How should oseltamivir be used seasonally and in pandemics

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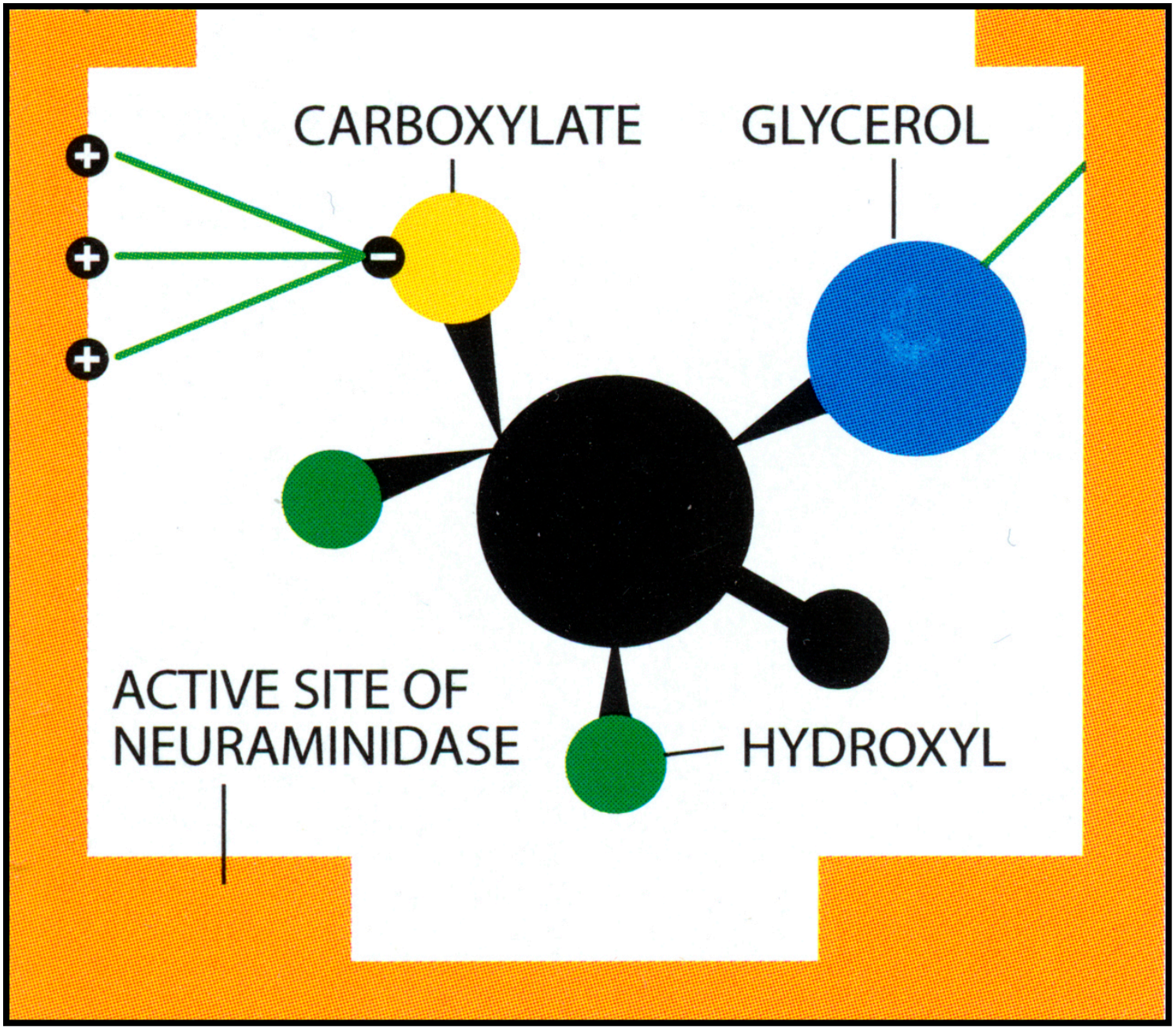
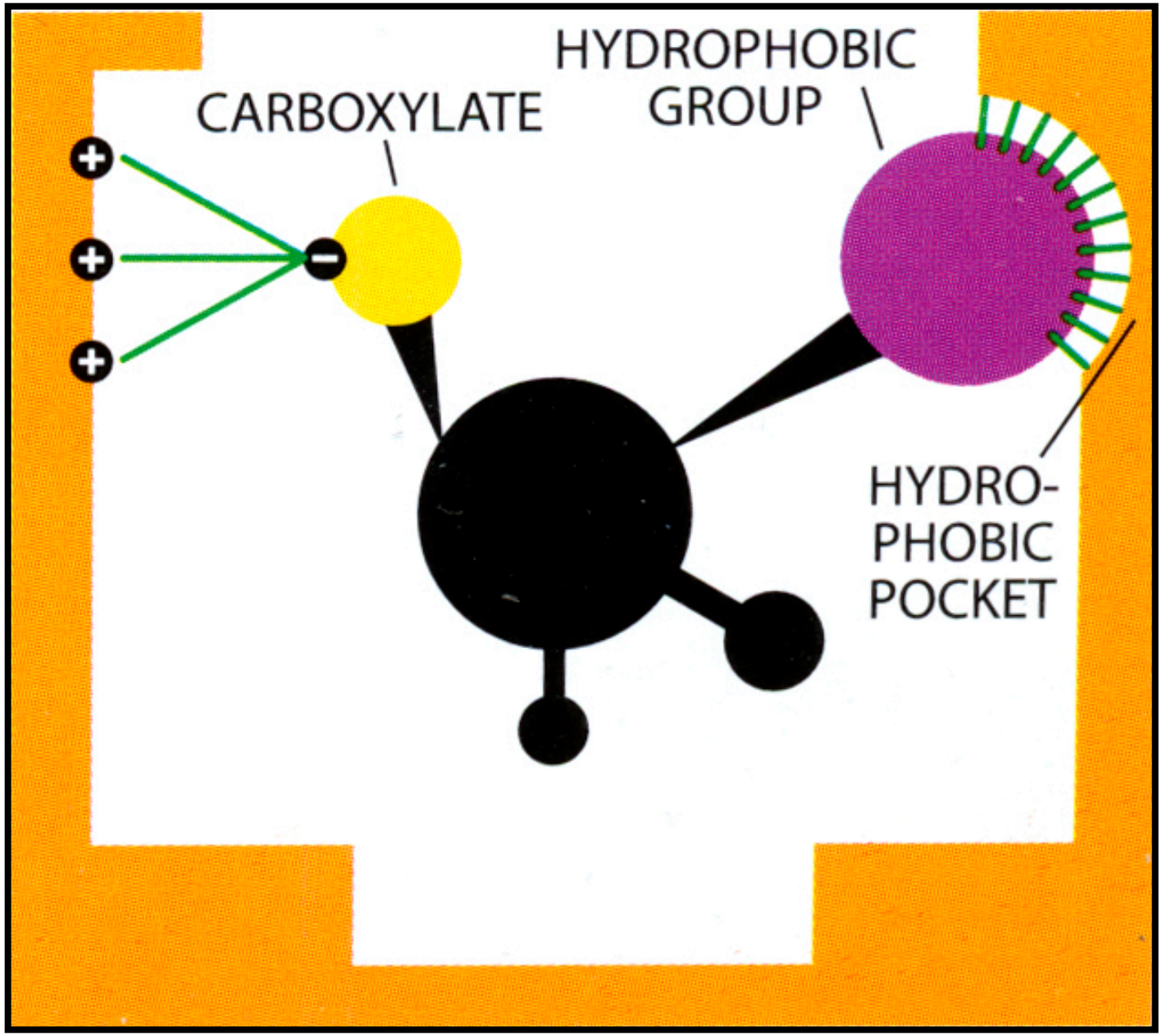
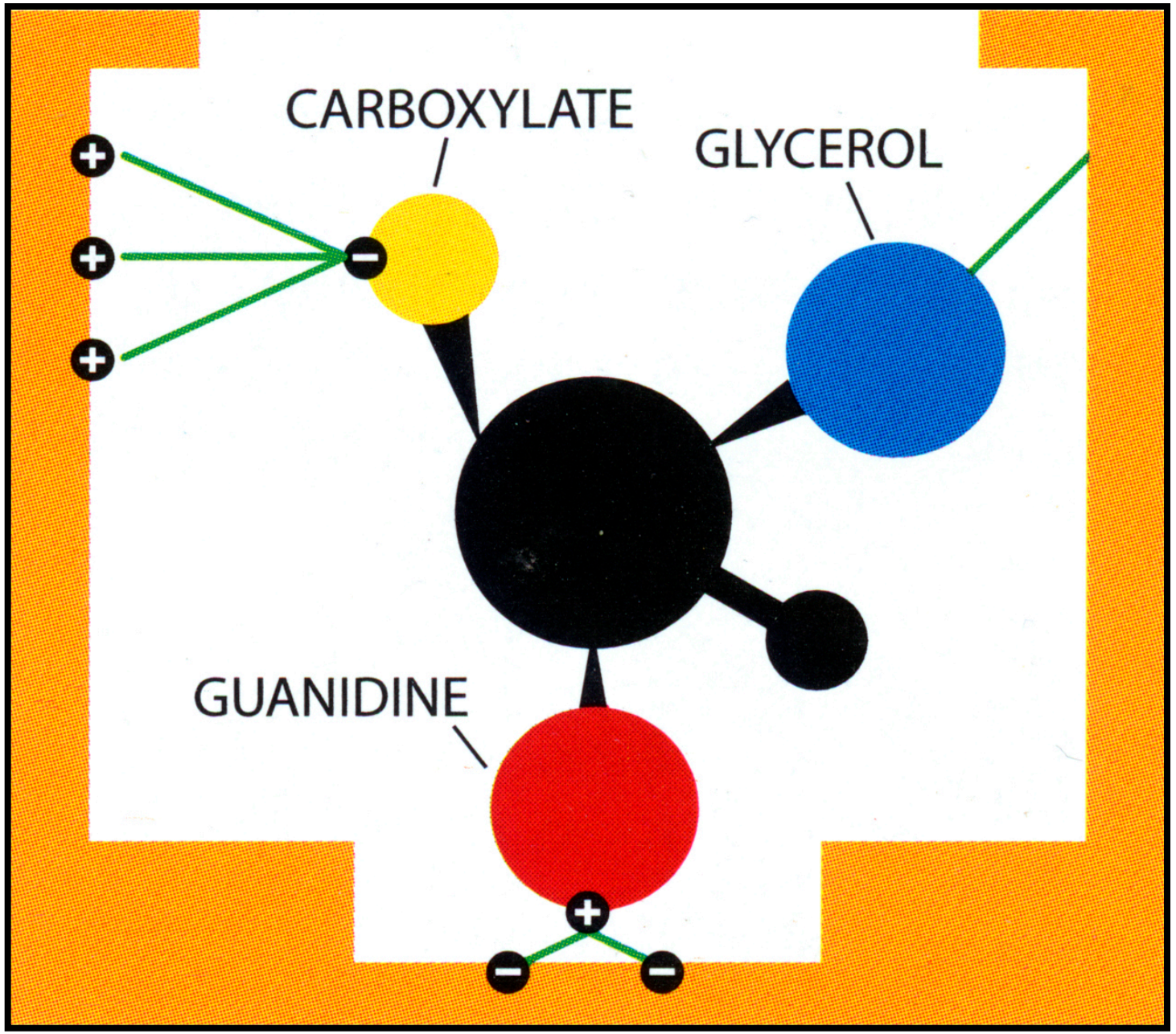
Sialic Acid


