

“New influenza antivirals”

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WHO Collaborating Centre
for Reference and
Research on Influenza
VIDRL



@hurt_lab
@WHOCCFluMelb





“New influenza antivirals”

Or more specifically...

“Polymerase inhibitors”

“Baloxavir”

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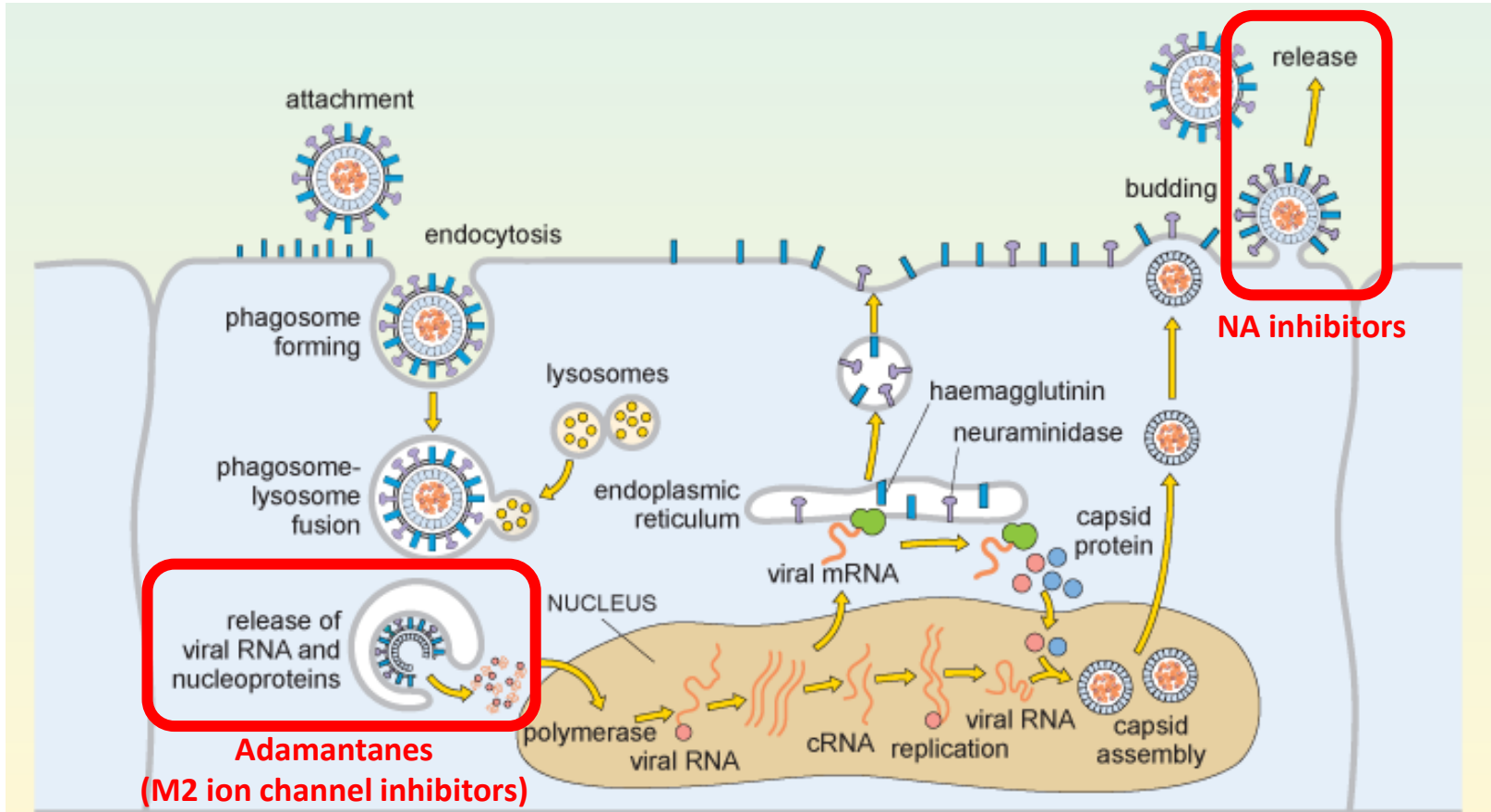
COI declaration

