OPTIONS IX for THE CONTROL OF INFLUENZA
24–28 AUGUST 2016
Sheraton Grand CHICAGO Hotel
10 YEARS isirv

Clinical Development Challenges: Trial Designs and Endpoints

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I have financial relationship(s) with:

Research grant: Crucell

Advisory Boards: Crucell, AIMM therapeutics, MedImmune, Avi Biopharma

AND

My presentation does include discussion of off-label or investigational use of antivirals.

Placebo-controlled RCTs of neuraminidase inhibitors:
mostly in previously healthy people with mild flu

Articles

Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial

K G Nicholson, F Y Aoki, A D M E Osterhaus, S Trottier, O Carewicz, C H Mercier, A Rode, N Kinnersley, P Ward, on behalf of the Neuraminidase Inhibitor Flu Treatment Investigator Group*

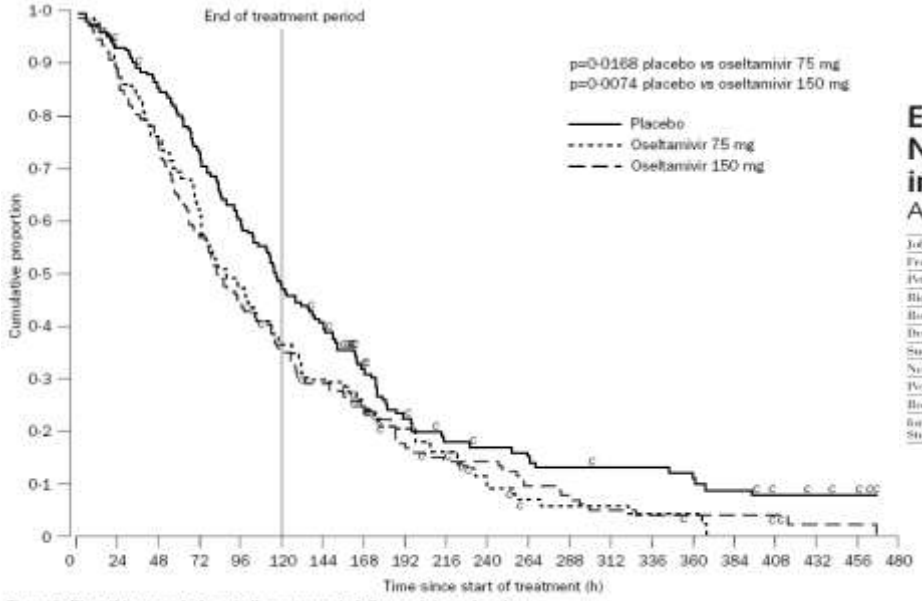


Figure 2: **Time (h) to resolution of all symptoms in influenza-infected patients**
c=censored patients who withdrew before resolution of symptoms.

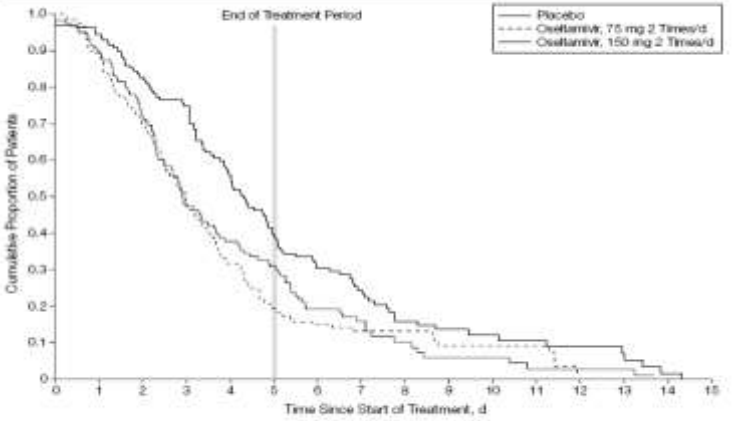
Lancet 2000; **355:** 1845–50

- Symptom relief as primary endpoint

Efficacy and Safety of the Oral Neuraminidase Inhibitor Oseltamivir in Treating Acute Influenza
A Randomized Controlled Trial

John J. Treanor, MD
Frederick G. Hayden, MD
Peter S. Vrooman, MD
Rick Barbarash, PharmD
Robert Bettis, MD
Dennis Riff, MD
Sudeep Singh, MD
Nelson Kinnersley
Penelope Ward, MD
Roger G. Mills, MD
for the US Oral Neuraminidase Study Group

Figure 2. Time to Alleviation of All Symptoms in Influenza-Infected Patients



Participants with missing values were censored. One patient (not shown, oseltamivir, 75-mg group) had a censored value of 20.3 days. P<.001 for placebo vs oseltamivir, 75 mg twice daily; P = .006 for placebo vs oseltamivir, 150 mg, twice daily.

