Emerging and antiviral-resistant influenza infections: new drug development and therapeutic options

Dominic Dwyer
ICPMR and Pathology West
University of Sydney and Westmead Hospital
Westmead NSW
Australia

PathologyWest
supporting hospitals and local communities

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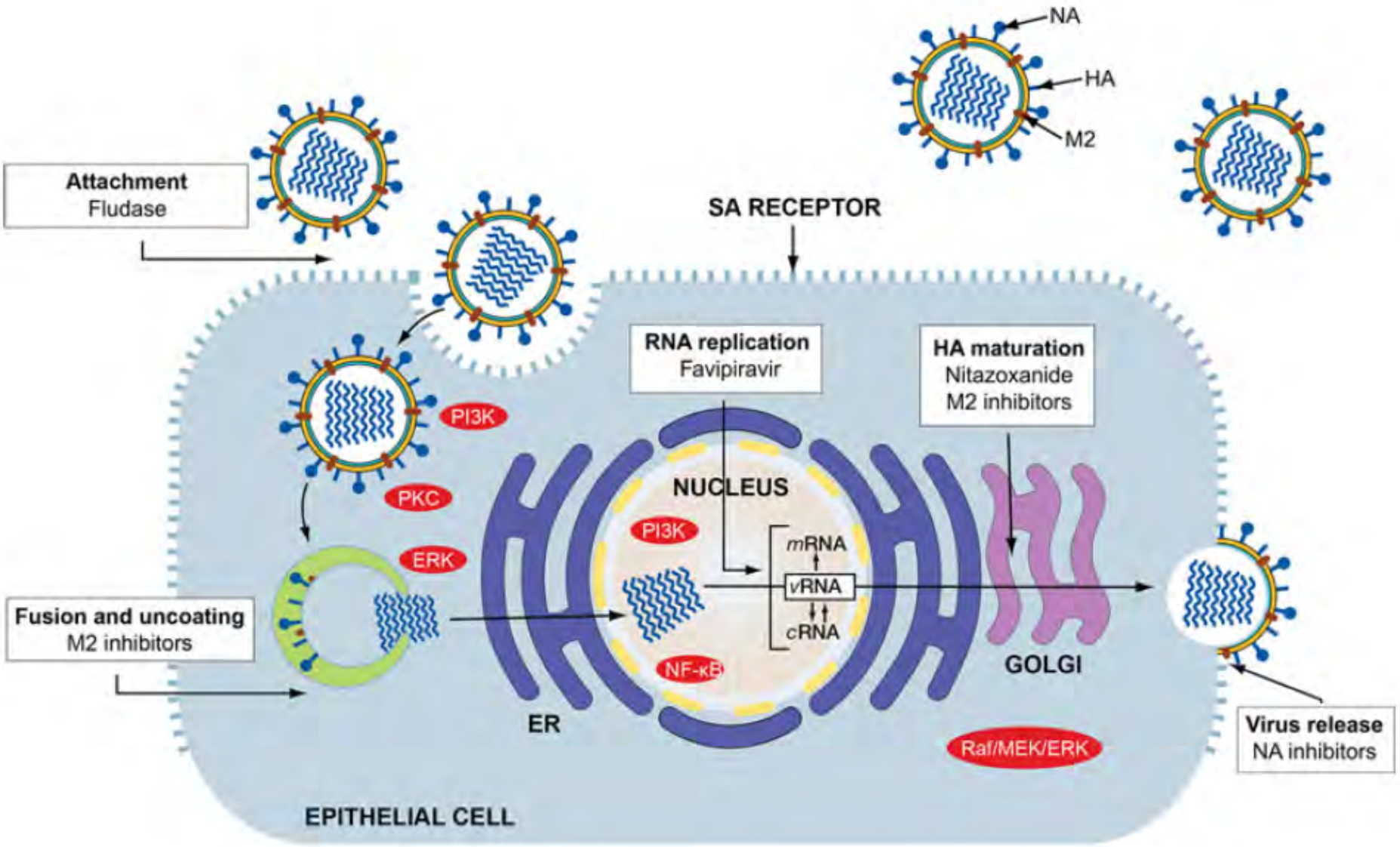
Influenza virus replication inhibitors



