemic over in July 2010 and, as such, we may be missing studies that address pandemic influenza after the 2009–10 season. To avoid this, our definition of ‘pandemic’ for this review reflected the fact that NIs would be used early on in a pandemic situation (before vaccination became available). Fourth, we included studies that evaluated the effectiveness (or safety) of NIs in general, precluding the identification of the effectiveness of a specific NI drug. It should be noted, however, that over half (65%) of the included studies evaluated the effects specifically of oseltamivir. Studies where it was unclear whether the antivirals mentioned were all NIs were also excluded. Lastly, our research question was very broad, resulting in a vast quantity of literature being obtained for final analysis. Despite identifying many studies, none evaluated NI effectiveness or safety in Aboriginal peoples, in residential community-based settings (including hostels, homeless shelters, non-healthcare residential settings such as university residences and group homes) or among individuals residing in remote and isolated communities.

Conclusions

Overall, the evidence evaluated in this systematic review indicates that NI treatment is likely effective in reducing mortality and possibly effective in reducing pneumonia, in general populations. It also appears likely that NIs are effective for reducing secondary transmission in general populations, when indicated for prophylaxis. There appears to be an increased benefit if NIs are administered within 48 h of symptom onset (or earlier) for all outcomes, but with limited and low-quality data we can only confirm a benefit for reducing mortality. It is also evident that gaps in knowledge remain with regard to NI effectiveness and safety for specific populations, in particular Aboriginal people, high-risk individuals (living with chronic and/or immune conditions) and the elderly (≥65 years old). Our results are consistent with similar systematic reviews conducted using observational studies. We found evidence further suggesting that NIs are likely safe for use in general populations and may be safe for use in children and pregnant women. However, the results of this review must be interpreted with caution as they are based on a small number of studies that are of very poor methodological quality. Knowledge gaps remain regarding NI effectiveness and safety for specific populations, namely Aboriginal people, high-risk individuals (living with chronic and/or immune conditions) and the elderly (≥65 years old).

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Transparency declarations

None to declare.

Supplementary data

Supplementary data (Parts 1–10) are available at JAC Online.

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