CARBOXYLATE
GLYCEROL
ACTIVE SITE OF
NEURAMINIDASE
HYDROXYL

Oseltamivir Carboxylate



Zanamivir



Differences between seasonal and pandemic use.

- Randomized trial data on efficacy comes from seasonal use, mainly in populations with some immunity
- Studies on use in the 2009 pandemic observational
- Goals of use different

  -Seasonal:

    Modification of illness duration and severity

    Prevention of complications, often secondary

    Vaccine available

  -Pandemic

    Prevention of complications major issue

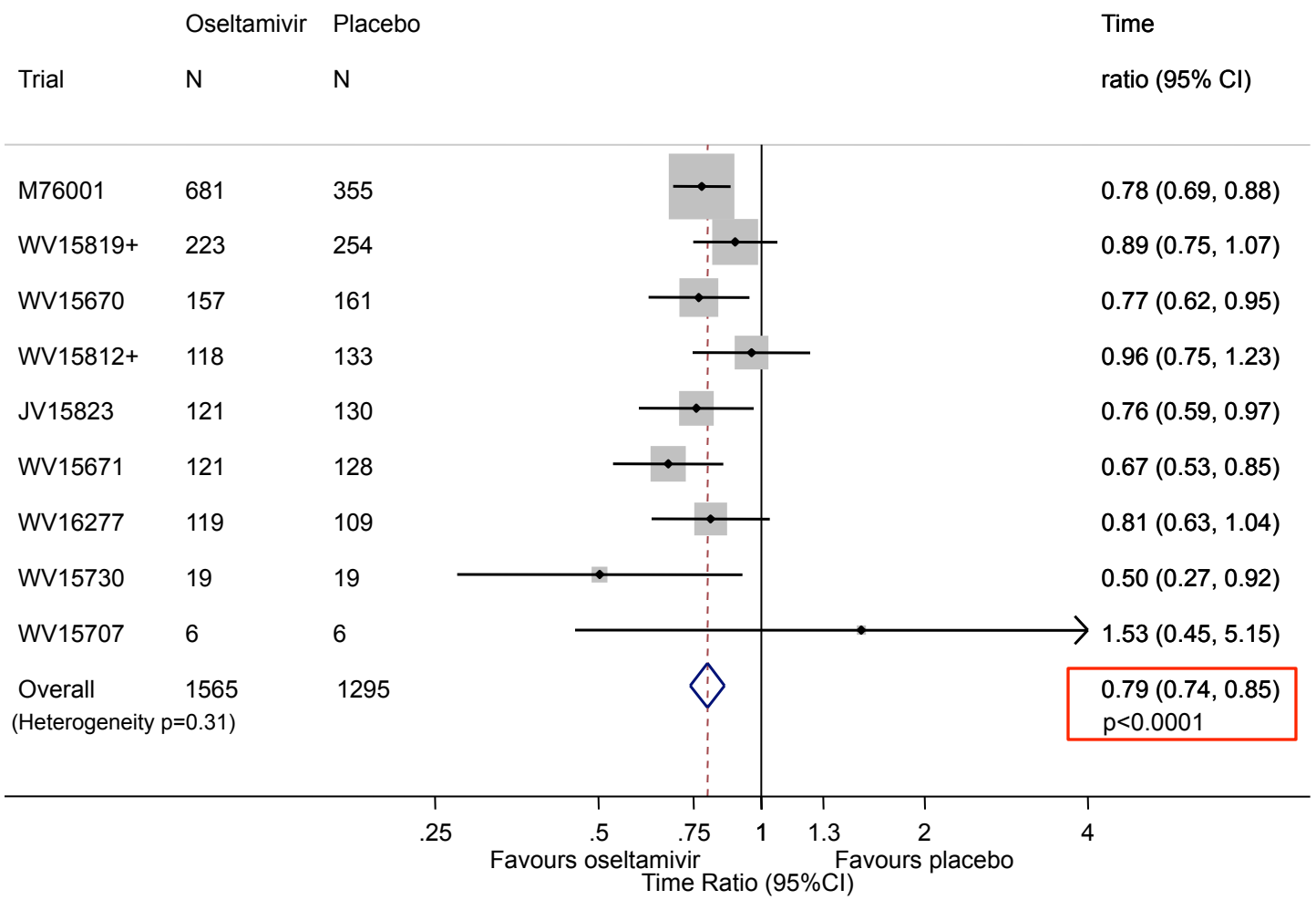
    Vaccine not available early. May use for prophylaxis and transmission control

