

# Controversies in the Prevention and Treatment of influenza

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# Regensburg



# Prevention of Influenza

- What are the benefits of influenza vaccination in the elderly?
- How best to prevent influenza in the elderly?
  - Can we induce herd immunity by influenza vaccines?

# Framework Influenza Vaccine Efficacy

- Endpoint: Influenza like-Illness (ILI), laboratory confirmed (clinical efficacy)
  - Difficult to measure, especially in pre-PCR times
- Serology as surrogate marker (serological efficacy)
  - Antibody titer in hemagglutinin-inhibition-Assay
  - Protection correlated to AIHA Titer, seen in experimental human infection, eg. AIHA 1:40 correlates with 50% reduction in ILI

# Claims

- Influenza vaccination in the elderly prevents
  - Influenza like illness (effectiveness 35%)
  - Influenza hospitalization (33%)
  - Influenza and pneumonia related deaths (47%)
  - All cause mortality (50%)

# Vaccination in the Elderly- Best evidence

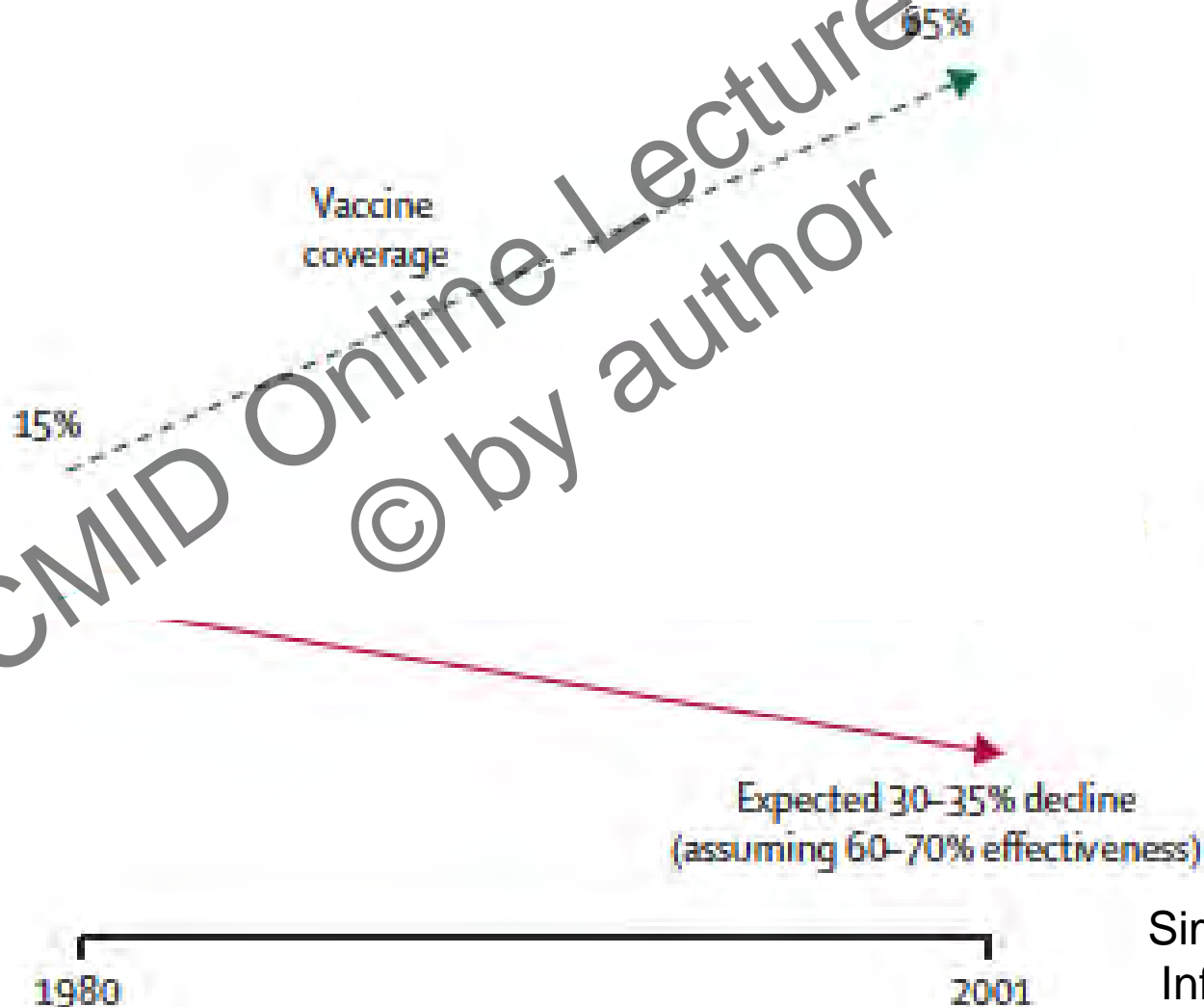
- One larger placebo controlled randomized controlled trial from 1994 (n=1838)

