Inhibidores de neuraminidasa para la prevención y el tratamiento de la influenza en adultos sanos

Jefferson TO, Demicheli V, Di Pietrantonj C, Jones M, Rivetti D

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RESUMEN

Antecedentes
Se recomienda el uso de los inhibidores de neuraminidasa (IN) en casos de influenza y sus complicaciones en años interpandémicos y en una pandemia.

Objetivos
Evaluar los efectos de los IN en la prevención de o la disminución de los trastornos causados por la influenza, su transmisión y sus complicaciones en adultos sanos y estimar la frecuencia de efectos adversos.

Estrategia de búsqueda
Se realizaron búsquedas en el Registro Cochrane Central de Ensayos Controlados (Cochrane Central Register of Controlled Trials - CENTRAL) (*The Cochrane Library* número 3, 2005), MEDLINE (2004 hasta septiembre, semana 4, 2005), EMBASE (2003 hasta junio 2005) se contactó con fabricantes, investigadores en este campo, y autores de estudios evaluadoss en la revisión.

Criterios de selección
Estudios aleatorios o cuasialeatorios controlados con placebo de IN en adultos sanos expuestos a casos de influenza naturales.

Recopilación y análisis de datos
Dos autores aplicaron los criterios de inclusión, evaluaron la calidad del ensayo y extrajeron los datos. Se organizaron las comparaciones en profilaxis, tratamiento y eventos adversos con una subdivisión adicional por resultado y dosis.

Resultados principales
Se identificaron cuatro ensayos de profilaxis, 13 de tratamiento y cuatro de profilaxis postexposición. En la profilaxis comparada con placebo, los IN no tiene ningún efecto en las enfermedades tipo influenza (ETI) (riesgo relativo [RR] 1,28; intervalo de confianza [IC] del 95%: 0,45 a 3,66 para oseltamivir oral 75 mg diarios; RR 1,51; IC del 95%: 0,77 a 2,95 para zanamivir inhalado 10 mg diarios). La eficacia de oseltamivir oral 75 mg diarios para la influenza sintomática es 61% (RR 0,39; IC del 95%: 0,18 a 0,85), o 73% (RR 0,27; IC del 95%: 0,11 a 0,67) con dosis de 150 mg diarios. La eficacia del zanamivir inhalado 10 mg diarios es 62% (RR 0,38; IC del 95%: 0,17 a 0,85). Ningún NI tiene un efecto considerable sobre la influenza asintomática. El oseltamivir provoca náuseas (odds-ratio [OR] 1,79; IC del 95%: 1,10 a 2,93). El oseltamivir para profilaxis posexposición tiene una eficacia de 58,5% (15,6 a 79,6%) para las viviendas y de 68% (34,9 a 84,2%) a 89% en los contactos de los casos índices. El zanamivir tiene un rendimiento similar. Los cocientes de riesgo del tiempo hasta el alivio de los síntomas de influenza favorecieron al grupo tratado 1,33 (1,29 a 1,37) para zanamivir y 1,30 (1,13 a 1,50) para oseltamivir. La carga viral nasal disminuyó significativamente con ambos IN. El oseltamivir 150 mg diarios previno las complicaciones de las vías respiratorias inferiores (OR 0,32; IC del 95%: 0,18 a 0,57). No se pudo encontrar datos comparativos sobre los efectos del oseltamivir en la influenza aviar.

Conclusiones de los autores
Debido a su baja efectividad, no deben usarse los IN en el control de la influenza estacional habitual. En una epidemia grave o pandemia, los IN deben usarse con otras medidas de salud pública. No se pueden generalizar las conclusiones sobre la influenza estacional a la influenza pandémica o aviar.

RESUMEN EN TÉRMINOS SENCILLOS

Influenza is an acute infection of the airways and the whole body, caused by a virus

Symptoms include fever, headache and cough. Serious complications such as pneumonia can also occur. This review of trials found that neuraminidase inhibitors (Nls) such as zanamivir and oseltamivir are effective in preventing ("prophylaxis") and treating ("treatment") the symptoms and complications of influenza but do not prevent infection or interrupt voidance of viruses from the nose. Oseltamivir causes nausea, vomiting and retching while zanamivir causes diarrhoea. There is no evidence that NIs may be effective against bird flu. Because of their performance, NI should not be used on their own, but alongside barrier (masks, gloves), personal hygiene and quarantine measures.

ANTECEDENTES

En años recientes, se ha desarrollado una nueva generación de fármacos antivirales. Estos compuestos, conocidos como inhibidores de neuraminidasa (IN), son el zanamivir nebulizado (Relenza) (anteriormente conocido como GG167) desarrollado por Glaxo Wellcome PLC (Reino Unido) y el oseltamivir oral (anteriormente conocido como RO 64-0796 o GS 4104) codesarrollado por Gilead Sciences Inc (Foster City, CA, EE.UU.) y Hoffman La Roche Ltd (Basilea, Suiza).

Los IN inhiben la liberación de viriones de la célula infectada ya que la neuraminidasa es esencial para la entrada y salida viral de la célula blanco. Recientemente, la Organización Mundial de la Salud ha alentado a los países miembros a que usen los antivirales en los "períodos interpandémicos" de influenza. La justificación para esta recomendación es la siguiente: "el uso en gran escala de antivirales y vacunas durante una pandemia dependerá de la familiaridad con una aplicación eficaz durante el período interpandémico. El mayor uso de estas modalidades ampliará la capacidad y mitigará la morbilidad y mortalidad de las epidemias anuales de influenza. Estudios realizados durante el período interpandémico pueden mejorar las estrategias para el uso durante una pandemia" (WHO 2005). La European Medicines Agency adoptó una perspectiva diferente por la que identifica a los IN (especialmente el oseltamivir) como compuestos con un efecto complementario a las vacunas que se usan en una pandemia de influenza (EMA 2005) para el tratamiento de los casos índices y la profilaxis de influenza en el personal en riesgo (policía, bomberos, trabajadores de la atención sanitaria). Aunque están disponibles varias revisiones sistemáticas de los efectos de los IN (Burls 2002; Cooper 2003; Jefferson 2000; Turner 2003), ninguna está actualizada y ninguna evaluó la función potencial de los IN en una pandemia de influenza, donde es común la alta carga viral y la transmisión significativa. En este contexto, cobra importancia la compensación entre dosificación y perfil de eventos adversos en la profilaxis, la actividad contra la infección por influenza, independientemente de los síntomas (influenza sintomática y asintomática) y la excreción vírica en los líquidos corporales (Ward 2005)).

OBJETIVOS

Evaluar la eficacia y efectividad de los IN en la prevención de los casos y las complicaciones de la influenza (profilaxis) en adultos sanos.
Evaluar la eficacia y efectividad de los IN en la prevención de los casos y las complicaciones de la influenza (tratamiento) en adultos sanos.
Evaluar la efectividad de los IN para interrumpir la propagación del virus de la influenza.
Estimar la frecuencia de los efectos adversos asociados con la administración de los IN en adultos sanos.

CRITERIOS PARA LA VALORACIÓN DE LOS ESTUDIOS DE ESTA REVISIÓN

Tipos de estudios

Cualquier estudio aleatorio o cuasialeatorio comparó el oseltamivir o el zanamivir en seres humanos con placebo, antivirales de control o ninguna intervención, o comparó dosis o regímenes de oseltamivir y zanamivir. Se consideraron los estudios que evaluaron la profilaxis o el tratamiento de la exposición a la influenza natural.

Tipos de participantes

Individuos sin patologías crónicas preexistentes que podrían agravar la evolución de la influenza. En base al objetivo de revisar las pruebas en adultos sanos, sólo se consideraron los estudios en los cuales no menos de 75% de los sujetos tenían entre 14 y 60 años de edad para excluir a sujetos de mayor edad que se encuentran en mayor riesgo de complicaciones

Tipos de intervención

Oseltamivir o zanamivir como profilaxis o tratamiento de la influenza (eficacia), o la enfermedad tipo influenza (ETI / efectividad).

Tipos de medidas de resultado

Clínicos

Número, distribución temporal y gravedad de los casos de influenza (definidos como los participantes con signos y síntomas clínicos de influenza con diagnóstico basado en pruebas positivas de laboratorios o en aumento en el nivel de anticuerpos o aislamiento viral o ambos) o casos de enfermedad tipo influenza (ETI, definidos como los participantes con signos y síntomas clínicos de influenza) y sus complicaciones.

Laboratorio

Medidas de carga viral (como concentración del virus de la influenza excretado en la mucosa nasal).

Efectos adversos

Número y gravedad de los efectos adversos.

ESTRATEGIA DE BÚSQUEDA PARA LA IDENTIFICACIÓN DE LOS ESTUDIOS

En la revisión original, se realizaron búsquedas en el Registro Cochrane de Ensayos Controlados (CCTR) (*The Cochrane Library* Número 1, 1999), MEDLINE (en mayo de 1999), EMBASE (1991 a 1998). Se revisó la bibliografía de los artículos recuperados para identificar otros ensayos. Se realizaron búsquedas manuales en la revista *Vaccine* desde su primera publicación hasta fines de 1997. Se estableció contacto con ambos fabricantes para localizar ensayos no publicados, ya que los IN están todavía en la fase de desarrollo previo al registro.

Se usaron los siguientes términos de búsqueda o grupos combinados en cualquier idioma:
Influenza Route (oral)
route (parenteral)
Neuraminidase inhibitors
Oseltamivir
RO/GS 4104
Zanamivir

En esta revisión actualizada, se realizaron búsquedas en el Registro Cochrane Central de Ensayos Controlados (CENTRAL) (*The Cochrane Library*, Número 3, 2005) MEDLINE (desde 2004 hasta la cuarta semana de septiembre de 2005) y EMBASE (desde 2003 hasta junio de 2005). También se estableció contacto con los fabricantes, los investigadores en el tema, y los autores de los estudios evaluados en la revisión.

Se utilizó la siguiente estrategia de búsqueda en MEDLINE conjuntamente con la estrategia de búsqueda sensible Cochrane para identificar ECA (Higgins 2005)). Se utilizó la misma estrategia para la búsqueda en CENTRAL No se aplicó ninguna restricción de idioma.

MEDLINE (OVID)
1 exp INFLUENZA/
2 influenza$.mp.
3 or/1-2
4 neuraminidase inhibitor$.mp.
5 oseltamivir.mp.
6 zanamivir.mp.
7 GS4071.mp.
8 or/4-7
9 3 and 8

Se hicieron búsquedas en EMBASE (WebSPIRS) mediante la estrategia siguiente:
#1 explode 'influenza-' /
#2 (influenza* in ti) or (influenza* in ab)
#3 #1 or #2
#4 explode 'sialidase-inhibitor' /
#5 (neuraminidase inhibitor* in ti) or (neuraminidase inhibitor* in ab)
#6 explode 'oseltamivir-' /
#7 (oseltamivir in ti) or (oseltamivir in ab)
#8 explode 'zanamivir-' /
#9 (ozanamivir in ti) or (zanamivir in ab)
#10 #4 or #5 or #6 or #7 or #8 or #9
#11 #3 and #10

También se verificaron las listas de referencias de otras revisiones sistemáticas sobre el tema (Burls 2002; Cooper 2003; Turner 2003)).

MÉTODOS DE LA REVISIÓN

Procedimiento de inclusión

Dos autores (VD y TOJ) leyeron todos los ensayos recuperados en las búsquedas y aplicaron los criterios de inclusión. La evaluación de la calidad metodológica de los ECA se realizó con los criterios del Manual Cochrane para Revisores (Cochrane Reviewers' Handbook) (Deeks 2004)). Se evaluaron los estudios según la adecuación de métodos de generación de la secuencia de asignación, ocultamiento de la asignación y cegamiento y el tratamiento de las pérdidas durante el seguimiento.

Procedimiento de mediación

VD medió en los casos en que hubo desacuerdos sobre la calidad de un ensayo entre TOJ y DR.

Recogida de datos

Los siguientes datos se extrajeron en formularios estandarizados, y luego se verificaron y registraron:
Características de los participantes
- Número de participantes.
- Edad, sexo, grupo étnico, grupo de riesgo.

Características de las intervenciones
- Tipo de IN, tipo de placebo, dosis, esquema de tratamiento o profilaxis, duración del seguimiento (en días).

Características de las medidas de resultado
- Número y gravedad de los casos de influenza en los grupos de IN y de placebo.
- Concentración de los virus de la influenza excretados en el moco nasal.
- Efectos adversos: presencia y tipo.
- Fecha del ensayo.
- Lugar del ensayo.
- Patrocinador del ensayo (especificado, conocido o desconocido).
- Estado de la publicación.

Síntesis de los datos
Se organizaron las comparaciones en profilaxis, tratamiento y eventos adversos con una subdivisión adicional por resultado y dosis. Los riesgos relativos de los eventos de los grupos de profilaxis versus placebo de los ensayos individuales se combinaron con el modelo de efectos aleatorios de DerSimonian y Laird, para incluir la variabilidad entre los ensayos. Se realizó un análisis de sensibilidad de los métodos usados y los resultados obtenidos se compararon con el modelo de efectos fijos y el de efectos aleatorios. En los ensayos de profilaxis, la eficacia se derivó según 1-RR (riesgo relativo) x 100 o el RR cuando no fuese significativa. Se usaron los odds-ratios (OR) para calcular la asociación de los efectos adversos con exposición a los antivirales. En los ensayos de tratamiento, el análisis de los resultados "tiempo hasta el alivio de los síntomas" y "tiempo para retomar la actividad normal" causó cierta dificultad debido a la inconsistencia y la falta de estandarización en el informe de la mayoría de los ensayos. La mayoría de los informes describieron estos resultados en términos de medianas para cada grupo de tratamiento. Sin embargo, la notificación estándar en un metanálisis exige que estos resultados se expresen como (log) cociente de riesgos. Si se supone que el efecto del tratamiento es constante con el transcurso del tiempo (lo que parece razonable), entonces puede usarse la razón de las medianas para calcular el cociente de riesgos. Para estimar la varianza del log del cociente de riesgos, se usó el método de Parmar y cols. (Parmar 1998). The number of events was estimated from survival curves when these were available or, when they were not available, assumed to be all patients completing the trial providing follow up was sufficiently long enough for this to be a reasonable assumption. In one study (Boivin 2000) follow up was possibly not long enough for this to be a reasonable assumption, however this was a small trial (27 participants in total) and follow up was sufficiently long enough for more than 90% of the patients to be expected to reach the endpoint. The impact of including this trial in the overall analysis is likely to be negligible. As a check to see if the estimation methods used are accurate, one study (Makela 2000) provided both hazard ratios and medians. The two methods provided identical results for the intention-to-treat (ITT) population and similar results for the influenza-positive population. The random effects inverse variance method was used for the meta-analysis of the log hazard ratio. Two studies presented nasal viral titre data as medians and ranges (Nicholson 2000; Treanor 2000). The data were converted into means and standard deviations (SDs) to be consistent with other studies and allow meta-analysis. Means were converted directly from the medians as both are measures of central tendency and should be similar for approximately symmetrical data. The range was converted to a SD using the method described by Hurlburt 1994. The inter-quartile range (IQR) was converted to SD by multiplying by 68/50 (as 50% of the data is contained within the IQR while +/- 1 SD contains 68% of the data providing it is approximately normally distributed) then dividing by 2 (to estimate 1 SD).

DESCRIPCIÓN DE LOS ESTUDIOS

- Prophylaxis trials

We identified four prophylaxis trials, two assessing zanamivir (Kaiser 2000; Monto 1999a) and two assessing oseltamivir (Hayden 1999a; Kashiwagi 2000a).
The mean and median zanamivir arm size was 492 individuals (25th percentile 461, 75th percentile 522) and the mean length of follow up was 22 days. The mean oseltamivir arm size was 598 (median 597, 25th percentile 376 and 75th percentile 818 individuals) and the mean length of follow up was 49 days.

- Treatment trials

We identified eight treatment trials of zanamivir (Aoki 2000; Boivin 2000; Hayden 1997; Makela 2000; Matsumoto 1999; MIST 1998; Monto 1999b; Puhakka 2003) and five of oseltamivir (Kaiser 2003; Kashiwagi 2000b; Li 2003; Nicholson 2000; Treanor 2000) fulfilling our inclusion criteria. Two zanamivir trials (Aoki 2000; Boivin 2000) were linked publications of the Monto 1999b and MIST 1998 trials. One oseltamivir study included supplementary outcome data from all treatment trials (Kaiser 2003). One oseltamivir trial (Li 2003) was linked to two redundant publications (Li 2001; Longuyn 2004).

The mean zanamivir arm size was 297 individuals (median 250, 25th percentile 149, 75th percentile 340), the mean oseltamivir arm size was 383.8 individuals (median 245, 25th percentile 216, 75th percentile 314) and the mean length of follow up was 26 days for zanamivir and 21 days for oseltamivir.

- Post-exposure prophylaxis (PEP) trials

We identified two PEP trials of different design assessing the effects of oseltamivir. Hayden 2004 is a C-RCT comparing the effects on household contacts of expectant treatment with

oseltamivir with commencing immediate PEP. Welliver 2001 investigated the effects of oseltamivir on the spread of influenza by randomising household contacts of index cases with influenza to the active principle or placebo. The mean and median oseltamivir arm size was 446.54 (25th percentile 422 and the 75th% percentile 470).
Two further PER trials assessed zanamivir (Hayden 2000a; Monto 2002). In both trials, household contacts of an index case with ILI were randomised to either placebo of zanamivir.

A full description of all trials is available in the 'Characteristics of included studies' table.

CALIDAD METODOLÓGICA

One prophylaxis trial had adequate methodological quality (Monto 1999a), one had an unclear measures to protect double blinding (Hayden 1999a) and two (Kaiser 2000; Kashiwagi 2000a) had unclearly described methods. Kaiser 2000 reported no dropouts from the trial. Four treatment studies (Makela 2000; MIST 1998; Nicholson 2000; Treanor 2000) had adequate methodological quality, four trials (Aoki 2000; Boivin 2000; Kaiser 2003; Kashiwagi 2000b) has unclearly described processes, although three (Aoki 2000; Boivin 2000; Kaiser 2003) were linked to larger studies. The remainder had at least one unclearly described item. One trial (Li 2003) did not include withdrawals in the analysis.

Withdrawals were included in all PEP trials but all other items were poorly described. Hayden 2004 was an open-label C-RCT. Allocation concealment was not described in the zanamivr trials.

RESULTADOS

We carried out three main comparisons with placebo: NIs in a pre-exposure, post-exposure prophylaxis (PEP) and treatment roles. We further subdivided each comparison according to outcome case definition. We did not meta-analyse data from the PEP trials, as they had different designs.

- Prophylaxis trials

Compared to placebo, NIs have no effect against ILI (RR 1.28, 95% CI 0.45 to 3.66 for oral oseltamivir 75 mg daily, RR 1.51, 95% CI 0.77 to 2.95 for inhaled zanamivir 10 mg daily). Higher dosages appear to make no difference, although this observation is based on single studies with very low viral circulation (Hayden 1999a; Kaiser 2000).

The efficacy of oral oseltamivir 75 mg daily against symptomatic influenza is 61% (RR 0.39, 95% CI 0.18 to 0.85), or 73% (RR 0.27, 95% CI 0.11 to 0.67) at 150 mg daily, although this last observation is based on a single study. Inhaled zanamivir 10 mg daily is 62% efficacious (RR 0.38, 95% CI 0.17 to 0.85). The addition of an intranasal dose does not seem to significantly enhance its prophylactic activity (RR 0.22, 95% CI 0.08 to 0.58), although again this last observation is based on a single study.

Oseltamivir confers 64% protection against symptomatic and a symptomatic influenza (RR 0.46, 95% CI 0.31 to 0.68) at a lower dose of 75 mg daily. An increase to 150 mg daily does not appear to enhance its activity (RR 0.48, 95% CI 0.29 to 0.80) although this observation is based on a single study. Similarly zanamivir has a 43% protective effect (RR 0.67, 95% CI 0.50 to 0.91) and based on a single study the addition of intranasal dose does not appear to enhance its activity (RR 0.77, 95% CI 0.38 to 1.56).

However, when the outcome is asymptomatic influenza no NI has significant effects (oseltamivir 75 mg daily RR 0.73, 95% CI 0.43 to 1.26; oseltamivir 150 mg daily RR 0.67, 95% CI 0.35 to 1.28; zanamivir 10 mg daily 1.63, 95% CI 0.99 to 2.67). These observations are based on three studies (Hayden 1999a; Kashiwagi 2000a; Monto 1999a) with a combined denominator of 2974 in the presence of relatively high viral circulation (5% in the combined placebo arms).

Oseltamivir induces nausea (OR 1.79, 95% CI 1.10 to 2.93), especially at the higher prophylactic dose of 150 mg daily (OR 2.29, 95% CI 1.34 to 3.92).

- Post-exposure prophylaxis (PEP) trials

Hayden 2004 reports that PEP provided an efficacy of 58.5% (15.6% to 79.6%) for households and of 68% (34.9% to 84.2%) for individual contacts. Given the high circulation of virus (184 out of 298 index cases had influenza, 66% of which had influenza AH1N1 and remainder influenza B virus) effectiveness was high 62.7% (26% to 81%).
Welliver 2001 reports 89% (67% to 97%) protective efficacy in contacts of index cases with influenza and 84% (45% to 95%) for index cases.
Neither trial reported the onset of viral resistance after five (Hayden 2004) and seven days (Welliver 2001) of prophylaxis at a dose of 75 mg twice daily (Hayden 2004) and once daily (Welliver 2001). Neither the background rate of infection in the community nor the viral strains are reported, although influenza A and B were co-circulating at the time.
Monto 2002 reports a 79% effectiveness and 81% efficacy (64% to 90%) for households and 82% for individuals against symptomatic influenza, 55% to 59% against all asymptomatic and symptomatic influenza. Zanamivir shortened duration of illness by 1.5 days and was well tolerated and no viral resistance was reported.
Hayden 2000a concludes that zanamivir was 79% (57% to 89%) effective and 72% (42% to 87%) effective in preventing contacts from developing symptomatic influenza and 53% (27% to 70%) effective and 48% (15% to 68%) efficacious in preventing symptomatic and asymptomatic influenza. Zanamivir also shortend duration of symptoms by 2.5 days. There was no evidence of the onset of resistance.