    Supply may be limited

Pandemic Use of Antivirals

- **Strong evidence from observational studies in the 2009 pandemic that oseltamivir treatment prevented severe outcomes**
- **No evidence that use led to the emergence of resistance, in spite of H1N1 being the subtype with greatest history of resistance development**
- **Used differently in different countries based on local factors**
  - **-In Japan used extensively. Said to have prevented mortality**
  - **-In UK, made available by calling a telephone number**
  - **-In US, use varied dependent on risk groups. Based on expected severity- eg. pregnant women. Restriction on use based on concern about supply.**
- **Early use in the course of illness critical. Do not wait for lab confirmation.**

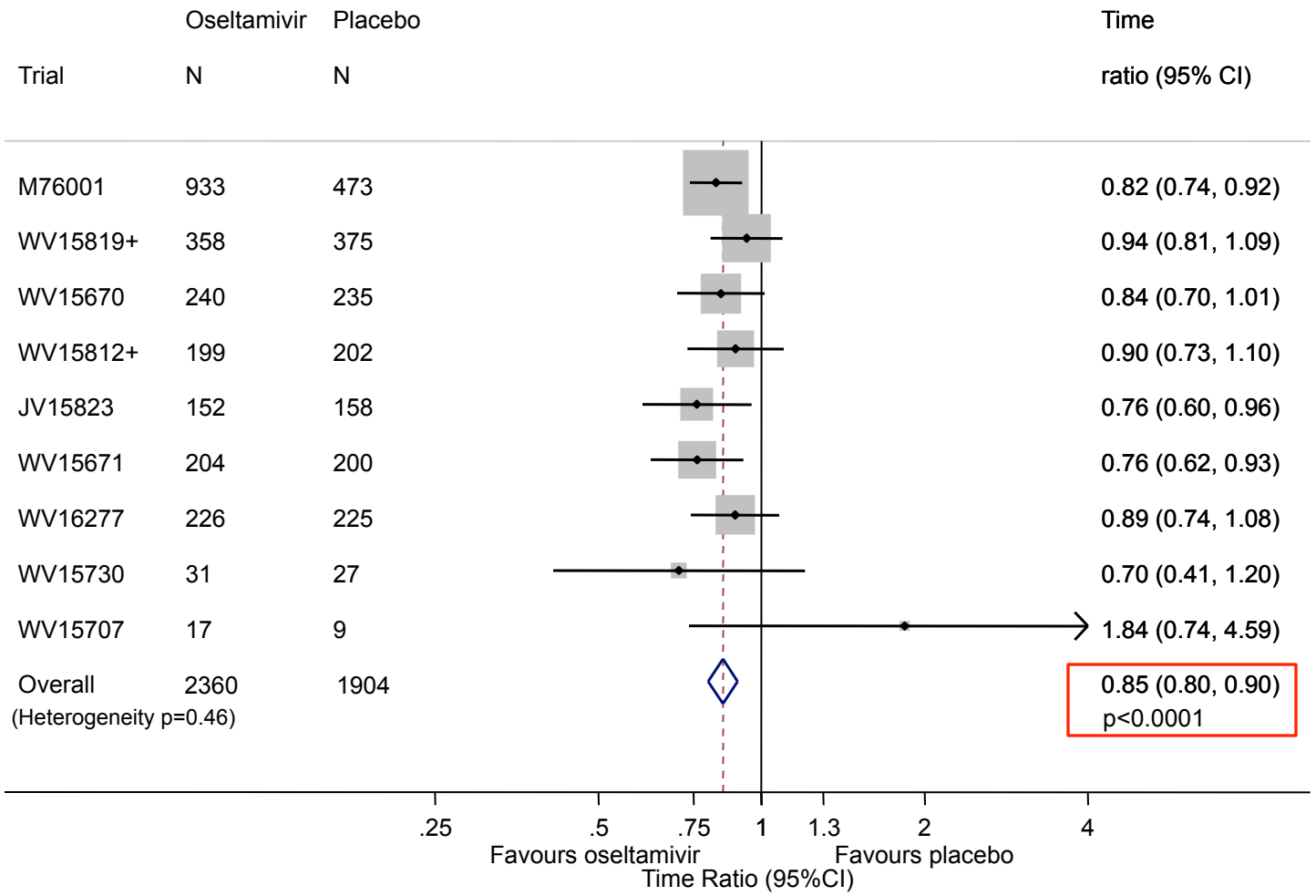
Time to alleviation of all symptoms – ITTI results



