INFLUENZA

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INFLUENZA

- Don’t confuse with the common cold
- Symptoms may be similar BUT

  those with influenza are sick

  those with coryza (cold) are unwell!

INFLUENZA

- Fever
- Headache
- Shivering perhaps genuine rigor
- Polyarthralgia
- Cough (non productive at first)
- Sore throat
- Rhinorrhoea
- Emotional Lability

INFLUENZA

	Common Cold	Influenza
Incubation	12 hrs – 5 days	1 – 3 days
Fever	+ or -	++
Cough	+ or -	+
Rhinitis	+	-
Polyarthralgia	-	+
Toxaemia	-	+

(After J Murtagh)

INFLUENZA

Complications

- Secondary chest infection
- Pneumonia (Staph or Strep - note mortality)
- Encephalitis

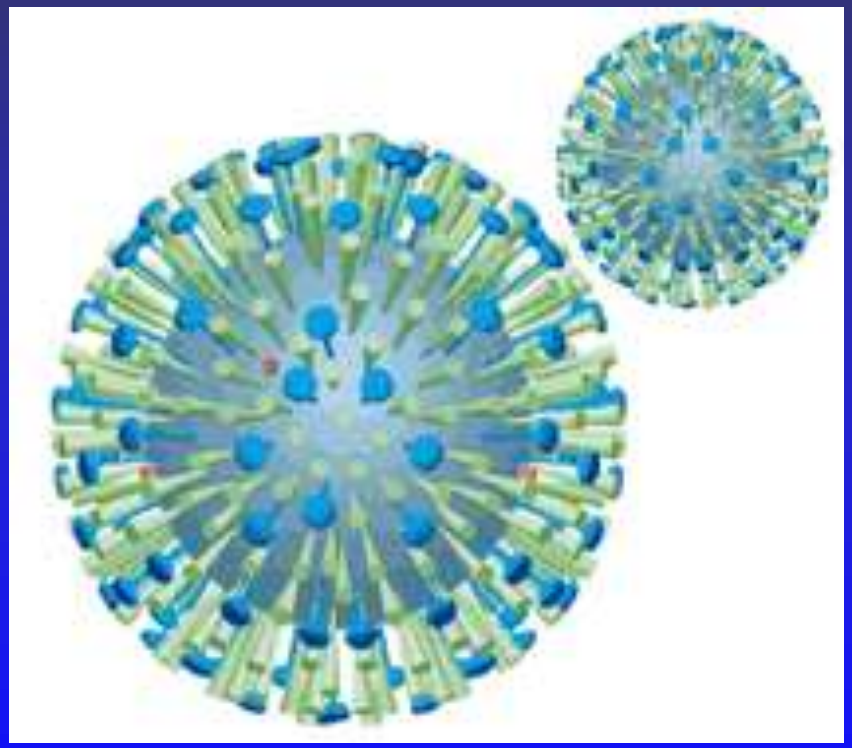
INFLUENZA

Call it INfluenza - Not “flu”