- Treatment trials

Time to alleviation of symptoms (considering intention to treat population) was assessed by nine trials (Hayden 1997; Li 2003; Makela 2000; Matsumoto 1999; MIST 1998; Monto 1999b; Nicholson 2000; Puhakka 2003; Treanor 2000). The estimated hazard ratios for zanamivir were greater than one, hence in favour of the treated group and there was no evidence of heterogeneity (I^2 = 0%). The pooled hazard ratio is 1.24 (95% CI 1.13 to 1.36) indicating that the treated group are 24% more likely to have their symptoms alleviated than the placebo group by a given time-point. We obtained a similar result for oseltamivir (hazard ratio 1.20, 95% CI 1.06 to 1.35). For time to alleviation of symptoms in influenza-positive participants, the hazard ratios were significantly in favour of the treated group 1.33 (95% CI 1.29 to 1.37) for zanamivir and 1.30 (95% CI 1.13 to 1.50) for oseltamivir. There was no evidence of heterogeneity for the zanamivir data meta-analysis, but I^2 was 37.5% for oseltamivir. Application of the fixed-effect model did not materially alter the hazard ratio (Boivin 2000; Hayden 1997; Kashiwagi 2000b; Li 2003; Makela 2000; Matsumoto 1999; MIST 1998; Monto 1999b; Nicholson 2000; Puhakka 2003; Treanor 2000).

Time to return to normal activities (considering intention to treat population) was assessed by four studies (Matsumoto 1999; MIST 1998; Monto 1999b; Treanor 2000). The pooled estimated hazard ratios for zanamivir was 1.28 (95% CI 1.13 to 1.45), while the single study assessing oseltamivir (Treanor 2000) had a non-significant hazard ratio (1.23, 95% CI 1.02 to 1.48). There was no heterogeneity (I^2 = 0). In influenza-positive participants the pooled hazard ratio was just below significance 1.17 (95% CI 1.00 to 1.37, P value 0.06) for zanamivir (Makela 2000; MIST 1998; Hayden 1997) and significant for oseltamivir (1.22, 95% CI 1.07 to 1.39) although this observation is based on a single study (Treanor 2000). There was no evidence of heterogeneity (I^2 = 0%).

Five studies reported assessing the effect of NI administration on viral load (as estimated by mean nasal titres of excreted viruses at 24 and 48 hours since randomisation) (Boivin 2000; Kashiwagi 2000b; Nicholson 2000; Puhakka 2003; Treanor 2000). Titres were significantly diminished by both zanamivir and oseltamivir (WMD -0.62, 95% CI -0.82 to -0.41). The effect is more marked the longer the time since randomisation (and commencement of treatment). Exclusion of data from the Treanor 2000 and Nicholson 2000 studies does not affect our conclusions. There was evidence of heterogeneity (I^2 = 34.6%) but analysis using a fixed-effect model did not materially affect our findings, except for the comparison zanamivir against placebo where the effect on mean nasal titres at 48 hours since randomisation is not significant when analysed using a fixed-effect model. Treatment did not, however, suppress viral excretion, apparently regardless of the dose. We found insufficient data to comment on the effects on nasal excretion of viruses of higher doses of medication.

Oseltamivir 150 mg daily is effective in preventing lower respiratory tract complications in influenza cases (OR 0.32, 95% CI 0.18 to 0.57), especially bronchitis (OR 0.40, 95% CI 0.21 to 0.76) and pneumonia (OR 0.15, 95% CI 0.03 to 0.69), but not in ILI cases (OR 0.21, 95% CI 0.02 to 2.04). Both NIs are effective in preventing complications of all types in the intention-to-treat (ITT) population (OR 0.49, 95% CI 0.38 to 0.62), although these observations are based on single studies (Kaiser 2003; Makela 2000) the combined denominator is fairly substantial (2991).

NIs are not associated with any adverse event in a treatment role, although this may be due to the difficulty in separating adverse events from the symptoms of influenza and to the relatively small denominators in the analysis. Finally, use of relief medications and antibiotics is unaffected by assumption of NIs (OR 0.81, 95% CI 0.59 to 1.12).

DISCUSIÓN

Role of NIs in seasonal influenza

We have assembled a good-quality uptodate evidence base of the prophylcacitc and treatment effects of NIs. These compounds have low effectivness, high efficacy and appear well tolerated, with the possible exception of oseltamivir-induced nausea and vomiting and zanamivir-induced diarrhoea. Existing trials on NIs were clearly designed and undertaken within a registration and regulation perspective. This is reflected in the cryptic reporting of continuous outcome data which forced us to resort to summary measures such as HR, which although methodologically virtuous, may not be relevant to workers in the field. Onset of resistance is a possibility. Although none of the studies included in the review reported it, Kiso and colleagues found an 18% isolation rate of NI-resistant A/H3N2 viruses in 50 very young children at day 4 of treatment, and a high prolonged viral excretion even after five days of treatment (Kiso 2004). Resistance to oseltamivir is reported to be the around 0.5% from other trials in the Roche database (Ward 2005). NIs affect influenza symptoms, either preventing their appearance or curtailing their duration and although we found clear evidence of their evidence in the interruption of transmission of seasonal influenza in households, NIs do not prevent infection and decrease but do not interrupt nasal shedding of seasonal influenza viruses. We cannot explain how NIs can affect respiratory complications of seasonal influenza such as bronchitis and pneumonia while not preventing infection and this effect should be further studied. An explanation for what we have observed is a possible effect in preventing a proportion of NI recipients to seroconvert into symptomatic influenza cases. This would explain the observed effects of NIs on serious complications and interruption of transmission in households during seasonal influenza. Whichever explanation is chosen, prophylactic use of NIs in a serious epidemic or a pandemic may enhance vulnerability to infection by preventing seroconversion and facilitating the

selection of NI-resistant mutant viruses. Because of their low effectiveness and the possibility of the onset of resistance we conclude that NIs should not be routinely used in seasonal influenza. In the case of a serious localised comfirmed epidemic, NIs could be used to prevent serious complications.

Role of NIs in avian influenza. We identified no comparative evidence of the role of NIs in avian influenza. Oseltamivir was used against three subtypes of avian influenza viruses with proven bird-to-human and human-to-human transmission: A/H5N1, A/H7N7 and H7N3. The virological and transmission profile of avian H5N1 influenza is not clear. One review reports that experience from the cases of avian influenza transmitted to man in South East Asia suggests that viral shedding commences before symptoms appear and ceases after 48 hours from symptoms onset (Yuen 2005). The WHO-led review of H5N1 influenza cases suggests that viral shedding and infectivity of index cases could be protracted (WHOWC 2005). What appears clear however, is that viral load can be up to 10 times greater than in seasonal influenza (WHOWC 2005). In the South East Asia outbreaks, use of oseltamivir was not associated with any obvious effect on mortality, although this could be due to late commencement of therapy and high initial viral load. Resistance to oseltamivir was detected in up 16% of children given the drug (WHOWC 2005), accordingly with evidence from Japan (Kiso 2004), a country with very high NI prescription rates, and in two of eight Vietnamese people aged 8 to 35 (de Jong 2005). The apparently common feature favouring the selection of resistant viruses is immunological naivety to the infecting viral subtype. A large outbreak of avian A/H7N7 influenza with bird-to-human and human-to-human transmission took place in chicken farms in the Netherlands between February and June 2003. Eighty-five of the 453 people who reported symptoms (mainly ILI and/or conjunctivitis) had A/H7N7 isolation from lacrimal fluid and/or upper airway swabs. Among other measures, PEP with oseltamivir 75 mg was started. Ninety people in the case registry probably had prophylactic treatment. Avian influenza virus infection was detected in one of 38 (2.6%) people who used oseltamivir, compared with five of 52 (9.6 %) who reported that they had not taken prophylactic medication. The difference was not significant (P value 0.38), probably because of small numbers and of the late nature of the commencement of PEP (Koopmans 2004). A similar outbreak of A/H7N3 took place in British Columbia, Canada in 2004. Twelve possible cases (22% of total) reported taking prophylactic oseltamivir at symptom onset, and 11 (20%) received oseltamivir for treatment. Maximum duration of oseltamivir assumption is thought to have been 12 weeks (Ward 2005). The remaining 22 patients with suspected cases were identified more than 48 hours after onset or refused treatment. All recovered fully (Tweed 2004). Evaluation of the effects of oseltamivir was outside a formal study and in all three cases data on the effectiveness of oseltamivir are insufficient to reach a conclusion. The use of NIs in avian influenza or in a possible pandemic is not supported by any credible data at present and we have doubts as to the generalisability of the evidence from seasonal influenza to avian influenza. Given the circumstances (ad hoc studies carried out during actual localised epidemics of avian influenza and the future characteristics of any pandemic) this is not surprising.

Finally, the inability of the NIs to prevent infection and to suppress viral nasal excretion raise doubts as to their effectiveness in interrupting viral spread in a pandemic, although NIs may have a role in addressing symptoms and complications. We conclude that in a pandemic, NIs should be used within a package of measures to interrupt spread, that is to say, together with barrier, distance and personal hygiene measures.

CONCLUSIONES DE LOS AUTORES

Implicaciones para la práctica

NIs are not recommended for routine use in seasonal influenza. In exceptional circumstances they could be used as an adjunct to public health measures.

Implicaciones para la investigación

Larger trials are required to assess the effects of NIs in epidemic influenza, especially their impact on complications and deaths. Further research on the possible effects of NIs on avian influenza subtypes is also required.

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POTENCIAL CONFLICTO DE INTERÉS

In 1998 to 1999 Dr Jefferson was an ad hoc consultant for Hoffman LaRoche Ltd.

Glossary

- **Efficacy**: the impact of an intervention (drug, vaccines etc) on a problem or disease in ideal conditions - in this case the capacity of NIs to prevent or treat influenza and its complications.
- **Effectiveness**: the impact of an intervention (drug, vaccines etc) on a problem or disease in field conditions - in this case the capacity of NIs to prevent or treat ILI and its complications.
- **Influenza**: an acute respiratory infection caused by a virus of the Orthomyxoviridae family. Three serotypes are known (A, B and C). Influenza causes an acute febrile illness with myalgia, headache and cough. Although the

median duration of the acute illness is three days, cough and malaise can persist for weeks. Complications of influenza include otitis media, pneumonia, secondary bacterial pneumonia, exacerbations of chronic respiratory disease and bronchiolitis in children. These illnesses may require treatment in a hospital and can be life-threatening especially in 'high-risk' people e.g. the elderly and people suffering from chronic heart disease. Additionally, influenza can cause a range of non-respiratory complications including febrile convulsions, Reye's syndrome and myocarditis. The influenza virus is composed of a protein envelope around an RNA core. On the envelope are two antigens: neuraminidase (N antigen) and hemagglutinin (H antigen). Hemagglutinin is an enzyme that facilitates the entry of the virus into cells of the respiratory epithelium, while neuraminidase facilitates the release of newly produced viral particles from infected cells. The influenza virus has a marked propensity to mutate its external antigenic composition to escape the hosts' immune defences. Given this extreme mutability, a classification of viral subtype A based on H and N typing has been introduced. Additionally, strains are classified on the basis of antigenic type of the nucleoprotein core (A, B), geographical location of first isolation, strain serial number and year of isolation. Every item is separated by a slash mark (e.g. A/Wuhan/359/95 (H3N2)). Unless otherwise specified such strains are of human origin. The production of antibodies against influenza beyond a conventional quantitative threshold is called **seroconversion**. Seroconversion in the abscence of symptoms is called **asymptomatic influenza**.

- **Influenza-like illness (ILI)**: an acute respiratory illness caused by scores of different viruses (including influenza A and B) presenting with symptoms and signs which are not distinguishable from those of influenza. ILI does not have documented laboratory isolation of the causative agent and is what comonly presents to physicians and patients (also known as the flu")
- **Mean**: a measure of central tendency of a group of viariables (such as age). It is calculated by adding all the individual vaules and then dividing by the number of values in the group.
- **Median**: a measure of central tendency of a group of viariables (such as age). It is the halfway mark of a set of viariables, the dividing point between lower and upper.
- **Randomised study**: when it appears that the individuals (or other experimental units) followed in the study were definitely or possibly assigned prospectively to one of two (or more) alternative forms of health care using random allocation - **randomised controlled trial (RCT)**. When the unit of allocation is a group (such as a family, or a military unit) the design is that of a **Cluster Randomised Trial (C-RCT).**
- **Quasi-randomised study**: when it appears that the individuals (or other experimental units) followed in the study were definitely or probably assigned prospectively to one of two (or more) alternative forms of health care using some quasi-random method of allocation (such as alternation, date of birth or case record number) - **clinical controlled trial (CCT)**.

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Recursos externos

- Ministry of Defence (1999 review) UK

Recursos internos

- The authors' own institutions (2005 update) ITALY
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** El asterisco señala los documentos más importantes para este estudio*

TABLAS

Characteristics of included studies

Study	**Aoki 2000**
Methods	Multicentre, randomised, double-blind parallel group study, performed in 14 countries in Europe and North America during the 1995 - 1996 winter. The Monto 99c
Participants	One thousand two hundred and fifty six patients were included in study, of which 722 had laboratory confirmed influenza. The report only includes data for the 722 influenza cases. Participants were healthy individuals over 13 years old with acute influenza like illness (ILI) lasting less than 48 hours. The patients had to be able to use the inhaler and nasal devices. Patients with unstable chronic illness (e.g., hospitalised) or were pregnant or breast feeding were excluded. Randomisation was carried out with an allocation schedule of 2:2:1:1 respectively
Interventions	Treatment lasted for five days
Outcomes	Serological: Serum samples were collected on days 1 and 21, and assayed for the presence of anti-influenza antibodies by haemagglutination inhibition Effectiveness: ILI (feverishness and at least two of the following symptoms: headache, myalgia, cough, or sore throat). Productivity Health status Sleep quality Healthcare utilisation Treatment satisfaction Social functioning Physical functioning Role functioning Body pain Current health perception Psychological distress The clinical efficacy of Zanamivir and was reported is the Monto 99c trial. Safety outcomes are not reported
Notes	The authors conclude that zanamivir treatment reduced absenteeism, improved patient productivity and well being, and reduced the additional use of healthcare resources in patients with influenza. It is very difficult to understand the basis for this conclusion when Table II shows equal proportion of influenza cases throughout the arms. The use of aggregate measures such as lest-squares mean scores for health status indicators and presentation in histogram form makes interpretation very difficult
Allocation concealment	B ? Unclear
Study	**Boivin 2000**
Methods	Double-blind, randomised, placebo controlled, multicentre sub-study, part of the MIST study, assessing the relationship between alleviation of all clinical important symptoms (as defined by no fever and other flu symptoms recorded as absent or mild for at least 24 hours) and reduction of viral load. The study was conducted during the 1997-1998 season in Qu?c and Winnipeg, Canada

Characteristics of included studies

Participants	Thirty-five patients were enrolled. 27 (77%) had an influenza virus infection laboratory-confirmed on day 1. All subjects had influenza A virus H3 infections. 10 received a placebo, 17 received zanamirvir. Three influenza virus positive high-risk subjects were enrolled (2 in the placebo, 1 in zanamivir group). Healthy adolescents and adults, older than 12 years, and high risk subjects (defined as those with chronic respiratory, cardiovascular, or renal disease) with naturally occurring influenza A virus infections
Interventions	Inhaled zanamivir 10 mg 2 x daily for 5 days
Outcomes	Laboratory: serial swabs viral resistance insurgence analysis viral load Effectiveness: fever time to alleviation of symptoms Safety: no safety outcomes are mentioned
Notes	The authors conclude that: 1) zanamivir produced a rapid antiviral effect following inhalation, and this was noted as early as 12 hours after beginning treatment, 2) the decrease in virus load induced by zanamivir correlated with a significant reduction in the median time to alleviation of symptoms. 3) neither phenotypic nor genotypic assays detected any evidence of emergence of zanamivir-resistant strains during therapy. This is a sub-study of the pivotal treatment trial MIST. The claim of the relation between decreased viral load and alleviation of symptoms does not appear to be substantiated in the text of the report. All outcomes reported are non-clinical
Allocation concealment	B ? Unclear
Study	**Hayden 1997**
Methods	Two multicentre trials in North America (38 centres, 220 individuals) and Europe (32 centres, 197 individuals) conducted during the 1994-1995 influenza season. Both trials assessed the treatment effects of zanamivir using a randomised, double-blind, placebo controlled design.
Participants	Otherwise healthy individuals with symptoms suggestive of influenza persisting longer than 48 hours. Mean ages of subjects in the three arms were 31 to 33 years
Interventions	Participants were randomised to receive either 10 mg of inhaled zanamivir by mouth plus 6.4 mg by intranasal spray or 10 mg of inhaled zanamivir and intranasal placebo spray or aqueous placebo by both routes twice daily for five days. During convalescence HAI titres were assessed and 262 individuals had laboratory confirmed influenza. Of these, 56% were due to A/H3N2 and 44% to B virus
Outcomes	Overall nine placebo patients and ten from each of the other arms withdrew or were lost to follow up (explained in the text as failure to at tend for the follow up visits). The major outcome assessed in the trial was ?time to alleviation of major symptoms? (defined as absence of fever and headache, muscle ache, sore throat and cough). Additionally, time to resumption of usual activities are also reported (Table 3)

Characteristics of included studies

Notes	Individuals who commenced treatment 30 hours or less from the onset of illness fared significantly better than those who commenced later. Both interventions significantly shortened duration of illness compared to placebo (5.3 and 5.4 days compared to 6.3 days). Inhaled and intranasal zanamivir significantly shortened non-effective time compared to placebo. Importantly, no effect was seen on non-influenza infected patients (although the data are not presented in the text). Adverse effects are presented in the text as overall and broken down by generalised (respiratory tract and gastrointestinal) and local (perinasal). The authors conclude that zanamivir is safe and effective treatment against influenza A and B if given early in the illness. Although clearly randomised, no details of allocation or double blinding are given. The intention to treat analysis has clearly taken place
Allocation concealment	B ? Unclear
Study	**Hayden 1999a**
Methods	Multicentre randomised double-blind placebo-controlled preventive phase III trials of oseltamivir. Follow up was 8 weeks. Medication continued for 6 weeks after recognition of the outbreak in the study area. Randomisation and allocation were carried by using a computer-generated sequence. Due to the low incidence of influenza (2.4% or 38/1559) the data from the two studies were combined. The study was conducted during the winter of 1997-1998 in Virginia, Texas and Kansas with circulating A/Sydney/5/97 H3N2 strain
Participants	One-thousand five-hundred and fifty-nine healthy unvaccinated adults aged 18 to 65. There were 33 withdrawals from the treatment arms and 21 from the placebo arm
Interventions	Oral oseltamivir 75 mg daily (n = 520), or twice daily (n = 520) or placebo (n = 519) for six weeks. Acetaminophen could also be taken by protocol agreement
Outcomes	Serological/Laboratory: viral isolation and paired sera for antibody titres were taken Effectiveness: influenza (presence of ILI symptoms and culture within two days of symptom onset and/or antibody rise) asymptomatic influenza (antibody rise in the absence of symptoms) ILI: oral temp of 37.2C or more with at least one respiratory (cough, sore throat, coryza) or one constitutional symptom (aches, fatigue, headache, chills, sweats) Safety: study withdrawals withdrawals due to Aminotransferase concentration increase withdrawals due to gastrointestinal events headache Nnausea vomiting
Notes	The authors conclude that protection of 76 per cent is satisfactory given the low level of influenza activity. The study is reasonably reported but procedures for double blinding are not described and effectiveness outcomes are very confusingly named and described
Allocation concealment	A ? Adequate
Study	**Hayden 2000a**
Methods	Multicentre, double-blind, randomised, placebo-controlled PEP trial that took place during the 1998 to 1999 winter in the USA
Participants	Two hundred and twenty one index cases aged 18 to 20 and 837 family contacts aged around 25 to 26 years in 337 families (168 assinged to placebo and 169 to zanamivir)

Characteristics of included studies

Interventions	Index cases recieved either inhaled zanamivir 10 mgs daily or placebo for five days. Family contacts received either zanamivir 10 mgs daily or placebo for ten days
Outcomes	Serological: serum assays, PCR and culture (with resistance assay) Effectiveness: ILI Efficacy: Influenza and duration of symptoms Safety: not better defined but authors report a profile similar to placebo
Notes	The authors conclude that zanamivir was 79% (57% to 89%) effective and 72% (42% to 87%) effective in preventing contacts from developing symptomatic influenza and 53% (27% to 70%) effective and 48% (15% to 68%) efficacious in symptmatic and asymptomatic influenza. Zanamivir shortend duration of symptoms by 2.5 days. There was no evidence of the onset of resistance. Allocation concealment is not described
Allocation concealment	D ? Not used
Study	**Hayden 2004**
Methods	(WV 16163) Multicentre, open-cluster randomised trial conducted in Europe and North America during the 2000-2001 influenza season. The aims of the study were to assess the effects of post-exposure prophylaxis (PEP) with oseltamivir compared with standard treatment (oseltamivir if symptoms occurred in contacts) and the possible onset of resistance. Eligible households had a maximum of 3 and a minimum of 8 members, including at least 1 index case and at least 2 eligible contacts aged 1 year or more. Children aged younger than 1 year were excluded. Randomization was stratified by the presence or absence of an infant (aged younger than 1 year) in the household and by the presence or absence of a second index case (IC) in the household. ICs and contacts recorded symptoms twice daily on diary cards for 30 days
Participants	Eight-hundred and twelve healthy and non-pregnant household contacts of 298 index cases presenting with an influenza-like illness (temperature 37.8C or more plus cough and/or coryza) during a documented community influenza outbreak were randomized by household (n = 277). There were 20 contact exclusions, 11 because of lack of information and 9 due to lack of laboratory infected status data
Interventions	PEP with oseltamivir for 10 days or treatment at the time of developing illness (expectant treatment) during the postexposure period beginning within 48 h of the reported onset of symptoms in the index case. All index cases received oseltamivir treatment twice daily for 5 days. Contacts in the expectant treatment arm were also given a standard 5-day treatment course if illness developed (adults and adolescents older than 12 years received 75 mg oseltamivir capsules twice daily, whereas children aged 1 to 2, 3 to 5, and 6 to 12 years received 30, 45, and 60 mg oseltamivir suspension, respectively, twice daily). A second course of treatment could be provided in the event that the subject developed an ILI after the completion of the first course of oseltamivir