- Estimated difference in median time to alleviation:
  -25.2 hrs (-36.2, -16.0), 97.5 hrs vs 122.7 hrs

Dobson J et al. *Lancet*. 2015; 385: 1729-1737

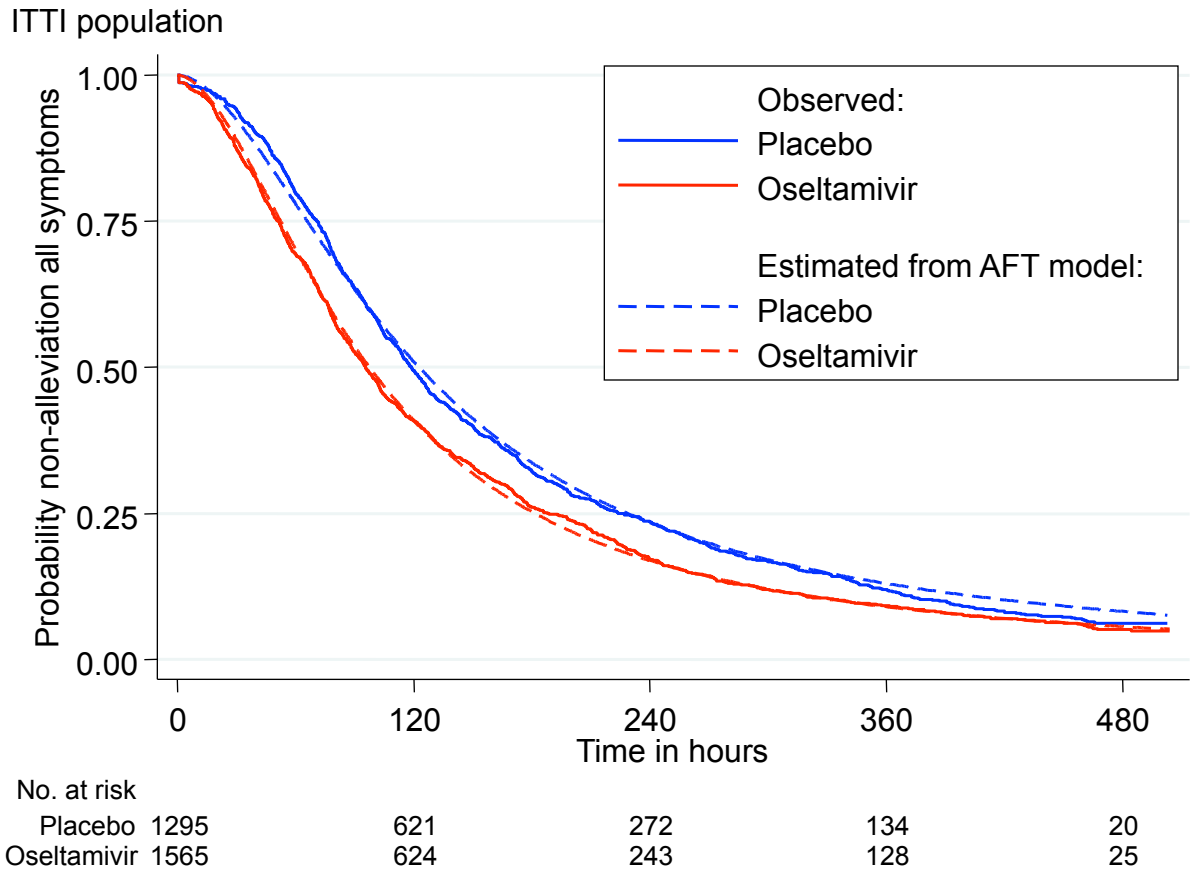
Time to alleviation of all symptoms – ITT results