	Placebo	Vaccine	Risk/Rate-Ratio	Efficacy
Lab. conf. Influenza				
all	16/927	38/911	0,42	58%
60-69y	12/649	29/645	0,41	59%
70 and more	4/278	9/256	0,43	57%
Seroprotection (AH3N2, AIHA 1:100)				
all	5,9%	66,1%	11,2 (8,6-14,2)	
60-69y	4,9%	66,5%	13,6 (9,6-19,2)	
70 and more	8,3%	65,3%	7,9 (5,2-11,9)	

# Accumulating evidence in the 1990s and later...

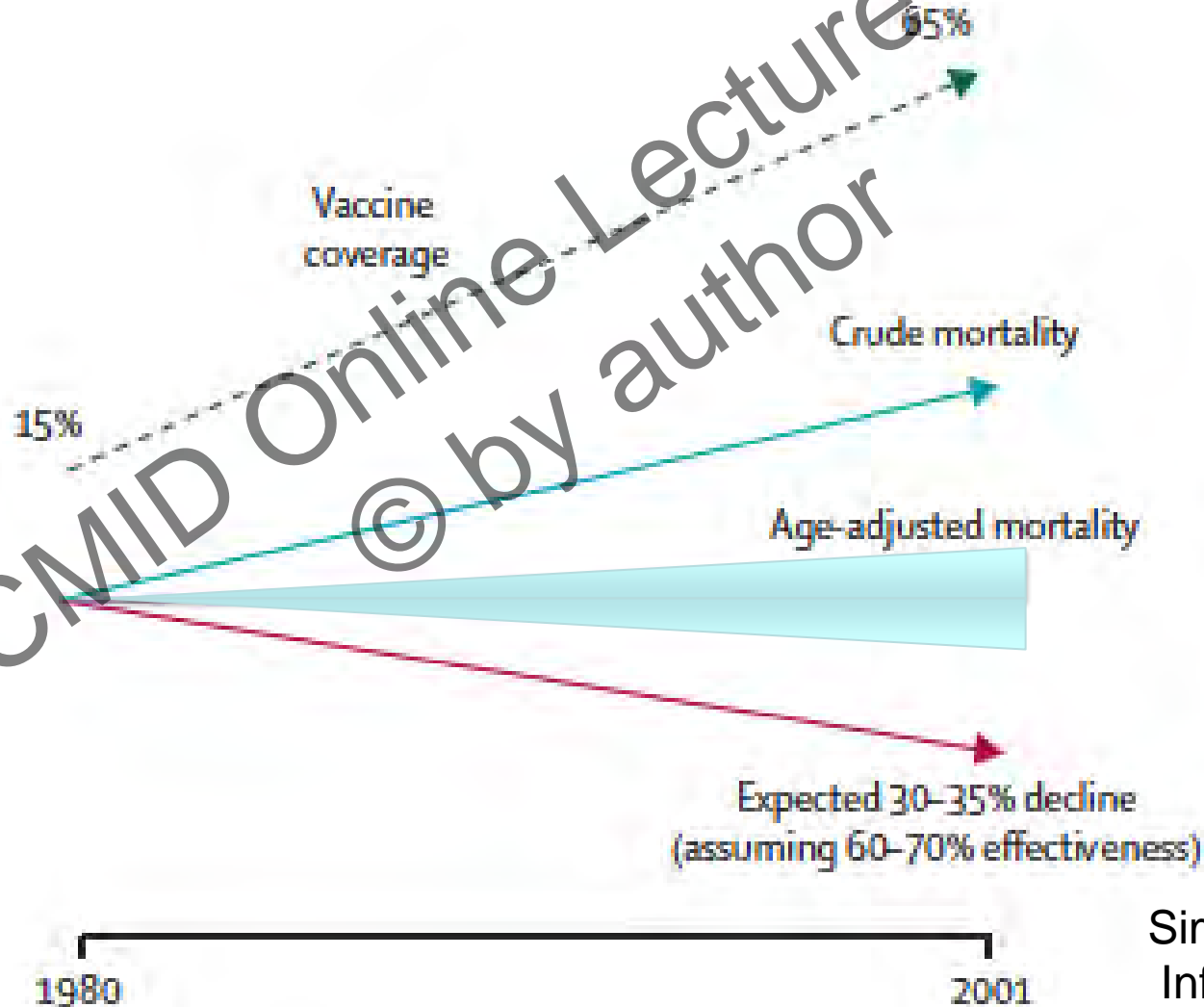
- Many cohort studies comparing outcomes of vaccinated and unvaccinated elder people
  - Within seasons with high viral circulation
  - Within seasons with good/bad match of vaccines
- Many cohort studies induce meta-analyses
  - Pre-1990s and post 1990 studies
  - Vaccine efficacy for all-cause mortality
    - In community living elderly >50%
    - In institutionalized elderly >68%