JAMA. 2000;283:1016-1024

Observational studies point to benefits of oseltamivir treatment in hospitalized patients

Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data

	Crude analysis		Adjusted* analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Laboratory confirmed or clinically diagnosed, all ages; n=29 234	0·92 (0·81–1·05)	0·21	0·81 (0·70–0·93)	0·0024
Laboratory confirmed cases, all ages; n=25 001	0·94 (0·81–1·09)	0·42	0·82 (0·70 to 0·95)	0·0104
Adults (≥16 years); n=19 816	0·82 (0·70–0·95)	0·0071	0·75 (0·64–0·87)	0·0002
Children (<16 years); n=9218	1·02 (0·73–1·42)	0·90	0·82 (0·58–1·17)	0·28
Pregnant women; n=2166	0·47 (0·24–0·90)	0·0228	0·46 (0·23–0·89)	0·0215
Critical care patients				
Adults (≥16 years); n=5103	0·74 (0·57–0·95)	0·0187	0·72 (0·56–0·94)	0·0155
Children (<16 years); n=1725	0·84 (0·52–1·37)	0·49	0·70 (0·42–1·16)	0·17

OR=odds ratio. *Adjusted for treatment propensity (by quintile), corticosteroid use, and antibiotic use.

Table 2: **Neuraminidase inhibitor treatment (at any time) versus none**

Muthuri SG et al. *Lancet Respir Med 2014*

Antivirals for influenza: current state of affairs

- Licensed agents only for treatment of ***acute uncomplicated*** flu
  - Adamantanes:
    - amantadine, rimantadine
    - not recommended due to resistance in circulating strains
  - Neuraminidase inhibitors:
    - oseltamivir (oral), zanamivir (inhaled)
    - US, Japan, S Korea: peramivir (IV); Japan: laninamivir (inhaled)

- No licensed agents for treatment of ***serious/hospitalized*** flu

Guidelines recommend (off-license) use of oseltamivir for severe influenza

WHO Guidelines for
Pharmacological Management of
Pandemic Influenza A(H1N1) 2009
and other Influenza Viruses

Revised February 2010

World Health Organization

Rec 01: Patients who have severe or progressive clinical illness should be treated with oseltamivir as soon as possible. (Strong recommendation, low quality evidence.)

Mind the gap

"Rational believers"

- Flu is caused by influenza viruses and can be severe
- Oseltamivir inhibits flu viruses
- Proven efficacy for uncomplicated flu
- Observational studies strongly suggest efficacy for severe flu

+

Treat patients with severe disease and those at risk for severe disease

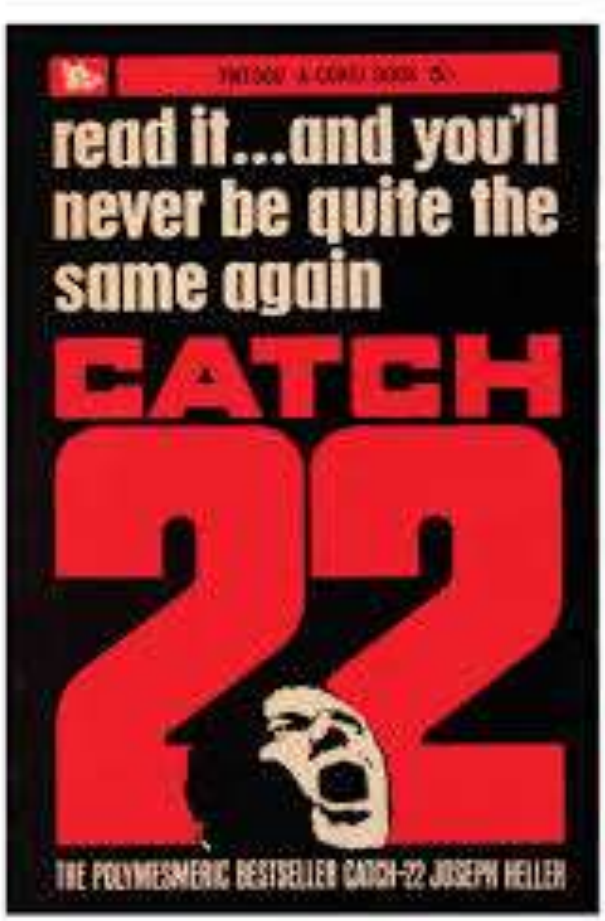
"Rational non-believers"

- No evidence from RCTs

↓

Not rational to treat at present

How to determine efficacy of new antivirals in patients with severe influenza?



Guidance for Industry

Influenza: Developing Drugs for Treatment and/or Prophylaxis

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2011

Efficacy studies in severe hospitalized influenza are very complicated

- No formal demonstration of clinical efficacy for any antiviral
  - *FDA: active-controlled non-inferiority trial is not an option*
- Current treatment guidelines prevent placebo controls
  - *FDA: dose-response, or superiority when added to 'standard of care'*
- No validated efficacy endpoints
  - *FDA: endpoints should demonstrate improvement in how the patient feels, functions or survives; primary virological endpoint not appropriate.*

Evaluation of Intravenous Peramivir for Treatment of Influenza in Hospitalized Patients

Menno D. de Jong,[1] Michael G. Ison,[2] Arnold S. Monto,[3] Hristo Metev,[8] Carol Clark,[4] Brian O'Neil,[5] Jenna Elder,[6] Amy McCullough,[7] Phil Collis,[7] and William P. Sheridan[7]

Clinical Infectious Diseases® 2014;59(12):e172–85

- Superiority trial: peramivir vs placebo added to standard-of-care (SOC)
- Primary efficacy analysis in population *not* receiving oseltamivir as SOC
- Hospitalized patients, broad inclusion criteria, broad geography
- Primary endpoint: time to clinical resolution (TTCR)

= resolution ≥ 4 of 5 vital signs:

		Resolution Criteria	
Assessment	Modality and Frequency	Children[a]	Adolescents and Adults[a]
Temperature	Thrice daily while hospitalized, once daily after discharge; all temperature measurements were performed ≥4 h after administration of antipyretic medication using a study-supplied electronic thermometer	≤37.2°C oral or ≤37.8°C rectal or tympanic	≤37.2°C oral or ≤37.8°C rectal or tympanic
Oxygen saturation	Thrice daily while hospitalized	≥92%	≥92%
Respiration rate	Thrice daily while hospitalized	≤30/min	≤24/min
Heart rate	Thrice daily while hospitalized	≤110/min	≤100/min
Systolic blood pressure	Thrice daily while hospitalized	≥80 mmHg	≥90 mmHg

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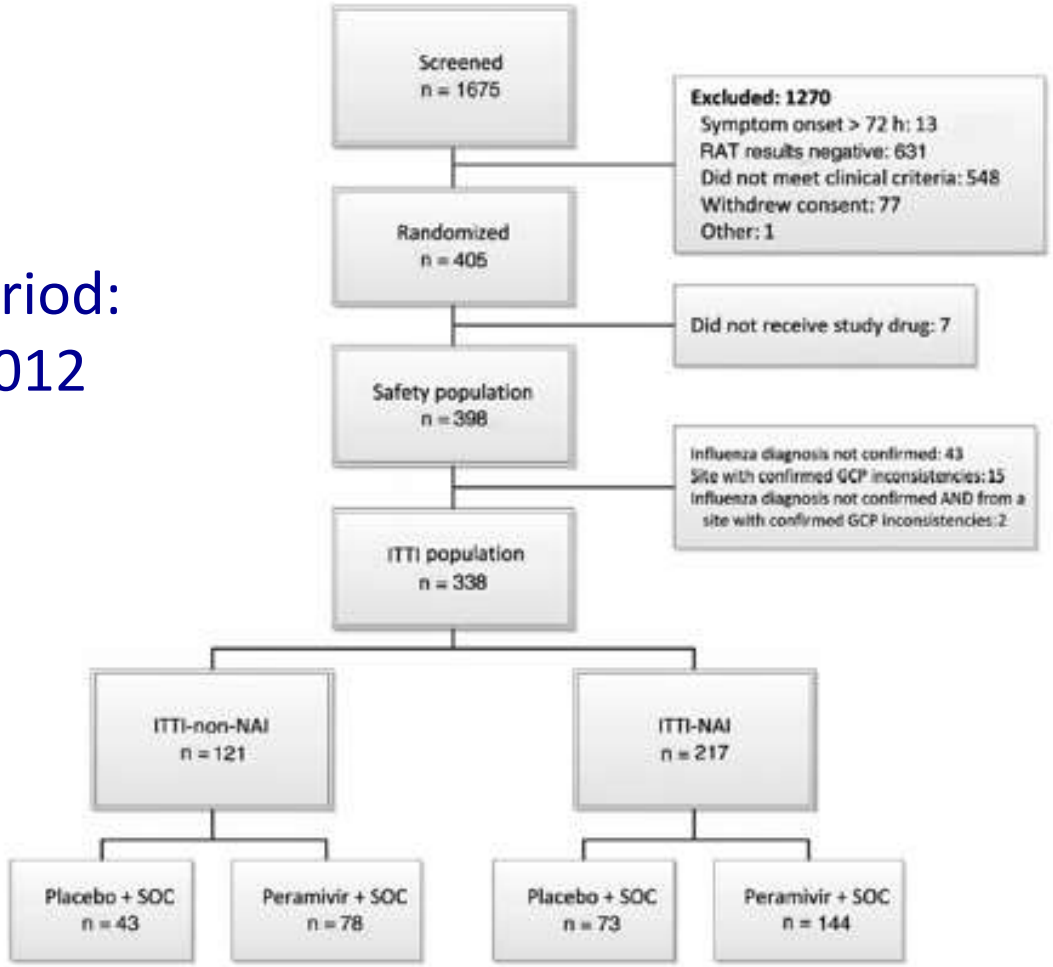
Clinical Infectious Diseases® 2014;59(12):e172–85

Study period:
2009-2012



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Clinical Infectious Diseases® 2014;59(12):e172–85

Table 5. TTCR for ITTI Non-NAI SOC Population and ITTI NAI SOC Population

	TTCR, Median (95% CI), h[a]			
	ITTI Non-NAI SOC Population[b]		ITTI NAI SOC Population[c]	
Subjects	Placebo + SOC	Peramivir + SOC	Placebo + SOC	Peramivir + SOC
All subjects	49.5 (40.0–61.9) (n = 43)	42.5 (34.0–57.9) (n = 78)[d]	48.9 (31.0–65.8) (n = 73)	41.8 (30.9–56.8) (n = 144)[e]
Symptoms ≤48 h at randomization	58.2 (37.0–71.1) (n = 32)	42.9 (35.4–63.0) (n = 50)	48.4 (35.7–80.1) (n = 38)	41.8 (27.8–67.3) (n = 76)
Symptoms >48 h at randomization	40.0 (20.0–42.5) (n = 11)	36.0 (23.3–65.0) (n = 28)	31.0 (18.9–62.0) (n = 35)	36.0 (25.0–61.4) (n = 68)
Admitted to ICU at baseline				
Yes	50.2 (7.8–61.9) (n = 8)	31.5 (22.8–47.5) (n = 15)	49.5 (37.0–65.5) (n = 35)	46.3 (38.3–64.0) (n = 63)
No	49.5 (37.0–65.5) (n = 35)	46.3 (38.3–64.0) (n = 63)	38.8 (25.0–60.8) (n = 66)	36.2 (27.8–48.3) (n = 132)

placebo vs peramivir

- Study terminated prematurely for futility after preplanned interim analysis

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Clinical Infectious Diseases® 2014;59(12):e172–85