Characteristics of included studies

Outcomes	Serological: throat and nose swabs and paired serum samples for determining influenza strain-specific hemagglutination-inhibition (HAI) antibody titers Effectiveness: percentage of households with at least 1 secondary case of influenza during the 10-day period after the start of treatment in the ICs (primary efficacy outcome) Percentage of households with at least 1 secondary case of ILI during the 10-day period after the start of treatment in the ICs Both outcomes were also calculated for individual contacts and for children aged 1 to 12 years. Duration of illness (time to alleviation of symptoms for treated ICs and for ill contacts: the first 24 h period in which the severity of all influenza symptoms were remained as mild or none) Efficacy analyses were carried out for: intention-to-treat index-infected (ITTII) population defined as those households and contacts of laboratory-confirmed, influenza-infected ICs. Subpopulation of contacts who were virus-negative at baseline (ITTIINAB) Overall intention-to-treat (ITT) population (all randomized households and contacts, regardless of infection status in the IC). Safety: withdrawals nausea vomiting The data for children aged 1 to 12 were not extracted
Notes	The authors conclude that oseltamivir is safe and effective in interrupting household transmission. A very confusing report with unclear alternative interventions and outcomes which had to be pieced together from fragments of text. Randomisation details are lacking together with cluster co-efficient data
Allocation concealment	D ? Not used
Study	**Kaiser 2000**
Methods	Multicentre, double-blind, placebo-controlled randomised controlled trial. The trial assessed the prophylactic activity of zanamivir after presumed exposure to influenza in the community. The study was conducted from November 1995 to March 1996 in Europe and North America when A/H3N2 was the predominant strain
Participants	Five hundred and seventy five asymptomatic subjects aged 13 to 65 years (mean age 34 to 35 years) who had been in close contact with index cases of influenza like illness of no longer than 4 days duration (ILI was defined as temp of 37.8C or more or feverishness with at least two of the following: headache, myalgia, cough and/or sore throat). No withdrawals are mentioned
Interventions	Participants were randomised to four treatment groups: 1) 2 intranasal sprays of zanamivir (16 mg/mL) per nostril (0.1 mL per spray) plus 2 placebo inhalations 2) 2 zanamivir inhalations (5mg per inhalation) plus 2 placebo sprays per nostril 3) inhaled and intranasal zanamirvir 4) 2 placebo inhalations and 2 placebo sprays per nostril All were self administered for 5 days

Characteristics of included studies

Outcomes	Serological/laboratory: serum samples (days 1 and 21) and viral upper airways samples were taken Effectiveness: six point scale of influenza like symptoms ILI, including: - headache sore throat feverishness, muscle aches, cough, nasal congestion, weakness loss of appetite Observations were recorded twice daily for 10 days Safety: no detailed outcome data are reported
Notes	The authors conclude that short term treatment with intranasal zanamivir was ineffective. However, inhaled zanamivir treatment reduced the rate of influenza, which was 2% to 3% among zanamivir recipients versus 6% among placebo recipients. The results in the text are reported in a very confusing fashion. It is likely that "influenza at 21 days" and "Symptomatic or asymptomatic influenza 21 days after initiation" are the same outcome reported twice differently in the text and table 2. Because of the possibility of error, data on asymptomatic influenza have not been extracted
Allocation concealment	B ? Unclear
Study	**Kaiser 2003**
Methods	Report of complications outcomes from ten placebo controlled RCTs of oseltamivir from the Roche clinical studies database. Only three are from healthy adult populations and are included in this review. Methods are those of the relevant studies. The studies were conducted in 1997-1998 in northern and southern hemispheres. 68% of the participants had influenza, predominantly H3N2, while 12% had influenza B. For further information see Treanor 2000 and Nicholson 2000
Participants	
Interventions	
Outcomes	
Notes	
Allocation concealment	D ? Not used
Study	**Kashiwagi 2000a**
Methods	Double-blind placebo-controlled randomised controlled trial of the preventive effects of oseltamivir against influenza A and B. The study was carried out in 33 centres in Japan. Both H3N2 and H1N1 were co-circulating at a low level the time with H3N2 accounting for 10 of the 13 cases in the placebo arm of the trial. Follow up and administration of the drug was for 42 days, with a further post-administration of 57 days' duration
Participants	Three hundred and eight healthy subjects aged 16 to 89 (mean 34 years), predominantly non-smokers. There were three withdrawals in the intervention arm (one each for adverse events, protocol violation and voluntary withdrawal)
Interventions	Oral oseltamivir (Roche) 75 mg or placebo daily for six weeks

Characteristics of included studies

Outcomes	Serological: viral antibody titres Effectiveness: Group 1: participants with fever of 37.5C or more and at least two other influenza symptoms with laboratory confirmed influenza Group 2: participants without fever of 37.5C or more or at least two other influenza symptoms with laboratory confirmed influenza Group 3: participants with no symptoms or signs with laboratory confirmed influenza Group 4: participants with symptoms without laboratory confirmed influenza Safety: diarrhoea, abdominal pain upper, nausea, abdominal pain, vomiting, abdo. distension, stomatitis, loose stools, retching, sore throat, faecal abnormality, gingivitis, constipation, oral discomfort, tooth loss, tooth ache, gingival oedema, dyspepsia, food poisoning, oesophagitis, glossitis, enterocolitis, headache, sneezing, dizziness, somnolence, insomnia, paraesthesia, cough, rhinorrhea, epistaxis, allergic rhinitis, nasal passage irritation, nasal congestion, tonsillitis. Other adv events are grouped by infectious, local, musculoskeletal, reproductive, metabolic, cutaneous, injury and poisoning, eye, vascular, ENT, renal. An extensive list of laboratory and diagnostic tests is reported
Notes	The authors conclude that oseltamivir is safe and effective in the prevention of influenza. Despite not being able to consult the text, the tables and abstract report sufficient information. The study appears well designed and well reported
Allocation concealment	B ? Unclear
Study	**Kashiwagi 2000b**
Methods	Double-blind placebo-controlled randomised trial of the treatment effects of oseltamivir against influenza A and B. The study was carried out in 79 centres in Japan. Both H3N2 and H1N1 were co-circulating at the time with H3N2 accounting for nearly 60% of infections in both arms of the trial. Follow up and administration of the drug was for 5 days, with a further post-administration of 21 days' duration
Participants	Three hundred and sixteen subjects were enrolled, 162 in the placebo arm and 154 in the active arm (including one in the placebo arm was given the study drug by mistake). There were 3 withdrawals from the active arm (one each for overdosing not turning up for follow up and voluntary withdrawal) and 11 from the placebo arm (4 for adverse events, 4 for voluntary withdrawal, 1 was given the study drug by mistake, 1 "other" and 1 for not turning up for follow up) so 151 in each arm completed the trial. Participants were aged 16 to 89 (mean age 35.5 in the active arm and 33.6 in the placebo arm). Five were inpatients. One hundred and twenty two participants were infected with influenza and 130 in the placebo arm. These represented the intention to treat infected (ITTI) population
Interventions	Oral oseltamivir (Roche) 75 mg or placebo twice daily for five days. In the ITTI population, administration took place within 36 hours of onset of symptoms for all but 8 in the active arm and 5 in the placebo arm

Characteristics of included studies

Outcomes	Serological: viral antibody titres Effectiveness: time to resolution of illness (ITTI) time to resolution of symptoms (ITTI) cases of influenza (ITTI) influenza viral titre severity (symptom scores) Safety: diarrhoea, abdominal pain upper, nausea, abdominal pain, vomiting, abdo. distension, stomatitis, loose stools, retching, sore throat, faecal abnormality, gingivitis, constipation, dry mouth, oral pain, tooth ache, gingival oedema, dyspepsia, tongue coated, oesophagitis, glossitis, enterocolitis, headache, sneezing, dizziness, somnolence, insomnia, paraesthesia, cough, rhinorrhea, dizziness, grand mal convulsion, epistaxis, allergic rhinitis, nasal passage irritation, nasal congestion, tonsillitis. Other adv events are grouped by infectious, local, musculoskeletal, reproductive, metabolic, cutaneous, injury and poisoning, eye, cardiac, ENT, renal. An extensive list of laboratory and diagnostic tests is reported
Notes	The authors concluded that oseltamivir is safe and effective in reducing length of illness. Lack of translation of parts of the text make assessment of quality difficult. The imbalance in denominators is not explained
Allocation concealment	B ? Unclear
Study	**Li 2003**
Methods	Double-blind randomised placebo-controlled trial to assess the efficacy of oseltamivir in the treatment of naturally occurring influenza. Background rates of infections are not described, nor strains isolated from participants are described
Participants	Four hundred and seventy eight healthy adults aged 18 to 65 with symptoms consistent with influenza (fever of 37. 8C or more, plus at least two others: coryza/nasal congestion, sore throat, cough, myalgia/muscles aches and pain, fatigue, headache or chills/sweats). People with influenza vaccination less than 12 months before the study were excluded. Sixteen participants were lost to follow up or refused to continue the trial, 3 were excluded prior to taking medication because they did not meet the entry criteria, and 8 were excluded because of protocol violation. Four hundred and fifty one individuals were analyzed for efficacy as the intention- to- treat population (ITT) (216 oseltamivir and 235 placebo) with 273 individuals were identified as influenza infected through laboratory test and were regarded as the intention- to- treat infected population (ITTI) (134 oseltamivir and 139 placebo) .For the safety analysis, 459 individuals were included (137 oseltamivir group with influenza, 84 oseltamivir group without influenza, 141 placebo group with influenza, and 97 placebo group without influenza)
Interventions	Oral oseltamivir phosphate or placebo (Roche) 75 mg bid for 5 days
Outcomes	Serological: culture or serological tests were used to confirm influenza cases (symptoms and a positive culture on day 1 and/or =4 fold increase in HAI antibody between baseline and day 21 of the study). Viral cultures were performed on all participants: 224 positive and 254 negative. Of 224 individuals with positive culture, serum HAI antibodies on days 1 and 21 were completed in 160 individuals (133 positive, 27 negative). Of 254 with negative cultures, HAI antibodies were completed in 146 individuals (58 positive, 88 negative) . Effectiveness:

Characteristics of included studies

	the primary outcome was time to resolution of symptoms (from the onset of symptoms to the time that all symptoms were resolved). A symptom severity scale was used (0 = no problem, 1 = minor, 2 = moderate, 3 = severe). Symptoms scores are reported as median areas under the curve of decreased total score and cumulative alleviation proportion by arm as survival curve Logrank test Safety: nausea, upset upper abdomen, vomiting, vertigo, insomnia, and rash were reported with an increased frequency in the active arm but the difference was not significant. Numerators are not reported. Follow up took place at days 3, 6, 8 and 21 (vital signs and laboratory examinations included blood routine, urine routine, liver and renal function)
Notes	The authors conclude that oseltamivir is well tolerated and efficacious in relieving symptoms within 36 of onset of influenza and could be used routinely on all symptomatic subjects during an outbreak. A very badly reported trial, with impenetrable outcome reporting
Allocation concealment	A ? Adequate
Study	**MIST 1998**
Methods	Multi-centre randomised placebo-controlled trial of the treatment and safety effects of zanamivir in healthy adults with ILI and influenza. Randomisation and allocation were centralised. Concealment was by means of sealed envelopes on site. Follow up was 28 days and symptoms were self-recorded with diaries. The study was conducted in 1997 in Australia, New Zealand and South Africa, with A/H3N2 being the dominant viral strain
Participants	Four hundred and fifty five healthy and non-pregnant persons aged 12 or more (mean 37 years) with influenza symptoms of no more than 36 h (temp of higher than 37.8C or feverishness or both and at least two of the following myalgia, sore throat, cough, headache). There were 76 participants (57 with respiratory diseases,15 aged 65 or more, 11 with a metabolic disease, 8 hypertensives and 2 immunocompromised) There were 58 withdrawals: 31 for adverse events (27 in the zanamivir arm and 4 on placebo), withdrawn consent (5 and 3), loss to follow-up (7 and 10) and 2 because of protocols violation (1 and 1)
Interventions	Inhaled zanamivir 10 mg bd or placebo for five days. An antipyretic and antitussive were also dispensed with a request not be used routinely

Characteristics of included studies

Outcomes	Serological/Laboratory: viral cultures and paired antibody titre estimations Effectiveness: symptoms (duration and severity): feverishness, cough, headache, sore throat, myalgia, nasal congestion, weakness and anorexia were rated on a 4-point scale (0 = no symptoms; 1 = mild; 2 = moderate; 3 = severe) temp sleep disturbance ability to perform normal activity complications antibiotic use Safety: adverse events bronchitis cough sinusitis LRTC diarrhoea nausea and vomiting
Notes	The authors conclude that zanamivir was effective and well-tolerated. A well reported study although safety outcome definitions are not given and it is difficult to see how adv events such as bronchitis could be distinguished from influenza disease. The format of reporting of outcomes ay lead to considerable loss of data
Allocation concealment	A ? Adequate
Study	**Makela 2000**
Methods	Randomised double-blind, placebo-controlled trial to assess the effectiveness of zanamivir in the treatment of subjects presenting with influenza symptoms during a period of influenza activity. The trial took place in 11 European countries during the winter of 1997-1998. The predominant strain was A/H3N2. Follow up was up to 28 days
Participants	Three hundred and fifty six patients aged 12 or more. Patients presenting with acute febrile influenza-like illness. Patients were required to have a fever (37.8C or more for patients aged less than 65, 37.2C or more for patients aged 65 or more, with at least two of the following symptoms: headache, myalgia, cough and sore throat. They had to start therapy within 2 days of symptom onset. Women who were pregnant or at risk of pregnancy were excluded
Interventions	Within two days of onset of typical influenza symptoms and received orally inhaled zanamivir 10 mg via diskhaler twice daily for five days or matching placebo

Characteristics of included studies

Outcomes	Serological: influenza was confirmed by diagnosis of virus culture, virus isolation, seroconversion, or by virus detection PCR. Influenza A subtyping was performed by serology and PCR Effectiveness: time until alleviation of clinically significant symptoms of influenza time to alleviation and no use of relief medication, time to return to normal activities influenza high risk influenza positive Safety: bronchitis sinusitis diarrhoea pharyngitis nausea and vomiting pneumonia
Notes	The authors conclude that zanamivir is effective in reducing the duration and severity of influenza illness and is well tolerated. No age breakdown is given and the whole text gives the idea of careful editing to enhance effect of zanamivir. Reporting of clinical outcomes is in the format of Area Under the Curve (AUC)
Allocation concealment	A ? Adequate
Study	**Matsumoto 1999**
Methods	Double-blind, randomised, placebo-controlled trial of the treatment efficacy of inhaled and intranasal zanamivir for five days. Follow up was up to 28 days. ITT analysis was carried out. The study was carried out in 28 centres in Japan during January to March 1995. The dominant strain was A/H3N2
Participants	One hundred and sixteen healthy subjects aged 16 to 65 recruited in 28 centres randomised to three arms. Participants with a set list of symptoms who presented themselves to their family doctor within 36 hours of onset were enrolled. Two participants dropped out from arm 1 and 2 from arm 3 because of lack of improvement
Interventions	Zanamivir (Nippon Glaxo) dry powder (5 mg/inhalation) or matching placebo or aqueous intranasal spray (1.6 mg/spray) or matching placebo were administered. Participants received either two inhalations (10mgs) plus intranasal placebo, or 10 mg inhaled zanamivir plus two spray per nostril (6.4 mg) or double placebo for five days. As initial analysis failed to detect any difference between arm 1 and arm 2, the data from the two arms was compared with placebo
Outcomes	Serological: serology and virological samples were taken and influenza viruses identified with PCR. Effectiveness: participants were instructed in the use of diaries to record symptoms. - Time to alleviation of: fever, headache and myalgia, cough and sore throat (used in the text as corporate indicator of lower fever, headache and myalgia). - Time to resumption of normal activities Safety: possible adverse events hoarse voice, headache, diarrhoea

Characteristics of included studies

Notes	The authors conclude that participants in the active arms recovered faster by one day compared to placebo recipients (3 days instead of four). Continuous outcomes are summarised in the text either median and interquartile ranges (time to alleviation) or as Kaplan-Meyer plots (time to resumption of normal activities). Average reporting quality but randomisation and double blinding are not described
Allocation concealment	B ? Unclear
Study	**Monto 1999a**
Methods	Double-blind randomised, placebo-controlled trial assessing the effects of zanamivir, administered once daily, in the prevention of influenza infection and disease. Follow up was for 35 days. Randomisation was stratified in blocks of 10 for each site and participant were assigned sequentially to pre-randomised packaged drug or placebo. The study was conducted during the 1997-1998 influenza season in two Midwest university communities, United States (Universities of Michigan and Missouri). A/Sydney/5/97 H3N2 was the dominant strain
Participants	One thousand one hundred and seven healthy adults, mean age 29, range 18 to 69 years, mainly students or community volunteers. 1107 included in the ITT analysis. Eleven discontinued the trial for adverse events, 16 for consent withdrawal or loss to follow-up. Follow-up was for up to 28 days with a final visit at day 35
Interventions	Zanamivir 10 mg or placebo for six days or more up to 28 days, administered by self-activating inhalation once daily using a Diskhaler device
Outcomes	Serological/Laboratory: serum samples and paired sera for antibody titres Effectiveness: influenza if had 2 of the following recorded successively in at least 3 diary entries: cough, headache, sore throat, myalgia, feverishness or temp of at least 37.8 C with a rise in antibody titres and/or viral isolation febrile influenza if temp of at least 37.8 C with a rise in antibody titres and/or viral isolation febrile illness if only temp of at least 37.8 C Safety is not mentioned in detail, only as any adverse event
Notes	The authors conclude that zanamivir administered once daily is efficacious and well tolerated in the prevention of influenza for a 4-week period in healthy adults. A reasonably reported study
Allocation concealment	A ? Adequate
Study	**Monto 1999b**
Methods	Double-blind randomised placebo-controlled multi-centre parallel group study. Follow up was for 21 days. The study was conducted in November to March 1996 in North America and Europe. The dominant strains were A/H3N2 and A/H1N1
Participants	One thousand two hundred and fifty six healthy patients, aged 13 years or more (mean around 35 to 36 years) who had symptoms of influenza up to 48 h duration were enrolled. See below for definition of symptoms. There were seventy four withdrawals, these were for adverse events, lost to follow up and other reasons. Seven hundred and twenty two (57%) participants were found to have influenza. There were 158 participants described as high risk (n = 69 with asthma; n = 31 with cardiovascular disease; n = 18 had metabolic conditions; n = 39 were aged 65 or more

Characteristics of included studies

Interventions	Zanamivir 10 mg 2 x daily by oral inhalation plus 6.4 mg 2 x daily nasal spray versus zanamivir 10 mg 4 x daily by oral inhalation plus 6.4 mg 4 x daily by nasal spray versus placebo by both routes 2 x daily versus placebo by both routes 4 x daily. Placebo groups were combined for analysis. Medication was self administered and patients were instructed to take the inhaled medication before the intranasal medication. All patients were provided with acetaminophen tablets and dextromethorphan cough suppressant but were instructed to avoid using these medications unless their symptoms became sufficient to warrant them
Outcomes	Serological: serum assays at days 1 and 21 and viral isolation from airways Effectiveness: oral temp severity of symptoms: rated on six point scale in which '0' corresponded to no symptoms and '5' corresponded to severe symptoms sleep disturbances level of ability to perform normal activities health questionnaire time to alleviation of clinically significant symptoms, defines as the absence of feverishness, a temperature less than 37.8C and a score of 0 (none) or 1 (mild) for other major symptoms (i.e., headache, myalgia, sore throat and cough) for at least 24 hrs or more time to return to normal activities use of acetaminophen and cough mixture to relieve symptoms Safety Diarrhoea Nausea and vomiting Nasal signs and symptoms Headaches Bronchitis Withdrawal due to possible adverse events
Notes	The authors conclude that zanamivir can significantly reduce the duration and overall symptomatic effect of influenza. A summarily reported trial with selective and heterogeneous reporting of outcomes
Allocation concealment	B ? Unclear
Study	**Monto 2002**
Methods	Double-blind randomised placebo controlled PEP trial
Participants	Four hundred and eighty seven households with 1291 contacts aged 5 or more (mean age around 19 years)
Interventions	Inhaled zanamivir 10 mgs once daily for ten days. Index patients with ILI received symptomatic medication only
Outcomes	Serological: serum assays, PCR and culture (with resistance assay) Effectiveness: ILI Efficacy: Influenza Safety: not better defined but authors report a profile similar to placebo (no cases of bronchospasm are reproted in the intervention arm, but two are reported in the placebo arm)