# Influenza Vaccine and All cause mortality US –scenario





# Influenza vaccine and Mortality - reality



## Some simple fact checking....

- If 50% of all cause mortality is averted by influenza vaccine, influenza mortality must cause at least 50% of all cause mortality
- Clearly in contradiction to epidemiological data
  - Influenza related death are at most 10% of all winter deaths in the US

# Checkpoints for Case control studies

- Seasonality:
  - Death rates should differ most in or shortly after high viral circulation
    - In contrast, reduction of mortality in vaccinated people was most pronounced before the circulation of influenza in several studies
- Severity /Match:
  - Influenza effects should be more pronounced in severe seasons and good vaccine match
- Selection bias: vaccine uptake higher in healthy elderly

# Better Designs for Case Control Studies?

- Test-negative design:
  - Outcome : influenza like illness with laboratory confirmation (positive test) vs. ILI with negative test (!)
  - Both groups show similar health care use
  - Outcome specific for influenza, relevant for evaluation of influenza effectiveness
  - If you want to have a closer look at design of clinical studies: ESCMID course on clinical studies, 26-28th October 2016, Seville

# Rating Influenza Vaccination in the Elderly

- Serologic responses good, even in the very old (>85 yo)
- Clinically effective (in preventing ILI or worse)
- Mortality benefit in community dwelling elders low, if at all
- Some mortality benefit in institutionalized elderly people (less bias prone case-control studies)

## Two Ladies...



Maria, 85yo, no chronic illness, still hikes in the Alps, albeit more slowly, works in the garden, cooks, 4 children, 7 grandchildren (7-40yo)



Hildegard, 95yo, no chronic illness, works in the garden, active in business, 2 children, 5 grandchildren 22-30yo

# How best to protect?

- Influenza Vaccination in the elderly
  - What is the best vaccine?
  - Is it good enough – should we add other preventive measures – such as vaccination of friends and families?

# How to make the Influenza vaccine more immunogenic?

- Intradermal vaccination – effect marginal
- Adjuvanted vaccine - more immunogenic (though in large trials superiority not clearly demonstrated), no data on clinical effectiveness
- High-dose vaccine – best data yet