The challenges encountered:

- Patient enrollment (n = 405)
  - Long study period (2009-2012), 6 influenza seasons
  - >300 sites, 21 countries:
    - no enrollment from > 70% of sites; 6% of sites enrolled 63% of patients
    - ≈ 90% of non-NAI SOC patients enrolled from India/Eastern Europe
- Heterogeneous patient population
  - broad spectrum of illness severity
  - ≈ 70% comorbidities and/or age > 60 years
  - variety of influenza (sub)types
- Unvalidated clinical endpoint (TTCR)

Guidance for Industry

Influenza: Developing Drugs for Treatment and/or Prophylaxis

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2011

Because outbreaks of influenza are unpredictable and enrollment of serious or hospitalized patients probably will be more difficult than enrollment of uncomplicated cases, sponsors should consider collaborating with clinical trial networks with a wide range of sites.

Effect of double dose oseltamivir on clinical and virological outcomes in children and adults admitted to hospital with severe influenza: double blind randomised controlled trial

BMJ 2013;346:f3039

South East Asia Infectious Disease Clinical Research Network

- 2007 – 2010
- 13 hospitals, 4 countries
- 699 screened, 326 randomized

ISARIC

ND4BB COMBACTE

Platform foR European Preparedness Against (Re-)emerging Epidemics

PREPARE

In early development:

European Clinical Research organization for Antimicrobial resistance and emerging Infectious Diseases (ECRAID)

Smarter trial designs
to improve efficiency

- Traditional RCTs:
  - long, slow & expensive to conduct
  - provide ‘average’ answers
    - fail to capture the nuances of real-life clinical care

- Adaptive design RCTs:
  - takes advantage of accumulating data during trial
  - earlier answers by *response-adaptive randomisation*
    - more patients randomized to effective intervention
    - reduce imbalances of subgroups between study arms
    - detect efficacy ‘signals’ in subgroups
  - flexible
    - test several interventions concurrently
    - add & delete study arms

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Definition of severe influenza requiring hospitalization?

- Reasons for admission vary, *e.g.*
  - Primary influenza viral pneumonia
  - Secondary bacterial pneumonia
  - Additional organ or systemic failure such as ARDS or shock
  - Exacerbation of underlying chronic illness such as diabetes, COPD, CHF
  - etcetera

- Thresholds for admission vary
  - Depending on comorbidity, culture, policy, socioeconomic status etc

- Clear case definitions of influenza severity are needed

ABSTRACT# O-74

Session Name: Oral Abstract Session: Clinical Science

Presentation Date: Saturday, 27 August 2016

Session Time: 11:00 AM - 12:30 PM

Oral Presentation Time: 12:00 PM

Harmonizing Disease Severity Assessments in Infants and Children: The PEDSIDEA Consortium

Maren Alchikh, Christian Hoppe, Maria-Alexandra Papagrigoriou-Theorodridou, Vassiliki Papaevangelou, Helena C. Maltezou, Brunhilde Schweiger, Barbara Rath

Vienna Vaccine Safety Initiative, Berlin, Germany

ABSTRACT# LBP-17

Presentation Date: Friday, 26 August 2016

Use of National Early Warning System score to evaluate impact of baseline disease severity on the therapeutic outcomes in hospitalized patients with influenza illness

Michael Ison, James Zhou, Jeremy Katzen, Yonghong Gao, Jessica Houk, John Tegeris, Melissa Willis, James King

Northwestern University, Chicago, IL, United States

Evaluation of Intravenous Peramivir for Treatment of Influenza in Hospitalized Patients

Menno D. de Jong,[1] Michael G. Ison,[2] Arnold S. Monto,[3] Hristo Metev,[8] Carol Clark,[4] Brian O'Neil,[5] Jenna Elder,[6] Amy McCullough,[7] Phil Collis,[7] and William P. Sheridan[7]

Clinical Infectious Diseases® 2014;59(12):e172–85

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- Heterogeneous patient population
  - broad spectrum of illness severity
  - ≈ 70% comorbidities and/or age > 60 years
  - variety of influenza (sub)types

- Unvalidated clinical endpoint (TTCR)

Hospitalized patient populations are heterogeneous

Who is at high risk for developing flu-related complications?

- Children younger than 5, but especially children younger than 2 years old
- Adults 65 years of age and older
- Pregnant women
- People who have medical conditions including:
  - Asthma (even if it's controlled or mild)
  - Neurological and neurodevelopmental conditions
  - Chronic lung disease (such as COPD and cystic fibrosis)
  - Heart disease (such as congenital heart disease, CHF and IHD)
  - Blood disorders (such as sickle cell disease)
  - Endocrine disorders (such as diabetes mellitus)
  - Kidney disorders
  - Liver disorders
  - Metabolic disorders
  - Weakened immune system due to disease or medication
  - Morbid obesity (BMI of 40 or greater)

www.cdc.gov/flu/keyfacts

➢ **Differences in the course of how patients feel, function and survive are likely..**

Guidance for Industry

Influenza: Developing Drugs for Treatment and/or Prophylaxis

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2011

For seriously ill influenza patients requiring hospitalization, a primary endpoint should include clinical signs and symptoms, duration of hospitalization, time to normalization of vital signs and oxygenation, requirements for supplemental oxygen or assisted ventilation, and mortality.