- Estimated difference in median time to alleviation:
  -17.8 hrs (-27.1, -9.3)

Dobson J et al. *Lancet*. 2015; 385: 1729-1737

Time to alleviation of all symptoms – model fit (ITTI)



- Exploratory analysis: significant difference between treatment groups by 24 hours

Efficacy of Oseltamivir in Preventing Lower Respiratory Tract Complications (LRTCs) Leading to Antibiotic Use- ITTI Population

	Percent Reduction		
LRTCs Leading to Antibiotic Use	Overall n=2413	Otherwise Healthy n=1644	At Risk n=769
All LRTC	55%	67%	34%
Bronchitis	52%	60%	34%
Unspecified		-	
Pneumonia	61%	77%	30%
Influenza A	55%	63%	34%
Influenza B	54%	71%	25%

* Comparison of oseltamivir vs placebo, P<.001.
† Comparison of oseltamivir vs placebo, P=.02.

Kaiser L, et al. *Arch Intern Med*. 2003; 163:1667-72.

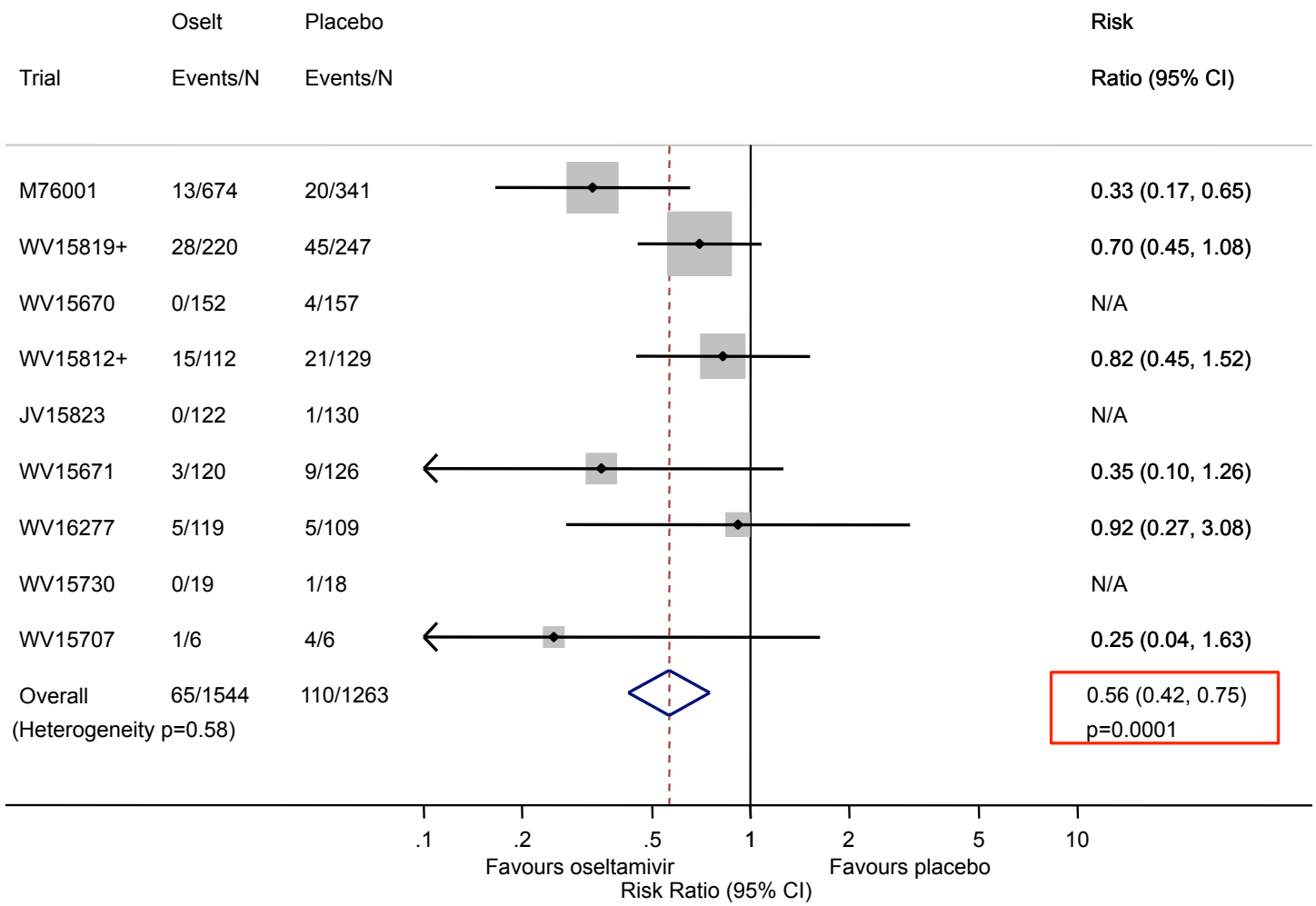
Lower respiratory tract complication (LRTC)

- **Definition:**
  - LRTC requiring antibiotics >48 hours after randomisation.
  - Preferred terms “bronchitis”, “pneumonia”, “LRT infection”
  - Self report and clinician judgement. No diagnostic tests required.