Webster RG et al. Ann NY Acad Sci 2014;1323:115

Antivirals for influenza

Class/agent	Brand name	Route
M2 inhibitors		
Amantadine	*Symmetrel*	*oral*
Rimantadine	*Flumadine*	*oral*
Neuraminidase inhibitors		
Zanamivir	*Relenza*	*inhaled, IV*
Oseltamivir	*Tamiflu*	*oral*
Peramivir	*Rapivab*	*IV (IM)*
Laninamivir	*Inavir*	*inhaled*

Antivirals for influenza

Class/agent	Brand name	Route
RNA polymerase inhibitors		
Favipiravir (T-305)	*Avigan*	*oral*
HA receptor inhibitors		
DAS181	*Fludas*	*inhaled*
Immunomodulators		
Nitazoxanide	*Alinia*	*oral*

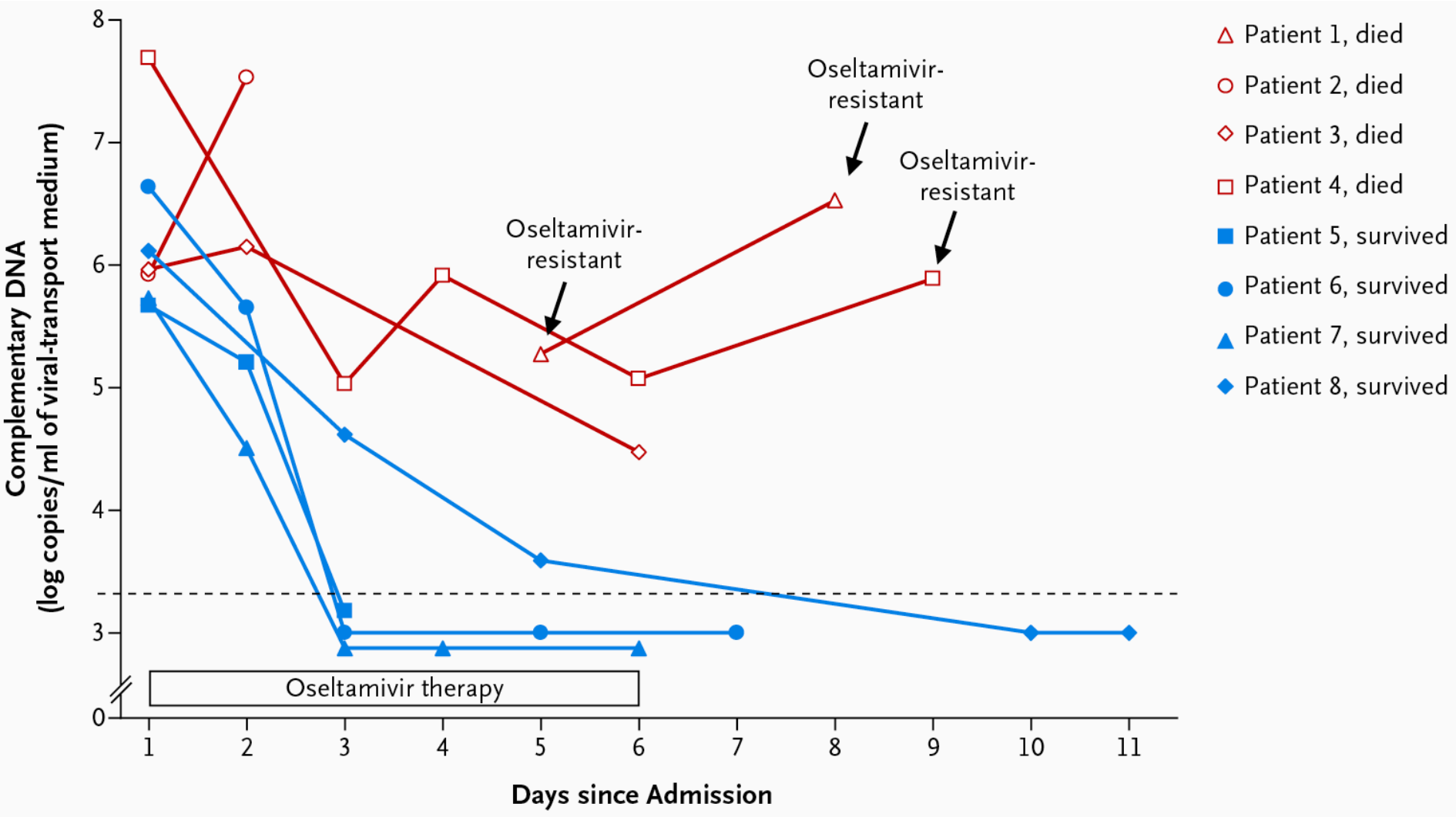
‘Intrinsic’ antiviral drug resistance

	Oseltamivir (Tamiflu)	Zanamivir (Relenza)	Adamantanes (amantadine)