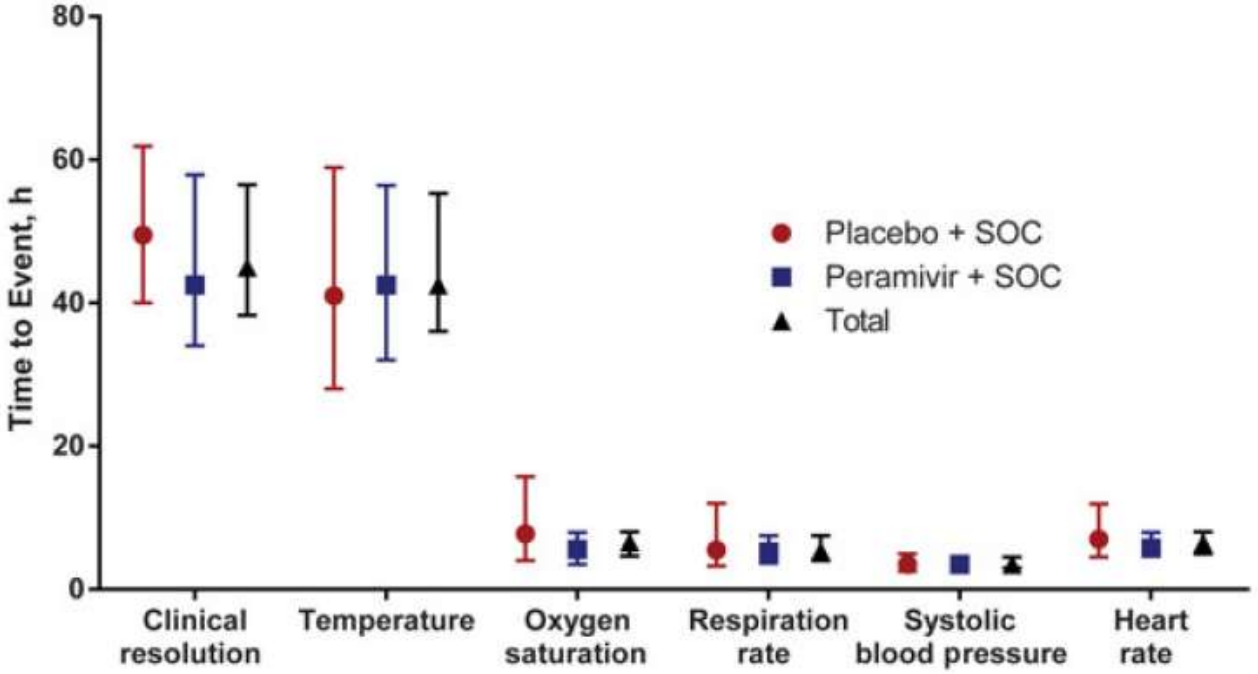
Choice of endpoint may depend on the clinical setting and/or viral strains. A single best endpoint has not been identified in seriously ill hospitalized patients

Evaluation of Intravenous Peramivir for Treatment of Influenza in Hospitalized Patients

Menno D. de Jong,[1] Michael G. Ison,[2] Arnold S. Monto,[3] Hristo Metev,[8] Carol Clark,[4] Brian O'Neil,[5] Jenna Elder,[6] Amy McCullough,[7] Phil Collis,[7] and William P. Sheridan[7]

Clinical Infectious Diseases® 2014;59(12):e172–85

- TTCR endpoint mainly driven by temperature



Ordinal scale endpoints

- Classification of clinical status over time based on discrete categories, *e.g.*
  a. death
  b. in ICU
  c. non-ICU hospitalization, requiring supplemental oxygen;
  d. non-ICU hospitalization, not requiring supplemental oxygen
  e. not hospitalized, unable to resume normal activities
  f. not hospitalized, full resumption of normal activities

- .Developed by INSIGHT/NIAID, used in antibody-based RCTs

ABSTRACT# O-73

Session Name: Oral Abstract Session: Clinical Science

Presentation Date: Saturday, 27 August 2016

Session Time: 11:00 AM - 12:30 PM

Oral Presentation Time: 11:45 AM

Clinical Trials for Hospitalized Influenza Patients - Options to Improve Enrollment, Data Quality, and Define Endpoints

Kimberly Armstrong, Karl Erlandson, Roxanne Shively, James King, John Tegeris, Melissa Willis

Biomedical Advanced Research and Development Authority, Washington, DC, United States

Patient-reported outcome (PRO) measures

- Patient-reported (severity of) symptoms and other measures
- Rigorous development and validation requirements from FDA
- Feasibility and usefulness in hospitalized patients tbd

Development and Validation of the Influenza Intensity and Impact Questionnaire (FluiiQ™)

Richard H. Osborne, BSc, PhD[1,], Josephine M. Norquist, MS[2], Gerald R. Elsworth, BSc, PhD[1], Lucy Busija, BA (Hons), MSci[1,3], Vinay Mehta, PhD, MS[2], Tim Herring, MPH[2], Swati B. Gupta, DrPH, MPH[2]*