- **Methods:**
  - Estimate overall risk ratio (RR) using Mantel-Haenszel method (without continuity correction)
  - Risk difference (RD) and 95% CI - use pooled placebo group risk and overall RR (95% CI)
  - Subjects on antibiotics at baseline excluded
  - ITTI and ITT populations

Dobson J et al. *Lancet*. 2015; 385: 1729-1737

LRTCs – ITTI results

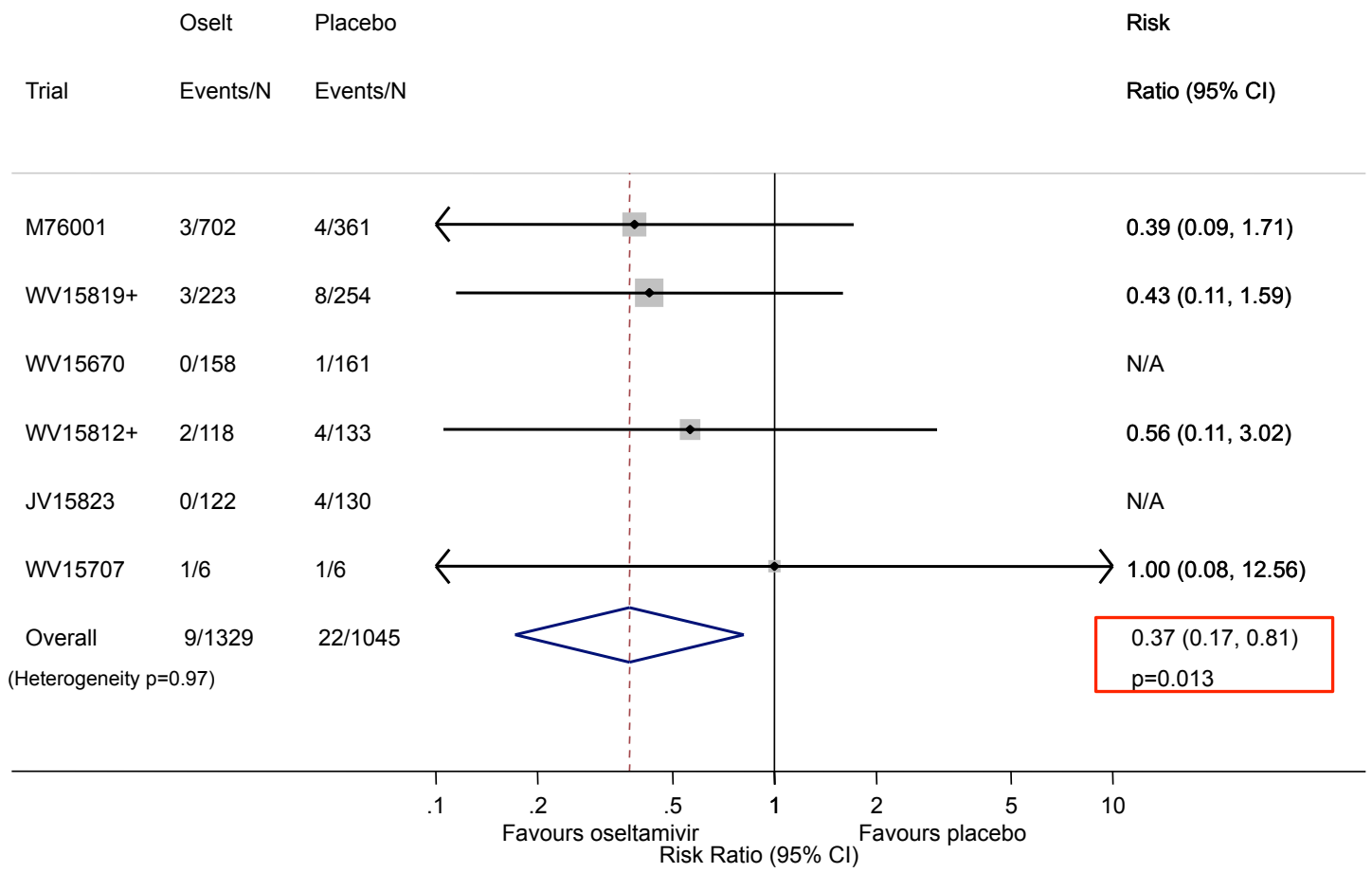


- Estimated risk difference: -3.8% (-5.0, -2.2)