There is “stomach flu”, “Flu”, “Flu Bug” etc but only one

INFLUENZA

What is Influenza



Influenza is

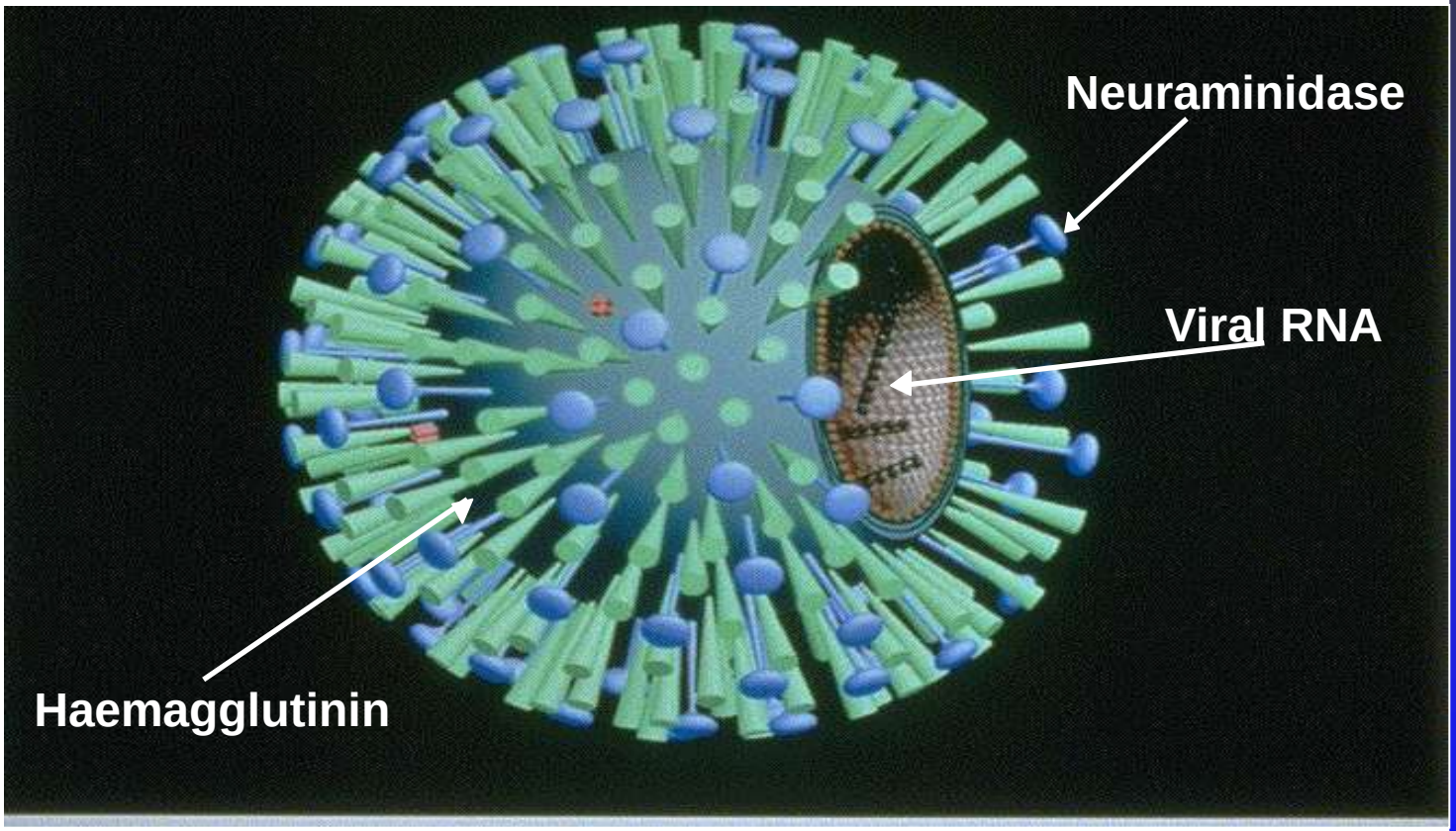
- a respiratory infection
- **caused by type A & type B viruses**
- most common in autumn & winter
- **enters through mucous membranes - mouth, nose, eyes**
- highly contagious - airborne
- **severe season >20% population infected**

Influenza

Types of influenza

- Clinically relevant strains are divided into type A and B
- **Type A**: Infects many different species (sea mammals, domestic fowl, swine, other farm animals, primates)
  - Responsible for epidemics and pandemics
  - The most highly mutating form
  - Type A viruses are subdivided based on the structure of their surface proteins (eg HxNy)
- **Type B**: Primarily infects humans
  - Less mutable
  - Cause regional epidemics
  - Antigenic drift but not shift

Structure of Influenza A virus



Adapted from Laver et al[6]

Swine Flu = Influenza A H1N1-09

Influenza Surface Proteins

Haemaglutinin

- Rod Shaped
- **Most common surface protein**
- Responsible for viral attachment to and penetration of host cells
- **Contains antigenic sites targeted by host immune system**
- 15 sub types identified
- **3 infect humans - H1, H2, H3**

Influenza Surface Proteins

Neuraminidase

- Mushroom shaped
- **Second most common surface protein**
- Plays an essential role in release and spread of virus from infected cells
- **Major target for host antibody**
- 9 sub types identified
  - two infect humans - N1 & N2

Swine Flu – NZ data (ESR)

Sampled 1696 people in the study

- Pre-March 2009
  - 11% population immune (mostly elderly)
- March 2009- 2010
  - 18% developed immunity
  - Mostly school age (one in 3 kids infected)
  - 50% with no symptoms
- 29% immune – greater with 2010 Flu vaccination

Swine Flu – NZ data (ESR)

Sampled 1696 people in the study

- Among newly infected
  - 29% overall
  - 50% in Pacific Islanders and 36% in Maori
  - ?Age structure, ?communal living, ?susceptibility
- High risk Groups
  - Pregnancy
  - School-age with co-morbidities (asthma)
  - Obese