VALUE IN HEALTH 14 (2011) 687–699

Development of the Flu-PRO: a patient-reported outcome (PRO) instrument to evaluate symptoms of influenza

John H. Powers[1,15*], M. Lourdes Guerrero[2], Nancy Kline Leidy[3], Mary P. Fairchok[4,5,6], Alice Rosenberg[1], Andrés Hernández[7], Sonja Stringer[3], Christina Schofield[6], Patricia Rodríguez-Zulueta[8], Katherine Kim[3], Patrick J. Danaher[9], Hilda Ortega-Gallegos[2], Elizabeth Dansie Bacci[3], Nathaniel Stepp[10], Arturo Galindo-Fraga[2], Kristina St. Clair[11], Michael Rajnik[12], Erin A. McDonough[13], Michelande Ridoré[4,5], John C. Arnold[14], Eugene V. Millar[4,5] and Guillermo M. Ruiz-Palacios[2]

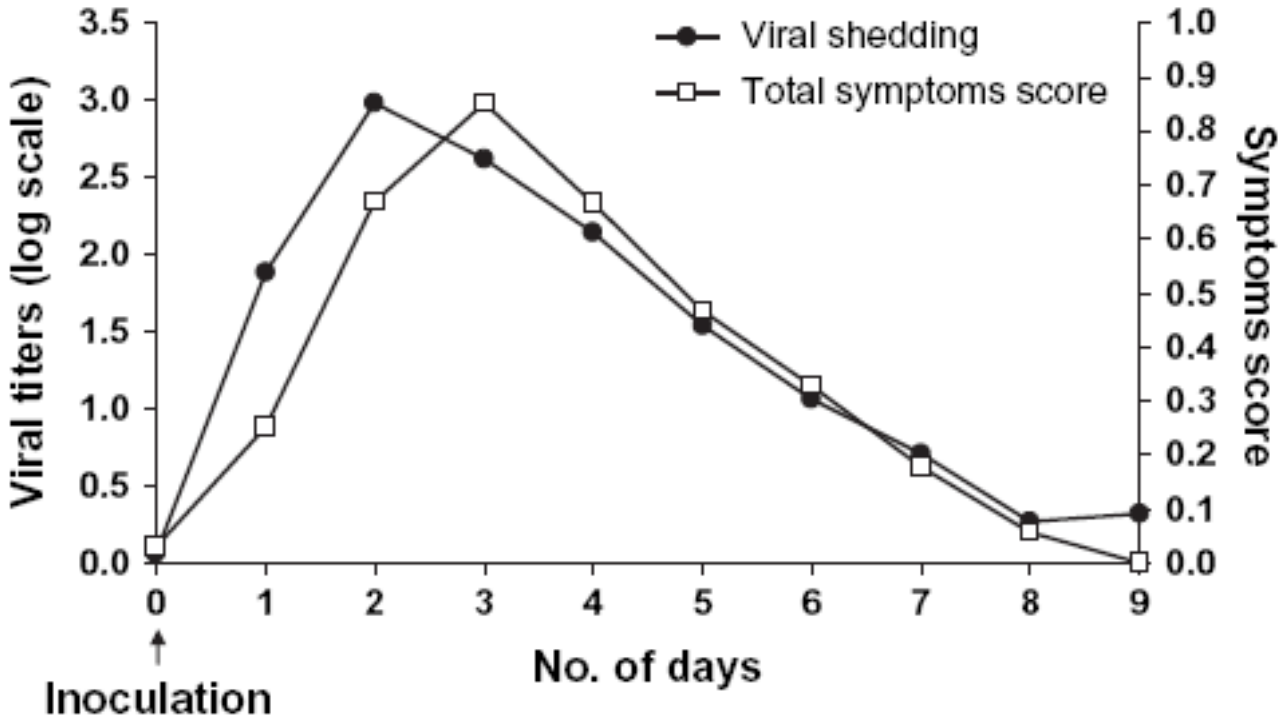
BMC Infectious Diseases (2016) 16:1

A virological endpoint makes sense

- It's the virus that causes the disease..
  - *rapid and complete viral clearance should be a primary aim of antiviral treatment to reduce disease, resistance and transmission*
- Virological endpoints reflect antivirals' mechanism of action
  - *should virological endpoints be considered surrogate markers?*
- Virological endpoints can potentially 'neutralize' the issues of clinical endpoints in hospitalized populations
- Virus shedding correlates with clinical measures

Viral shedding correlates with symptoms in human volunteer studies

(meta-analysis 56 studies, 1280 volunteers)



