Efficacy and side effects of neuraminidase inhibitors for influenza: who should be treated and who not?

Evidence from randomised controlled trials

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Influenza

- Every year, in the world, seasonal influenza responsible for
  - 3 to 5 million severe cases
  - 250 000 to 500 000 deaths

- In France, each year
  - Mean duration of epidemic: 10 weeks
  - November to March:
    - Responsible for 700 000 to 4.8 M consultations for ILI
    - ≈ 1 to 8% of the total population
  - Around 3 work days lost per individual consulting for ILI

World Health Organization. Influenza (Seasonal). Fact Sheet n°211. Genève: The institute; 2014; Available from: http://www.who.int/mediacentre/factsheets/fs211/en/index.html.

Influenza

- ILI corresponds Non specific respiratory symptoms occurring during the flu virus circulation

- ILI definitions differ according to countries, organizations …
  - **Centers for Disease Control and Prevention (CDC)**
    - fever (≥37.8°C, ≥100°F)
    - AND cough, and /or sore throat,
  - **European CDC**
    - At least one systemic symptom : fever, dizziness, headache, myalgia

    and
    - At least one respiratory symptom : cough, sore throat or dyspnea

Different viruses responsible for influenza-like illness according to the calendar week in Sept 2014- April 2015

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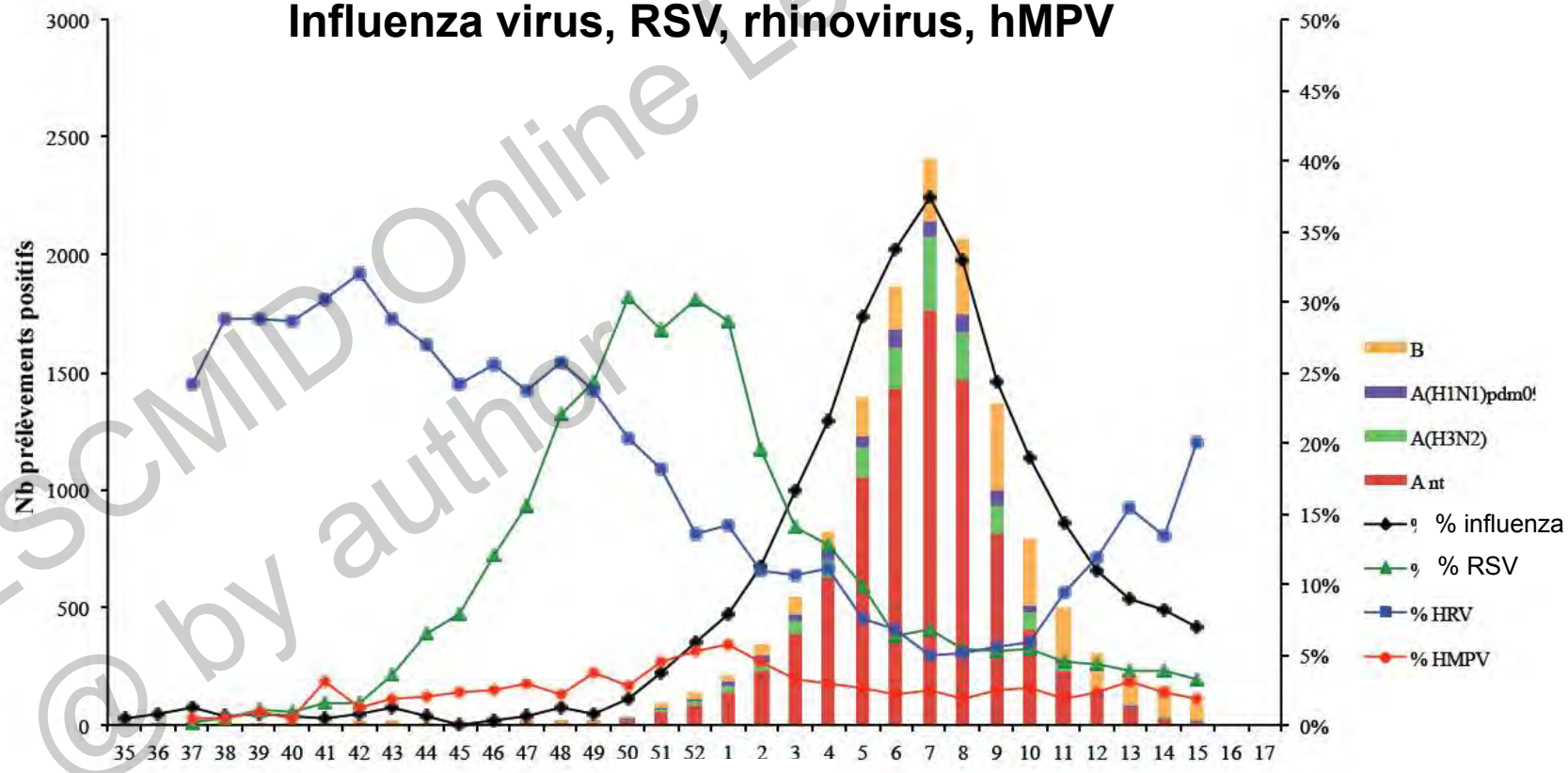
ces Civils de Lyon

RENAL, 2014-2015 season

Emergency room or hospitalized patients

Influenza virus, RSV, rhinovirus, hMPV



Influenza

- Vaccination is the main preventive measure
- Antiviral drugs are available for the treatment of infections
  - in non-vaccinated individuals
  - in case of reduced vaccine effectiveness due to
    - weak vaccine immunogenicity (elderly population)
    - circulating viruses antigenically different from those included in the vaccine

Anti influenza drugs

- M2 inhibitors Amantadine, rimantadine
- Neuraminidase inhibitors
  - Approved in most countries
    - Oseltamivir
    - Zanamivir
  - More limited approval
    - Laninamivir (approved in Japan……)
    - Peramivir (FDA approved in Dec 2014, approved in Japan)
- Polymerase inhibitors (favipiravir)
- Fusion inhibitors (**DAS181 ou fludase)**
- Thiazolide anti-infective nitazoxanide

Neuraminidase inhibitors

	Oseltamivir	Zanamivir	Laninamivir	Peramivir
Route of administration	Oral capsules Oral suspension	Inhalation IV infusion	Inhalation	Solutions for IV use
Dosage	75 mg BID 5 days	5 mg BID 5 days	20 mg ONE day	150 to 600mg 1 to 5 days
	Prodrog		Prodrog	
Activity Influenza A	Active	Comparable in vitro activity to O	Active	Active
Neuraminidase H275Y mutation	Confers high level resistance	NO impact		Reduced susceptibility
Influenza B	Less active in vitro	More active than Oseltamivir		

Seasonal influenza Guidelines

Table 1. Existing guidelines for the treatment and prevention of influenza

World Health Organization WHO guidelines for pharmacological management of pandemic influenza A(H1N1) 2009 and other influenza viruses http://www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceutical_mngt.pdf
US Advisory Committee on Immunization Practices (ACIP) Fiore AE, *et al.* Antiviral agents for the treatment and chemoprophylaxis of influenza. *MMWR*. 2011; 60(RR01): 1–24[4] http://www.cdc.gov/flu
UK National Institute for Health and Clinical Excellence TA168: Amantadine, oseltamivir, and zanamivir for the treatment of influenza http://egap.evidence.nhs.uk/amantadine-oseltamivir-and-zanamivir-for-the-treatment-of-influenza-ta168

US advisory committee on Immunization practices Antiviral agents for the treatment and chemoprophylaxis of influenza http:www.cdc.gov/flu

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CDC guidelines (Jan 9th 2015)

CDC Antiviral Recommendations 2014-2015 flu Season

- "CDC recommends antiviral medications for treatment of influenza"….