# High Dose vs SD Vaccine in the Elderly

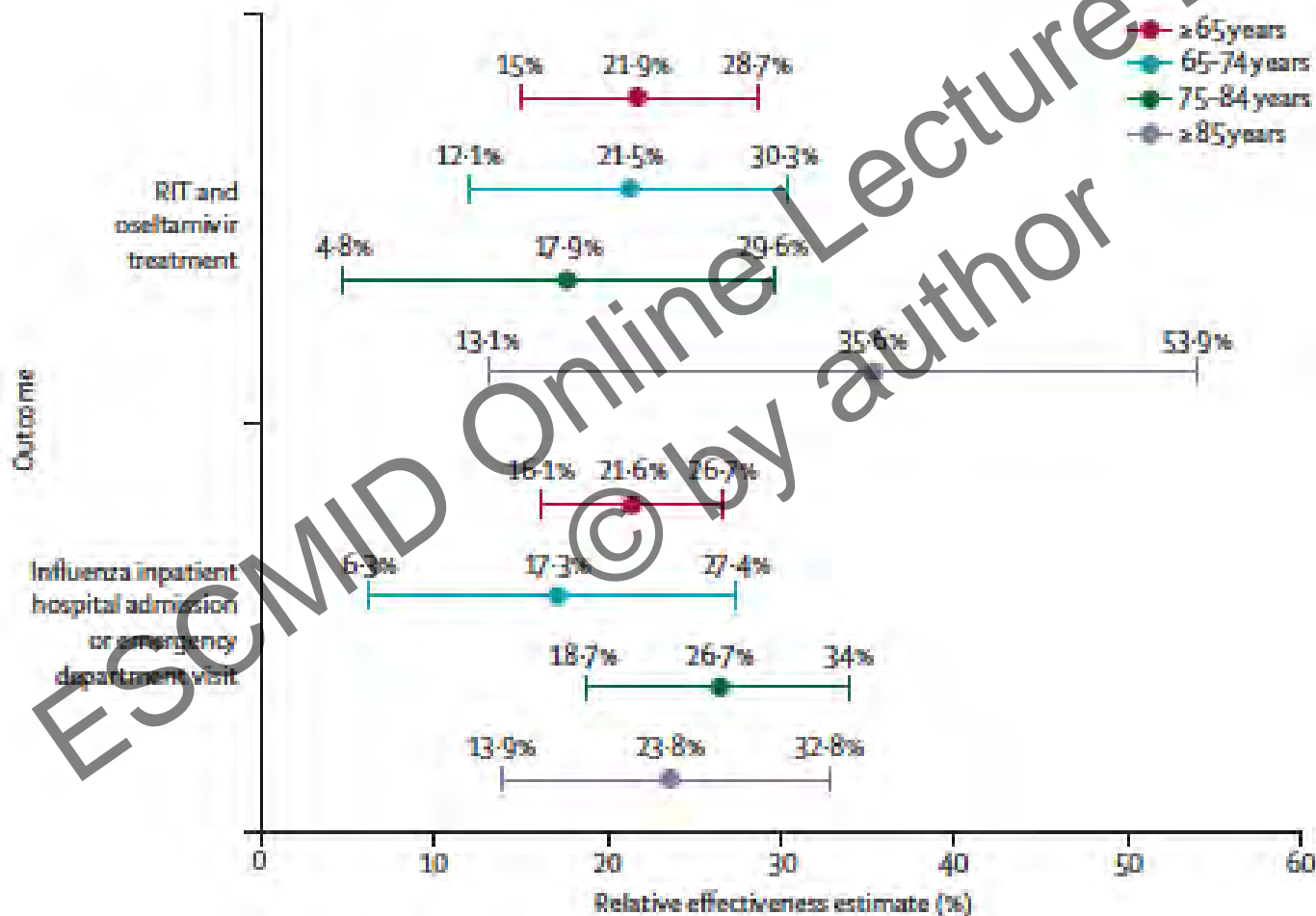
- 2975 HD vs. 1276 SD pts., median age 73y, 67% one, 34% two comorbidities

	SD (>75yo)	HD (>75yo)	HAI-GMT- Ratio	Rate Difference
Mean AIHA -Titers				
AH1N1	67 (62)	116 (104)	1,7	-
AH3N2	333 (339)	609 (533)	1,8	-
B	52 (64)	69 (68)	1,3	-
Seoprotection (AIHA 1:40)				
AH1N1	89,9%	76,8%	-	13,1
AH3N2	99,3%	96,5%	-	2,8
B	79,3%	67,6%	-	11,7

# HD-Vaccine: Clinical effective?

- Randomized study with 32.000 elderly, 66% < 75 yo, 34% 75 yo and more
  - HD vs. SD vaccine: 23% Efficacy in preventing lab confirmend ILI, resp. illness and related outcomes
  - Serologic and clinical efficacy in all age groups
- Case-control study
  - 900.000 pts. with HD, 130.000 pts with SD vaccine, 50% 65-75 yo, 36% 75-85 yo, 13% > 85yo
  - ILI defined as consultation with rapid test and prescription of oseltamivir (HD 22% effective)
  - Influenza-hospitalization (HD 22% effective)