H1N1 09 (‘swine’ flu)	sensitive	sensitive	*resistant*
H1N1 (seasonal)	*resistant (2B)* sensitive (2C)	sensitive sensitive	sensitive *resistant*
H3N2 (seasonal)	sensitive	sensitive	*mostly resistant*
B	sensitive	sensitive	n/a

‘Acquired’ oseltamivir resistance in A/H5N1

All WT

H274Y



De Jong M et al, NEJM 2005;353:2667-72

How should we use antivirals in influenza treatment?

- Typical influenza-like illness (if <48 hours)
- Severe clinical illness
  - Admitted to hospital
  - Admitted to ICU
- Immunosuppressed patients
- Pregnant women
- After 48 hours of illness?
- As prophylaxis?
- Oral, inhaled, intravenous?

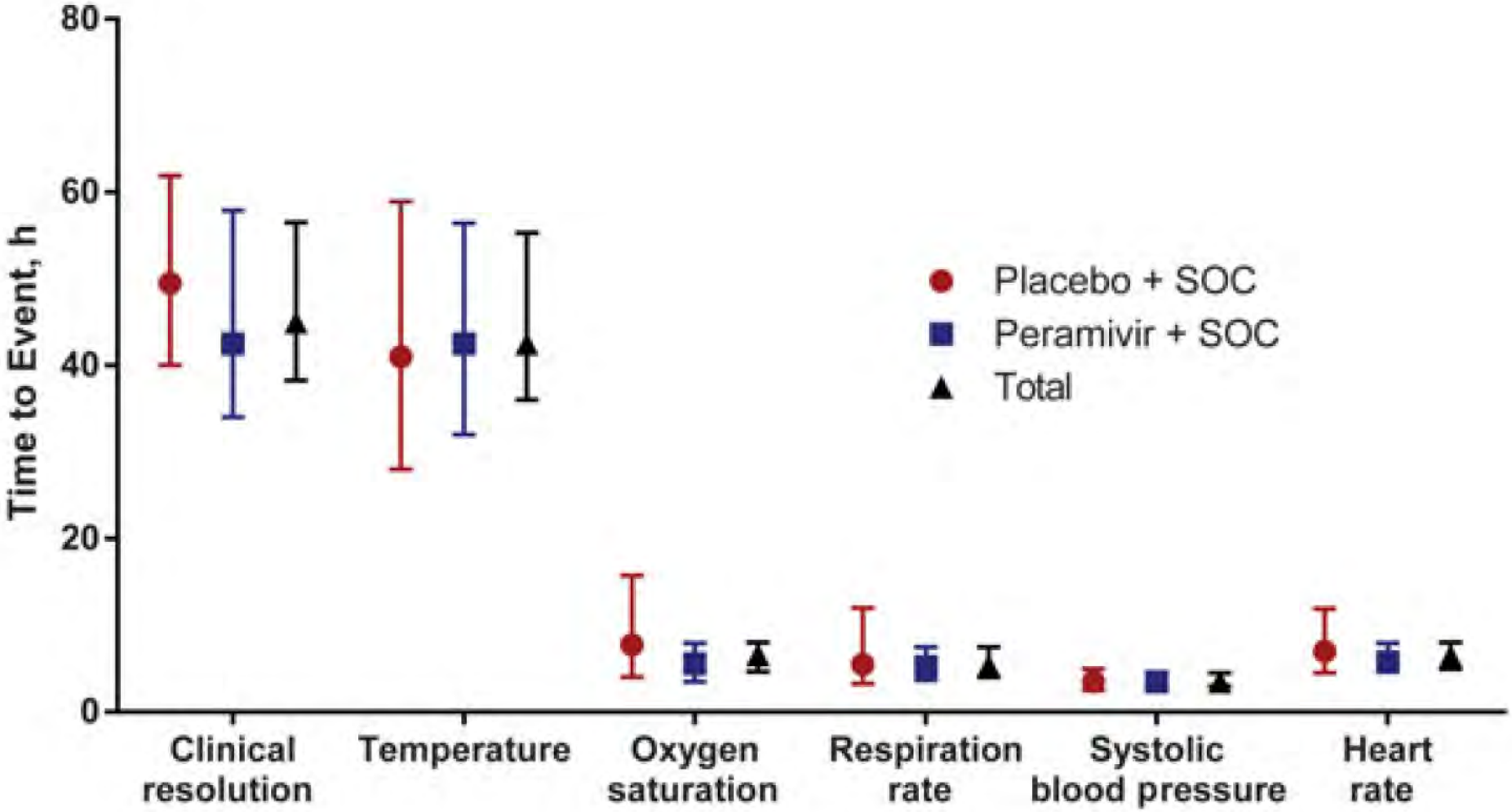
Measuring influenza antiviral efficacy is difficult