- **"All Hospitalized, Severely ill, and High Risk Patients with Suspected Influenza Should Be Treated with Antivirals"**

Centers for Disease Control and Prevention (USA). Seasonal Influenza (Flu) - Antiviral Medications: Summary for Clinicians. Atlanta: The Institute; 2014. http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

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CDC guidelines (Jan 9th 2015)

High risk patients: for influenza complications (in or outpatient):

- Children younger than 2 years
- Adults aged 65 years and older
- Adults younger than 65 years with comorbidities
- Women who are pregnant or postpartum (within 2 weeks after delivery)
- Persons younger than 19 years who are receiving long-term aspirin therapy;
- Persons who are morbidly obese
- Residents of nursing homes and other chronic-care facilities.

Centers for Disease Control and Prevention (USA). Seasonal Influenza (Flu) - Antiviral Medications: Summary for Clinicians. Atlanta: The Institute; 2014. http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

What supports CDC statement ?

- **CDC statement :**

  "Neuraminidase inhibitors … has been shown to have clinical and public health benefit, **as evidenced from randomized controlled trials, meta-analyses of randomized controlled trials,"** ……

NI Randomized clinical trials

Different

- **Setting of the trial**
  - Outpatients or hospitalized patients
- **Background characteristics** of included populations
  - Age : children, adults, elderly
  - Healthy individuals or patients with comorbidities
- **Included-ILI population**
  - Only influenza Infected population (rapid diagnostic tests at inclusion)
  - All patients whether infected or not

NAI Randomized clinical trials

- **Endpoints:**
  - **Primary :** Time to alleviation of symptoms
    Rarely virological endpoint
  - **Secondary :**
    Complications:
    - otitis
    - sinusitis
    - pneumonia
    - antibiotic use
    - hospitalisation
    - death

    Viral load; viral shedding

NB: pneumoniae generally not radiologically confirmed

Effectiveness of Oseltamivir

Effectiveness of Oseltamivir

- The interest of oseltamivir has been the subject of much debate
- Five meta-analyses have been published to date

Oseltamivir RCT meta-analyses

	Authors	Journal Year	Number of analysed RCT	Published / Unpublished	Number of included patients Oselta/PCB	Analysis
Skewed data	J Bursch	Lancet ID 2009	4	3/1	1410 700/710	Agregated metanalysis
Skewed data	T Jefferson	BMJ 2009	3	3/0	1797 1118/679	Agregated metanalysis
More valid data	MH Ebel	Family practice 2013	11	3/8	4327 2633/1694	Agregated metanalysis
More valid data	T Jefferson	BMJ 2014	8	3/5	3954 pts 2208/1746	Agregated metanalysis
More valid data	J Dobson	Lancet 2015	9	3/6	4328 pts 2360/1904	Individual patient data

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Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials

Joanna Dobson, Richard J Whitley, Stuart Pocock, Arnold S Monto

RCT performed between 1997 and 2001
Adults with ILI onset of symptoms less than 36h
Three ITT analyses

- ITT analysis of pts who received at least on dose (total population)
- ITT analysis of influenza-infected pts
- ITT non-influenza-infected population

Primary outcome

- Time to alleviation of symptoms

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Time to alleviation of Symptoms

Intention-to-treat				
Oseltamivir N	Placebo N	Estimates of median time and their difference (h)		
		Oseltamivir	Placebo	Difference
2360	1904	99·4	117·2	−17·8 (-27·1 to −9·3)

*Medians and differences in medians for individual trials are from Kaplan-Meier estimates. The overall estimated medians, differences (and 95% CI) are from the accelerated failure time model adjusted for trial.

Table 1: Estimates of median time to alleviation of all symptoms by treatment group in the intention-to-treat infected and intention-to-treat populations, both overall and for each trial

4264 pts

Total population

ITT total population:
17.8 hours shorter in O
Time ratio 0.85 (0.80-0.90)
15% shorter time
P<0.0001

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Time to alleviation of Symptoms

Intention-to-treat				
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4264 pts

Total population

ITT total population:
17.8 hours shorter in O
Time ratio 0.85 (0.80-0.90)
15% shorter time
P<0.0001

33%

Non- Infected population

ITT non-infected pts:
Time ratio 0.99 (0.88-1.12)
No reduction

Only participant identified as influenza-infected benefited from oseltamivir

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Time to alleviation of Symptoms

	Intention-to-treat infected					Intention-to-treat				
	Oseltamivir N	Placebo N	Estimates of median time and their difference (h)			Oseltamivir N	Placebo N	Estimates of median time and their difference (h)		
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Overall*	1565	1295	97·5	122·7	−25·2 (−36·2 to −16·0)	2360	1904	99·4	117·2	−17·8 (−27·1 to −9·3)

4 days 5 days

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Table 1: Estimates of median time to alleviation of all symptoms by treatment group in the intention-to-treat infected and intention-to-treat populations, both overall and for each trial

2860 pts — 66% (2/3) — 4264 pts

Infected population

ITT infected-patients:
Oseltamivir : 4 d
PCB: 5 days
25.2 hours shorter
Time ratio 0.79 (0.74-0.85)
21% shorter time
P<0.0001

Total population

ITT total population:
17.8 hours shorter in O
Time ratio 0.85 (0.80-0.90)
15% shorter time
P<0.0001