Characteristics of included studies

Notes	The authors conclude that zanamivir is effective in in prophylaxis and interrupting transmission (79% effectiveness and 81% efficacy - 64% to 90% - for households and 82% for individuals and was well tolerated. Zanamivir shortened duration of illness by 1.5 days. No viral resistance was reported. A reasonably reported trial
Allocation concealment	B ? Unclear
Study	**Nicholson 2000**
Methods	(WV 15670). Randomised double-blind placebo-controlled preventive phase IIIa trials of Ro 64-0796. WV 15670 was conducted in Europe, Canada and China during the 1997-1998 winter. 473 otherwise healthy individuals who presented with at least on respiratory and one constitutional symptom were randomised within 36 hours of onset. AH3N2 was the dominant strain
Participants	Seven hundred and twenty six healthy (apart from ILI symptoms) participants aged 18 to 65 were enrolled. Four hundred and seventy five participants had influenza (161, 158, 156 respectively). There were seven withdrawals for lack of compliance and 15 because of adverse events and 23 protocol violations
Interventions	Either oseltamivir 75 mg daily orally (n = 155), or twice daily (n = 157), or "matching" placebo (n = 161) for five days
Outcomes	Serological: culture and serological specimens were used to diagnose influenza infection. Effectiveness: the main outcome was the time to alleviation of symptoms expressed in days and type and incidence of adverse events. Additionally severity of illness was also assessed by means of a symptom score and antibiotic use was recorded in each arm. influenza was defined as viral isolation and/or antibody titre (at 3/52 interval) increase. The laboratory assessment was done in a blinded fashion Safety: nausea vomiting (reported as mean frequencies by arm). all outcomes were assessed twice daily for 21 days
Notes	The authors conclude that the time to alleviation of symptoms was significantly reduced in the active arms. Equally there was a 30% reduction in the symptoms scores of the active arms of both trials. As in the prophylaxis/prevention trials of oseltamivir, nausea was the most reported systemic adverse event, especially at the higher dose. The methodological quality of the study is reasonable. Randomisation by centralised computer and robust allocation concealment procedures are explicitly mentioned in the text
Allocation concealment	A ? Adequate
Study	**Puhakka 2003**
Methods	Multi-centre double-blind randomised placebo-controlled trial of treatment effects of zanamivir in Finnish armed forces conscripts Randomisation was computerised in blocks of 6. Only investigator-prescribed paracetamol was allowed. The study was conducted (2000-2001) over two influenza seasons with A/H3N2 and A/H1N1 respectively as dominant strains

Characteristics of included studies

Participants	Five hundred and eighty eight conscripts aged around 19 and mainly males, presenting with symptoms of ILI of less than 48 h duration with a temp of 38C or more and at least 2 of the following: headache, muscle/joint aches sore throat or cough during periods of influenza viral circulation. Surveillance was carried out throughout the influenza season. Diary cards were kept by participants for 28 days
Interventions	Inhaled zanamivir 5 mg per inhalation or placebo (lactose powder) bid for 5 days
Outcomes	Laboratory: real-time PCR, nasal and throat swabs (at 0, 8, 24 and 48h) and antibody titres (days 1 and 28) were collected Effectiveness: time to alleviation of symptoms (temp less than 37.8C and feverishness score as "none" and other symptoms recorded as 0 or 1 for 24 h) time to alleviation of symptoms with no use of relief medication (temp less than 37.8C and feverishness score as "none" and other symptoms recorded as 0 or 1 for 24 h in patients who have not taken relief medication) viral load use of relief medication severity of symptoms (overall symptoms, headache, cough, feverishness, sore throat, anorexia, muscle/joint aches and pains, weakness; on a scale: 0 = no symptoms; 1 = mild; 2 = moderate; 3 = severe) Complications: use of antibiotics for complications use of diagnostic procedures general well being was assessed using the - measure yourself medical outcomes - MYMOP questionnaire Safety: ILI symptoms that got worse bronchitis COPD or asthma that got worse Acceptability: ease of use of diskhaler device (data not extracted)
Notes	The authors conclude that zanamivir significantly reduces viral load, however startling improvements in symptoms could not be observed because of the characteristics of this very healthy population. In the discussion the authors observe the short and benign duration of the illness (median 2.33 d in the placebo arm). A reasonably reported study with no mention of blinding procedures. Data are not reported for a number of outcomes (e.g. general well-being, use of relief medication etc) for which data were apparently collected
Allocation concealment	B ? Unclear
Study	**Treanor 2000**
Methods	(WV 15671) Multicentre double-blind placebo-controlled randomised trial of the efficacy of oseltamivir in cases of influenza of 36 hours' duration or more. Randomisation and allocation were centralised through an automated phone programme. Although the aim of the study is to test the efficacy of the drug, data for both efficacy influenza) and effectiveness (ILI) are reported. The study was conducted between January and March 1998 in the USA. A/H3N2 was the dominant viral strain

Characteristics of included studies

Participants	Six hundred and twenty nine unvaccinated previously healthy adults aged 18 to 65 presenting within 36 h of symptom onset (oral temp 38C or more and at least one of the following: cough, sore throat, nasal symptoms and headache, malaise, myalgia, sweats/chills, fatigue). There were 46 withdrawals (16, 19 and 11 respectively) Follow up was 21 days, with twice daily observations recorded on diaries
Interventions	Oral oseltamivir 75 mg or 150 bd or placebo for 5 days
Outcomes	Serological/laboratory: viral culture for airway swabs and antibody titres at days 1 and 21 Effectiveness: symptom severity (graded on a 4 point scale) ability to perform usual activities and health status (11-point visual analogue scales) oral temp number and type of complications Safety: nausea vomiting withdrawals due to adverse effects
Notes	The authors conclude that oseltamivir reduces duration of illness and may reduce complications. Convoluted reporting and extensive use of medians may lead to loss of important data
Allocation concealment	A ? Adequate
Study	**Welliver 2001**
Methods	Multicentre double-blind placebo-controlled cluster randomised controlled trial (C-RCT) of the effects of oseltamivir in the interruption of transmission of influenza in families. The study was conducted in the winter of 1989-1999 in North America and Europe (76 centres)
Participants	Three hundred and seventy four households (962 healthy contacts with a mean age of 33, minimum 2 members and maximum 8 members per household) of 377 index cases (ICs) presenting within 48h of onset of cough and coryza. Children aged up to 12 were enrolled only if other contacts in the household met the enrolment criteria. A household represented a cluster (all members were randomised to the same treatment). There were 4 withdrawals due to contact not taking study medication and 7 withdrawals due to adverse events (5 in the active and 2 in the placebo arm)
Interventions	Oseltamivir 75 mg die or placebo within 48 h of symptom onset for 7 days and 500 mg of acetaminophen if needed. ICs were not treated
Outcomes	Serological: nasal swabs and paired antibody titres Effectiveness: proportion of contacts of IC with influenza within days 1 to 7 of the intervention ILI (oral temp of 37.2C or more and at least cough, nasal congestion or sore throat and headache, fatigue, chills or myalgia within 24 h) influenza (ILI plus laboratory confirmation) Safety: GI adverse events nausea wthdrawals due to adverse events

Characteristics of included studies

Notes	The authors conclude that oseltamivir was well tolerated and prevented spread of influenza. Poor reporting of randomisation, cluster correlation calculations and allocation procedures
Allocation concealment	B ? Unclear

Notas:
h = hourENT = ear, nose and throatbd = twice dailyd = day

Characteristics of excluded studies

Study	Reason for exclusion
Aoki 2003	No control arm (Roche study code WV 76006)
Calfee 1999	Experimental influenza only
Cass 1999	No denominator breakdown by arm
Hayden 1999	Experimental influenza only
Hayden 2000b	Experimental influenza only
Ison 2003	Population of persons with underlying medical conditions
Li 2001	Same data set as Li 2003
Longuyn 2004	Redundants publication of Li 2003
Massarella 2000	Phase 2a study with no safety outcomes reported
Monto 1999	Meta-analysis. No original data presented
Murphy 2000	At risk participants
Peng 2000	Dose-ranging study

CARÁTULA

Titulo	**Inhibidores de neuraminidasa para la prevención y el tratamiento de la influenza en adultos sanos**
Autor(es)	**Jefferson TO, Demicheli V, Di Pietrantonj C, Jones M, Rivetti D**
Contribución de los autores	Para la actualización de 2006: TOJ y DR aplicaron los criterios de inclusión y extrajeron los datos, y VD supervisó la extracción y actuó como tercer revisor cuando fuera necesario. MJ y CD verificaron y transformaron los datos, y supervisaron el metanálisis revisado. TOJ editó el texto, con contribuciones de todos los autores.
Número de protocolo publicado inicialmente	1999/1
Número de revisión publicada inicialmente	1999/2

Fecha de la modificación más reciente"	15 mayo 2006
"Fecha de la modificación SIGNIFICATIVA más reciente	15 mayo 2006
Cambios más recientes	**En la actualización de 2005 se revisó completamente el texto y se agregó una sección sobre pruebas de una epidemia de influenza aviar registrada en los Países Bajos en 2003, que causó una muerte. También se agregó una sección sobre la profilaxis postexposición. Se descartaron los estudios que analizan los efectos de los inhibidores de neuraminidasa (IN) en casos de influenza experimental (es decir, en sujetos que fueron infectados deliberadamente como parte del experimento) y se centró la atención en los numerosos estudios de casos de influenza contraída naturalmente. Los términos "influenza confirmada en laboratorio" e "influenza clínicamente confirmada" han sido reemplazados por términos más apropiados como "influenza" y "enfermedad tipo influenza" (ETI). Se cree que estos términos reflejan la diferencia entre la influenza real (causada por los virus A y B), y lo que se conoce coloquialmente como "gripe". Ambas enfermedades son rara vez clínicamente distinguibles en el tiempo real, a menos que se implemente un muy buen sistema de vigilancia, como ocurrió en la mayoría de los ensayos de esta revisión.**
Fecha de búsqueda de nuevos estudios no localizados	El autor no facilitó la información
Fecha de localización de nuevos estudios aún no incluidos/excluidos	El autor no facilitó la información
Fecha de localización de nuevos estudios incluidos/excluidos	13 octubre 2005
Fecha de modificación de la sección conclusiones de los autores	El autor no facilitó la información
Dirección de contacto	Prof Tom Jefferson Via Adige 28a Anguillara Sabazia Roma 00061 ITALY Télefono: +39 06 999 009 89 E-mail: toj1@aol.com
Número de la Cochrane Library	CD001265
Grupo editorial	Cochrane Acute Respiratory Infections Group
Código del grupo editorial	HM-ARI

RESUMEN DEL METANÁLISIS

01 NI versus placebo for prophylaxis				
Resultado	Nº de estudios	Nº de participantes	Método estadístico	Tamaño del efecto
01 Influenza-like illness	7	3549	Riesgo relativo (efectos aleatorios) IC del 95%	1.20 [0.77, 1.87]
02 Influenza (symptomatic)	7	3549	Riesgo relativo (efectos aleatorios) IC del 95%	0.41 [0.25, 0.65]
03 Influenza (symptomatic and asymptomatic)	7	3549	Riesgo relativo (efectos aleatorios) IC del 95%	0.61 [0.49, 0.76]
04 Influenza (asymptomatic)	4	2974	Riesgo relativo (efectos aleatorios) IC del 95%	0.93 [0.57, 1.51]
05 Adverse events - nausea			Odds-ratio (efectos aleatorios) IC del 95%	Subtotales únicamente
06 Adverse events - vomiting			Odds-ratio (efectos aleatorios) IC del 95%	Subtotales únicamente
07 Adverse events - diarrhoea			Odds-ratio (efectos aleatorios) IC del 95%	Subtotales únicamente
08 Adverse events - abdominal pain			Odds-ratio (efectos aleatorios) IC del 95%	Subtotales únicamente
09 Adverse events - others			Odds-ratio (efectos aleatorios) IC del 95%	Subtotales únicamente
10 Adverse events - withdrawals due to gastrointestinal events			Odds-ratio (efectos aleatorios) IC del 95%	Subtotales únicament

02 NI versus placebo for treatment				
Resultado	Nº de estudios	Nº de participantes	Método estadístico	Tamaño del efecto
01 Time to alleviation of symptoms (ITT)	9	4985	Cociente de riesgos (efectos aleatorios) IC del 95%	1.22 [1.14, 1.31]
02 Time to alleviation of symptoms (influenza cases only)	11	3491	Cociente de riesgos (efectos aleatorios) IC del 95%	1.32 [1.26, 1.38]
03 Time to return to normal activity (ITT)	4	2454	Cociente de riesgos (efectos aleatorios) IC del 95%	1.26 [1.14, 1.40]
04 Time to return to normal activity (influenza cases only)	4	1234	Cociente de riesgos (efectos aleatorios) IC del 95%	1.22 [1.07, 1.39]
05 Complications - bronchitis (ILI cases only)	1	714	Odds-ratio (efectos aleatorios) IC del 95%	0.87 [0.35, 2.20]
06 Complications - bronchitis (influenza cases only)	1	1644	Odds-ratio (efectos aleatorios) IC del 95%	0.40 [0.21, 0.76]
07 Complications - all lower respiratory tract complications (ILI cases only)	1	714	Odds-ratio (efectos aleatorios) IC del 95%	0.69 [0.30, 1.58]

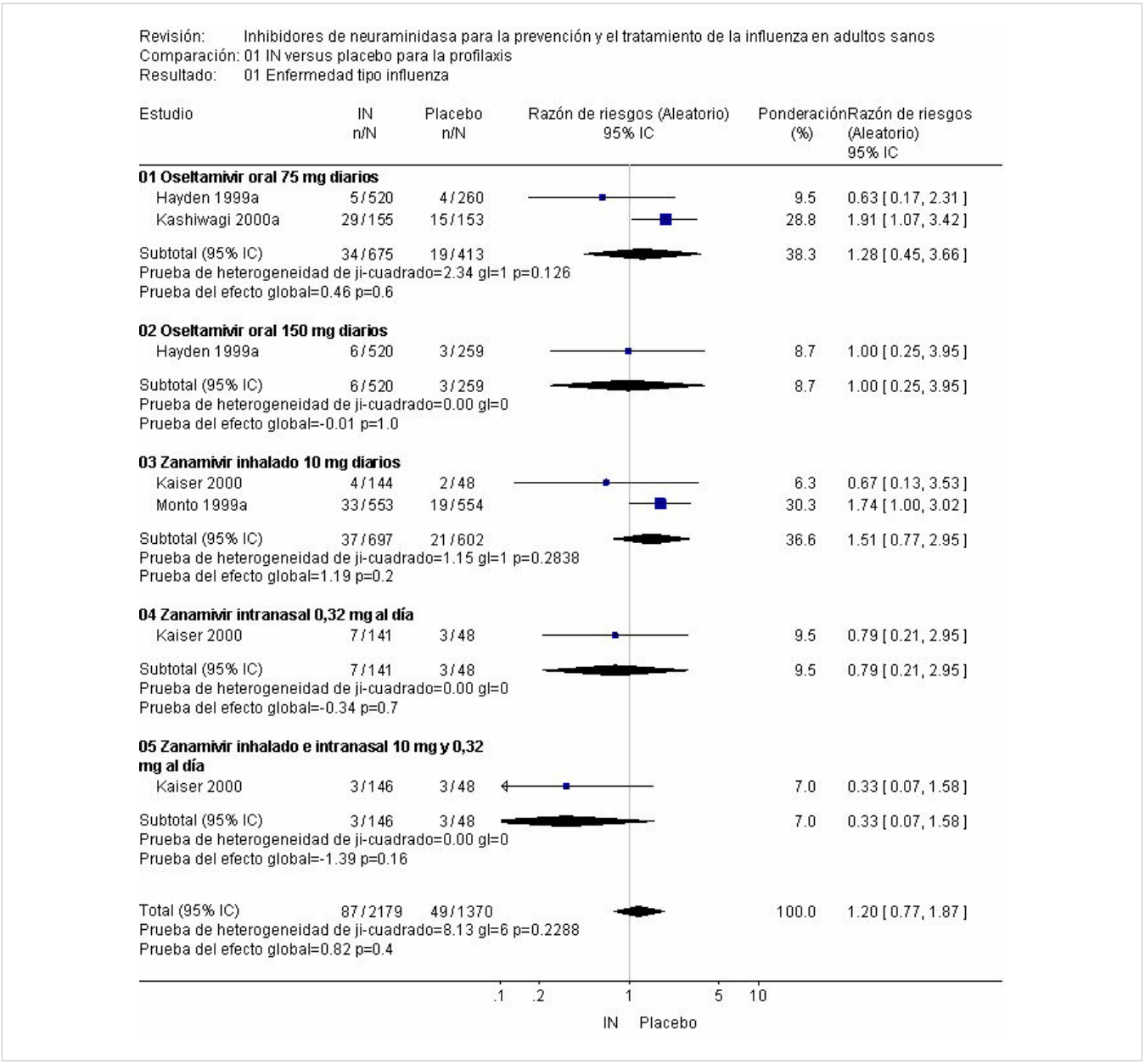
02 NI versus placebo for treatment				
08 Complications - all lower respiratory tract complications (influenza cases only)	1	1644	Odds-ratio (efectos aleatorios) IC del 95%	0.32 [0.18, 0.57]
09 Complications - pneumonia (ILI cases only)	1	714	Odds-ratio (efectos aleatorios) IC del 95%	0.21 [0.02, 2.04]
10 Complications - pneumonia (influenza cases only)	1	1644	Odds-ratio (efectos aleatorios) IC del 95%	0.15 [0.03, 0.69]
11 Complications - all hospitalisations (ILI cases only)	1	714	Odds-ratio (efectos aleatorios) IC del 95%	2.25 [0.46, 10.92]
12 Complications - all hospitalisations (influenza cases only)	1	1644	Odds-ratio (efectos aleatorios) IC del 95%	0.40 [0.10, 1.69]
13 Complications - hospitalisations possibly caused by influenza (ILI cases only)	1	714	Odds-ratio (efectos aleatorios) IC del 95%	4.50 [0.23, 87.40]
14 Complications - hospitalisations possibly caused by influenza (influenza cases only)	1	1644	Odds-ratio (efectos aleatorios) IC del 95%	0.22 [0.02, 2.16]
15 Complications - all types (ILI cases only)	2	1070	Odds-ratio (efectos aleatorios) IC del 95%	0.62 [0.43, 0.90]
16 Complications - all types (influenza cases only)	2	1921	Odds-ratio (efectos aleatorios) IC del 95%	0.43 [0.21, 0.90]
17 Complications - all types (ITT)	2	2714	Odds-ratio (efectos aleatorios) IC del 95%	0.43 [0.33, 0.56]
18 Adverse events - cough			Odds-ratio (efectos aleatorios) IC del 95%	Subtotales únicamente
19 Adverse events - headache			Odds-ratio (efectos aleatorios) IC del 95%	Subtotales únicamente
20 Adverse events - diarrhoea			Odds-ratio (efectos aleatorios) IC del 95%	Subtotales únicamente
21 Adverse events - nasal symptoms (congestion, rhinits, dry or sore throat)			Odds-ratio (efectos aleatorios) IC del 95%	Subtotales únicamente
22 Adverse events - nausea			Odds-ratio (efectos aleatorios) IC del 95%	Subtotales únicamente
23 Adverse events - bronchitis or pneumonia			Odds-ratio (efectos aleatorios) IC del 95%	Subtotales únicamente
24 Adverse events - all types			Odds-ratio (efectos aleatorios) IC del 95%	Subtotales únicamente
25 Use of relief medications and antibiotics	4	1830	Odds-ratio (efectos aleatorios) IC del 95%	0.82 [0.60, 1.11]
27 Mean nasal viral titres (at 24 hours since randomisation)	4	1002	Diferencia de medias ponderada (efectos aleatorios) IC del 95%	-0,62 (-0,82, -0,41)

02 NI versus placebo for treatment				
28 Mean nasal viral titres (at 48 hours since randomisation)	3	659	Diferencia de medias ponderada (efectos aleatorios) IC del 95%	-0.63 [-1.13, -0.13]