# HD-vaccine: Is it clinically effective?



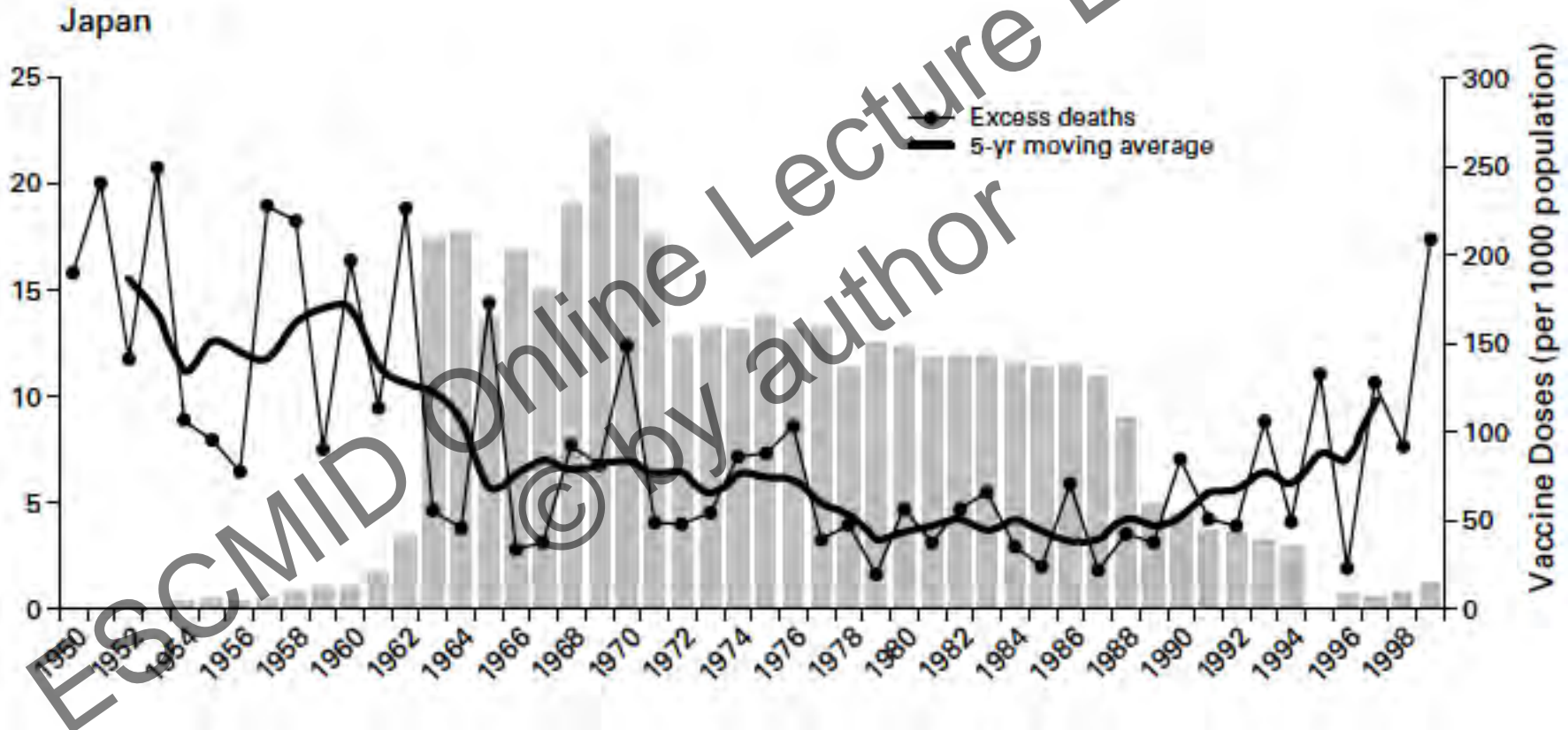
# Herd Immunity for the Protection of Elderly?