- *In vitro* tissue cultures
- Various animal models
- Human studies
  - Healthy adults and children
  - Outpatients and hospitalised patients
  - At-risk groups
- Measures of efficacy
  - Clinical markers
  - Complications
  - Laboratory confirmation and markers

Peramivir

- IV single, or daily dosing for 5 days
- IM dosing unsuccessful
- Tight binding to NA, with slow dissociation
- Resistance profile similar to oseltamivir (H275Y)

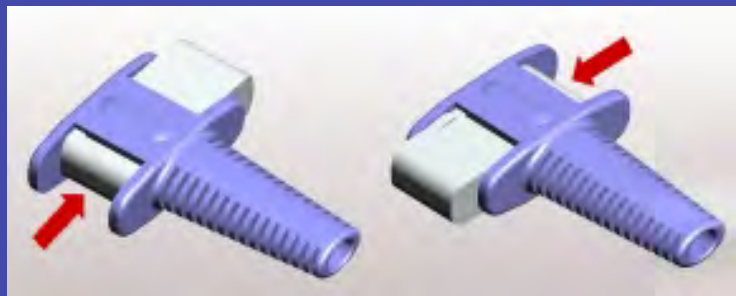
Time to clinical resolution in peramivir vs non-NAI treated hospitalised patients



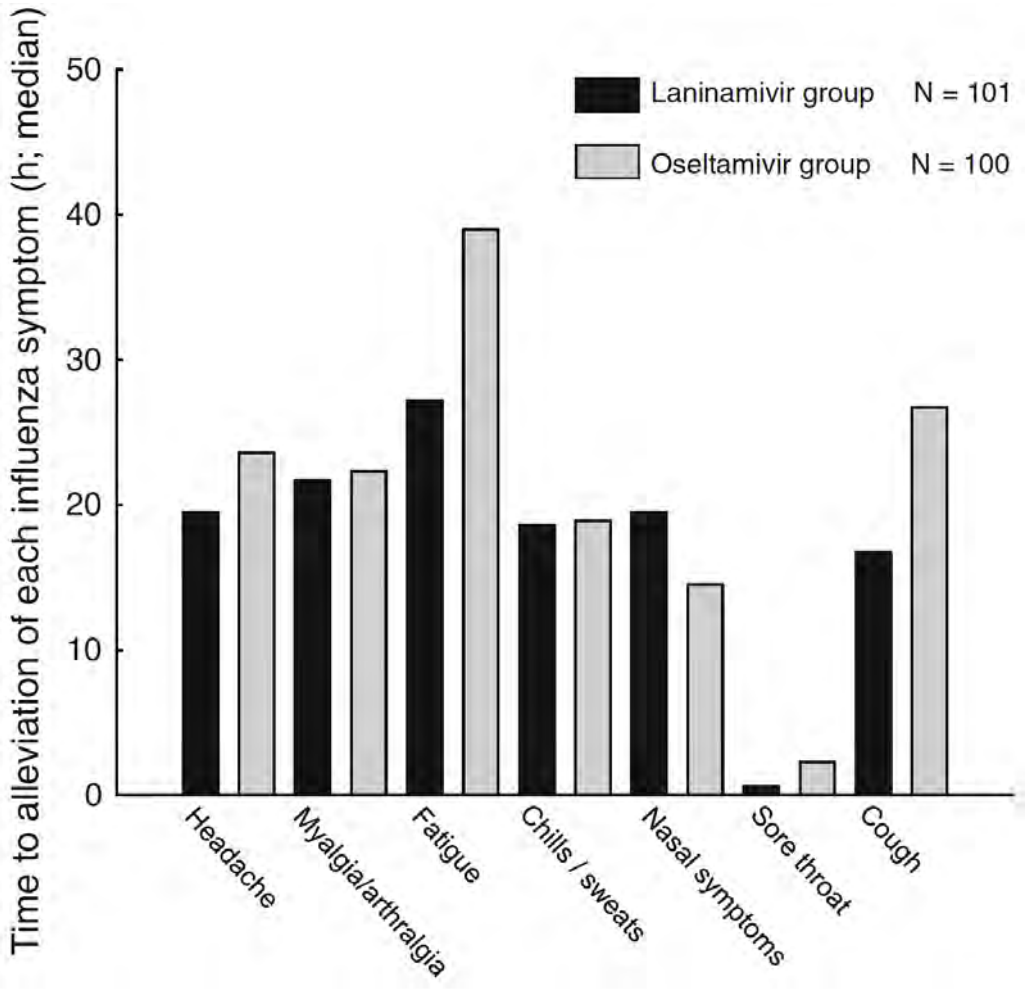
De Jong MD et al, CID 2014;59:e172

Laninamivir

- Laninamivr octanoate
- Inhaled (20-40mg) with high lung concentrations for 5 days
- Similar to zanamivir
- Use in oseltamivir-resistant seasonal A/H1N1



Time to alleviation of symptoms in patients with chronic respiratory disease
(single dose LMV vs OTV for 5 days)



Watanabe A. J Infect Chemother 2013;19:89

Favipiravir (T-705)

- Purine analogue
  - targets influenza RNA-dependent RNA polymerase
  - tri-ribophosphorylated (FVP-RTP) via cellular enzymes