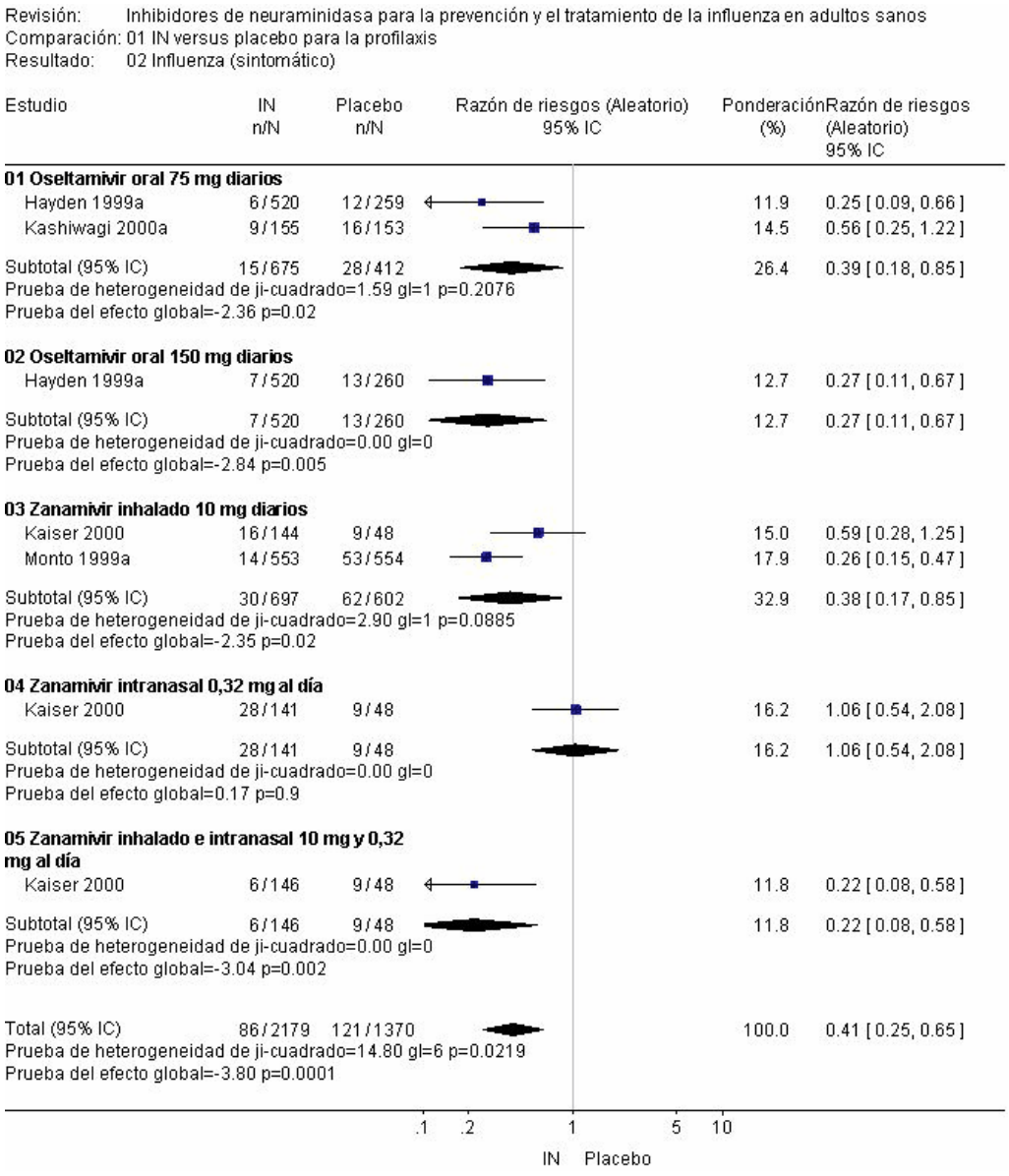
GRÁFICOS Y OTRAS TABLAS

Fig. 01 NI versus placebo for prophylaxis

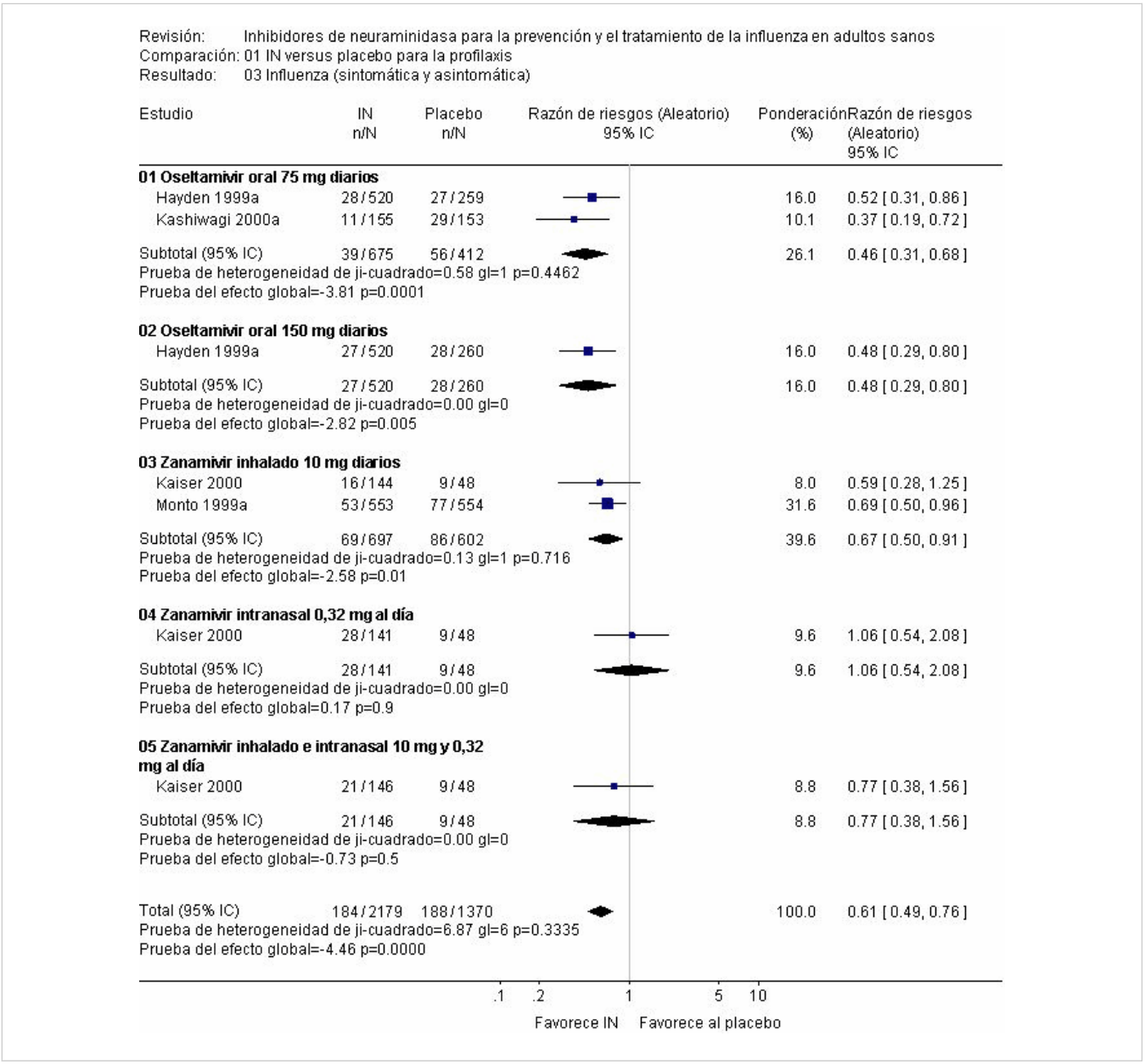
01.01 Influenza-like illness



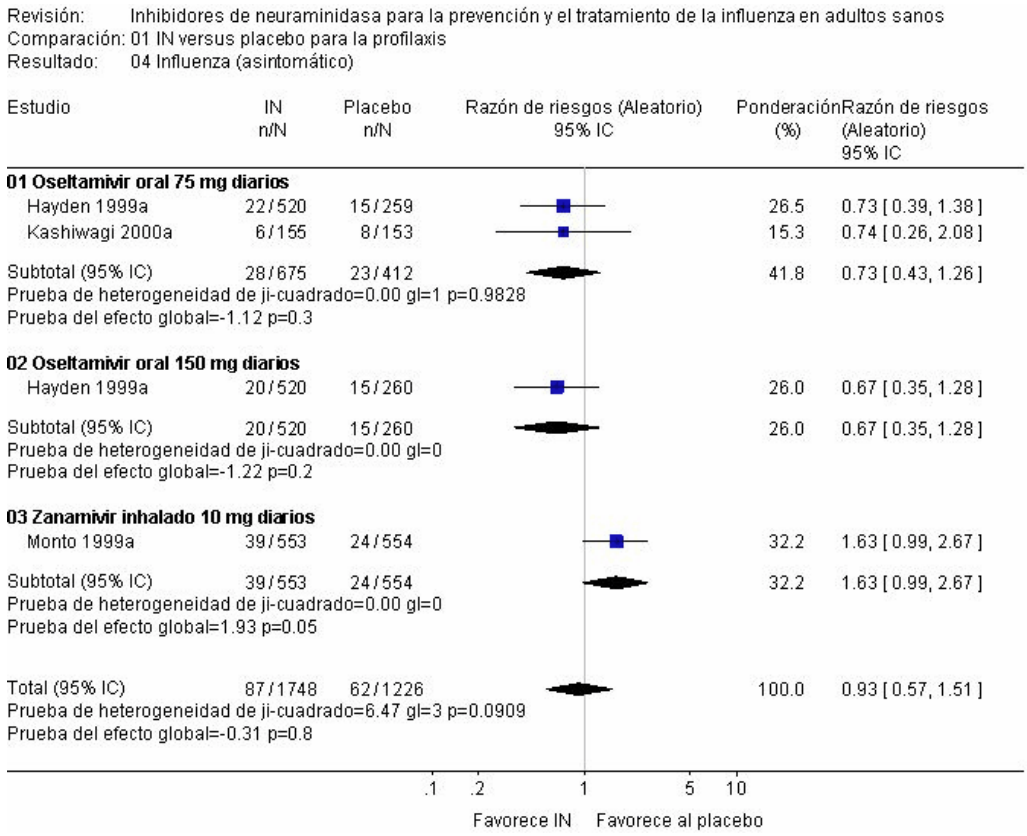
01.02 Influenza (symptomatic)



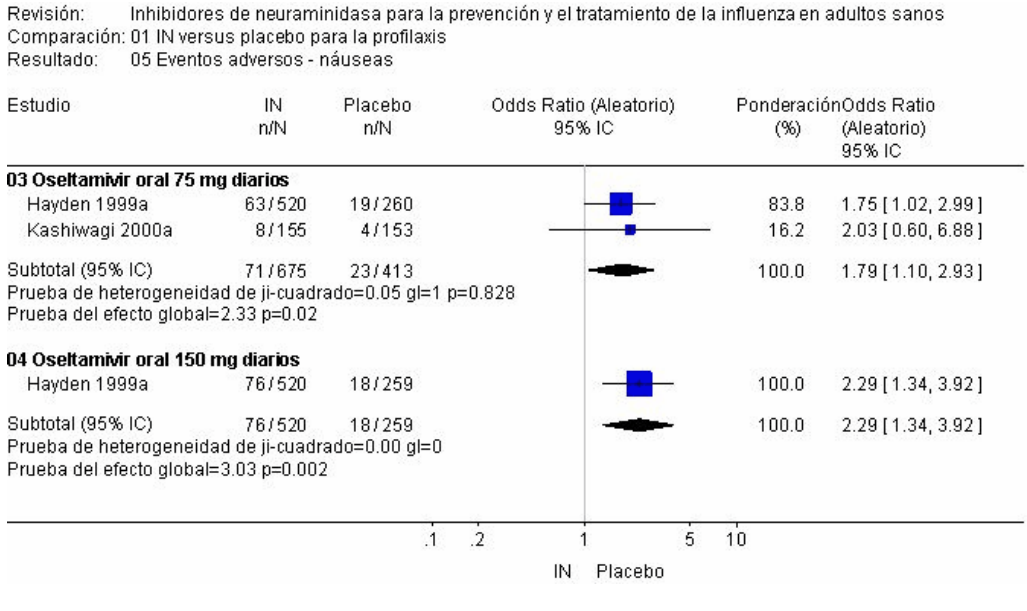
01.03 Influenza (symptomatic and asymptomatic)



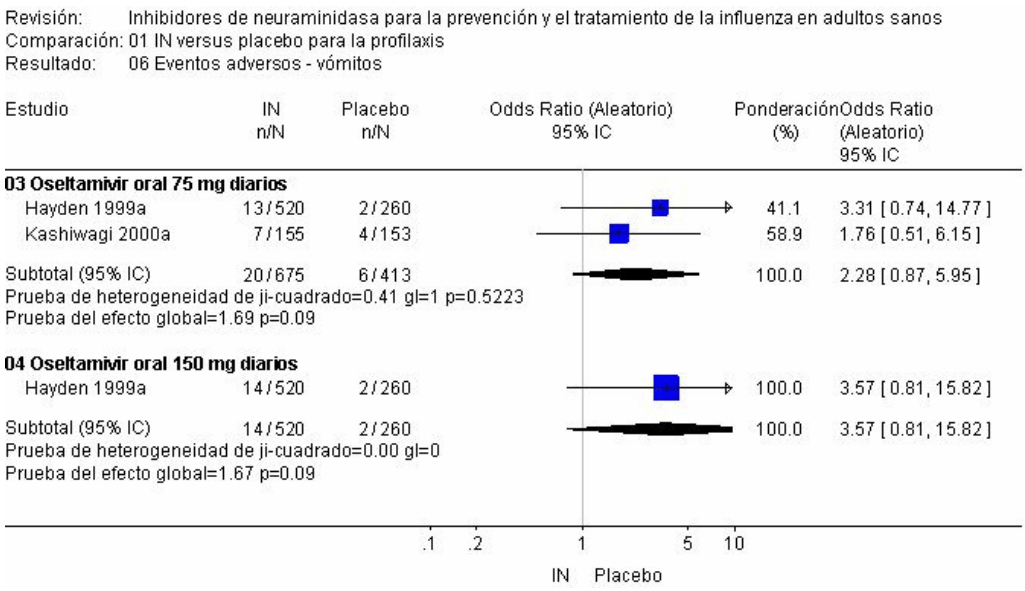
01.04 Influenza (asymptomatic)



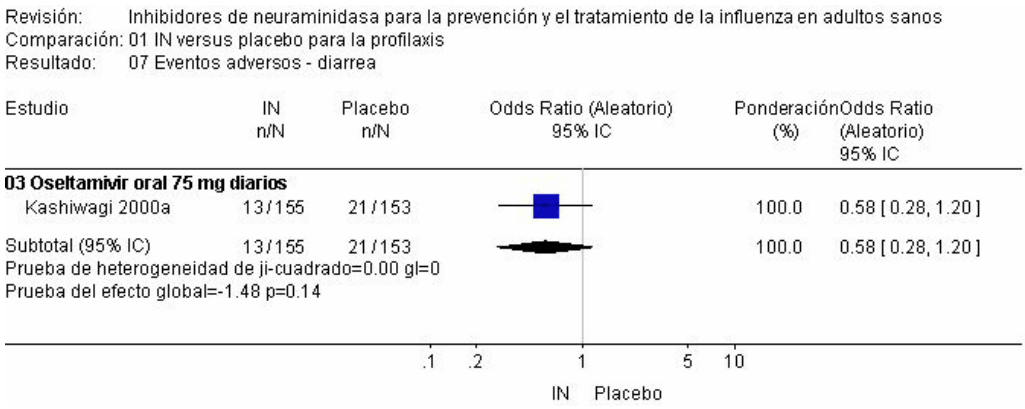
01.05 Adverse events - nausea



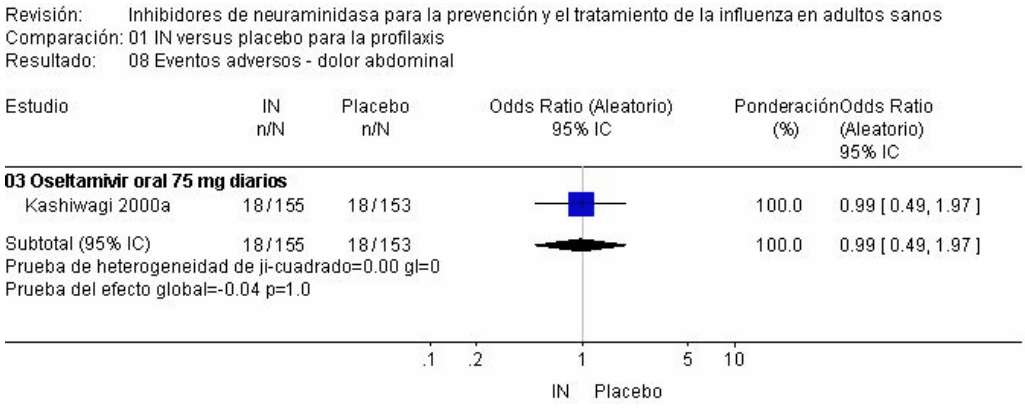
01.06 Adverse events - vomiting



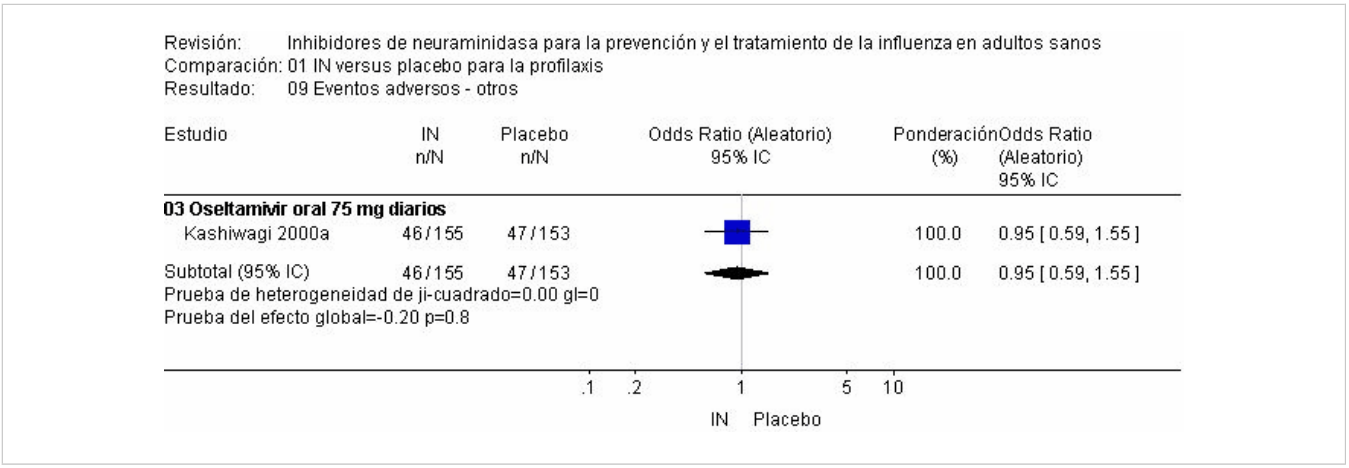
01.07 Adverse events - diarrhoea



01.08 Adverse events - abdominal pain



01.09 Adverse events - others



01.10 Adverse events - withdrawals due to gastrointestinal events

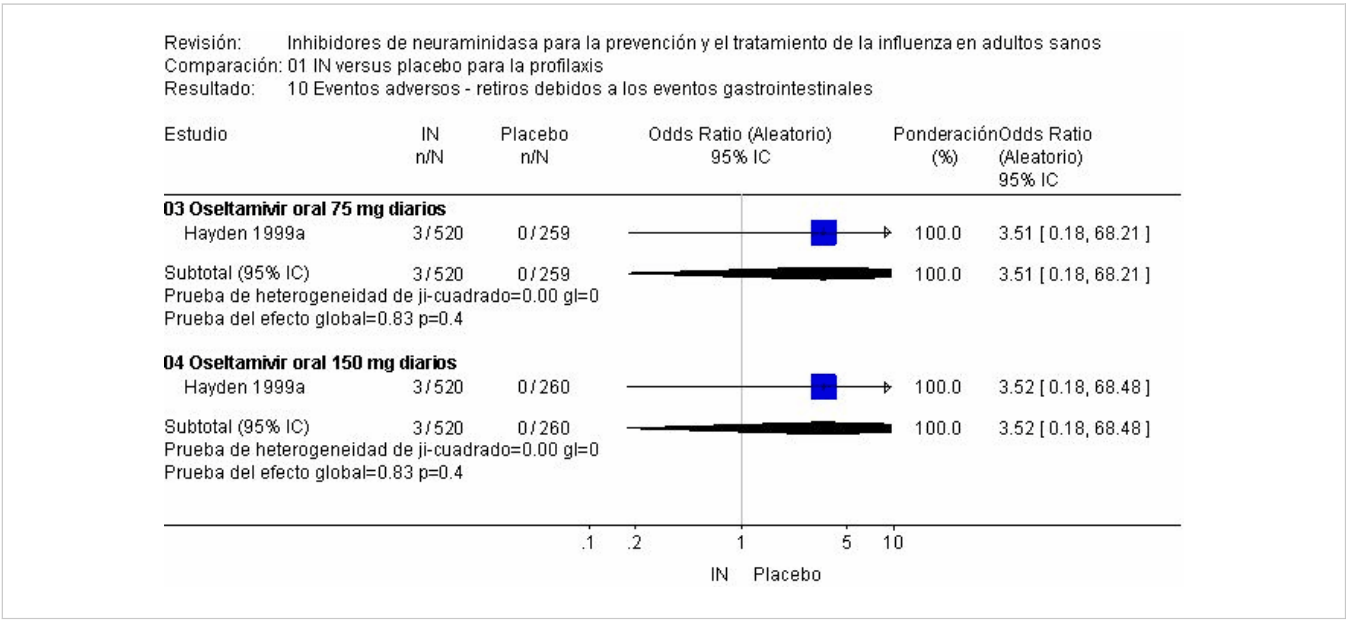
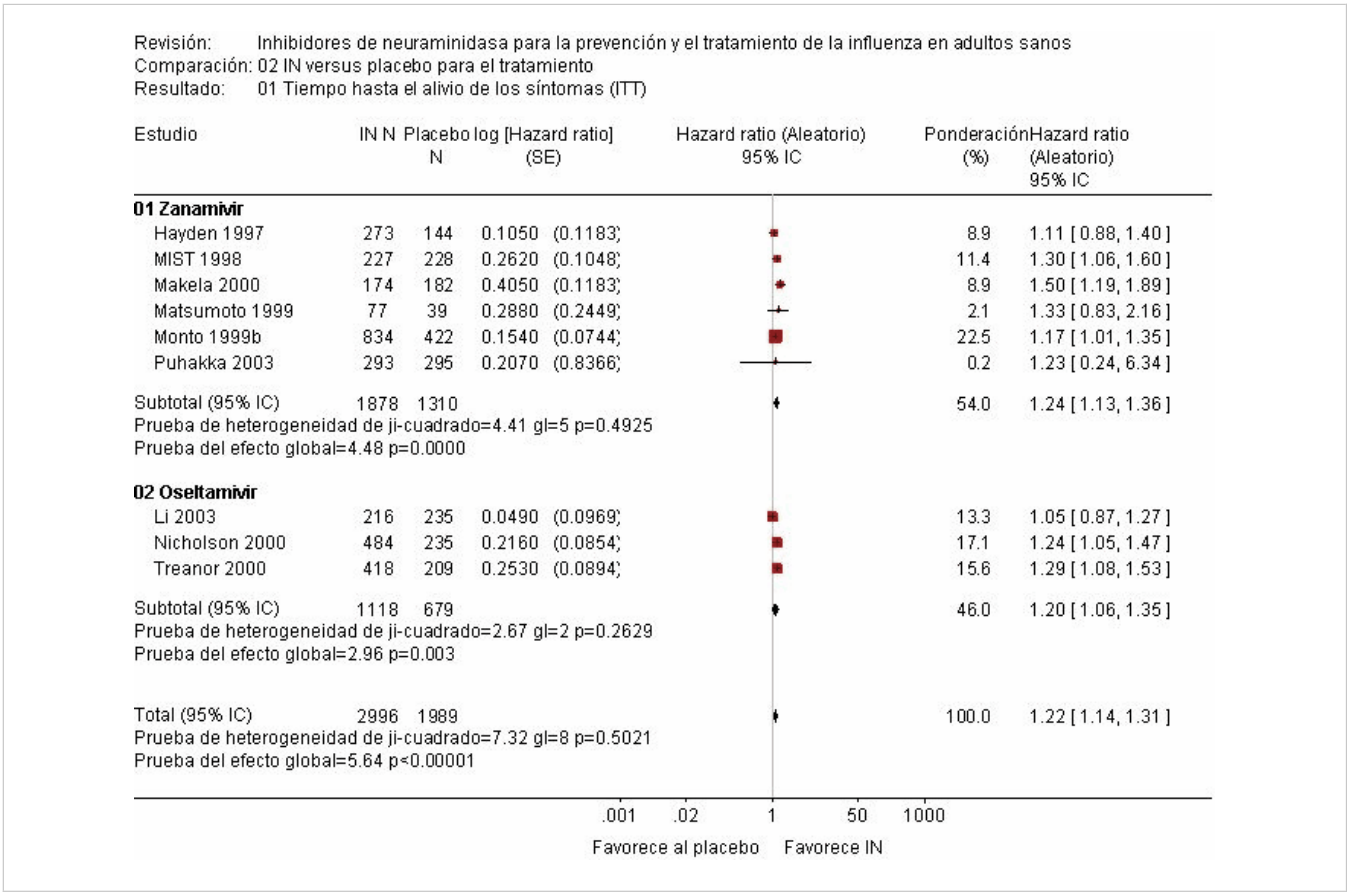