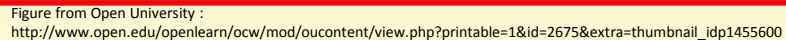
- Member of baloxavir publication steering committee organized by Shionogi
- Research group has received funding to conduct research studies from the following antiviral companies:
 - Shionogi
 - Romark
 - AusBio

Acknowledgments

- Thanks to the following people for providing data/information/figures used in the talk:
 - Dr. Zuzana Dobbie, Roche, Switzerland
 - Dr. Takeki Uehara, Shionogi, Japan
 - Dr. Harsha Shetty, Seqirus, Australia

Action of the 'current' influenza antivirals



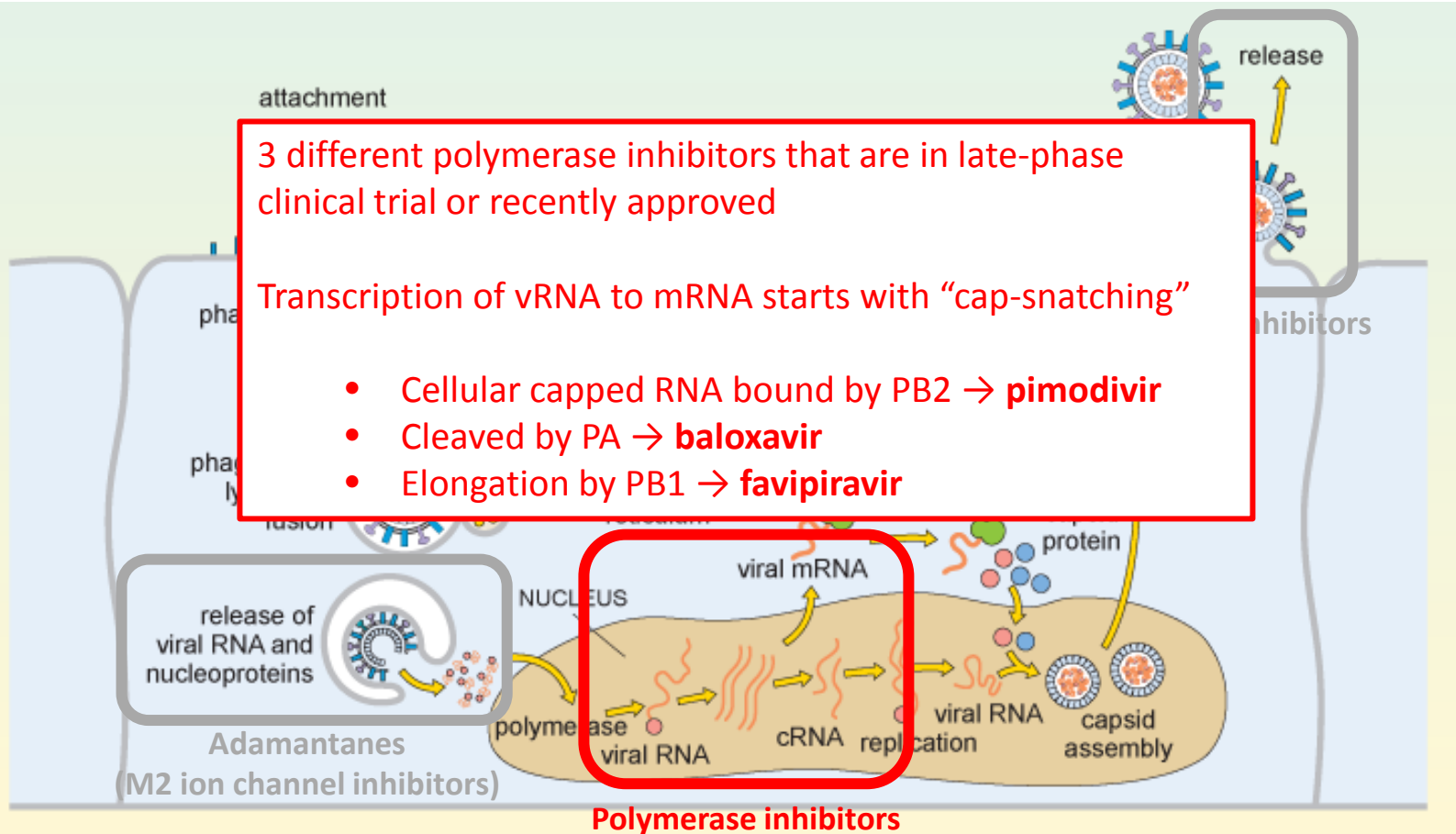


Action of the polymerase inhibitors

3 different polymerase inhibitors that are in late-phase clinical trial or recently approved