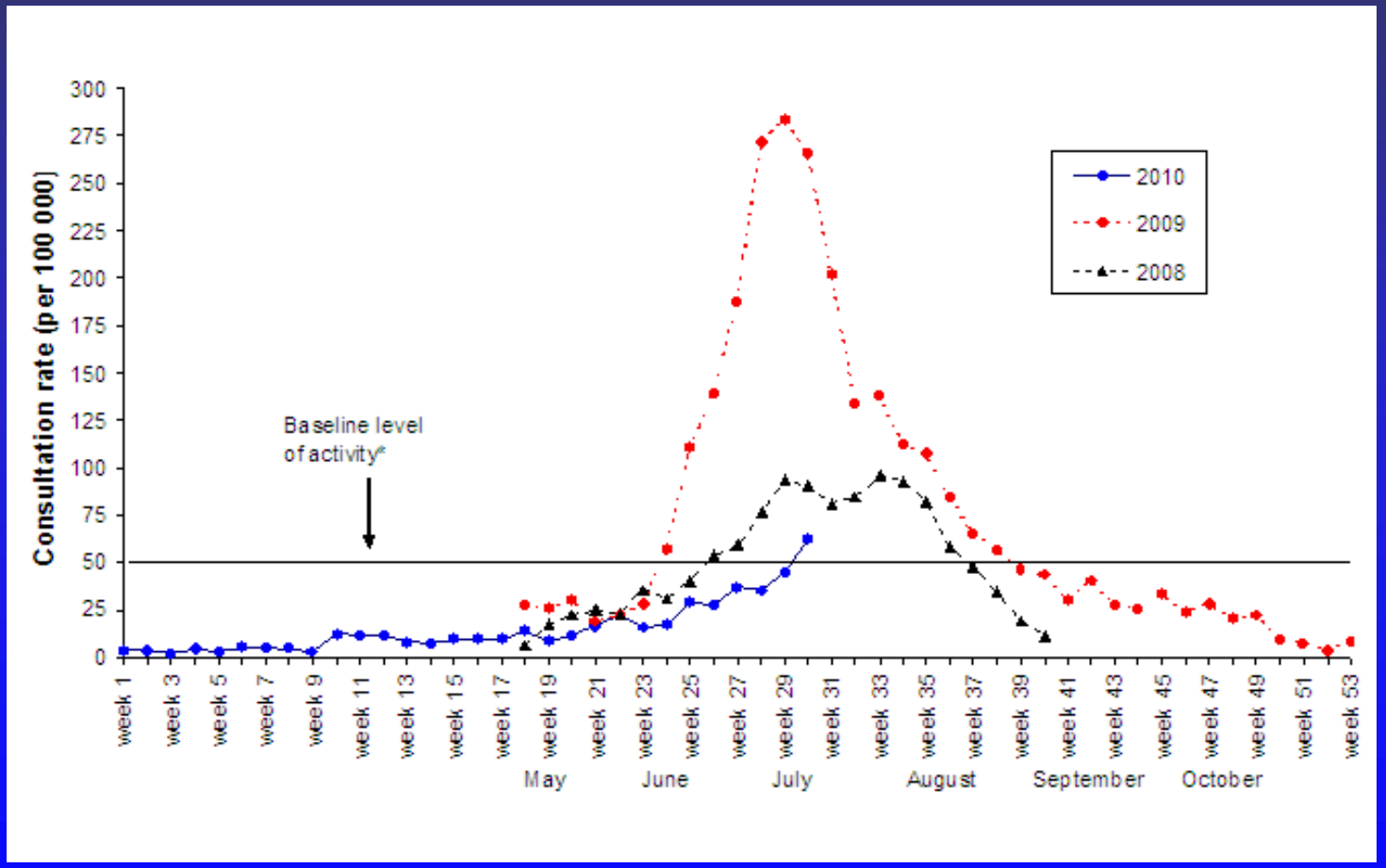
Swine Flu – NZ data (ESR)

Sampled 1696 people in the study

- 18% newly infected (780,000)
  - 1000 hospitalised (1 in 780 or 0.1%)
  - 35 deaths (1 in 22,000 infected or 1 in 30 hospitalised or 4% of hospitalised)
  - No increase in health care workers
- Activity low at present – outbreak in Nth Island.