» 2-3 log higher viral load in symptomatics than in asymptomatics

» positive correlation between viral load and illness severity

Carrat F et al. Am J Epidemiol 2008; 167: 775-85

Viral shedding correlates with symptoms in uncomplicated influenza

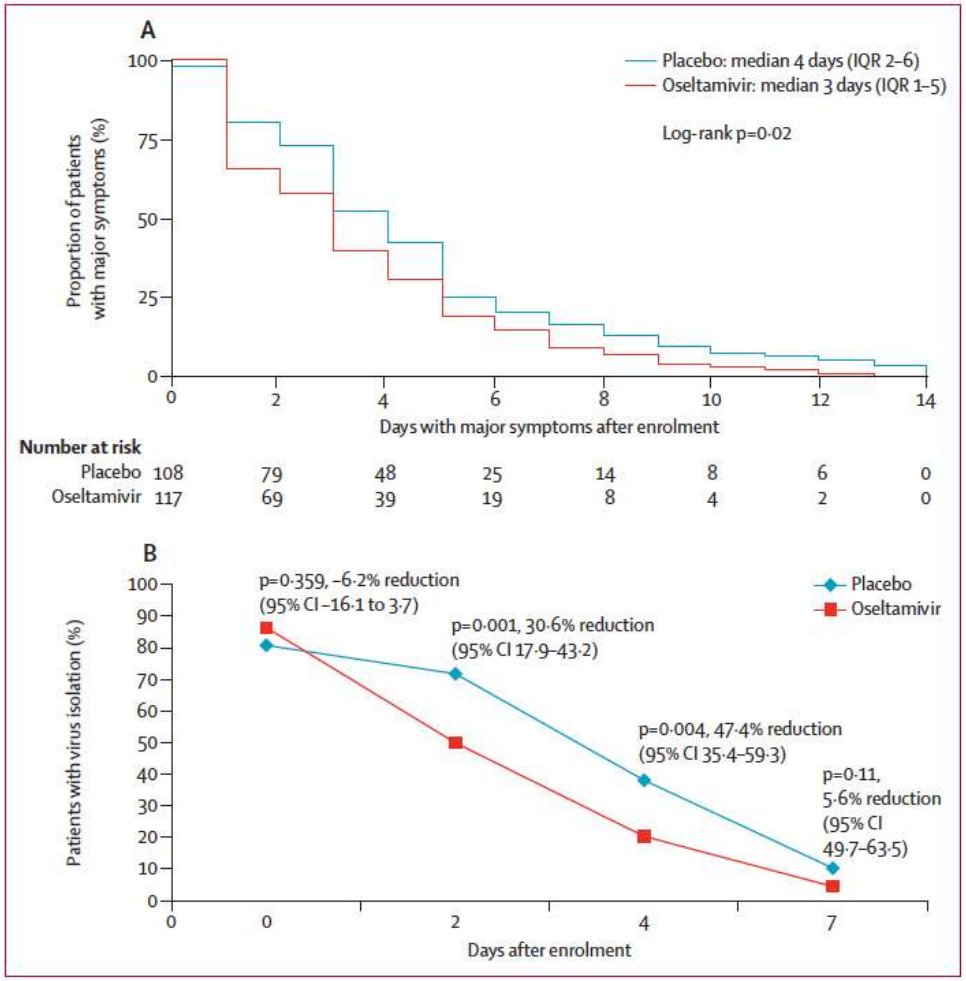
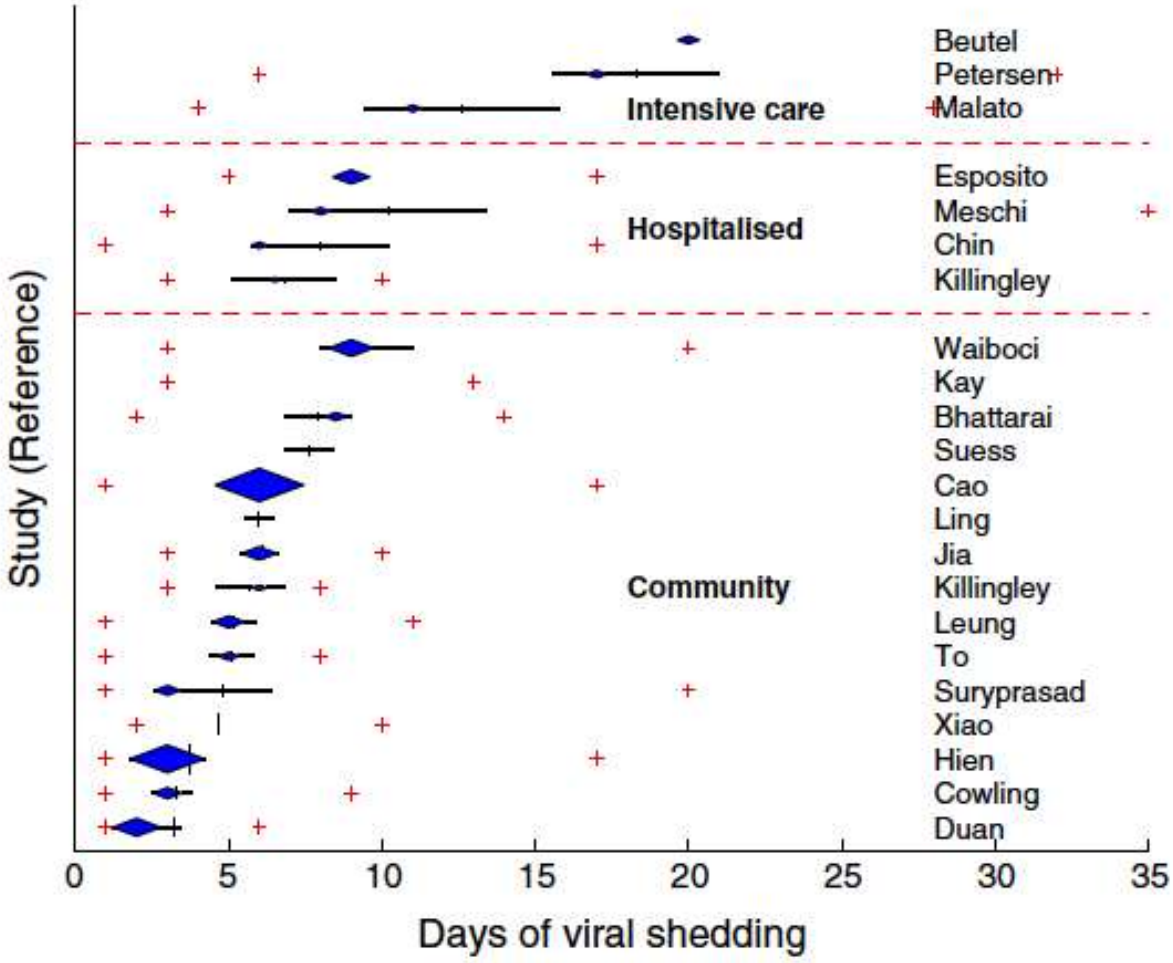