33%

Non- Infected population

ITT non-infected pts:
Time ratio 0.99 (0.88-1.12)
No reduction

Only participant identified as influenza-infected benefited from oseltamivir

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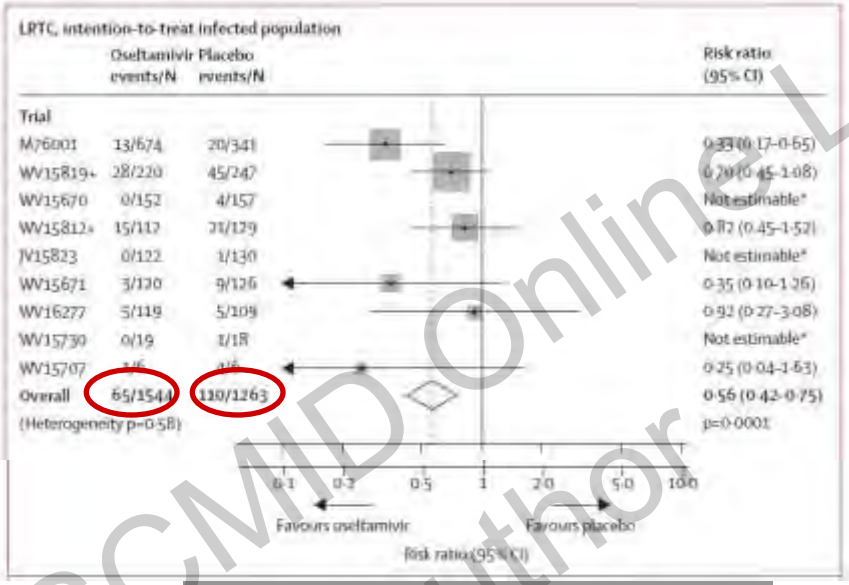
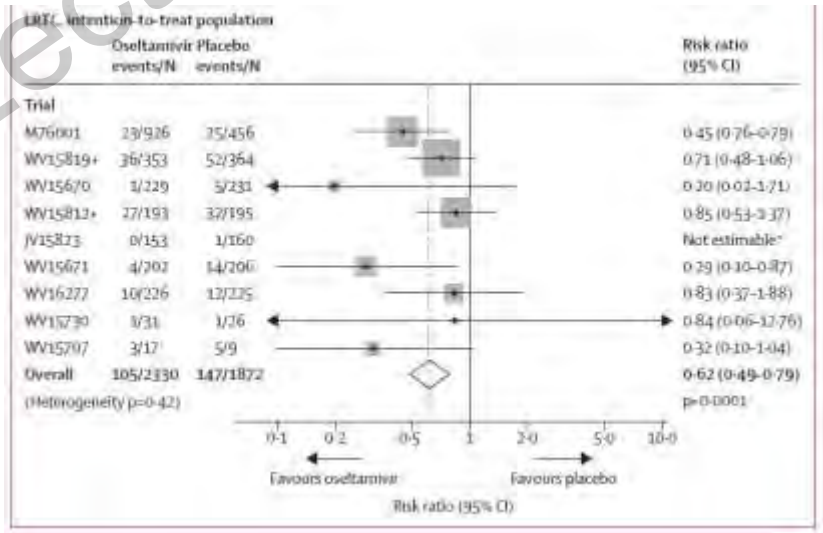
Oseltamivir vs PCB

Lower respiratory tract infection





Infected population

LRTI

Oseltamivir: 65/1544 **4.5%**

PCB: 110/1263 **8.7%**

RR 0.56 (CI95% 0.42-0.75)

Pneumonia

Oseltamivir **0.5% vs** PCB **1.6%;**

RR:0.40 (0.19-0.84, p=0.015)

Limits: not-predefined primary outcome

no radiological validation

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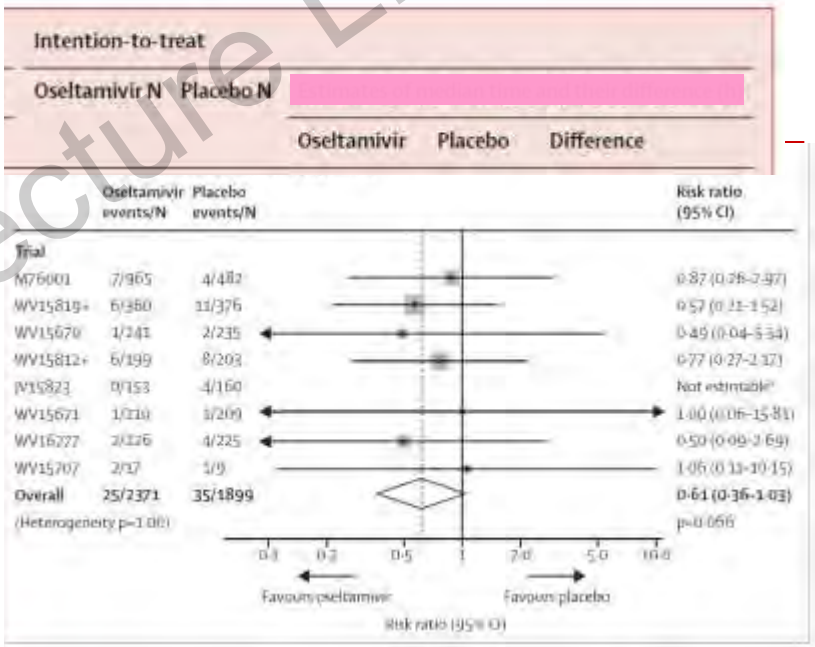
Oseltamivir vs PCB

Hospital admission



Total population

NON-significant reduction

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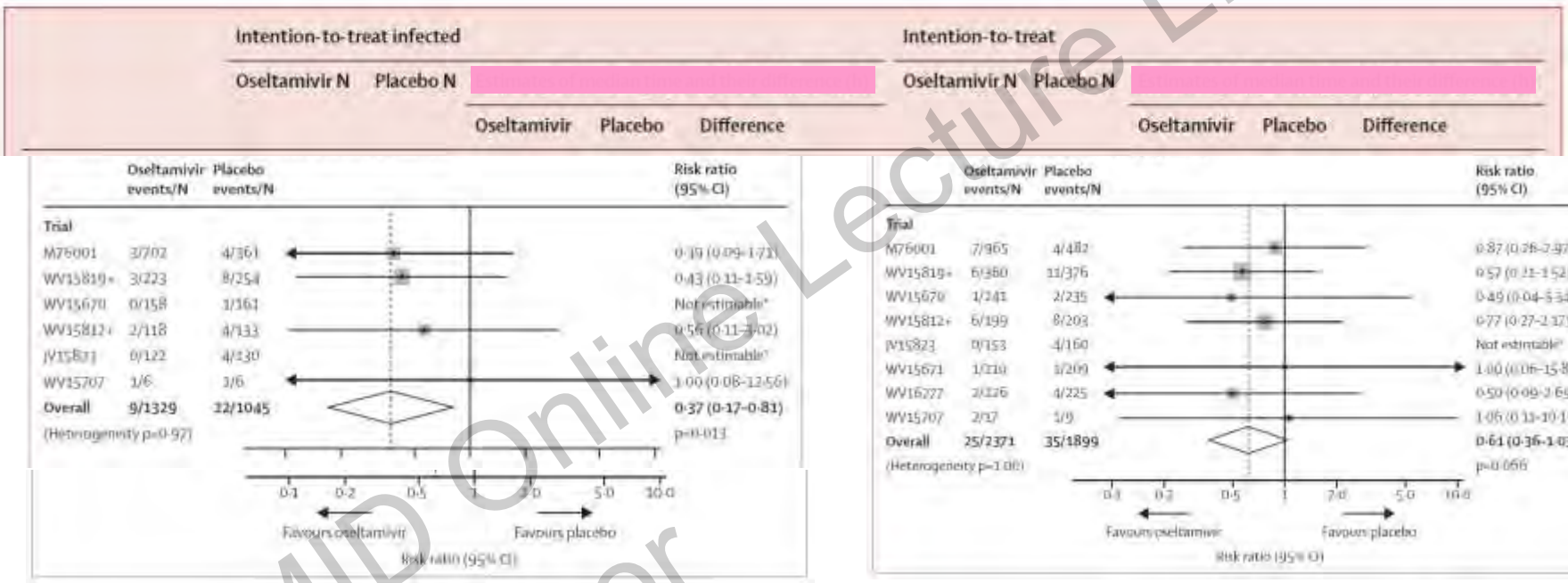
Oseltamivir vs PCB

Hospital admission



Infected population

(9/1329) 0.6% vs (22/1045) 1.7%

RR 0.37 (CI 95% 0.17- 0.81)

Total population

NON-significant reduction

An estimated 63% risk reduction of the number of hospitalized patients in oseltamivir receiving patients