- Young children central for influenza epidemiology– high rates of infection, high number of contact
- Does vaccination of young children/school children protect elderly patients
  - For pneumococcal infections clearly demonstrated

# The Japanese Experience

- Introduction of Influenza vaccination for Schoolchildren in 1962, mandatory since 1972
- Coverage rates up to 85% in schoolchildren
- Growing concern of parents and doubt about efficacy led to termination of program in 1994

# The Japanese Experience



# Recommendations

- Influenza vaccination – is effective, does prevent respiratory illness (or worse)
  - Do not promise much more!
- Highdose vaccine –
  - best choice currently
  - modest higher efficacy, no concerns regarding safety
- Vaccination of children protects elderly – not generally accepted

# What to do with the two Ladies...



High dose vaccine (unfortunately not licensed in the EU)  
Vaccinate 7yo grandson?



Same  
Grandchildren are too old for herd protection criteria  
If institutionalized: vaccinate staff!



# Treatment of Influenza

- Are neuraminidase inhibitors effective at all?
- Are there cutoffs – when not to start or use neuraminidase inhibitors any longer?
- Is there a rationale for combination antiviral therapy?

## Let's take a poll

- Neuraminidase inhibitors have clinical efficacy
- Neuraminidase inhibitors have efficacy in vitro, not in vivo

# Efficacy of NIs in Influenza Complications

- Up to 2010 in all metaanalyses.
  - Use of NI prevents complications (lower resp. Infection, otitis media)
- Growing concern about data quality
  - Cochrane group went to original datasets
    - Endpoints not validated
    - Some adverse effects not properly reported
- Cochrane group (T. Jefferson) asked for complete original study data (not compilations)