Swine Flu – NZ data (MOH)

Weekly consultation rates for influenza-like illness in New Zealand, 2008-2010



Source

Prevention and containment

Healthy

- Vaccination

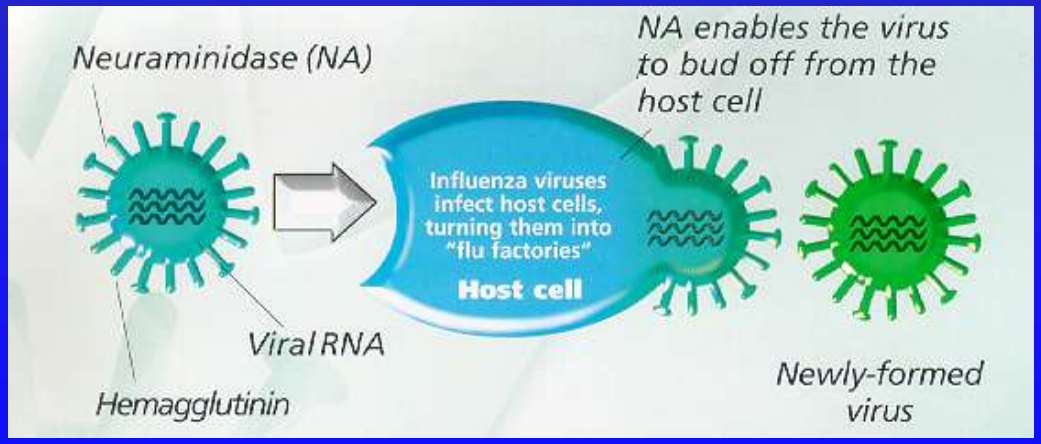
Unwell

- Hand-washing
- Cover sneezes
- Stay at home

Neuraminidase Inhibition - New Directions

How influenza infects you:

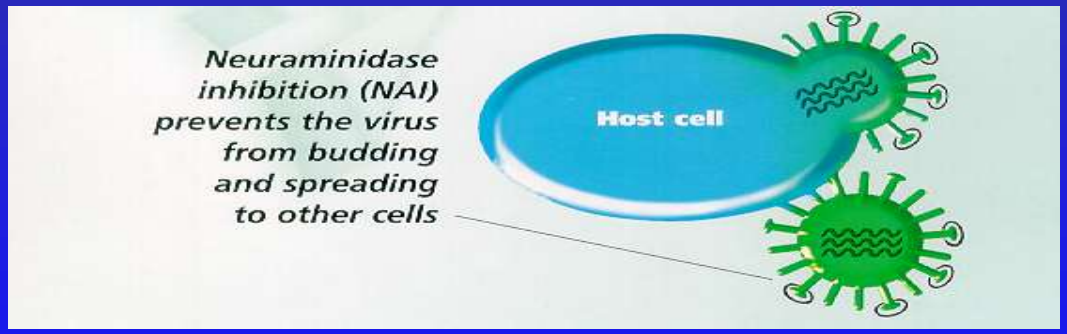
- viruses cannot multiply by themselves - must take over a living cell
- the influenza virus multiplies in the following ways:
  - virus particle lands on cell in respiratory tract
  - particle enters cell, releases genetic material
  - genetic material takes over the cell forcing the production of new influenza virus
  - new virus particles assembled and preparation for release
  - Neuraminidase enables the virus to bud from the host cell



Adapted from Laver et al[6]

Neuraminidase Inhibition - New Directions

- NAI's inhibit the release of new virus
- Prevent the virus from budding and spreading to other cells



Adapted from Laver et al

Influenza Surface Proteins

- **The influenza viruses are highly variable and each subtype can exist in many different strains**
- Most parts of the surface proteins (haemaglutinin and neuraminidase) vary year by year
- **HOWEVER, the active site of neuraminidase is conserved in all strains**