Figure 3: Kaplan-Meier curves of duration of (A) major symptoms (n=225) and (B) comparison of virus isolation in participants enrolled on day 3 after illness onset (n=216)

Fry AM et al. Lancet Inf Dis 2014; 14: 109-118

Duration (and level) of viral shedding correlates with illness severity



Fielding JE, et al. *Influenza Other Resp Viruses* **8,** 142–50 (2014).

Duration of viral shedding correlates with length of hospital stay

Table 3. Factors associated with total length of stay (LOS) in 99 consecutive influenza patients recruited in the viral shedding study

Characteristics	Unadjusted median LOS (IQR), days*	Adjusted HR (95% CI) for hospital discharge†	*P*-value
Prolonged viral RNA detection‡			
Yes	18.0 (12.4–23.6)	0.36 (0.19–0.71)	0.003
No	6.0 (4.9–7.1)	1.00	
Complication			
Yes	8.0 (4.2–11.8)	0.31 (0.17–0.57)	<0.0001
No	5.0 (3.8–6.2)	1.00	
Oseltamivir within 2 days			
Yes	6.0 (4.6–7.4)	2.12 (1.30–3.47)	0.003
No	13.0 (7.3–18.7)	1.00	
Influenza vaccination§			
Yes	5.0 (3.6–6.4)	2.14 (1.18–3.85)	0.012
No	7.0 (6.0–8.0)	1.00	

Lee N et al.
Antiviral Ther 2007; 12: 501-8

Level of viral shedding correlates with length of hospital stay

ABSTRACT# LBP-5

Presentation Date: Thursday, 25 August 2016

Viral load and length of stay in adults hospitalised with viral acute respiratory illness

Tristan Clark, Karl Nicholson

University of Southampton, Southampton, Hampshire, United Kingdom

Conclusion: High viral loads are associated with prolonged hospital length of stay in adults with viral acute respiratory illness. This further supports evidence suggesting that viral acute respiratory illness is a viral load driven process and suggests that viral load could be used in clinical practise to predict prolonged hospitalisation and prioritise antivirals.

Should co-primary clinical & virological endpoints be considered?

precedent from complicated UTIs

Complicated Urinary Tract Infections: Developing Drugs for Treatment

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2015

The primary efficacy endpoint should be a responder outcome.

- **Clinical and microbiologic response:** Resolution of the symptoms of cUTI present at trial entry (and no new symptoms) and the demonstration that the bacterial pathogen found at trial entry is reduced to fewer than 10^4 CFU/mL on urine culture (microbiological success).[11]

Virological endpoints: challenges

- *Choice of specimen*
  - oral, nasal, nasopharyngeal
  - upper vs lower
- *Method of detection*
  - culture vs PCR
  - quantitation
- *Standardization*
  - specimen collection
  - sample quality
  - detection methods
- *Choice of endpoint*
  - time to viral clearance?
  - negativity at day x?
  - reduction of titers/kinetics (AUC)?
  - …….?

ABSTRACT# LBO-6

Session Name: Late Breaking Oral Abstract Session

Presentation Date: Sunday, 28 August 2016

Session Time: 8:00 AM - 8:30 AM

Oral Presentation Time: 8:00 AM

The Evaluation of Virologic Endpoints for Efficacy Studies of Anti-influenza agent

John Beigel, Michael Hughes, Yajing Bao, Michael Ison, Justin Hoopes, Chris Myers, Richard Davey

Leidos in support of NIH/NIAID, Bethesda, MD, United States

ABSTRACT# P-659

Presentation Date: Saturday, 27 August 2016

Validation of Assays to Quantify Housekeeping Gene Expression to Determine the Impact of Sample Quality on Measured Viral Load in NP and OP Samples

Melinda Balansay-Ames

NHRC- Henry M. Jackson Foundation Contractor, San Diego, CA, United States

What is needed to study efficacy of antivirals in patients with severe influenza?

- Prospective & retrospective studies
  - to identify and validate appropriate ‘case definitions’ for severe influenza
  - to identify and validate appropriate clinical endpoints
  - to identify, standardize and validate virological endpoints

- Randomized controlled trials
  - need for improved efficiency
    - operational clinical networks?
    - novel (adaptive) designs?
  - controversy persists regarding oseltamivir efficacy for severe influenza
    - need for a placebo-controlled RCT in hospitalized patients?
  - only viable regulatory pathway at present = RCT in uncomplicated flu..?

Thank you