Transcription of vRNA to mRNA starts with “cap-snatching”

- Cellular capped RNA bound by PB2 → **pimodivir**
- Cleaved by PA → **baloxavir**
- Elongation by PB1 → **favipiravir**



Summary of the polymerase inhibitors

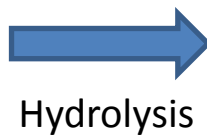
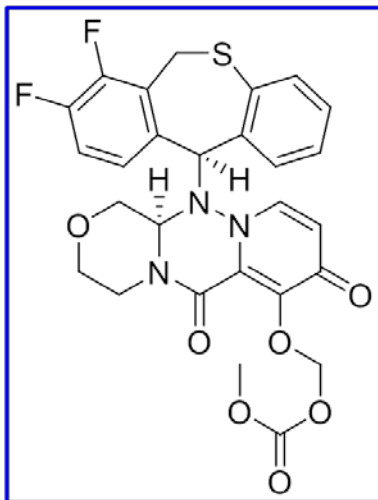
	Baloxavir	Favipiravir	Pimodivir
Polymerase target	PA	PB1	PB2
Influenza specificity	A & B	A, B & C	A
Can inhibit non-influenza viruses?	No	Yes	No
Approved for use in some countries?	Yes, in Japan (Feb '18) and US (Nov '18). Many countries in 2019.	Yes, Japan. (But limited to pandemic use under certain conditions). Variable efficacy in US trials	No, currently in Phase III
Dosing routes	Oral	Oral	Oral
Has been tested in combination with oseltamivir in clinical trials?	No	No	Yes
Ability to inhibit NAI resistant strains?	Yes	Yes	Yes
Antiviral- resistant mutants identified in vitro?	Yes	Yes	Yes
Antiviral resistant strains identified in clinical trials?	Yes	No	Yes

Efficacy of Baloxavir marboxil - Xofluza



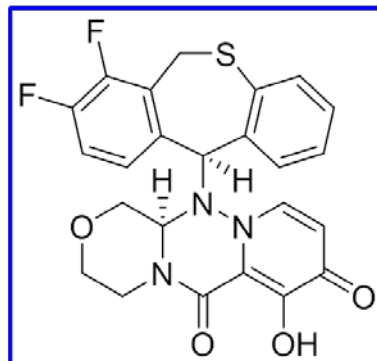
Baloxavir

Baloxavir Marboxil
(pro drug)



Long retention time
(half-life: 79.1 h)

Baloxavir Acid
(active form)



 **SHIONOGI INC.**

Japan
Taiwan

Genentech
A Member of the Roche Group



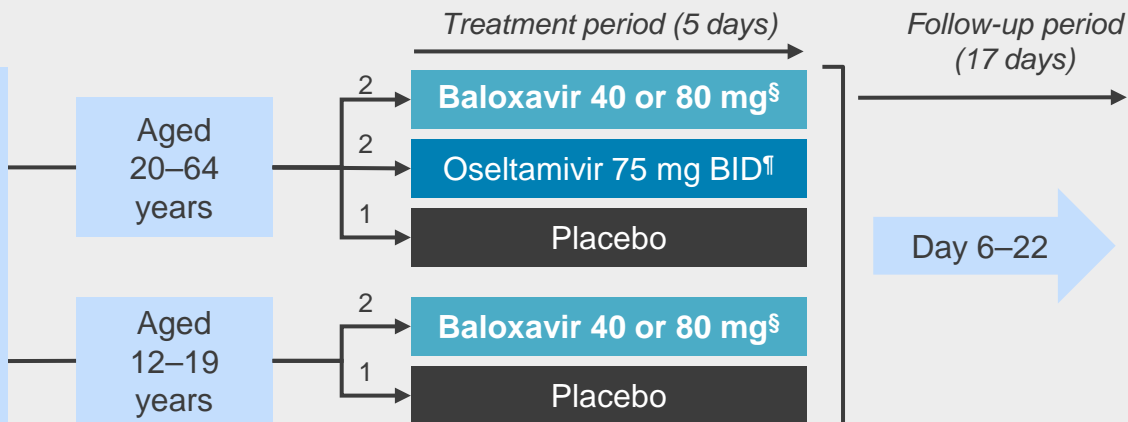
Rest of the world

- Single dose delivery
- US approved for uncomplicated influenza in >12 years of age
- Japan also approved for use in children <12 years