- Efficacy against
  - A(H1N1)pdm09, H3N2, H5N1, H7N9, influenza B
  - oseltamivir (H275Y), pan-NI (E119D) and M2 inhibitor resistant strains
- *In vitro*
  - *s*ynergy with oseltamivir
  - efficacy against many RNA viruses (arenaviruses, phleboviruses, hantaviruses, flaviviruses, enteroviruses, alphavirus, RSV, noroviruses)
- Limited human data

Furuta Y et al. Antiviral Res 2013;100:446, L'Huillier AG et al. JID 2015 May 17

DAS181 (Fludas)

- Conjugated sialidase that removes human (α2,6-) and avian (α2,3-) linked sialic acid from cell receptors
- *In vitro* effectiveness against
  - A(H1N1)pdm09, A(H5N1), A(H7N9), influenza B
  - oseltamivir-resistant (H275Y) strains
- Efficacy against parainfluenzaviruses

Marjuki H et al. JID 2014;210:435. Nguyen HT et al. EID 2013;19:1963

Time to ≥1 log drop in sustained viral shedding from day 1

	Multiple Dose DAS181 (N = 56)	Single Dose DAS181 (N = 69)	Placebo (N = 52)
Time to ≥1 log drop sustained (days)			
Event[b]/censored[c]	49/7	56/12	39/13
Median time	2	4	4
95% confidence interval	(1, 4)	(2, 4)	(4, 5)
Log-rank test[a]			
P value	.007	.164	