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Metanalysis Lancet 2015

			Dobson Oseltamivir vs PCB	
Oseltamivir effect			**Infected population**	**Total population**
Time to symptom alleviation			**25.2 h shorter 21% reduction (p<0.05)**	**17.8h shorter (p<0.05)**
Lower respiratory infection			**4.5 vs 8.7% 44% risk reduction (p<0.05)**	**38% risk reduction (p<0.05)**
Pneumoniae			**0.5 vs 1.6% 60% risk reduction (p<0.05)**	**66% risk reduction (p<0.05)**
Hospital admission			**0.6% vs 1.7% 63% risk reduction (p<0.05)**	**NON significant**

Metanalysis BMJ 2014 vs Lancet 2015

Oseltamivir effect	BMJ Jefferson Oseltamivir vs PCB		THE LANCET Dobson Oseltamivir vs PCB	
	Infected population	Total population	Infected population	Total population
Time to symptom alleviation	Not analyzed	16.7h shorter (p<0.05)		17.8h shorter (p<0.05)
Lower respiratory infection		NA		38% risk reduction (p<0.05)
Pneumoniae		1 vs 2.2% 45% risk reduction (p<0.05)		66% risk reduction (p<0.05)
Hospital admission		1.4 vs 1.8% 8% risk reduction NON significant		NON significant

HARM

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Oseltamivir vs PCB

Adult / ITT population

Adverse events

	Number of events		Overall risk ratio (95% CI)	p value	Placebo group risk (%)*	Oseltamivir group risk (%)†	Risk difference (95% CI)
	Oseltamivir (n=2401)	Placebo (n=1917)					
All adverse events	1033	819	0·97 (0·91 to 1·04)	0·41	42·7	41·5	−1·2% (−4·0 to 1·8)
Serious adverse events	21	22	0·79 (0·43 to 1·47)	0·46	1·1	0·9	−0·2% (−0·7 to 0·5)
Gastrointestinal disorders	574	370	1·21 (1·07 to 1·36)	0·0019	19·3	23·3	4·0% (1·4 to 6·9)
Nausea	247	118	1·60 (1·29 to 1·99)	<0·0001	6·2	9·9	3·7% (1·8 to 6·1)
Vomiting	201	63	2·43 (1·83 to 3·23)	<0·0001	3·3	8·0	4·7% (2·7 to 7·3)
Diarrhoea	147	147	0·75 (0·60 to 0·95)	0·016	7·7	5·8	−1·9% (−3·1 to −0·4)
Neurological disorders	124	93	1·00 (0·76 to 1·30)	0·97	4·9	4·8	−0·0% (−1·2 to 1·5)
Psychiatric disorders	11	13	0·62 (0·26 to 1·45)	0·27	0·7	0·4	−0·3% (−0·5 to 0·3)

Significant increase of nausea (9.9% vs 6.2%), vomiting (8.0% vs 3.3%)

Less diarrhea (5.8% vs 7.7%)

No evidence of treatment difference for neurological or psychiatric disorders

CDC statement

- « All high-risk patients (in or outpatient) with **suspected** influenza should be treated **as soon as possible** … »

As soon as possible

Early treatment within 6 hours is associated with the greatest reduction in the duration of symptoms

FY Aoki et al

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Time to alleviation of symptoms Sub group analyses

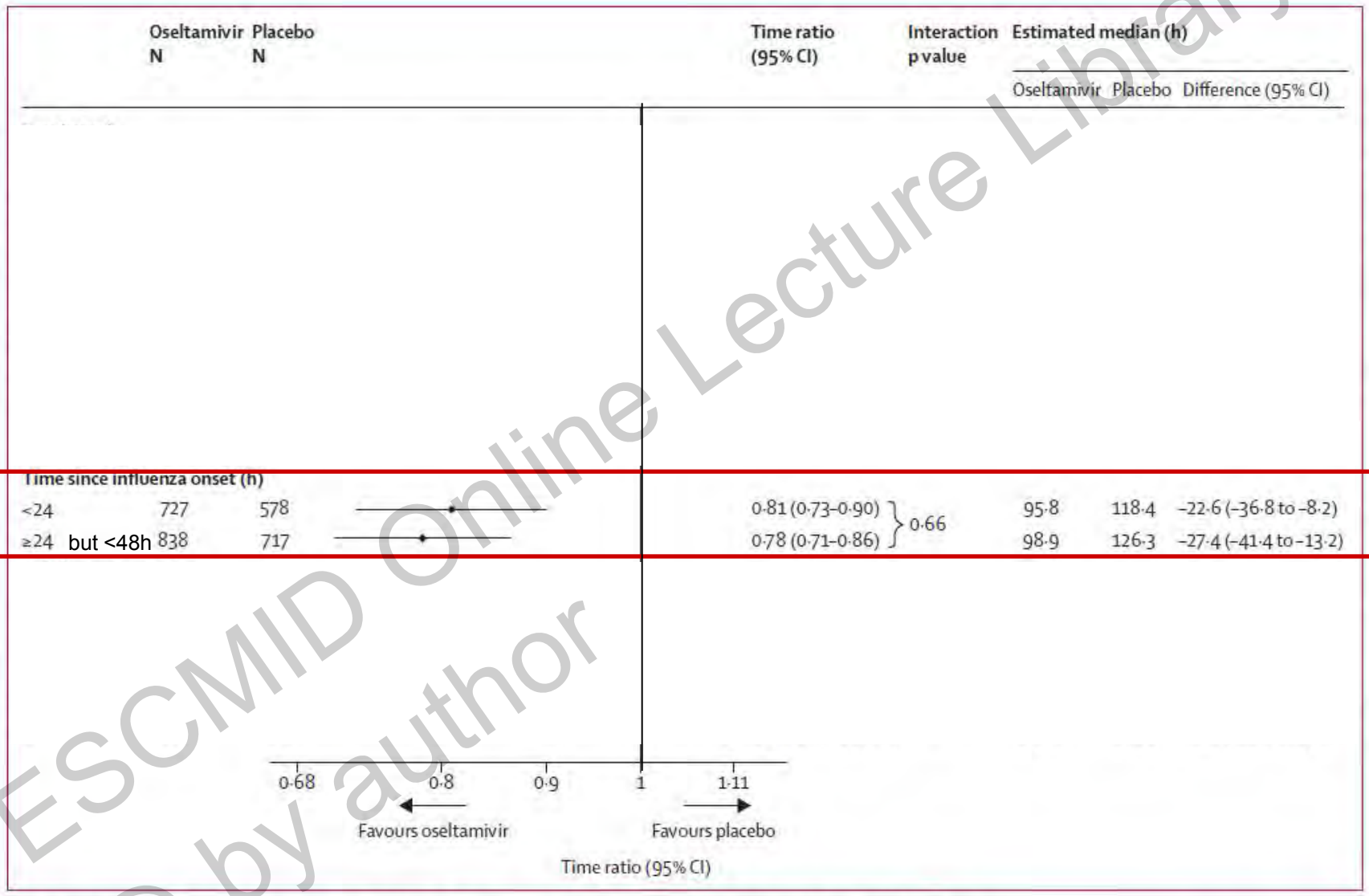
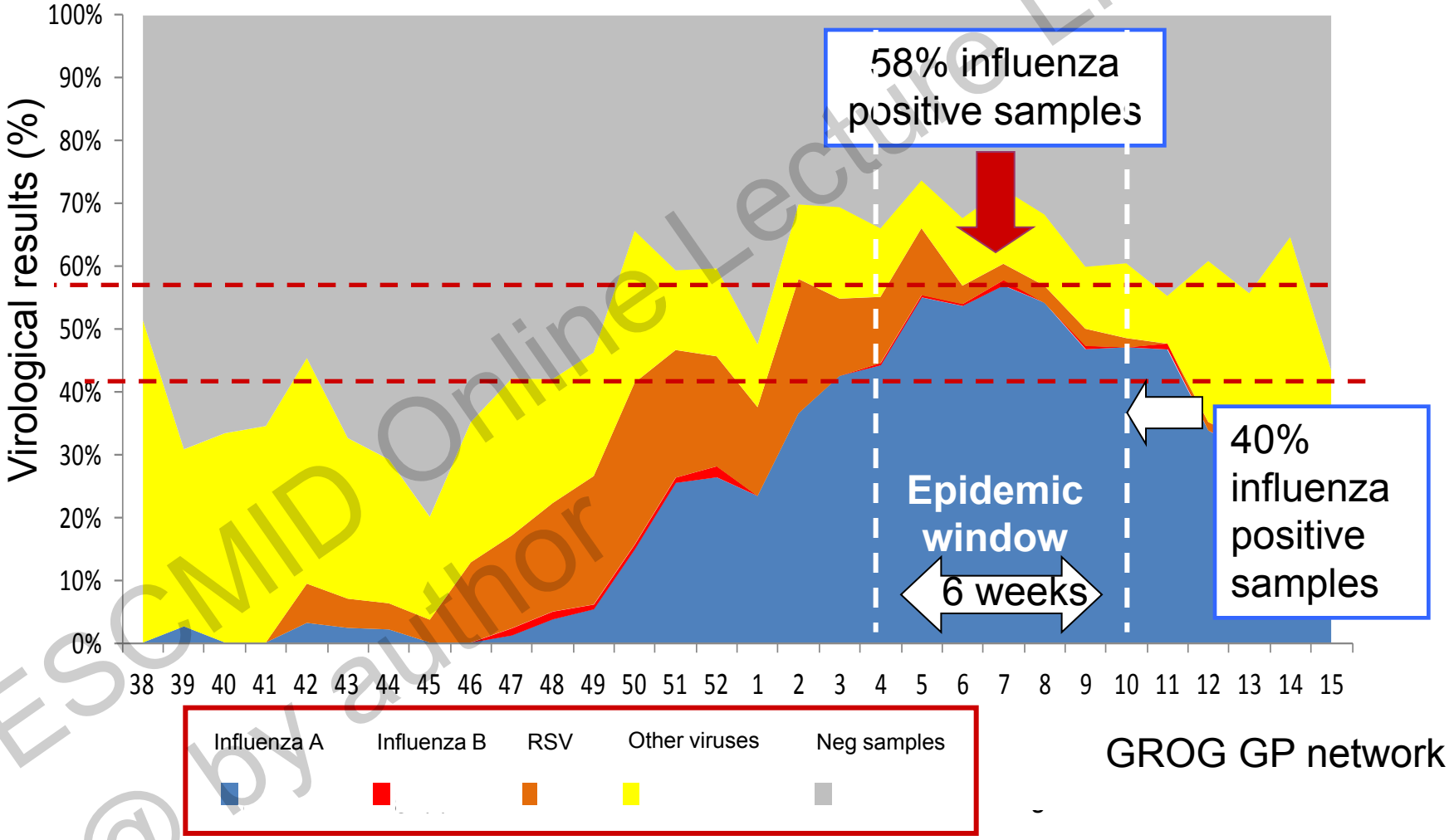