CAPSTONE-1: Phase III study of baloxavir vs. placebo or oseltamivir in OwH influenza patients

▶ Study design

- Aged 12–64 years
 - Otherwise healthy
 - Fever ($\geq 38^{\circ}\text{C}$ axillary), ≥ 1 systemic symptom* and ≥ 1 respiratory symptom**
 - ≤ 48 hours from symptom onset
- N=1436 (ITT N=1064)



▶ Key exclusion criteria

- Hospitalisation
- High risk of influenza complications

▶ Study endpoints

- **Primary endpoint:** time to alleviation of symptoms
- **Key secondary endpoints:** virological outcomes, time to fever resolution
- **Primary safety endpoints:** incidence of TEAEs

*Headache, feverishness/chills; muscle/joint pain or fatigue of moderate or greater severity.

**Cough, sore throat or nasal congestion of moderate or greater severity;

[§]Single dose on Day 1 (40 mg for body weight <80 kg, 80 mg for ≥ 80 kg); [¶]For 5 days.

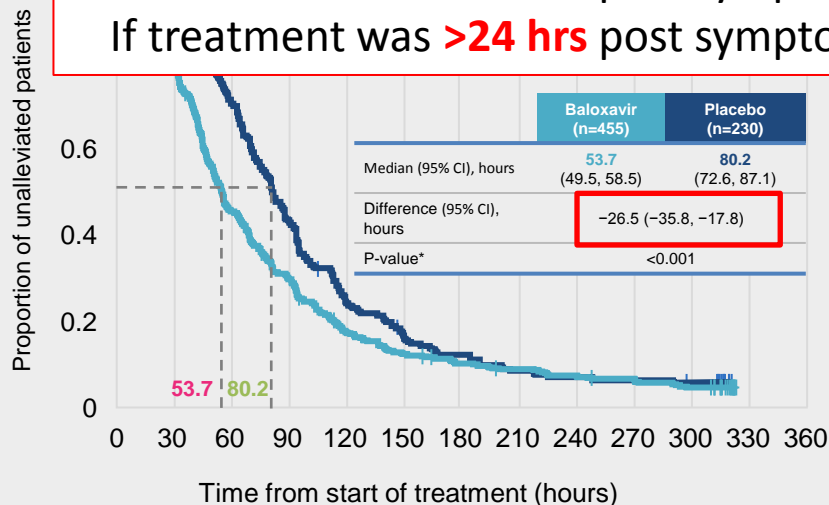
Hayden et al. N Engl J Med 2018

Adapted from slide kindly provided by Zuzana Dobbie, Roche

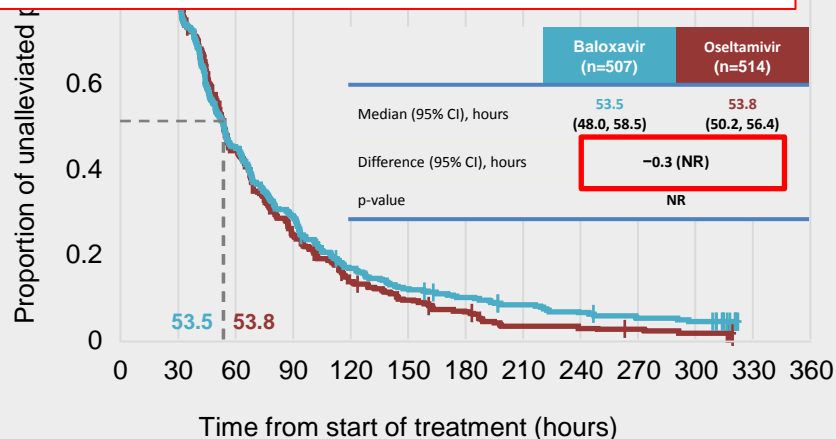
Baloxavir significantly reduced TTAS by >24 hours vs. placebo and was comparable with oseltamivir

Proportion of patients with symptoms

If treatment was <24 hrs post symptom onset: **32.8 hr** improvement in TTAS
 If treatment was >24 hrs post symptom onset: **13.2 hr** improvement in TTAS