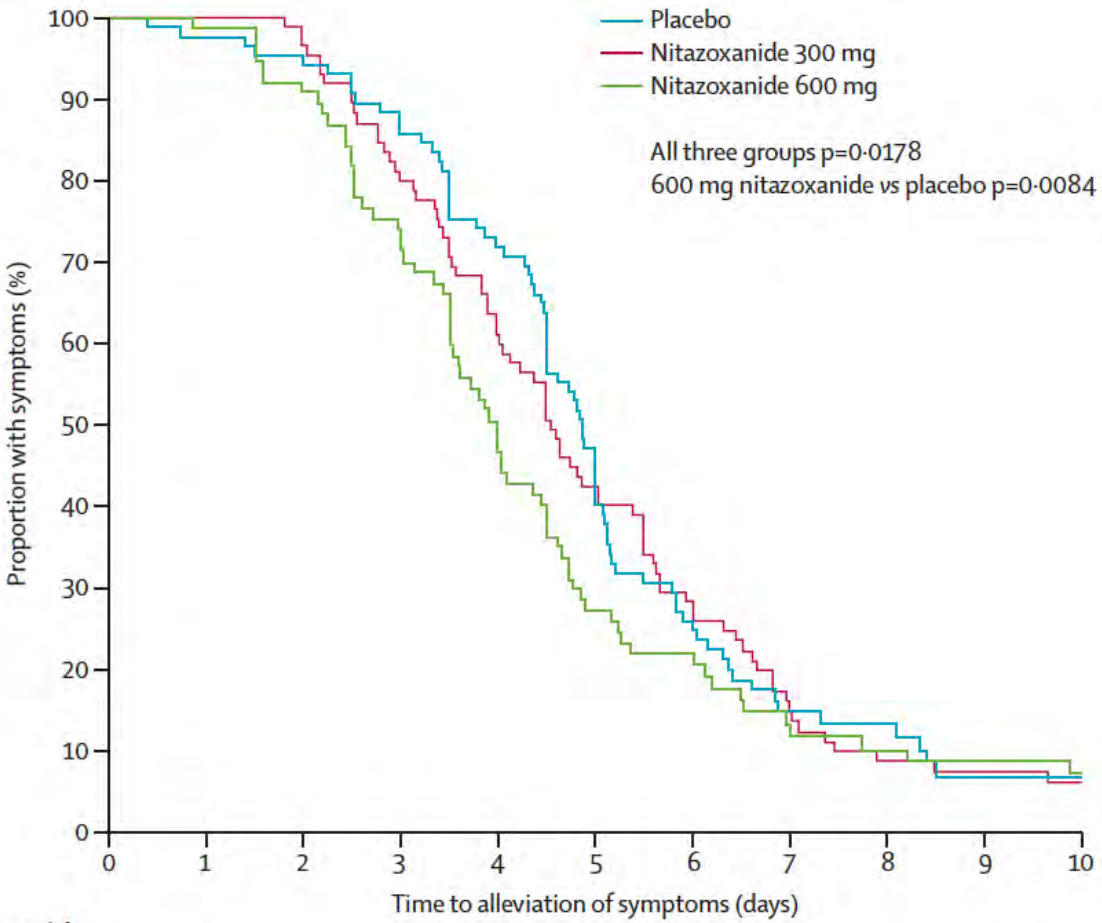
(NB: change in ILI symptoms not significant)

Moss RB et al. JID 2012; 206: 1844

Nitazoxanide

- Oral anti-parasitic agent
- Mode of action
  - immunomodulatory effects: upregulates interferon and INF-inducible genes
  - blocks HA maturation
- A(H1N1)pdm09, A/H3N2, influenza B
- *In vitro* synergy with oseltamivir
- *In vitro* activity against parainfluenzaviruses, coronaviruses, RSV

Time from first dose of nitazoxanide to alleviation of symptoms in confirmed influenza infection



Number with symptoms (at risk) at each timepoint											
Placebo	87	83	81	74	61	38	21	11	8	4	4
Nitazoxanide 300 mg	89	87	83	68	52	36	24	12	7	6	5
Nitazoxanide 600 mg	79	76	70	55	36	21	14	8	7	6	5

Haffizulla J et al. Lancet ID 2014;14:609-18

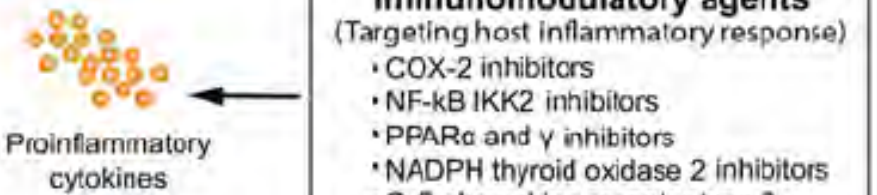
Antiviral combinations in clinical trials