TREATMENT

Neuraminidase Inhibitors

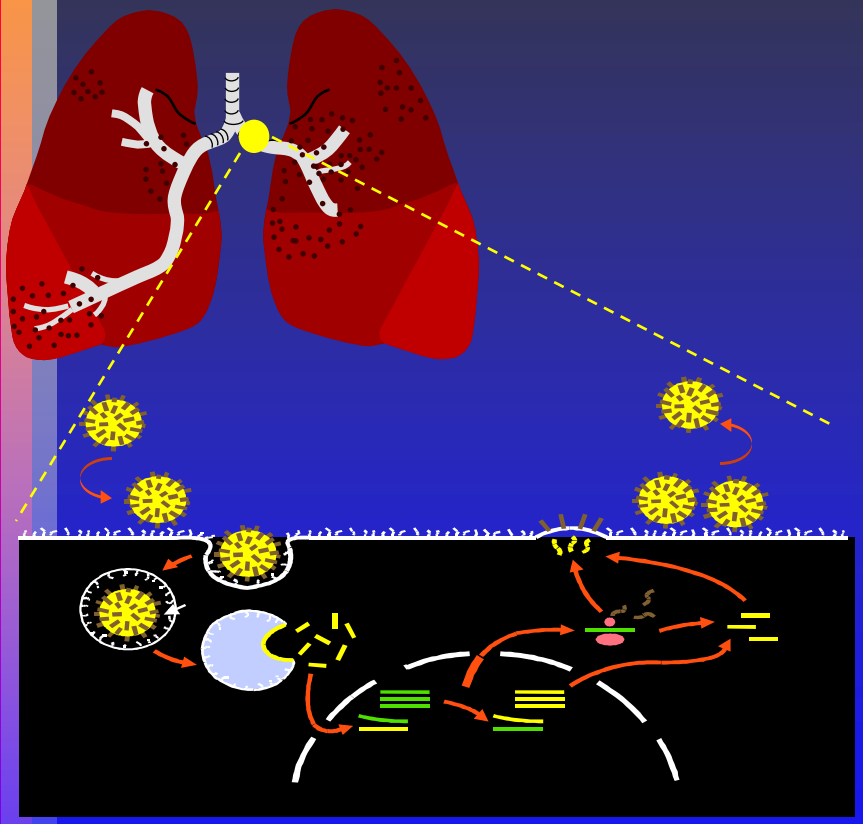
- Zanamavir (RELENZA) - inhaled
- Oseltamivir (TAMIFLU) - oral

Effective against both influenza A and B

Neuraminidase Inhibition

- **A new class of antiviral**
- **Zanamivir (RELENZA) and** oseltamivir (TAMIFLU) are in this class
- **Block the active site of the NA protein, prevents virus budding and spreading to other cells**
- Fewer infected cells reduces symptom severity
- Effective against type A and B viruses
- **Initial lab studies suggest low incidence of resistance**

Relenza - Mechanism of Action



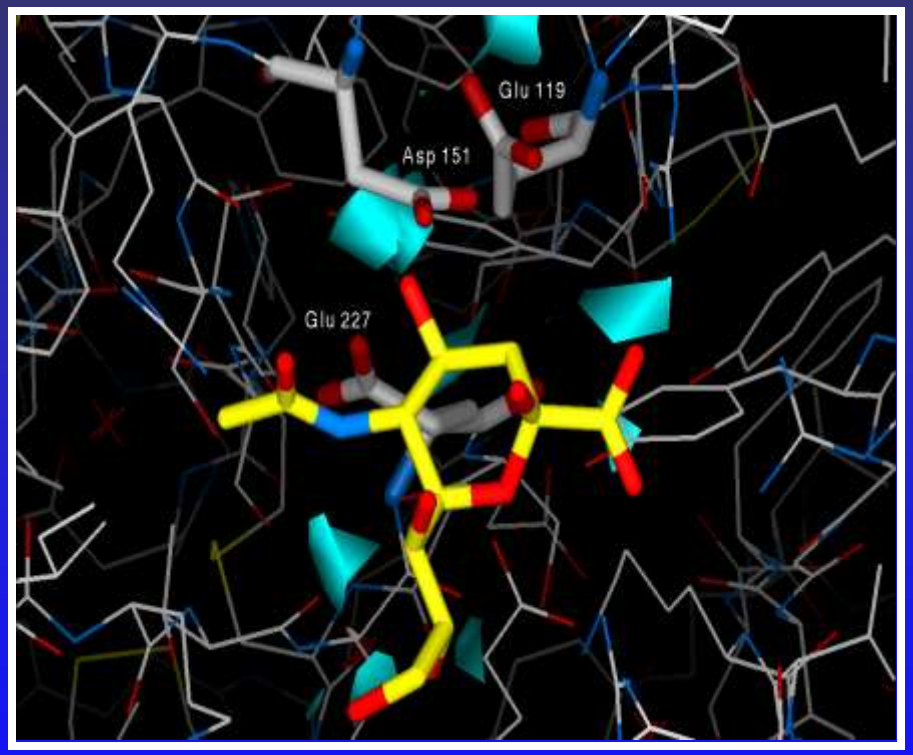
Virus attaches to airway cells

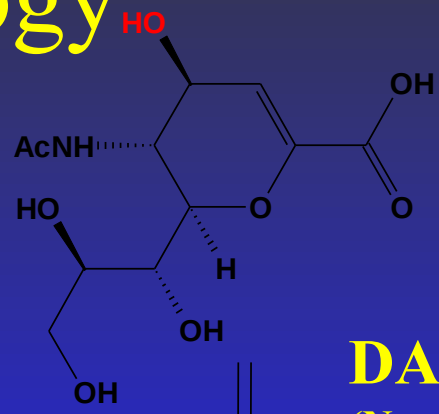
Viral growth

Virus neuraminidase releases new virus into airway

- Novel inhaled product for the treatment of influenza A & B (all subtype
- Potent, highly selective inhibitor of virus neuraminidase
- Site of action is in the airway itself - inhaled delivery is logical
- Topical delivery - very high drug levels at site of action, low systemic exposure (no safety issues)