Fig. 02 NI versus placebo for treatment

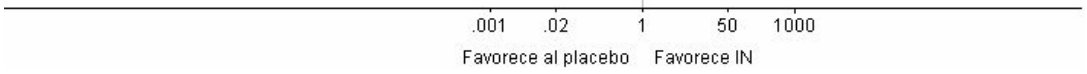
02.01 Time to alleviation of symptoms (ITT)



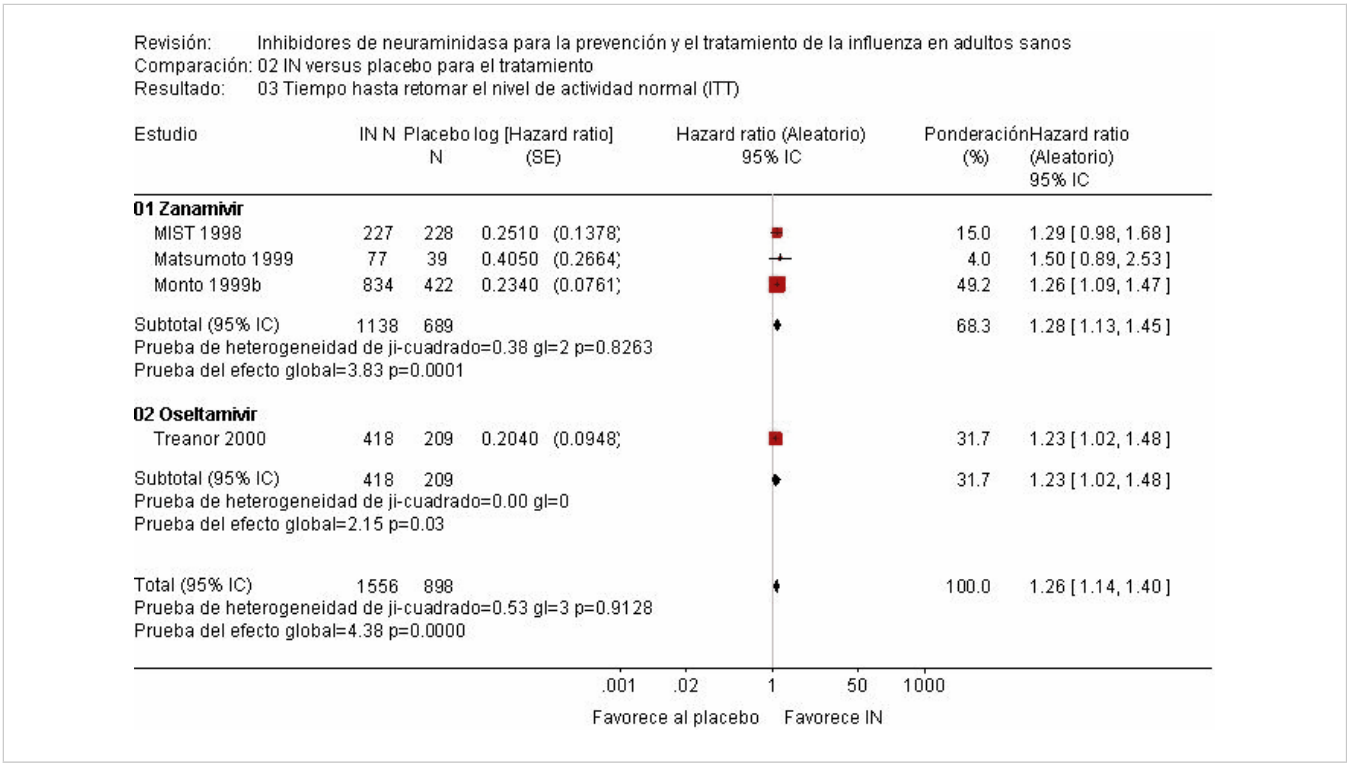
02.02 Time to alleviation of symptoms (influenza cases only)

Revisión: Inhibidores de neuraminidasa para la prevención y el tratamiento de la influenza en adultos sanos
Comparación: 02 IN versus placebo para el tratamiento
Resultado: 02 Tiempo hasta el alivio de los síntomas (casos de influenza solamente)

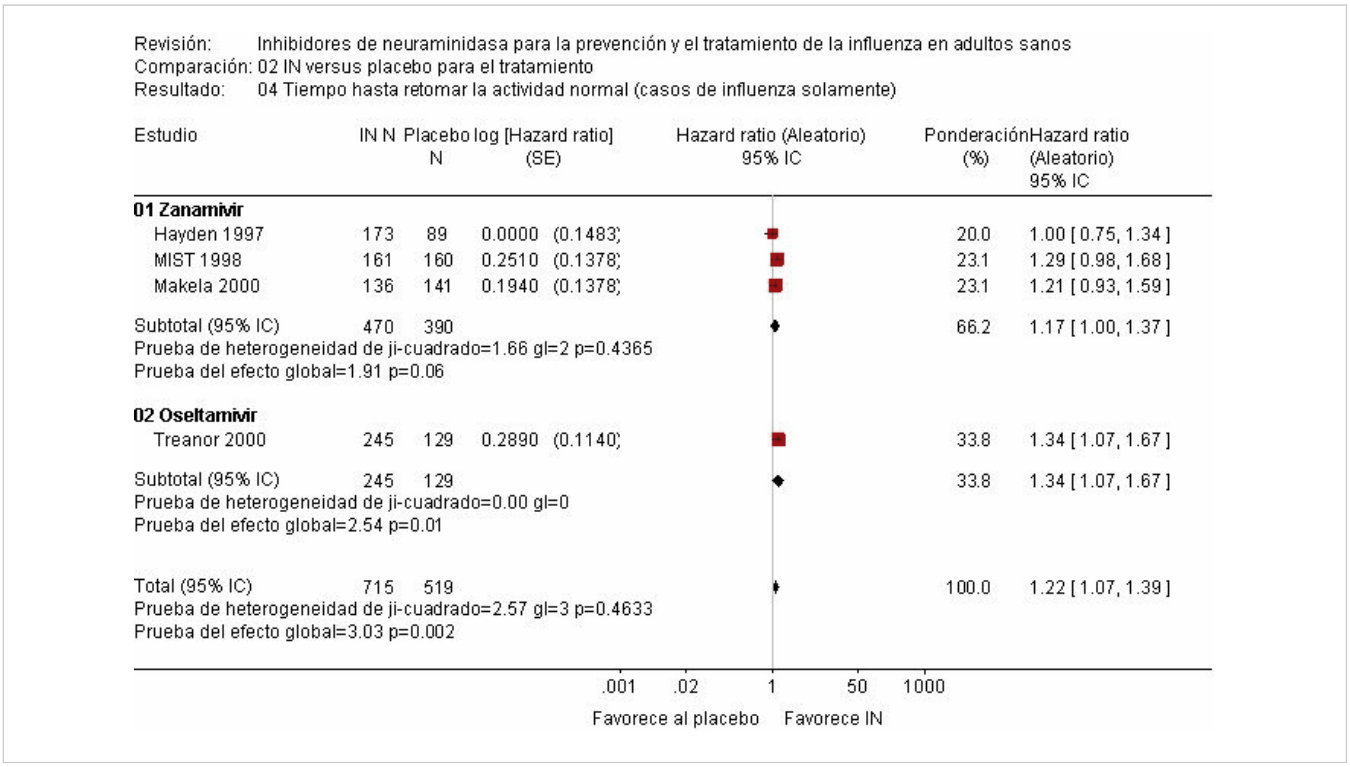
Estudio	IN N	Placebo N	log [Hazard ratio] (SE)	Hazard ratio (Aleatorio) 95% IC	Ponderación (%)	Hazard ratio (Aleatorio) 95% IC
01 Zanamivir						
Boivin 2000	17	10	0.6420 (0.3987)		0.4	1.90 [0.87, 4.15]
Hayden 1997	173	89	0.2230 (0.1483)		2.6	1.25 [0.93, 1.67]
MIST 1998	161	160	0.2880 (0.0160)		64.6	1.33 [1.29, 1.38]
Makela 2000	136	141	0.4700 (0.1378)		3.0	1.60 [1.22, 2.10]
Matsumoto 1999	44	29	0.0000 (0.2863)		0.7	1.00 [0.57, 1.75]
Monto 1999b	481	241	0.2410 (0.1000)		5.6	1.27 [1.05, 1.55]
Puhakka 2003	222	213	0.1530 (0.0959)		6.0	1.17 [0.97, 1.41]
Subtotal (95% IC)	1234	883			93.3	1.33 [1.29, 1.37]
Prueba de heterogeneidad de ji-cuadrado=5.89 gl=6 p=0.4353						
Prueba del efecto global=18.52 p<0.00001						
02 Oseltamivir						
Kashiwagi 2000a	122	130	0.2870 (0.1264)		3.6	1.33 [1.04, 1.71]
Li 2003	134	139	0.0360 (0.1240)		3.7	1.04 [0.81, 1.32]
Nicholson 2000	314	161	0.3200 (0.1048)		5.1	1.38 [1.12, 1.69]
Treanor 2000	245	129	0.3790 (0.1095)		4.7	1.46 [1.18, 1.81]
Subtotal (95% IC)	815	559			6.7	1.30 [1.13, 1.50]
Prueba de heterogeneidad de ji-cuadrado=4.80 gl=3 p=0.1873						
Prueba del efecto global=3.61 p=0.0003						
Total (95% IC)	2049	1442			100.0	1.32 [1.26, 1.38]
Prueba de heterogeneidad de ji-cuadrado=10.77 gl=10 p=0.3761						
Prueba del efecto global=11.37 p<0.00001						



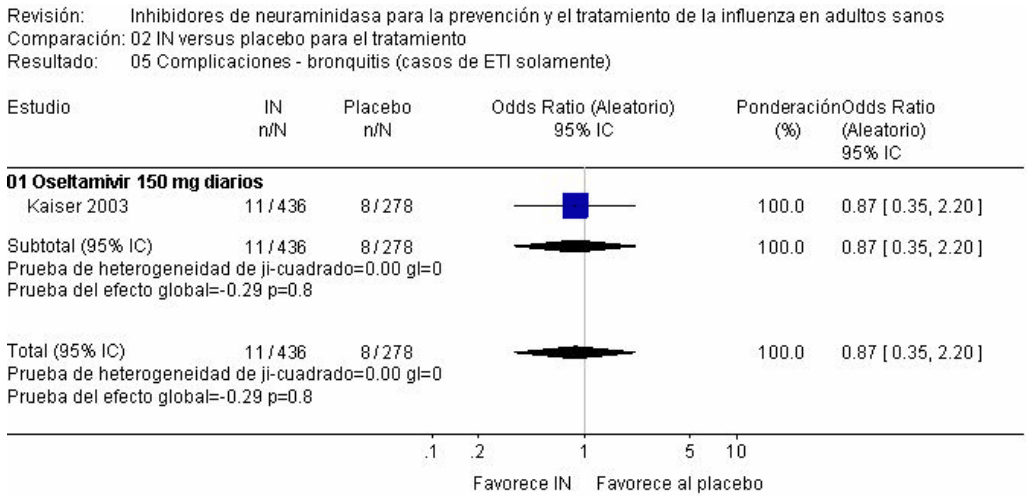
02.03 Time to return to normal activity (ITT)



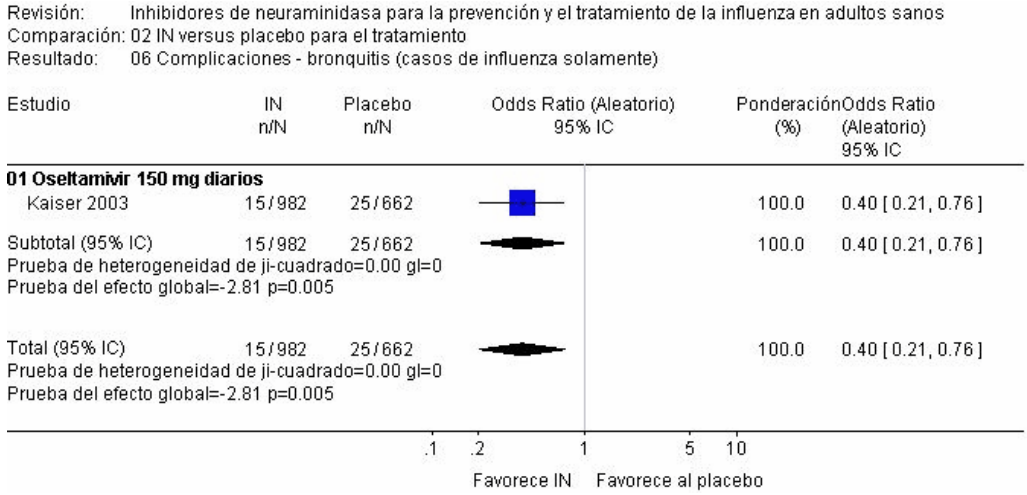
02.04 Time to return to normal activity (influenza cases only)



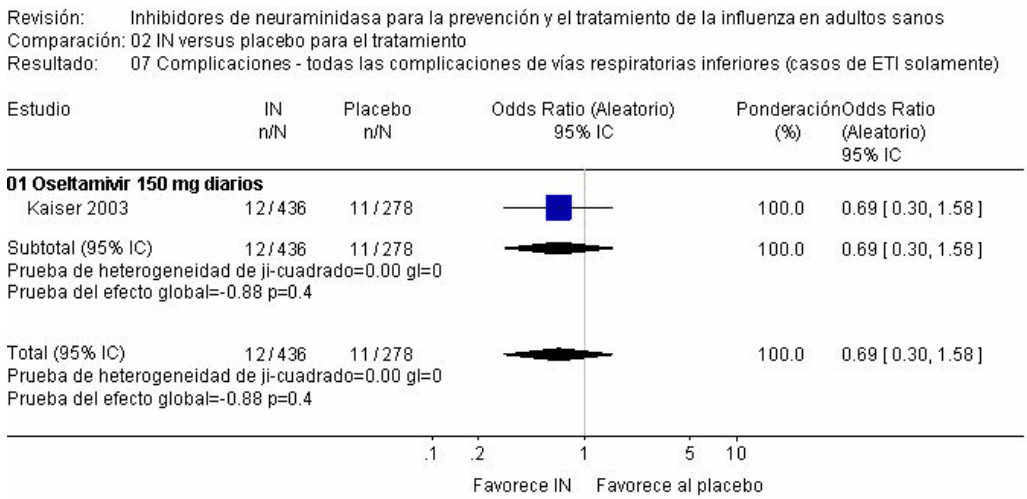
02.05 Complications - bronchitis (ILI cases only)



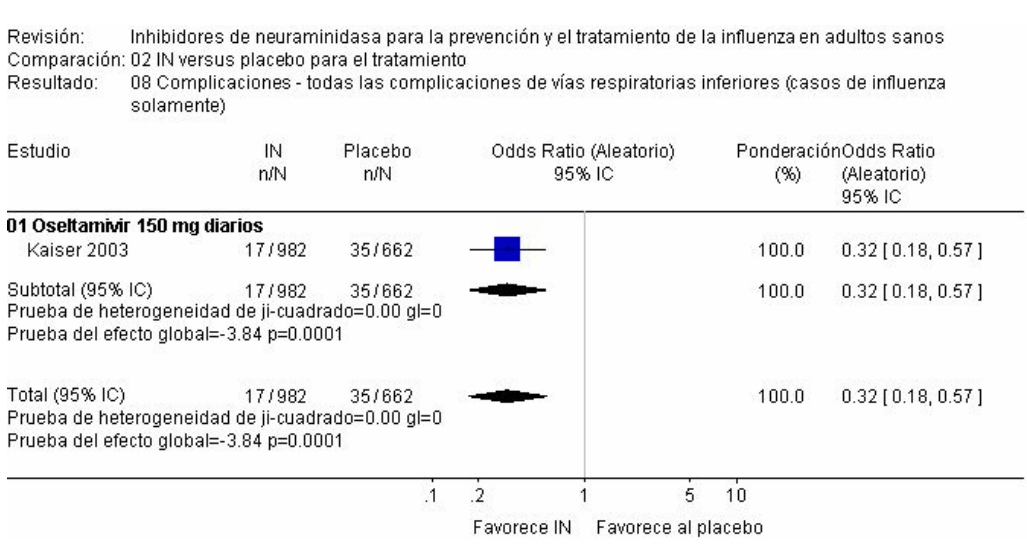
02.06 Complications - bronchitis (influenza cases only)



02.07 Complications - all lower respiratory tract complications (ILI cases only)

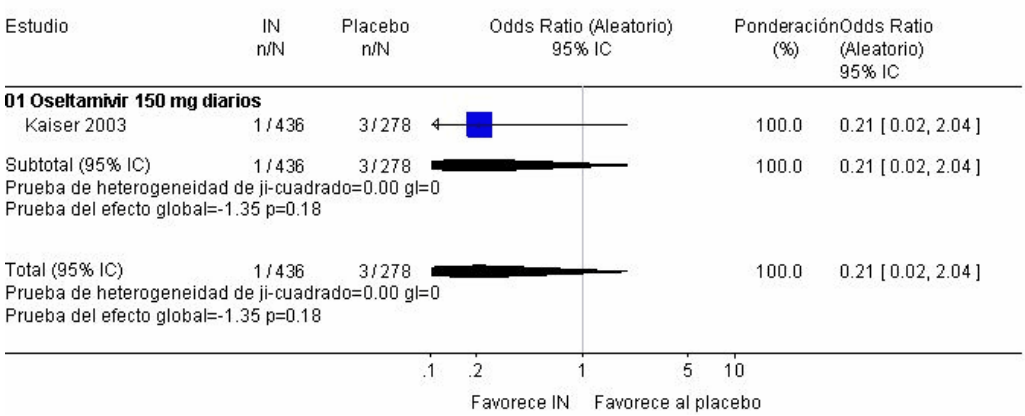


02.08 Complications - all lower respiratory tract complications (influenza cases only)



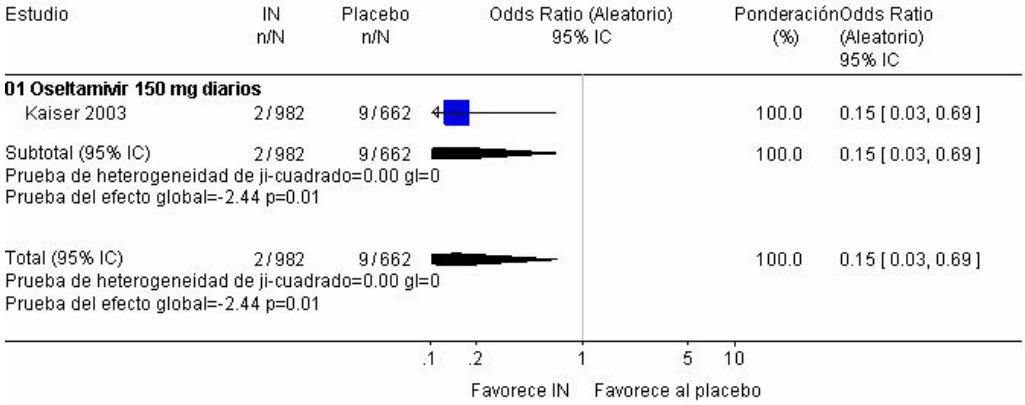
02.09 Complications - pneumonia (ILI cases only)

Revisión: Inhibidores de neuraminidasa para la prevención y el tratamiento de la influenza en adultos sanos
Comparación: 02 IN versus placebo para el tratamiento
Resultado: 09 Complicaciones - neumonía (casos de ETI solamente)