	Drugs tested	Target population
Pharmacokinetic interactions	Oral oseltamivir + oral amantadine (NCT00416962)	Healthy volunteers
	Oral oseltamivir + oral favipiravir (unpublished)	Healthy volunteers
	Intravenous peramivir + oral rimantadine[43]	Healthy volunteers
	Intravenous peramivir + oral oseltamivir[43]	Healthy volunteers
	Intravenous zanamivir + oral oseltamivir[44]	Healthy volunteers
	Oral amantadine + oral ribavirin + oral oseltamivir (NCT00867139)	Healthy volunteers
Completed controlled trails of clinical efficacy	Oral rimantadine + nebulised zanamivir[4]	Hospitalised adults
	Oral oseltamivir + inhaled zanamivir[42]	Ambulatory adults
	Oral oseltamivir + pH1N1 convalescent plasma[45]	Critically ill patients
	Oral oseltamivir + pH1N1 hyperimmune globulin (NCT01617317)	Critically ill patients
	Oral oseltamivir + maxingshigan/yinqiaosan (NCT00935194)	Ambulatory adults
	Oral oseltamivir + sirolimus + corticosteroids[46]	Critically ill patients
	Oral amantadine + ribavirin + oseltamivir (TCAD; NCT01617317)	Critically ill patients
Continuing randomised controlled trials of clinical efficacy	Oral oseltamivir + convalescent plasma or hyperimmune globulin (NCT01052480)	Hospitalised adults
		High-risk outpatients
	Oral amantadine + ribavirin + oseltamivir (TCAD; NCT01227967)	Ambulatory adults
	Oseltamivir + nitazoxanide (NCT01610245)	

TCAD= triple combination antiviral drug.

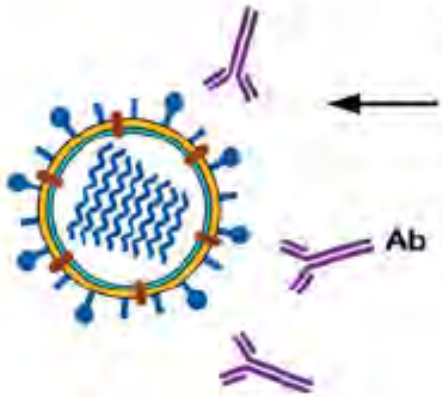
Dunning J et al. Lancet ID, 2014;14:1259

Modulation of host immune responses



Immunomodulatory agents
(Targeting host inflammatory response)
- COX-2 inhibitors
- NF-kB IKK2 inhibitors
- PPARα and γ inhibitors
- NADPH thyroid oxidase 2 inhibitors
- C-C chemokine receptor type 2

Lung endothelium (ARDS)
Tie2-agonist peptide (Vasculotide)



Immunomodulatory agents
(Targeting virus)
- Monoclonal antibodies
- Passive immunotherapy

Convalescent plasma to A(H5N1), A(H1N1)pdm09, seasonal influenza. MAbs to Group 1 and 2 HA stem conserved epitopes; other epitopes (M2e, NA, NP).

Webster RG et al. Ann NY Acad Sci 2014;1323:115
Sugiyama MG et al. Sci Rep 2015;5:11030

Further *in vitro* approaches

- RNA inhibition with siRNAs (eg. AVI-7100 to M1 and M2 mRNAs)
- Novel M2 inhibitors, NS1, polymerase PB2 (VX-787), nucleoprotein
- Targeting cellular signaling pathways
- Adjunctive treatments eg steroids, aspirin, statins etc

Hayden FG, Inf Other Resp Viruses 2012;7:63
Webster RG et al. Ann NY Acad Sci 2014;1323:115
Byrn RA et al. Antimicrob Agents Chemother 2015;59:1569

Ongoing issues with antivirals

- Careful messaging about clinical use
  - linkage with infection control measures
- Drug resistance monitoring and determining phenotypic significance of mutations
- No clear approach to treating drug-resistant infections
- Multiple causes of treatment failure other than resistance
- How is efficacy measured?
- Adverse effects, availability and cost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