Relenza™ (zanamivir) was rationally designed using computer-aided technology





DANA
(Neu5Ac2en)

Zanamivir
(4-guanidino - Neu5Ac2en)

The MIST Study Group

Randomised trial of efficacy and safety of inhaled zanamivir in treatment of Influenza A and B virus infections.

Methodology

- **Multicentre study - Australia, New Zealand & South Africa**
- **Randomised, double blind, placebo controlled trial of 455 patients with influenza-like symptoms.**
- **Treated with 10 mg inhaled zanamivir twice daily for 5 days or placebo.**
- **Analysed by intention to treat (ITT), influenza positive (IP) and high risk patients.**

The Lancet,1998, Vol. 352, pp 1877-1881

The MIST Study Group Primary End Point

Median time from initiation of treatment (Day 0) to alleviation of clinically significant symptoms of influenza:

- Temperature < 37.8°C, no feverishness
- Myalgia, cough, sore throat and headache scored as ‘none’ or ‘mild’
- Maintained for 3 diary card readings (≥24h)

The Lancet,1998, Vol. 352, pp 1877-1881

The MIST Study Group
Patient eligibility

- 12 years and over
- First dose of medication within 36 hours
- Fever/feverishness and two of the following symptoms: headache, cough, myalgia, sore throat
- Influenza circulating in the community
- Patient will not be compromised by receiving treatment
- Not pregnant, likely to become pregnant or breastfeeding