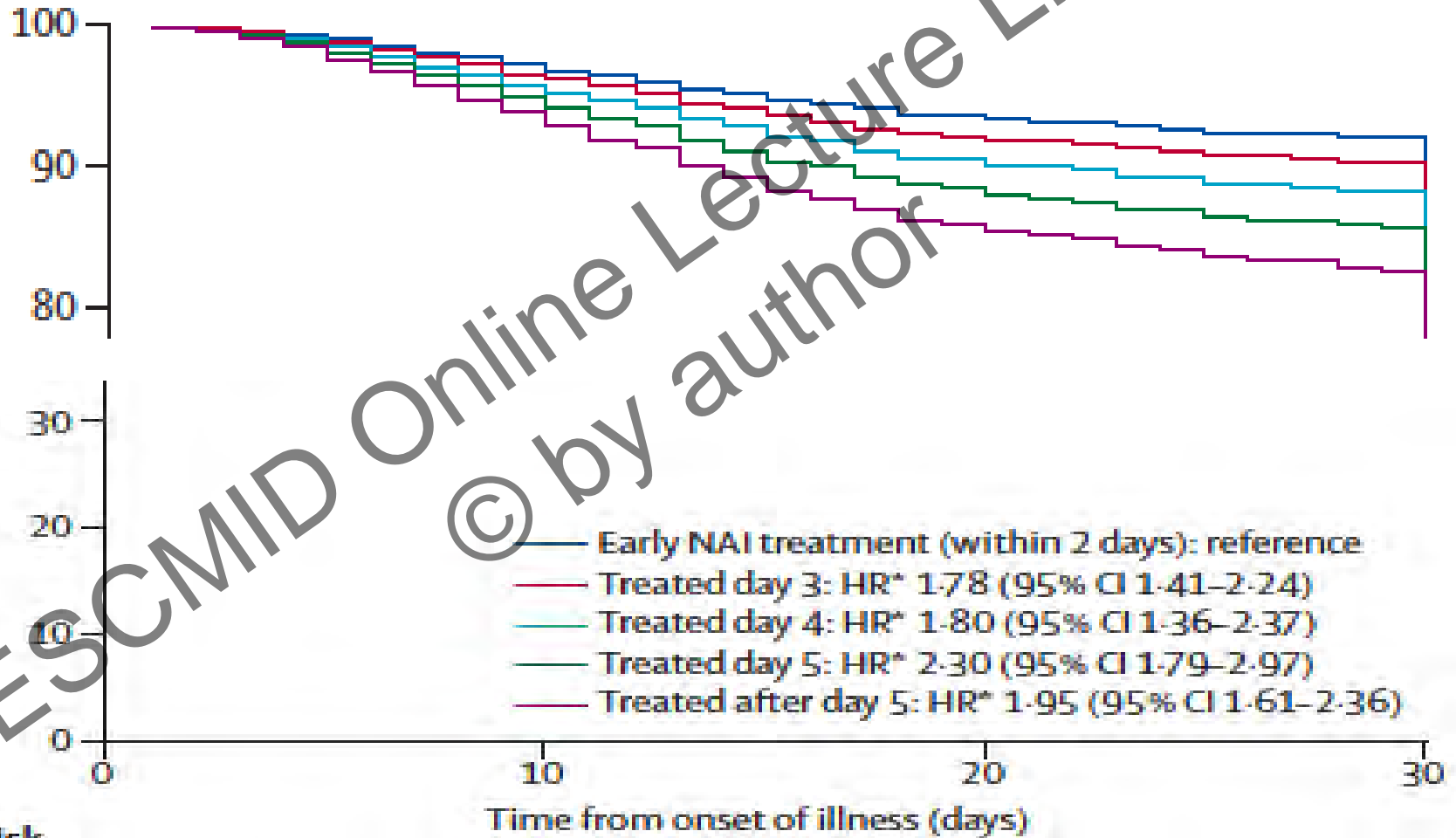
## Two new metaanalyses

- Oseltamivir/Zanamivir are effective in reducing time to symptom relief in children and adults (17h/24H)
- Oseltamivir/Zanamivir are effective in preventing infection after exposure
- No effect on complications (endpoints not validated, only low risk study participants)

# Clinical Efficacy of NIs in Other Studies

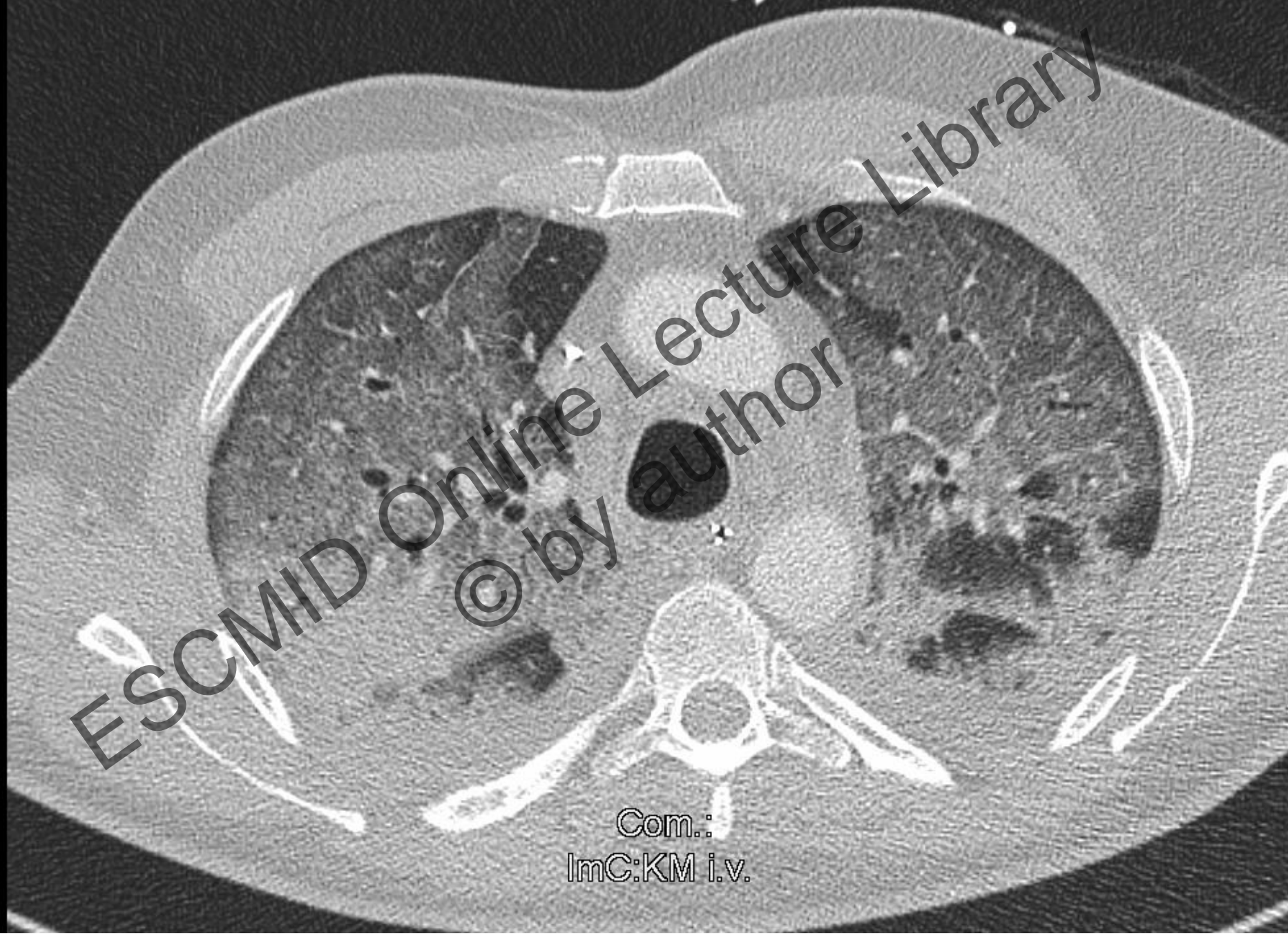
- Clinical efficacy demonstrated in many cohorts
- Metaanalysis of 78 cohorts with approx. 30.000 pts. 2009-11
  - median age 26y., 23% pregnant, 38% at least one comorbidity
  - 25% Pneumonie, 23% ICU
  - 36% untreated, 64% treated (92% oral oseltamivir, 8% other neuraminidase inhibit.)
  - Over all reduction of mortality (OR 0,48), significant with start until day 4 of symptoms
  - Reduction of mortality in pregnancy (OR 0.16-0.27)