Figure 3: **Subgroup analyses for time to alleviation of all symptoms in the intention-to-treat infected population**
COAD=chronic obstructive airways disease. Estimated median (h)=estimated median time to alleviation of all symptoms from accelerated failure time model adjusted for trial. Diff (95% CI)=the difference in the estimated medians with bootstrap 95% CI.

CDC

- « All high-risk patients (in or outpatient) with **suspected** influenza should be treated as soon as possible, …. **without waiting for virological confirmation of influenza »**

France : Respiratory viruses during 2013-2014 winter-GP



ILI : sudden onset of fever >39°C and myalgia and respiratory symptoms

CDC

- All high-risk patients (in or outpatient) with suspected influenza should be treated as soon as possible, without waiting for the confirmatory influenza testing.
- « While antiviral drugs work best when given early, therapeutic benefit has been observed even when treatment is initiated later »

Oseltamivir vs PCB
Children, onset of ILI ≤ 5 days

- **1190 people**, median age 5 years (IQR 2-9),
- TDR positive (21% of the screened population)
- Oseltamivir **started within 5 d** of symptom onset
- Onset of disease ≤ 5 days
  - 67% < 48 hours
  - 33% > 48 hours

- Median duration of symptoms **shorter** in oseltamivir group (3 days versus 4 days)
- Reduction of viral shedding at days 2, 4 and 7