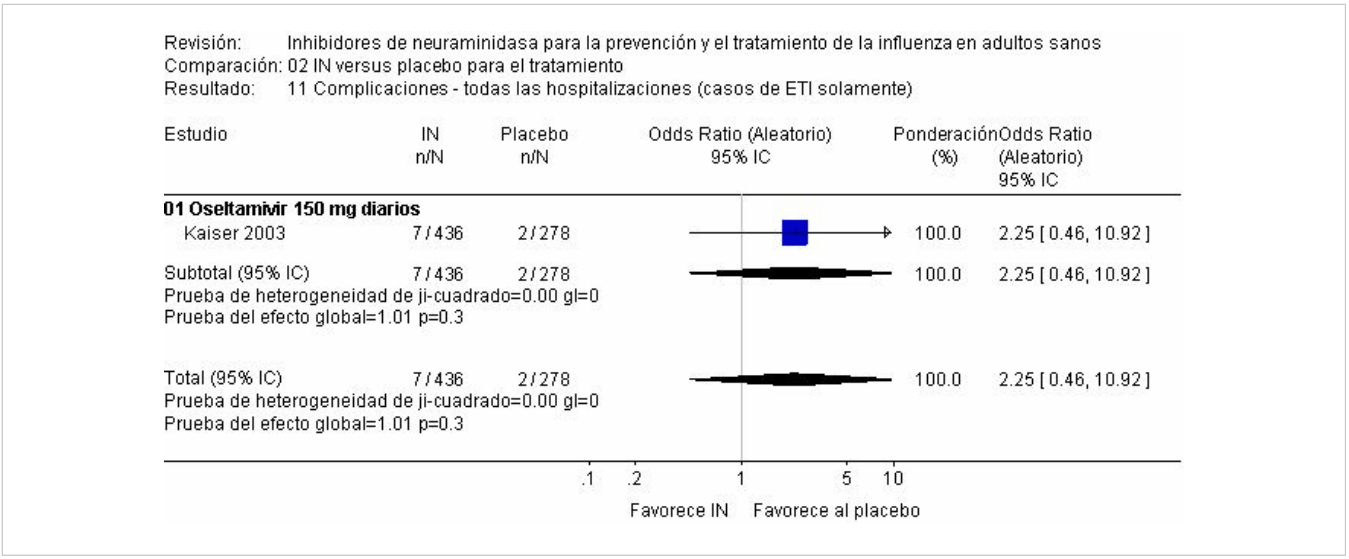


02.10 Complications - pneumonia (influenza cases only)

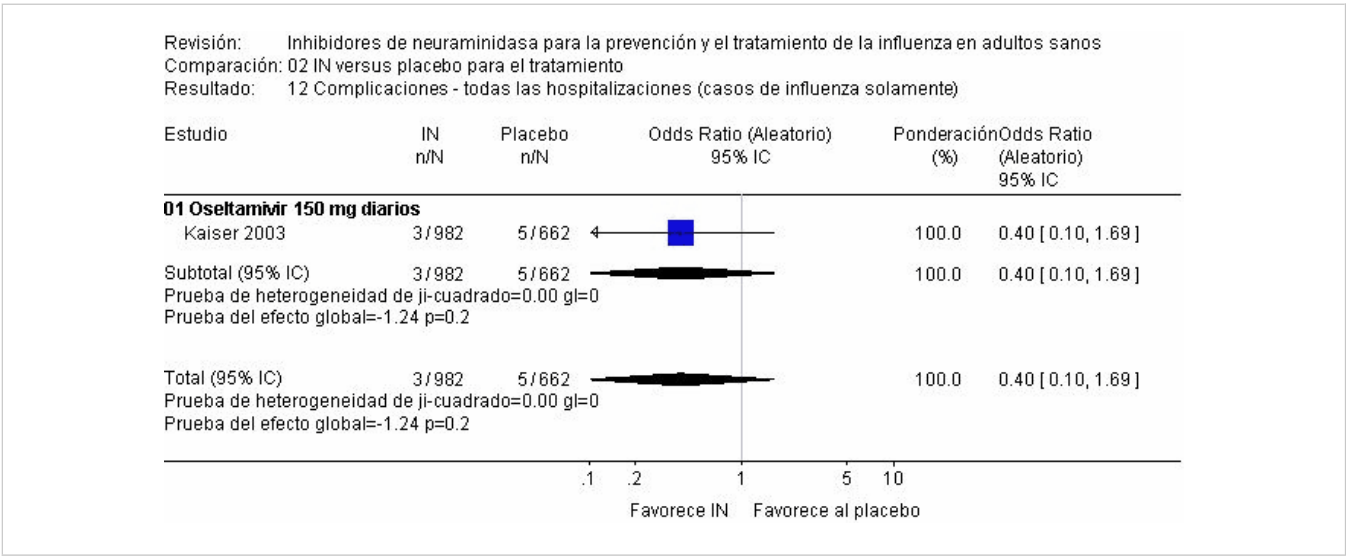
Revisión: Inhibidores de neuraminidasa para la prevención y el tratamiento de la influenza en adultos sanos
Comparación: 02 IN versus placebo para el tratamiento
Resultado: 10 Complicaciones - neumonía (casos de influenza solamente)



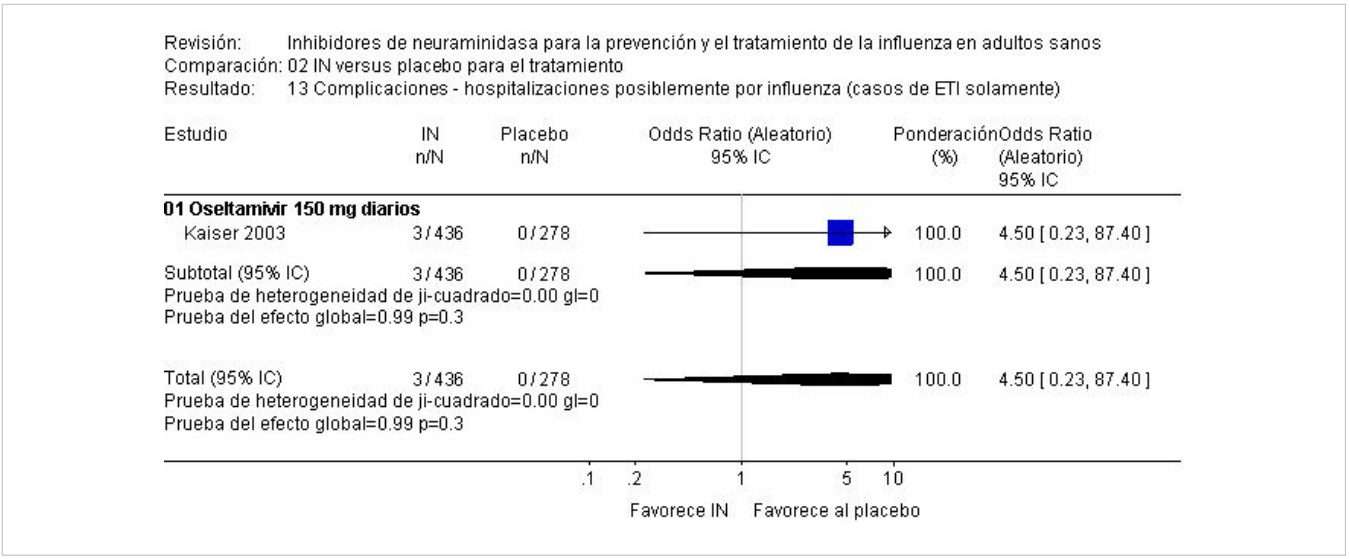
02.11 Complications - all hospitalisations (ILI cases only)



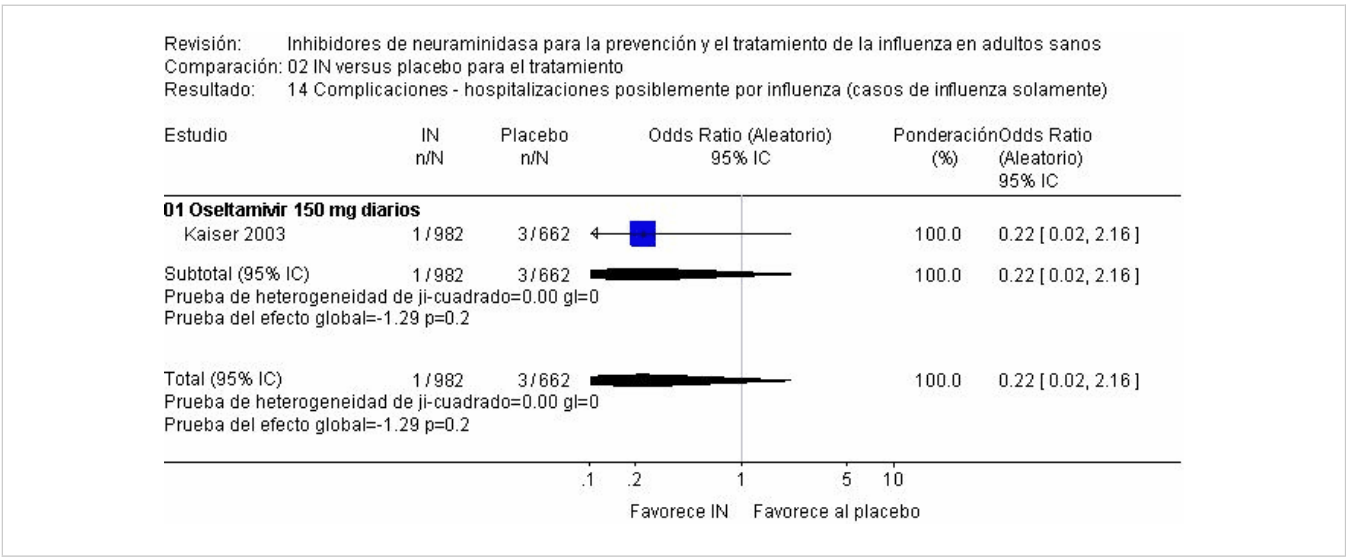
02.12 Complications - all hospitalisations (influenza cases only)



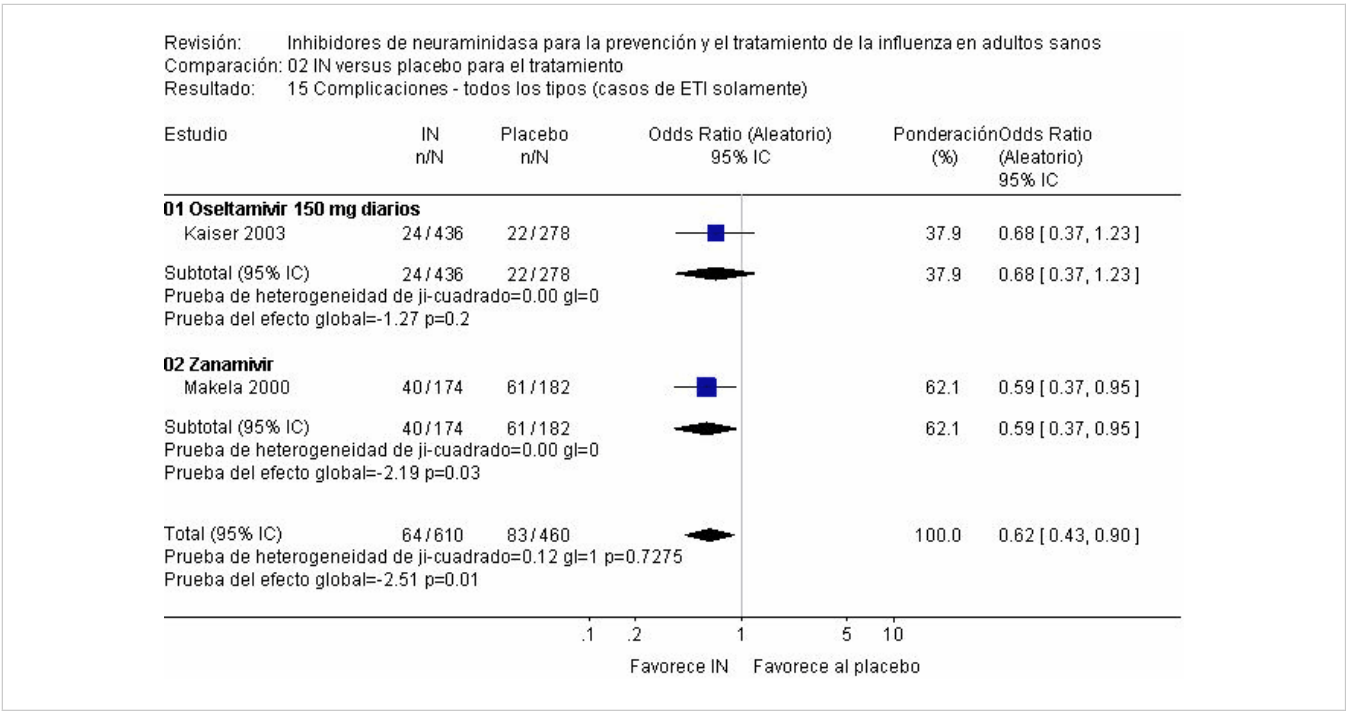
02.13 Complications - hospitalisations possibly caused by influenza (ILI cases only)



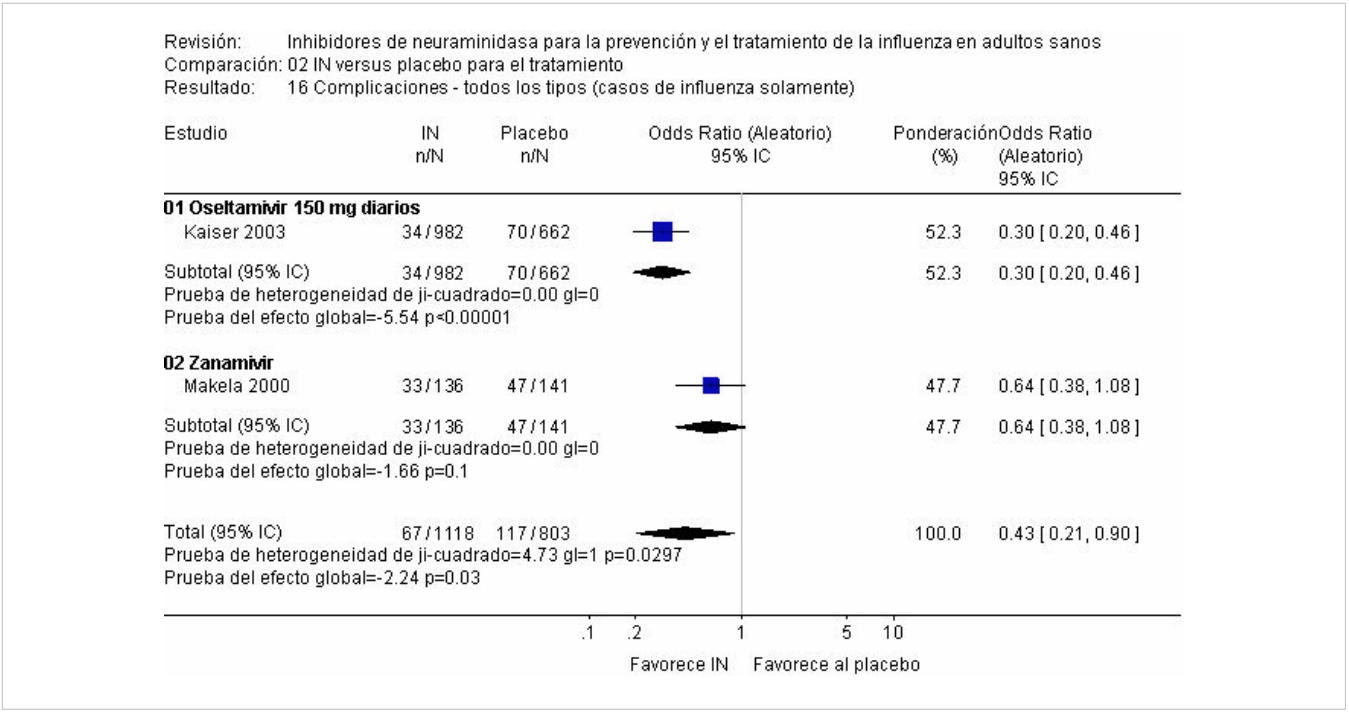
02.14 Complications - hospitalisations possibly caused by influenza (influenza cases only)



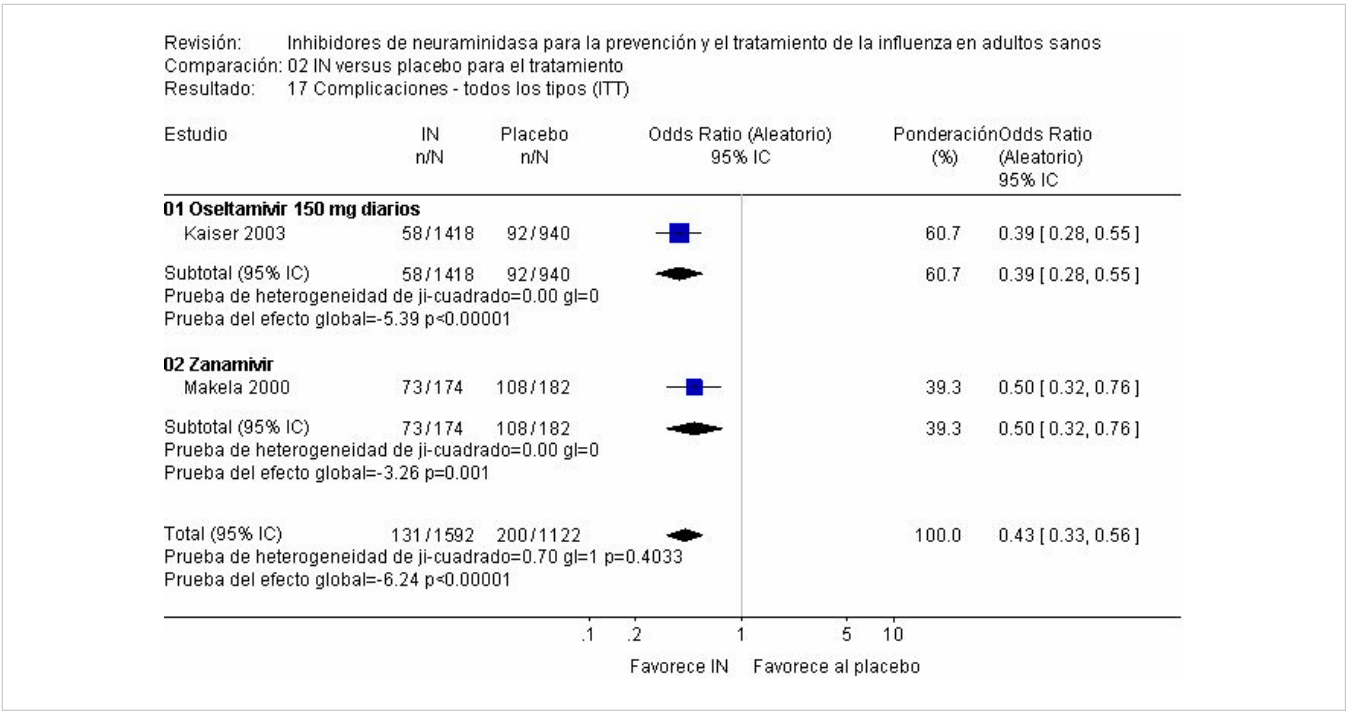
02.15 Complications - all types (ILI cases only)



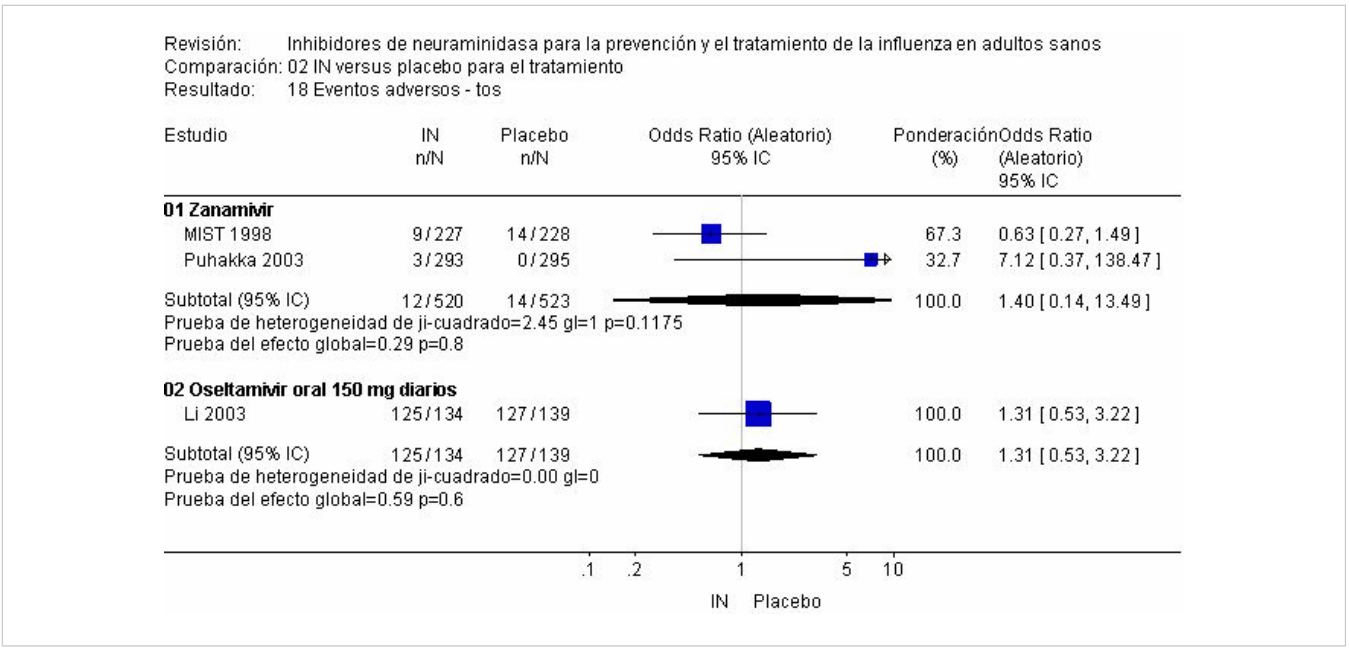
02.16 Complications - all types (influenza cases only)