The Lancet,1998, Vol. 352, pp 1877-1881

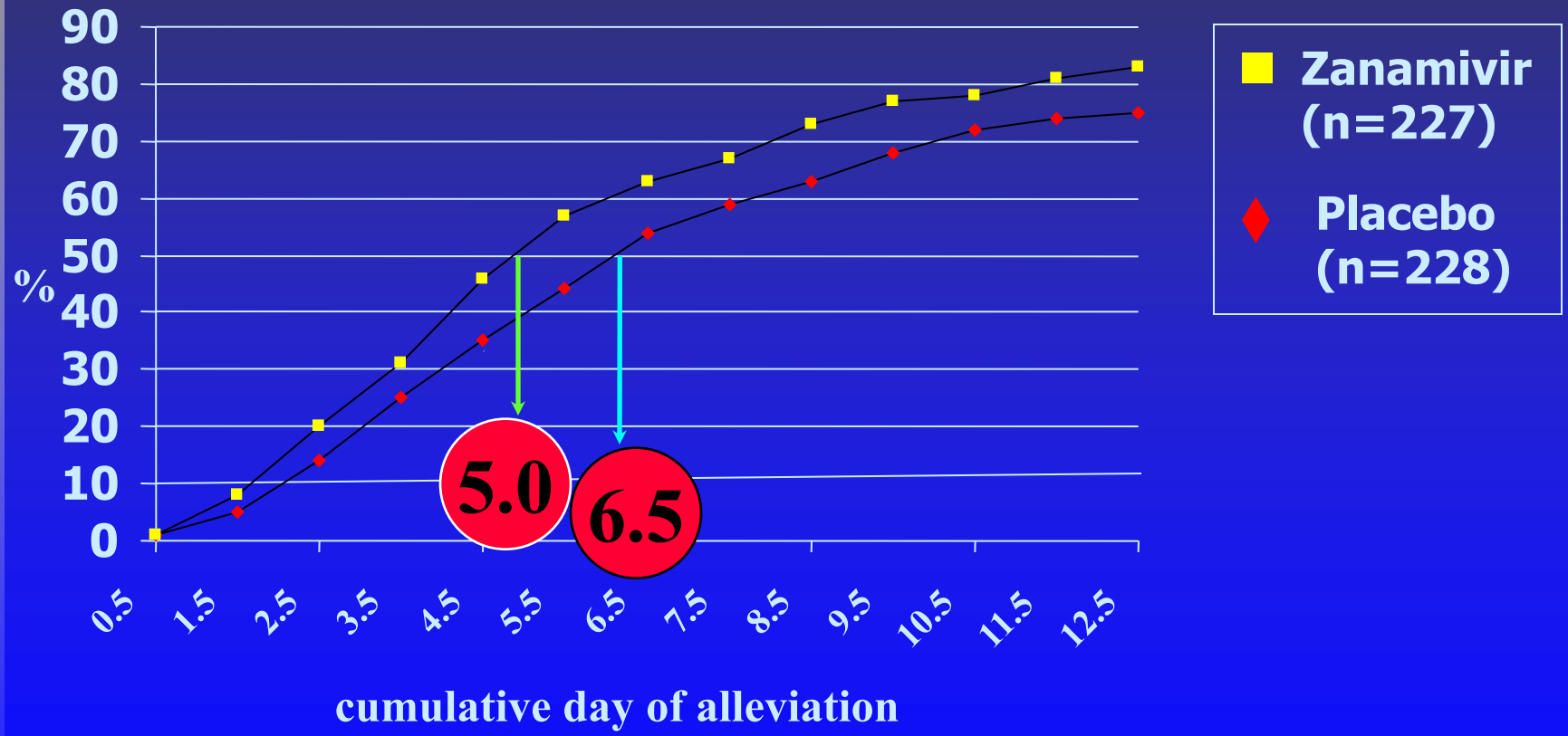
The MIST Study Group Demographics

- 53% male
- Mean age 37 years (range 12-82)
- 22% smokers
- Median duration of symptoms 26 hours
- 6% were vaccinated
- 91% took all the medication
- 71% flu positive
- 17% high risk

The Lancet,1998, Vol. 352, pp 1877-1881

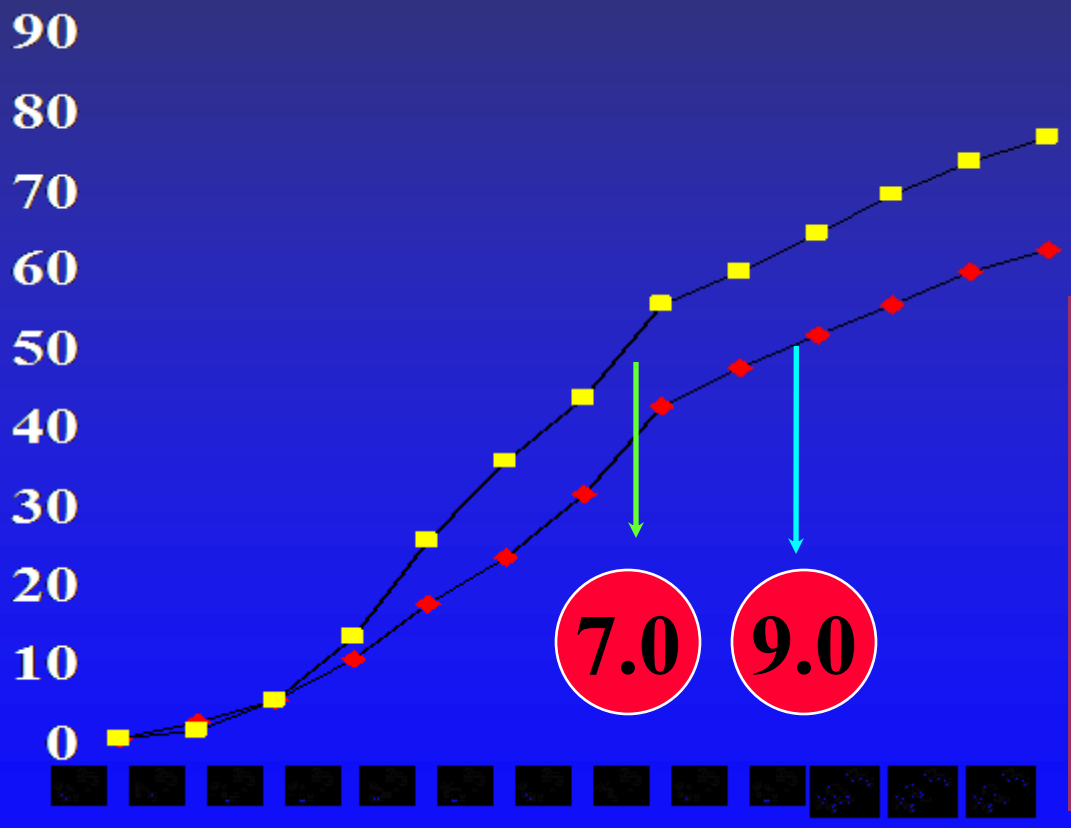
The MIST Study Group

Intent to treat - Alleviation of clinically significant symptoms (p=0.011)