Fry A Lancet ID 2014

Oseltamivir vs PCB
Children, onset of ILI ≤ 5 days

- **Pts included on day 3:**

Significant reduction of

- symptom duration (1 day)
- viral shedding at days 2, and 4

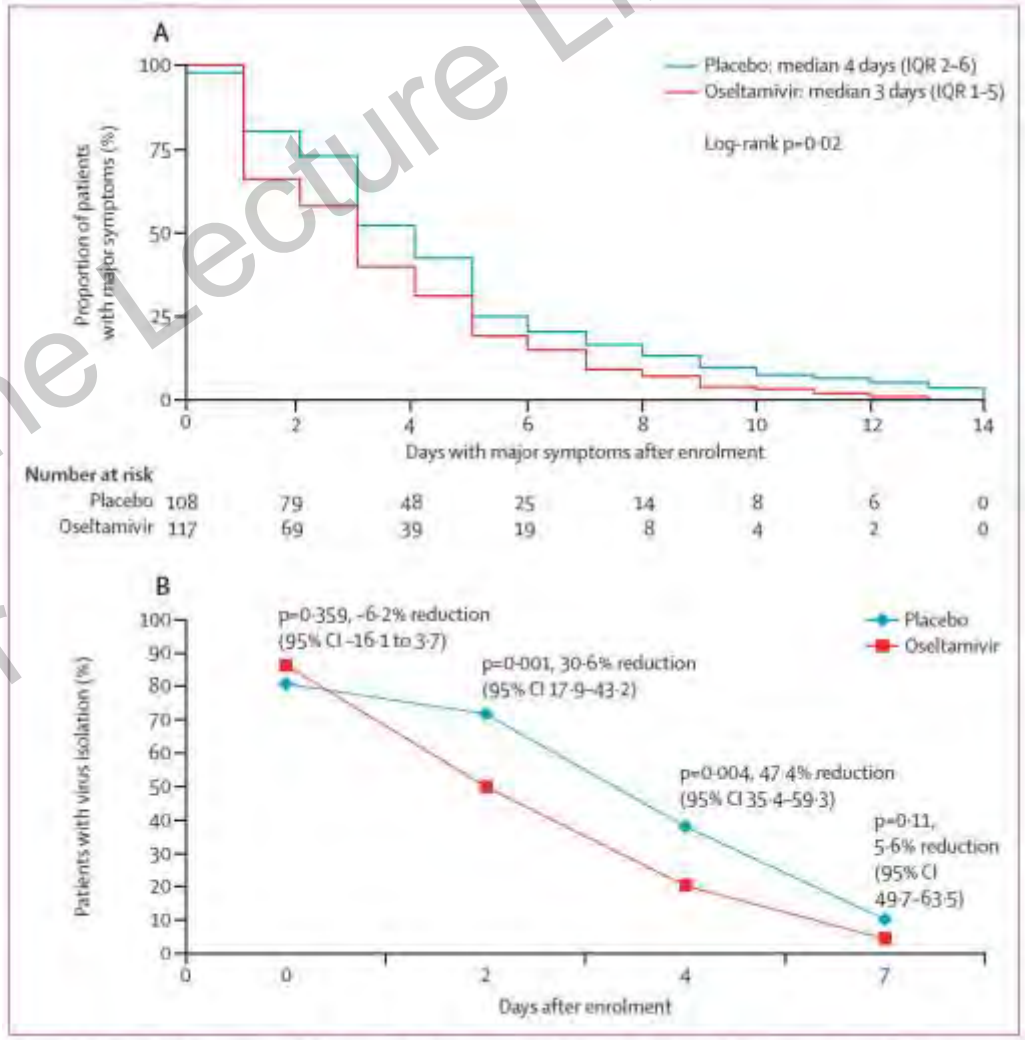


Figure 3: Kaplan-Meier curves of duration of (A) major symptoms (n=225) and (B) comparison of virus isolation in participants enrolled on day 3 after illness onset (n=216)

Fry A Lancet ID 2014

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CDC guidelines (Jan 9th 2015)

CDC Antiviral Recommendations 2014-2015 flu Season

- "CDC recommends antiviral medications for treatment of influenza"….

WHO should be treated ?

- **"All Hospitalized, Severely ill, and High Risk Patients with Suspected Influenza Should Be Treated with Antivirals"**

Centers for Disease Control and Prevention (USA). Seasonal Influenza (Flu) - Antiviral Medications: Summary for Clinicians. Atlanta: The Institute; 2014. http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

What population was included in Randomized Clinical trials ?

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Included population in the Nine Oseltamivir RCT

Trial number, timing and location	Key inclusion criteria
M76001[8] 1998-1999 USA	1) Aged ≥13 to 80 yrs 2) Fever ≥100°F, ≥ 1 respiratory symptom and ≥1 constitutional symptom of influenza, and within 36 hours of onset of influenza symptoms.
WV15819/WV15876/WV15978[9] 1999-2000 Europe, Israel, USA, Canada, South Africa, New Zealand, Australia	1) Aged ≥65 years. 2) Fever ≥37·5°C, ≥ 1 respiratory symptom and ≥1 constitutional symptom of influenza, and within 36 hours of onset of influenza symptoms.
WV15670[10] 1997-1998 Europe, Canada, China	1) Aged ≥18 and ≤ 65 yrs. 2) Fever ≥38·0°C, ≥ 1 respiratory symptom and ≥1 constitutional symptom of influenza, and within 36 hours of onset of influenza symptoms.
WV15812/WV15872[9] 1999 Australia, New Zealand, South Africa, Europe, USA, Canada	1) Aged ≥13 years. 2) Fever ≥38°C (100° F) if <65yrs / fever ≥37·5°C (99·5°F) if ≥65yrs, ≥ 1 respiratory symptom and ≥1 constitutional symptom of influenza, and within 36 hours of onset of influenza symptoms. 3) Chronic cardiac and/or respiratory disease.
JV15823[11] 1999-2000 Japan	1) Aged >16 yrs. 2) Fever >38·0°C, >2 clinical symptoms of influenza, and within 36 hours of onset of influenza symptoms.
WV15671[12] 1997-1998 USA	1) Aged ≥18 and ≤65 years. 2) Fever ≥38·0°C, ≥ 1 respiratory symptom and ≥1 constitutional symptom of influenza, and within 36 hours of onset of influenza symptoms.
WV16277 2001 Europe	1) Aged ≥13 yrs 2) Fever ≥37·8°C, ≥ 1 respiratory symptom and ≥1 constitutional symptom of influenza, and within 36 hours of onset of influenza symptoms.
WV15730[13] 1998 Australia, South Africa	1) Aged ≥18 and ≤65 years. 2) Fever ≥38·0°C, ≥ 1 respiratory symptom and ≥1 constitutional symptom of influenza, and within 36 hours of onset of influenza symptoms.
WV15707 1998 Australia, South Africa, South America	1) Aged >65 years. 2) Fever ≥37·5 deg C, ≥ 1 respiratory symptom and ≥1 constitutional symptom of influenza, and within 36 hours of onset of influenza symptoms.

Elderly population

Chronic cardiac pulmonary diseases

Elderly population

- **No RCT included hospitalized pts**
- **Only 2 RCT were specifically devoted to the elderly population**
- **Only 1 RCT included specifically pts with chronic cardiac or pulmonary diseases**

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Time to alleviation of Symptoms

	Intention-to-treat infected					Intention-to-treat				
	Oseltamivir N	Placebo N	Estimates of median time and their difference (h)			Oseltamivir N	Placebo N	Estimates of median time and their difference (h)		
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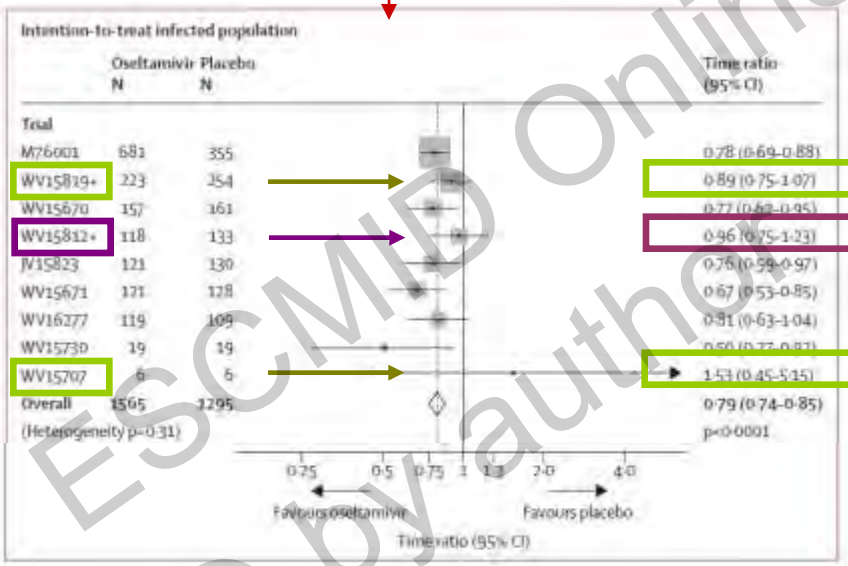
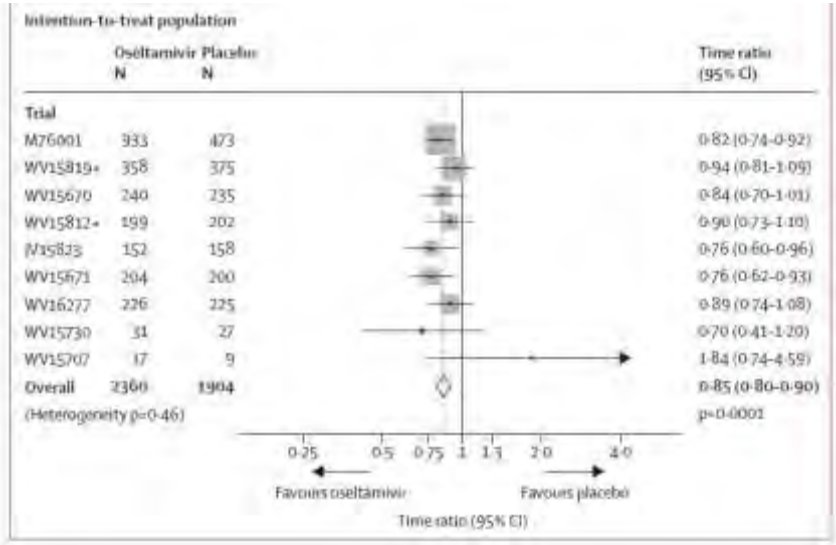
2860 pts ← **66% (2/3)** → **4264 pts**