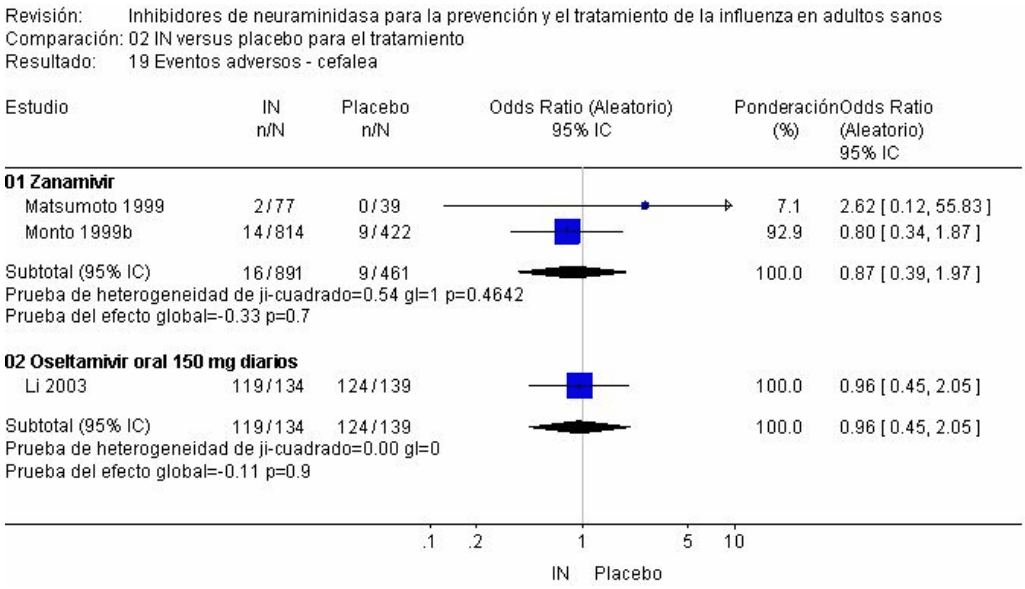
02.17 Complications - all types (ITT)



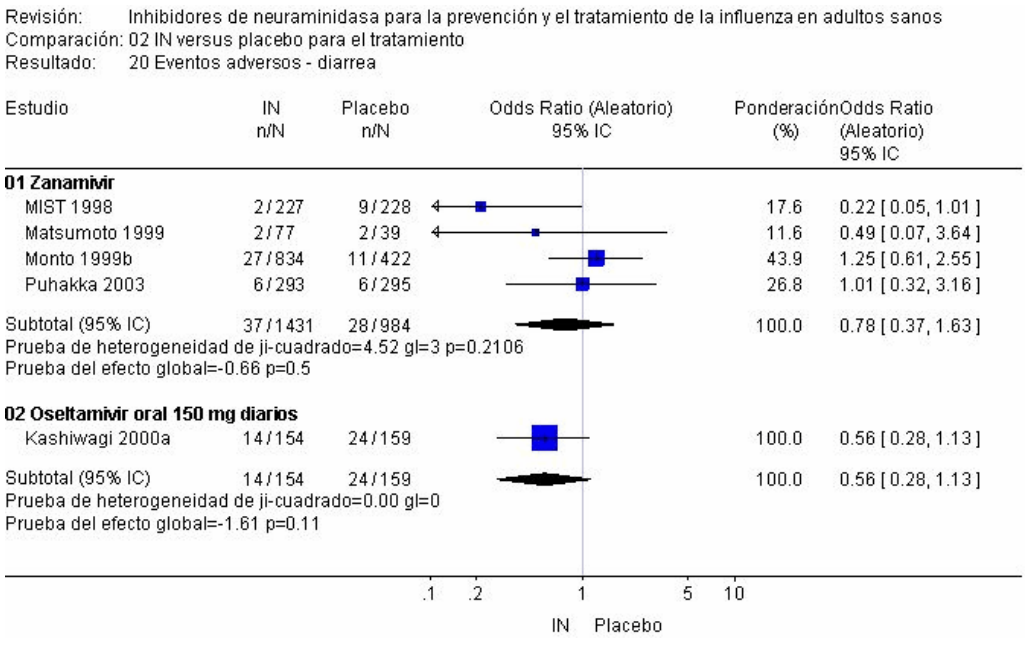
02.18 Adverse events - cough



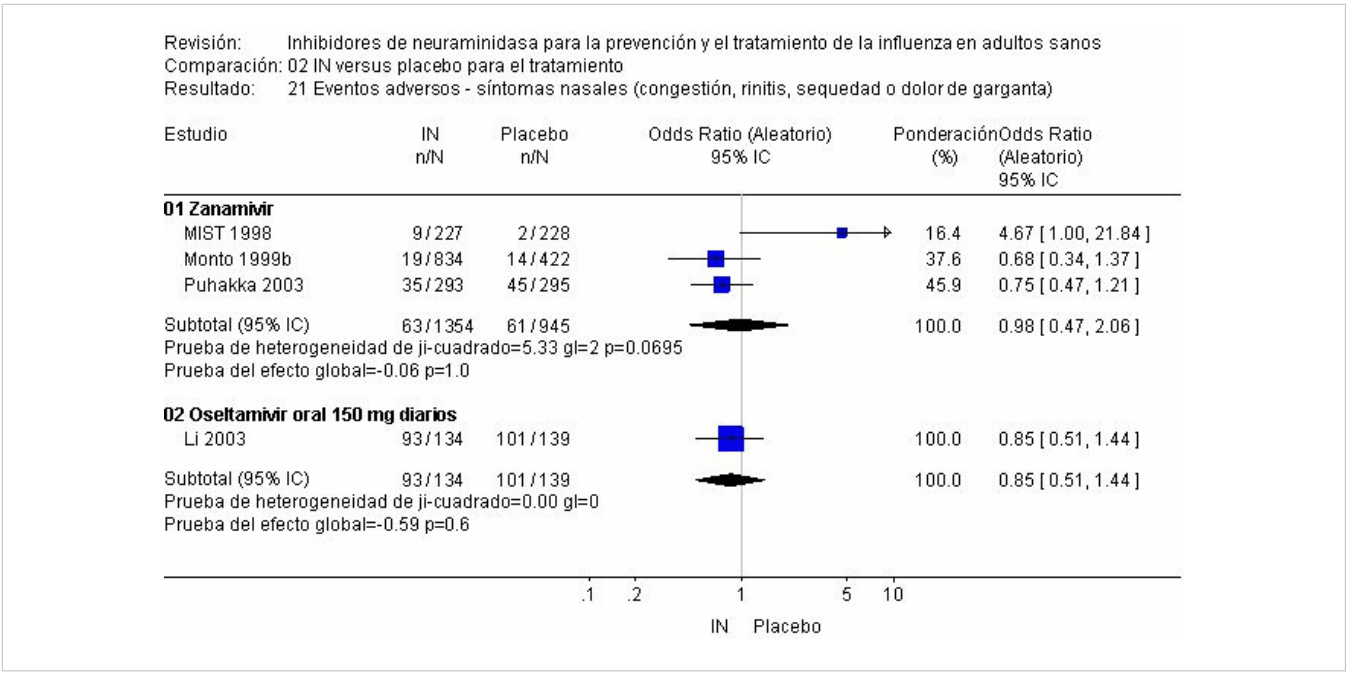
02.19 Adverse events - headache



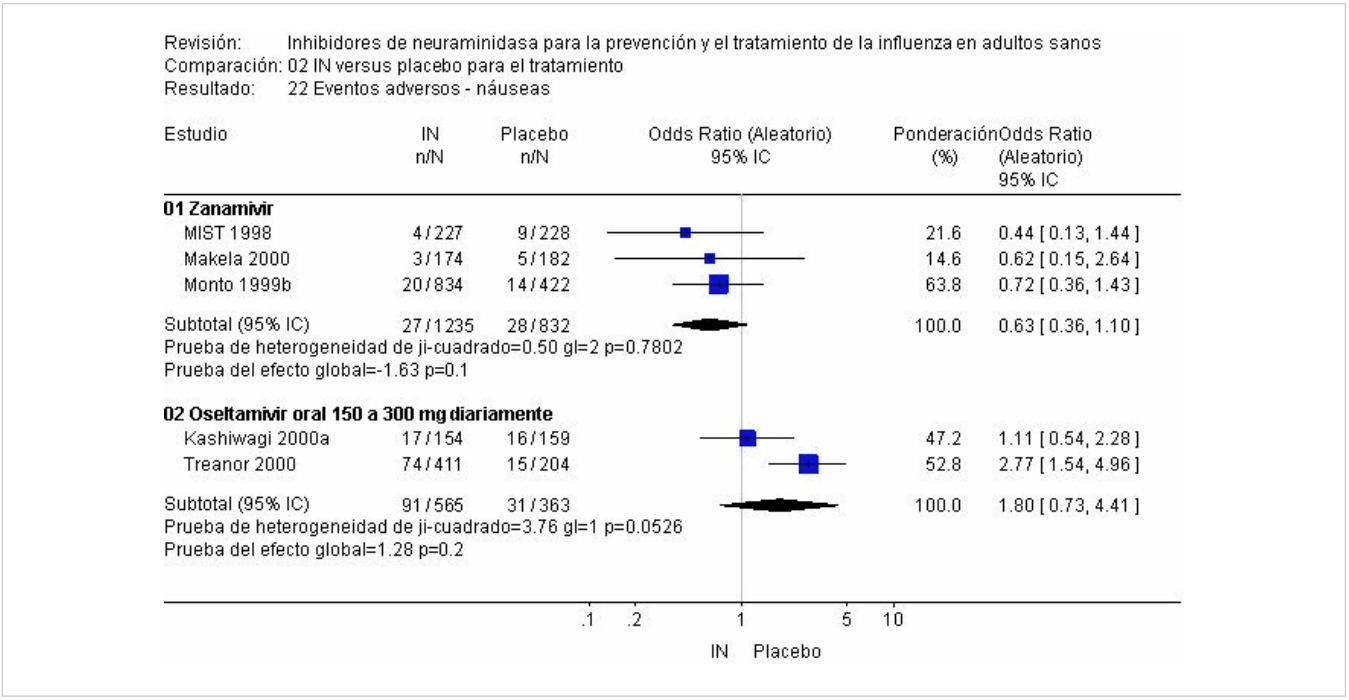
02.20 Adverse events - diarrhoea



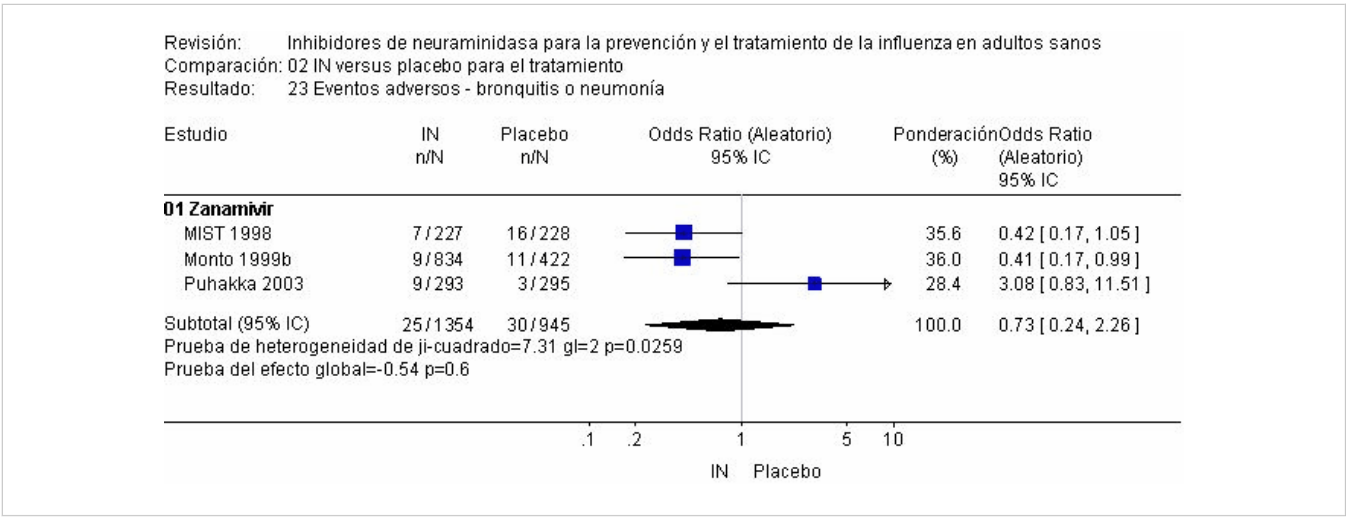
02.21 Adverse events - nasal symptoms (congestion, rhinits, dry or sore throat)



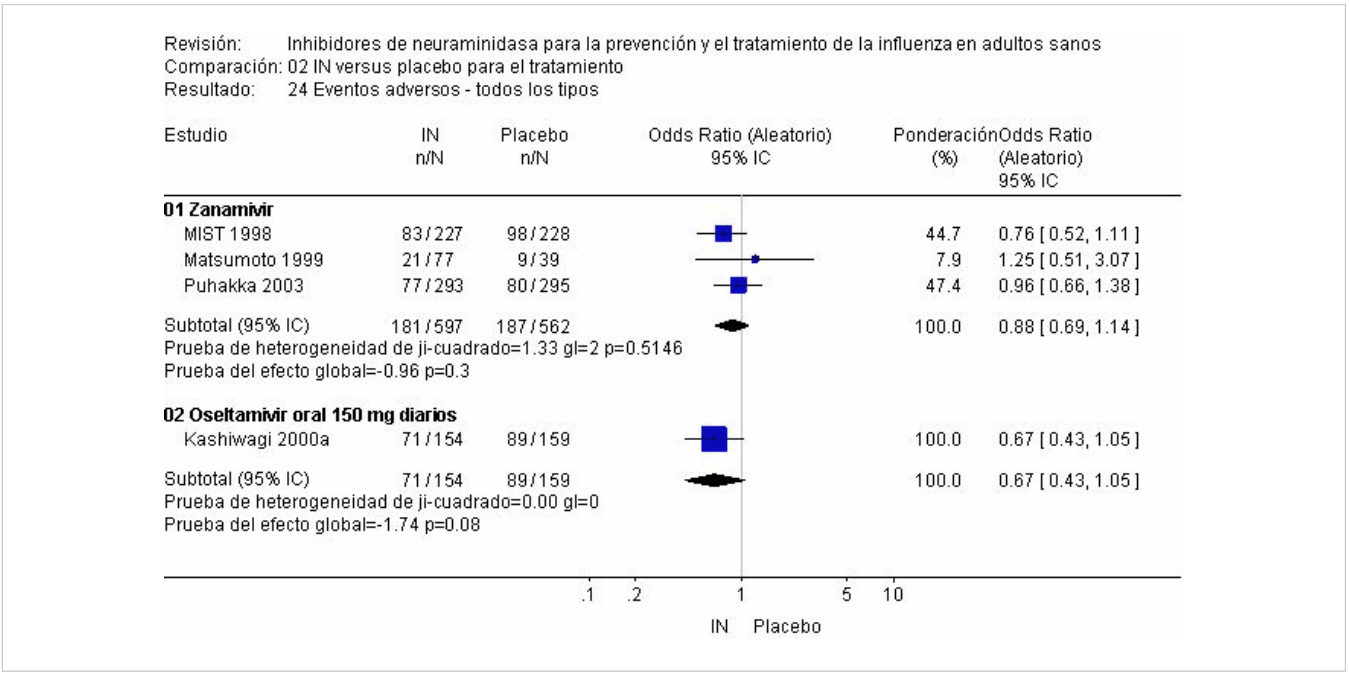
02.22 Adverse events - nausea



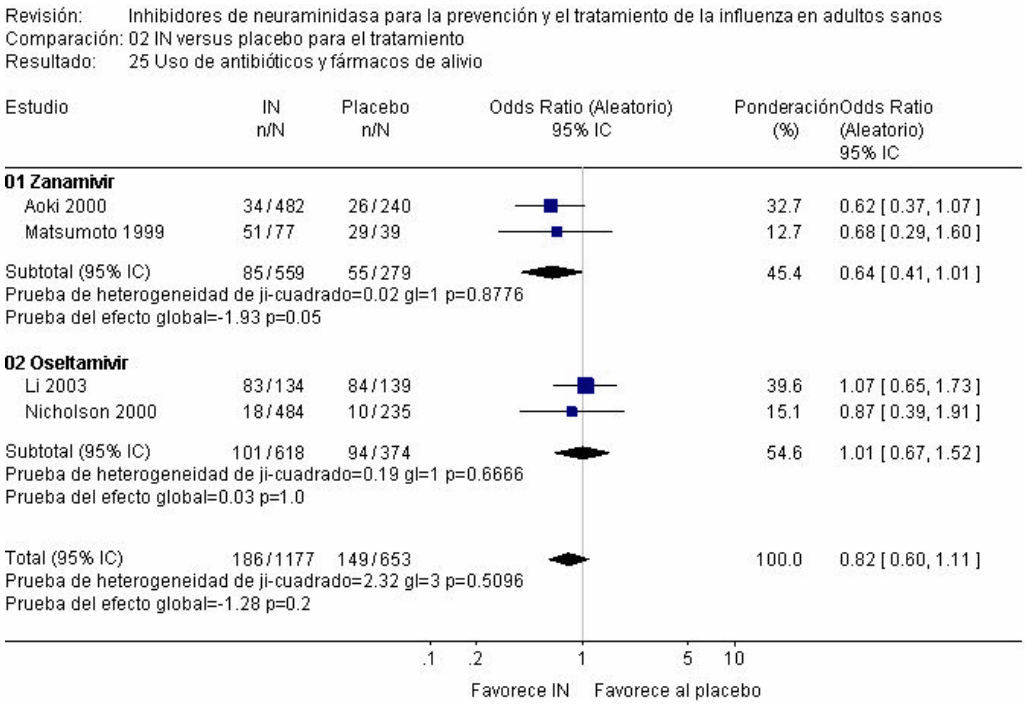
02.23 Adverse events - bronchitis or pneumonia



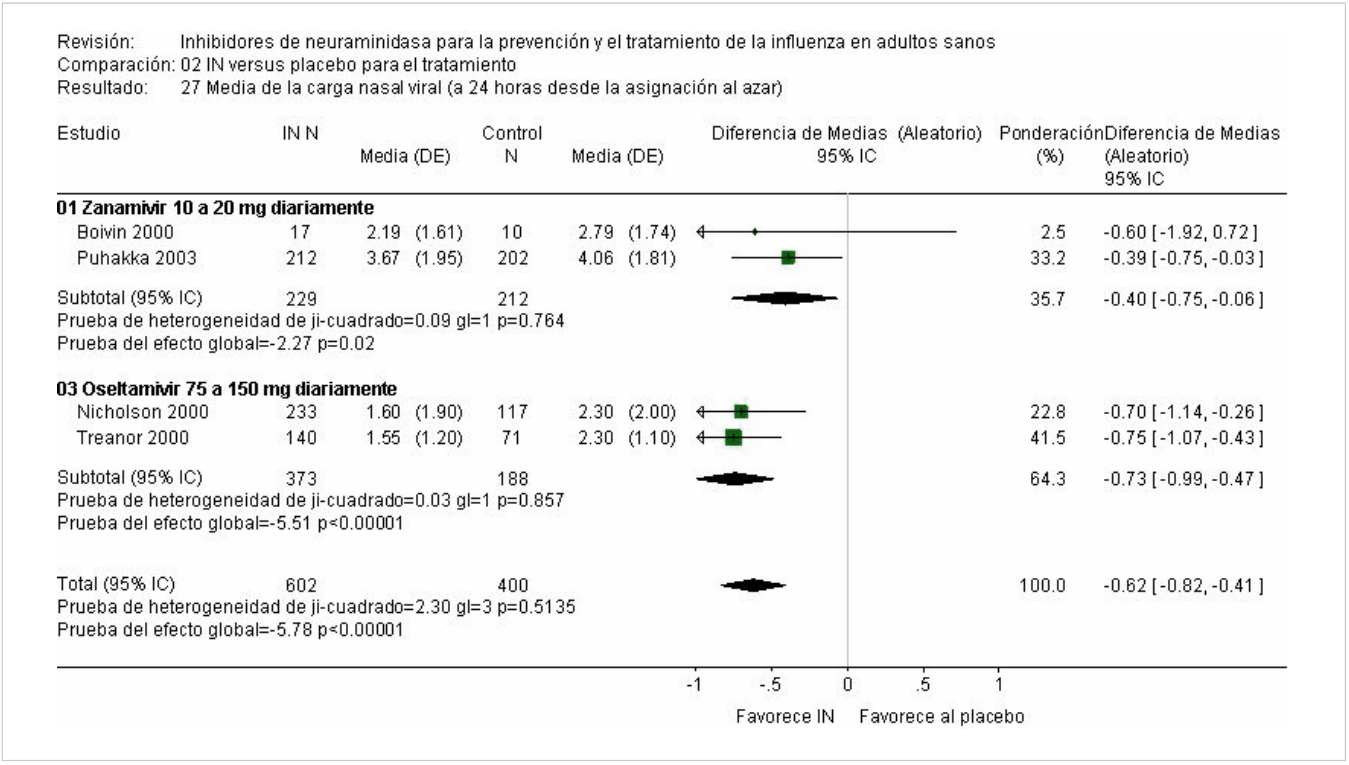
02.24 Adverse events - all types



02.25 Use of relief medications and antibiotics



02.27 Mean nasal viral titres (at 24 hours since randomisation)



02.28 Mean nasal viral titres (at 48 hours since randomisation)

Revisión: Inhibidores de neuraminidasa para la prevención y el tratamiento de la influenza en adultos sanos
Comparación: 02 IN versus placebo para el tratamiento
Resultado: 28 Media de la carga nasal viral (a 48 horas desde la asignación al azar)