  4.9% oseltamivir versus 8.7% placebo

Dobson J et al. *Lancet*. 2015; 385: 1729-1737

Hospitalizations – ITTI results (6 trials)



- Estimated risk difference: -1.1% (-1.4, -0.3)
  0.6% oseltamivir versus 1.7% placebo
- Some evidence of fewer hospitalisation on oseltamivir

Dobson J et al. *Lancet*. 2015; 385: 1729-1737

Reduction in Events Following Oseltamivir Treatment of Children 1-12 Years of Age ITTI Population

Endpoint	Reductions
Illness Duration until Alleviation	1.5 days
Duration of Fever	1.1 days
Physician Diagnosed Complications Requiring Antibiotics	40%
Physician Diagnosed Otitis Media	44%
Tympanometric Confirmed Otitis Media	50%

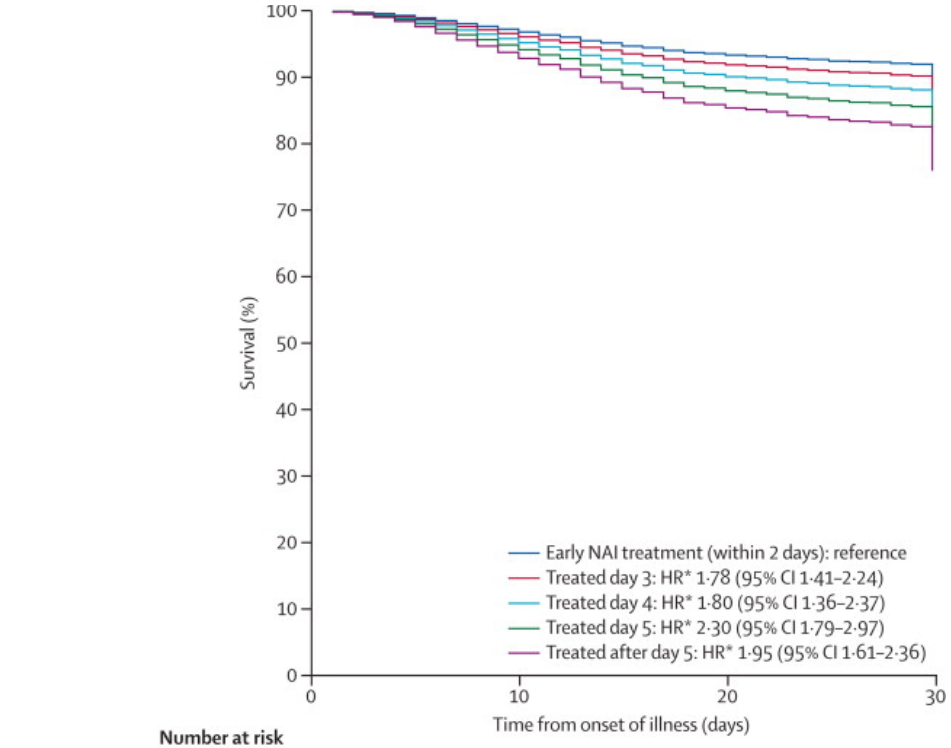
Whitley RJ, et al. *Pediatr Infect Dis J.* 2001; 20:127-33.

Efficacy of Seasonal Prophylaxis of Influenza with Zanamivir (4 weeks) and Oseltamivir (6 weeks)

	Zanamivir	Oseltamivir
Prevention of Symptomatic Laboratory Confirmed Influenza	67%	74%
Prevention of Influenza with Fever	84%	82%

Monto AS, et al. JAMA. 1999; 282:31-5.
Hayden FG, et al. NEJM. 1999; 341-1336-43.

Survival by time of oseltamivir treatment H1N1 pandemic. Individual level meta-analysis



Number at risk				
Early NAI treatment (within 2 days)	5192	2414	1939	1843
Treated with NAI day 3	1477	689	492	460
Treated with NAI day 4	1012	567	322	282
Treated with NAI day 5	812	541	272	241
Treated with NAI after day 5	2298	1981	1009	735

Survival by time to treatment
HR=hazard ratio. NAI=neuraminidase inhibitor. *Cox regression shared frailty model (adjusted for treatment propensity and in hospital steroid or antibiotic use).

Muthuri SG et al, Lancet Respir Med. 2014; 2:401

Conclusions

- Seasonal use of oseltamivir even when used extensively has not resulted in development of resistance. Seasonal A(H1N1) resistance in 2008 resulted from spontaneous mutation.
- Until universal vaccines are available, it is critical to use an antiviral for treatment and perhaps prophylaxis. Effect ofn avian viruses confirm.
- Availability might become an issue in a severe pandemic.
- Important to monitor the severity of the pandemic to create guidelines for use. Need to be specific and flexible
- Guidelines should identify those who are at particular risk.
- Early use essential. Even more important with avian viruses.
- New antivirals with different mode of action may be valuable in conjunction with oseltamivir Need to be studied.