Proportion of patients with symptoms



Primary endpoint. Intention-to-treat infected patients population

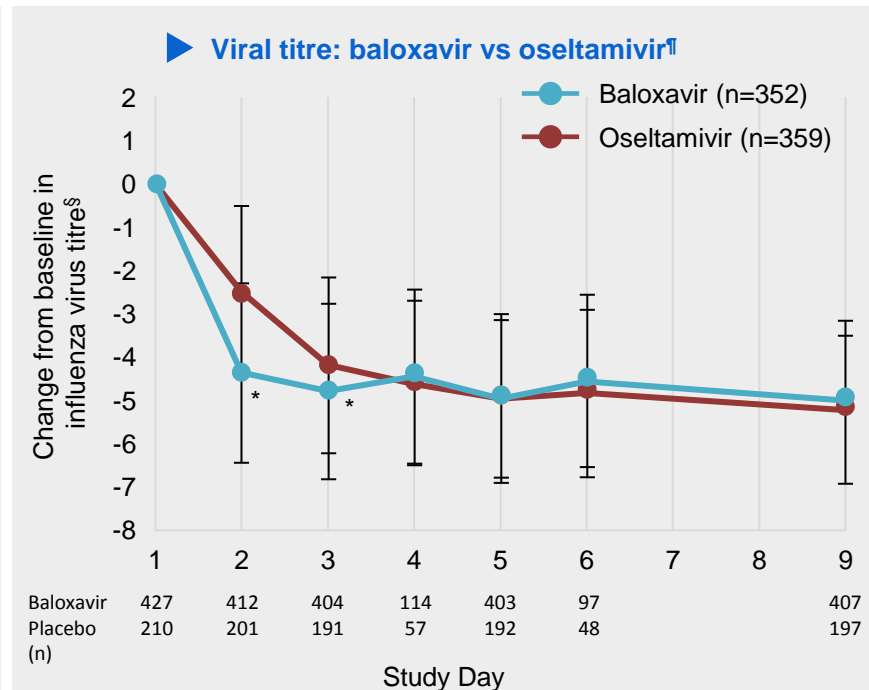
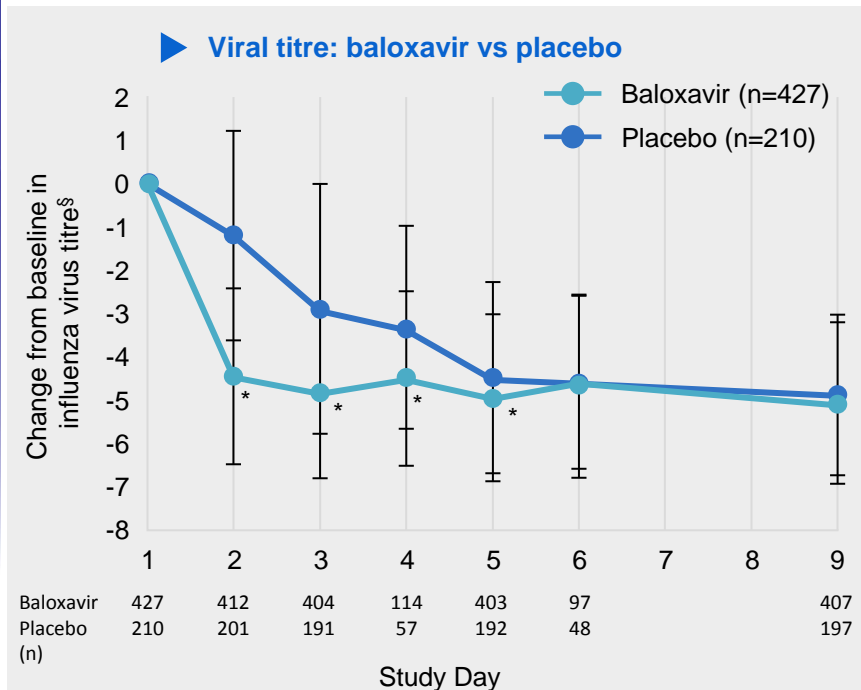
*Stratified generalised Wilcoxon test (stratification factors: country and symptoms score at baseline)

Patients who did not experience alleviation of symptoms were censored at the last observation time point. Subset of patients whose TTAS was not missing