Elderly population

Chronic cardiac pulmonary diseases

Figure 1: Fixed effect meta-analysis for time to alleviation of all symptoms
The overall time ratio is calculated from an accelerated failure time model adjusted for trial.

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Time to alleviation of symptoms:

prespecified exploratory Sub group analyses

≥ 65 years : 20%; non significant

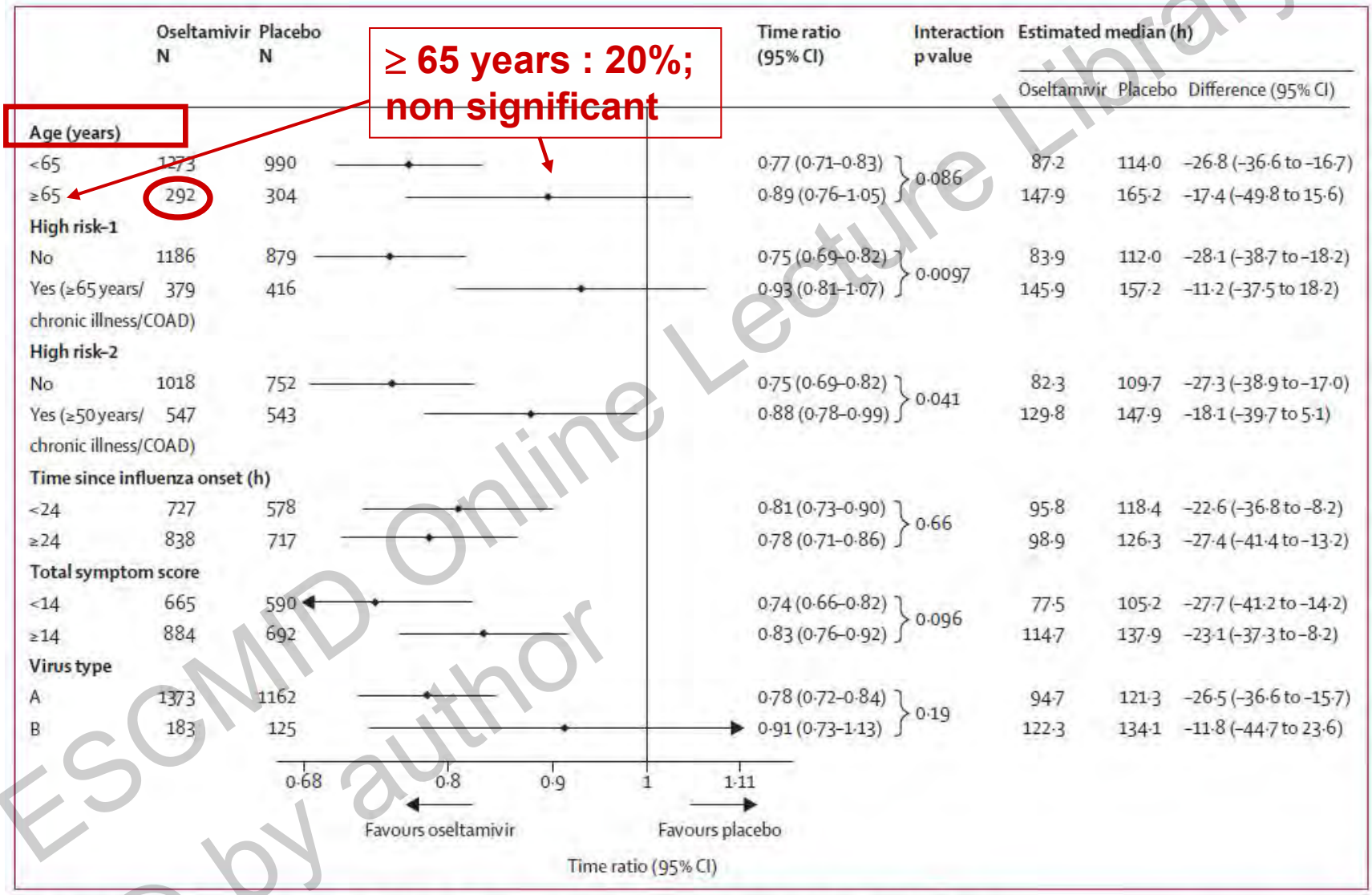

Figure 3: **Subgroup analyses for time to alleviation of all symptoms in the intention-to-treat infected population**
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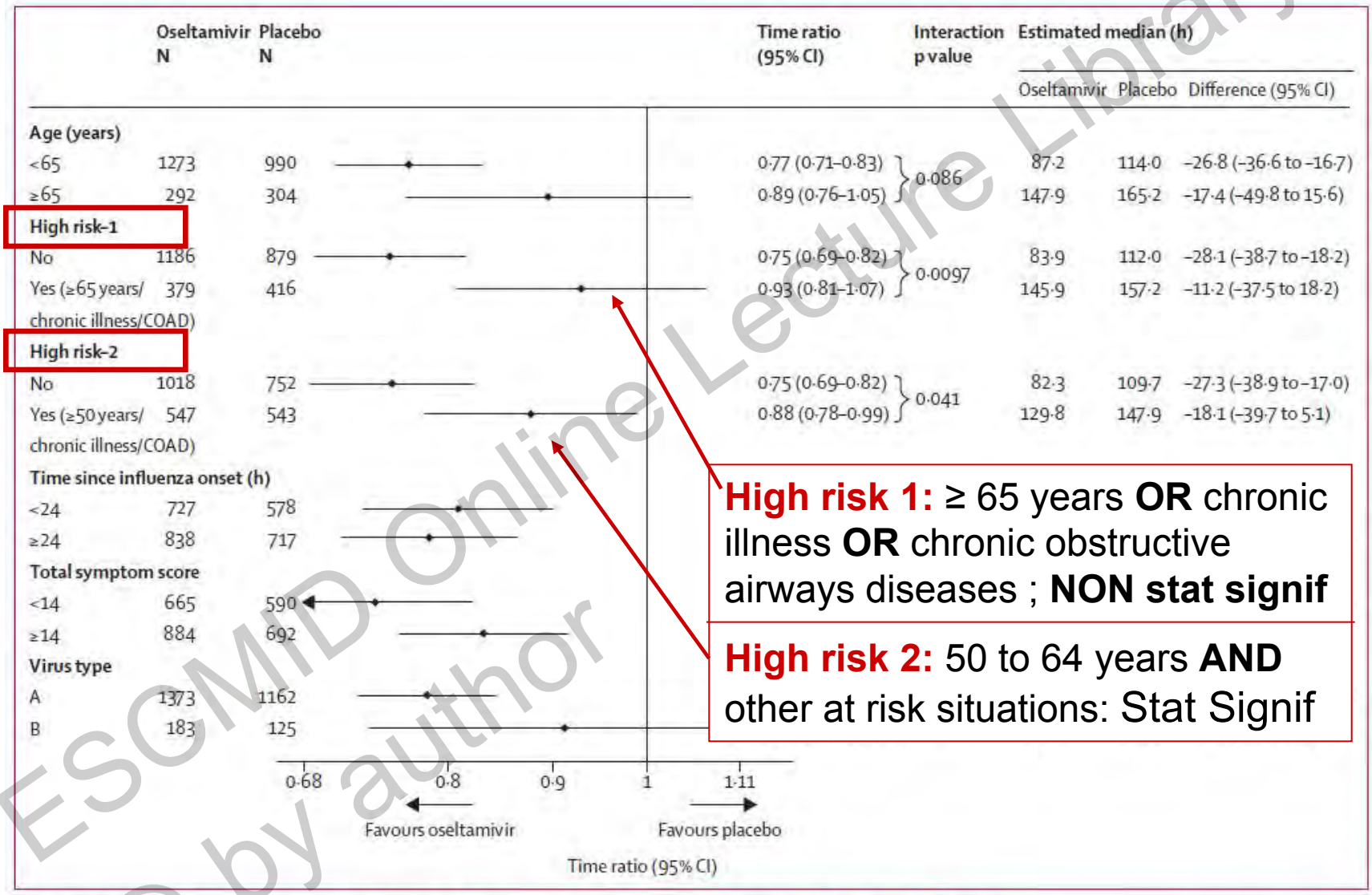

High risk 1: ≥ 65 years **OR** chronic illness **OR** chronic obstructive airways diseases ; **NON stat signif**

High risk 2: 50 to 64 years **AND** other at risk situations: Stat Signif

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Effectiveness of Zanamivir

Zanamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments

BMJ

BMJ 2014;348:g2547

- **Zanamivir** vs PCB for the treatment of influenza in healthy adults and children
- 16 RCT (treatment):
  - 2 RCT in children
  - 14 RCT in adults
- Unpublished clinical study reports and relevant regulatory comments

Carl J Heneghan BMJ 2014

Metanalysis BMJ 2014

	ZANAMIVIR	
Zanamivir effect	**Infected population (63.5%; 3094 pts)**	**Total population 4873 pts**
Time to symptom alleviation	0.67 day (95% CI 0.35 to 0.99)	0.6 day reduction 14.4h shorter 10% reduction 6.6 days to 6 days (p<0.05)
Bronchitis		5.0% (Z) vs 7.1% (PCB) RR 0.75 (0.61-0.91); (p<0.05)
Pneumoniae		1.3% (Z) vs 1.7% PCB RR 0.90 (0.58-1.40); NON significant
Hospital admission		NON significant

Carl J Heneghan BMJ 2014

Zanamivir HARM

In adult:

- No evidence of an increased risk of reported AE
- Nausea and vomiting were **less frequent**

  RR 0.60; 0.39-0.94

Combination of NI
Oseltamivir plus zanamivir

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Efficacy of Oseltamivir-Zanamivir Combination Compared to Each Monotherapy for Seasonal Influenza: A Randomized Placebo-Controlled Trial

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Table 2. Virological and clinical response according to treatment arms in the 541 enrolled patients, between day 0 and day 2 (ITT analysis).

Type of Response	Virological and Clinical Response Variables	Combined Oseltamivir and Zanamivir	Oseltamivir Plus Placebo	O+Z versus O		Zanamivir Plus Placebo	O+Z Versus Z		O Versus Z
				p-Value	Difference [95% CI]		*p*-Value	Difference [95% CI]	Difference [95% CI][a]
	n patients	192	176			173			
Virological	**Primary virological endpoint**								