The Lancet,1998, Vol. 352, pp 1877-1881

The MIST Study Group
Intent to treat - Return to normal activities



Median day

Zanamivir 7.0 days

Placebo 9.0 days

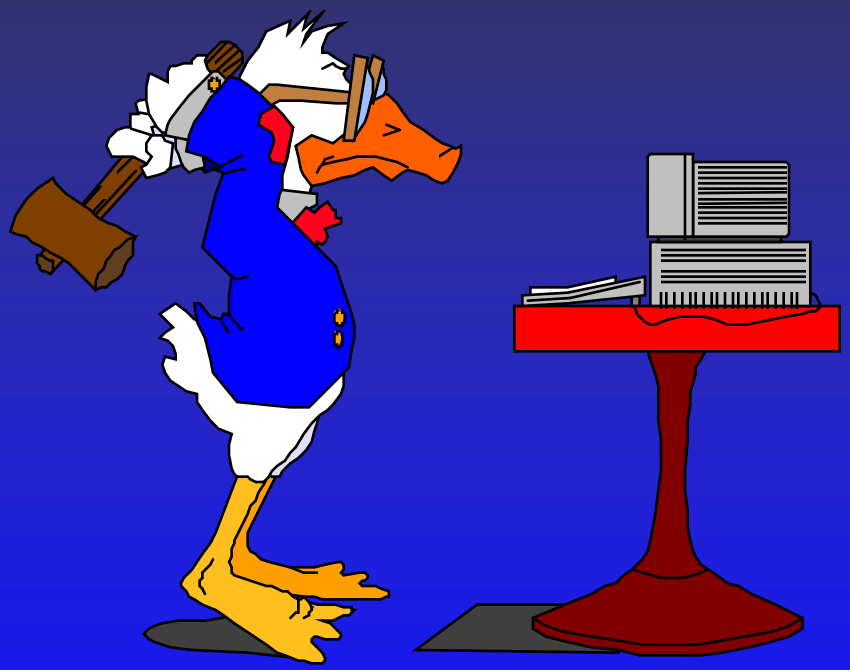
$p<0.001$

The Lancet,1998, Vol. 352, pp 1877-1881

The MIST Study Group Conclusions

- Clinical efficacy of inhaled zanamivir confirmed, 1.5 days benefit in ITT population (up to 2.5 day benefit in high risk patients).
- Reduction of severity of symptoms as well as reduced duration of illness compared to placebo.
- Significantly earlier return to normal activities in zanamivir treated patients compared to placebo.
- Similar adverse event profile to placebo reported in ITT population and high risk patients.
- Significantly less complications (32%) and associated antibiotic use (25%) in high risk patients compared to placebo.

The Lancet,1998, Vol. 352, pp 1877-1881



Influenza;
Groups at Higher Risk of Complications

- Elderly, especially in residential care units

- Patients with:
  - chronic respiratory disease e.g. asthma, COPD
  - chronic heart disease
  - chronic metabolic disease e.g. diabetes mellitus
  - immuno-suppression due to treatment or disease
  - haematological disorders
  - chronic renal failure

The MIST Study Group
% Complications and Associated Antibiotic Use in High Risk Patients

	Placebo	Zanamivir	Difference	p-value
Complications	46%	14%	32%	0.004
Antibiotic use	38%	14%	25%	0.025

The Lancet,1998, Vol. 352, pp 1877-1881

The MIST Study Group Adverse events

- A similar adverse event profile was reported for zanamivir treated patients compared to placebo.
- High Risk population - fewer adverse events reported for zanamivir patients compared to placebo
  - 38% vs 56%

The Lancet,1998, Vol. 352, pp 1877-1881

Relenza - Safety

- Assessed in 6138 subjects and patients
- Favorable safety profile consistent with:
  - **Specificity for influenza virus neuraminidase**
  - **Topical delivery / low systemic exposure**
  - **Non-metabolized**
- In randomized Phase II / III studies

- 2289 patients treated with zanamivir, all dosing regimens

Learning from Clinical Phase II / III Studies

- **Influenza can be diagnosed clinically.**
- **Treatment must be initiated within 48 hours of symptom onset .**
- **Treatment offers a 67% to 84% protective efficacy against influenza symptoms.**
- **Complication rates in all groups , but especially high risk , falls significantly.**

Influenza Can Be Diagnosed Clinically

- **Importance of surveillance data : ESR-GlaxoWellcome**
- **Awareness of local and community symptom clusters and risk groups**
- **70% correct diagnosis with**

  fever>37.8 : *plus two of*

  myalgia

  sore throat

  headache

  respiratory symptoms