# Survival and NI Therapy



## 53 yo man in the ICU

- Progressive dyspnea, cough, fever for 4 days
- Family called ambulance, admission through ED
- 53yo man, CLL, allogeneic stem cell tx 1/2015, recurrent CLL therapy with donor lymphocytes
- Infection bacterial/viral? GvHD? Lung edema with cardiac failure
- CRP 150 mg/l (UN 3), PCT 0.27ng/ml (UN 0.2)
- Leukocytes 3800/mcl, 46% neutrophils
- Start Antibiotics, Steroids and noninvasive ventilation



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## 53yo man, ICU 3.3.2016

- 3.3. Influenza A positiv; no other pathogens – start Oseltamivir
- 8.3 Influenza PCR positive
- 15.3. positive
- ..
- 19.4. positive (low titre) -
- 26.4. negative

## Rules for using NIs

- If you have a patient with severe influenza (eg pneumonia) with replication – treat
- Treatment course 5days, can be repeated
- There is no data on the maximum time, but 14days seems sensible to most
  - All eminence base (R.G. Webster)
- What if there is still replication?

## 53yo man, ICU 3.3.2016

- 3.3. Influenza A positiv, B , RSV, Adenovirus negativ – start Oseltamivir
  - Sequence shows wild type virus
- 8.3 Influenza PCR positive
- 15.3. positive
- 5.4. positive
  - Sequence: H275Y mutation
- 19.4. positive
- 26.4. negative

# Viral Turnover and Resistance

- Studies in experimental influenza infection:  
10<sup>exp11</sup> virus particles within 7 days infection
- Mutation rates of RNA-viruses are high - all single and dual mutants will be produced in one infection cycle
- Resistance to Oseltamivir with one nucleoside change.....
- Use more drugs or raise the barrier to resistance!

# Combination antiviral therapy for Influenza

- Amantadine and Ribavirin more effective, reduction of resistance development in animal models
- Amantadine, Ribavirine and Oseltamivir currently in clinical trials

## Conclusions

- Neuraminidase inhibitors have clinical efficacy – but the evidence for severe influenza is low
- Open questions about the optimal use of Nis:
  - Which patient to treat?
  - Cutoffs for starting and stopping therapy?
- There is a rationale for combination therapy – new strategies in development and clinicals studies

# Other Controversies Worthy Studying

- Pathogenesis: Virus vs. Host Reaction
- Mandatory Vaccination of Health Care Workers
- Cause of Mortality: Viral or Bacterial Pneumonia
- What defines best immunity: T-cells or Antibodies?
- Does yearly vaccination yield additional benefit?