	Day 2 influenza RT-PCR<200 cgeq/µl (% patients)	52.6%	62.5%	0.055	−9.9% [−19,9 to 0,2]	40.5%	0.020	+12.1% [2.02–22.3]	+22.0% [12,1–32,0]
Clinical	Time to resolution of illness in days (median, IQR)	3.5 [2.5–14]	3.0 [2–7]	0.015	+0.5 [0.0–1.5]	4.0 [2.5–14]	0.78	−0.5 [−1.0 to 0.5]	−1.0 [−1.5 to −0.5]

Better response in oseltamivir group as compared to oseltamivir + zanamivir or zanamvir alone

LANINAMIVIR

LANINAMIVIR

Laninamivir SINGLE dose vs Oseltamivir 5 days

- **In heathy adults**
  - Laninamivir **non-inferior** to oseltamivir
    - Less virus shedding
    - But during this season, many viruses were resistant to oseltamivir as the result of the H275Y mutation
- **In adults with pulmonary diseases**
  - Laninamivir **non-inferior** to oseltamivir

Similar rate of nausea, lower rate of vomiting

Similar or higher rate of diarrhea

Higher rate of dizziness (0.9-1.8%)

Watanabe A Clin Infect Dis. 2010

PERAMIVIR

PERAMIVIR

Peramivir SINGLE infusion vs PCB

- **In heathy adults**
  - **Shorter time** to alleviation of symptoms than PCB

Peramivir SINGLE infusion vs Oseltamivir 5 days

- **non-inferior to** 5-days oseltamivir

Peramivir multiple infusion vs Oseltamivir 5 days

- Trend toward a more rapid resumption of usual activities in Peramivir treated pts

Kohno S. Antimicrob Agents Chemother. 2010
Kohno S, Antimicrob Agents Chemother 2011
Ison MG Antivir Ther. 2013

CONCLUSIONS

- **Influenza**
  - Non-specific symptoms
  - At most, 60% of pts are influenza-infected (epidemic peak)
  - Flu-related complications are rare
- **INA benefit:**
  - Only noted in the influenza-infected population
  - Highly dependent on the proportion of the infected population which varies throughout the flu epidemic
- **INA Harm**
  - Noted in all (10%) receiving pts whether infected or NOT
  - Essentially mild

CONCLUSIONS

- **INA efficacy**
  - Probable but modest reduction of symptoms duration (20% ; 1 day out of 5)
  - Possible reduction of flu complications but a high number of pts must be treated to avoid a single case
  - When initiated within the first 48h (72H ?)
  - When the circulating virus is sensitive to NI (oseltamivir)
- **Very few data with other NIs**

Conclusions: Who should be treated ?

- **From a statistical point of view:**
  - The same population as the one included in RCT:
  - Young adults with or without comorbidities
  - Elderly with several comorbidities
- From a "**Common sense" point of view:**
  - The population which could benefit the most:
    - The elderly population with comorbidities
    - Infected Patients: positive rapid diagnostic test
    - or presenting flu at the peak of the epidemic
    - Influenza A > B
    - Circulating susceptible virus without NA mutation