Hayden et al. N Engl J Med 2018

Adapted from slide kindly provided by Zuzana Dobbie, Roche

Baloxavir significantly reduced viral titres vs. placebo or oseltamivir from 1 day post dose



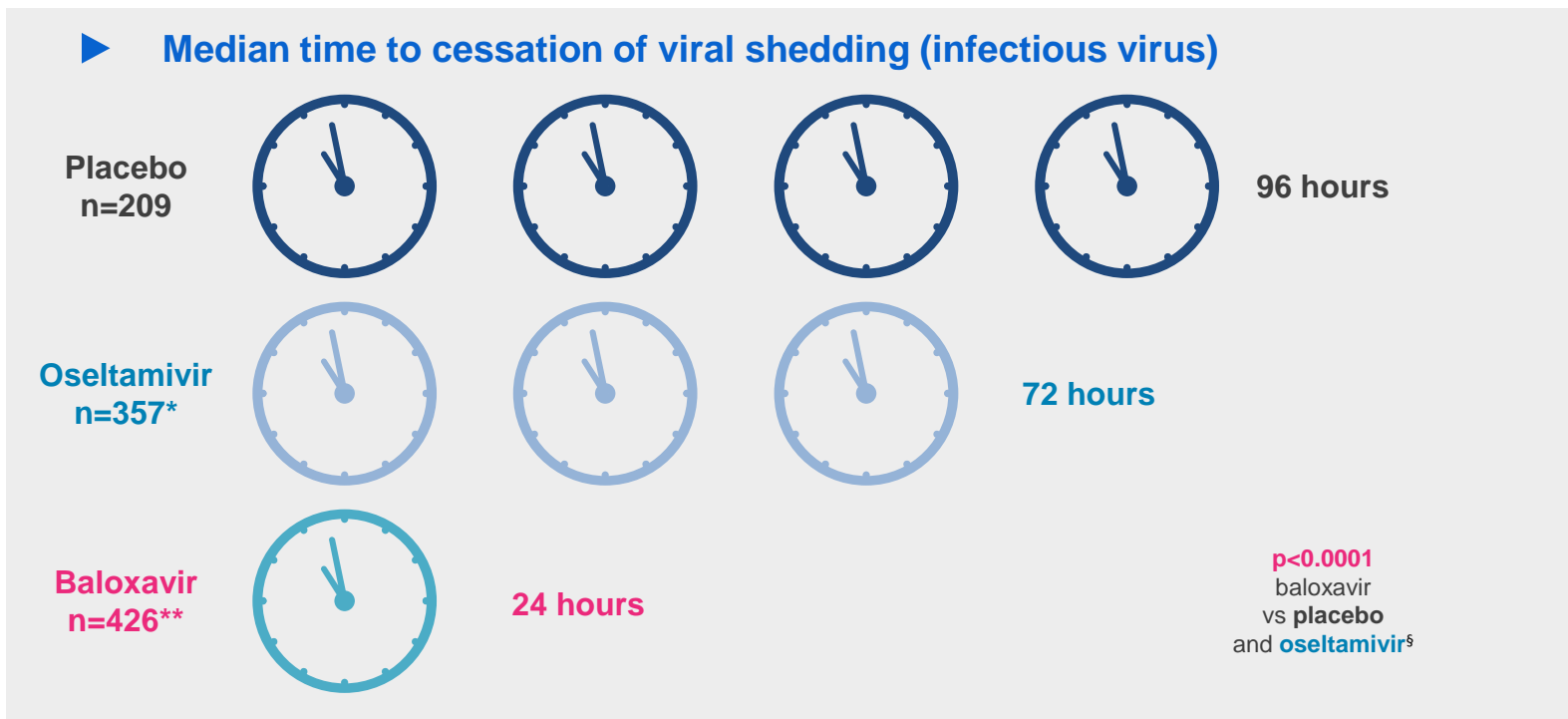
Secondary endpoint. ITTI population

*p<0.05 vs placebo or oseltamivir; [§]Mean log₁₀ (TCID₅₀/ml); [¶]Adults aged 20–64 years

Hayden et al. N Engl J Med 2018

Adapted from slide kindly provided by Zuzana Dobbie, Roche

The median time to cessation of viral shedding was 24 hours following baloxavir treatment



*Adults aged 20–64 years; **n=351 for comparison vs oseltamivir (adults aged 20–64 years)

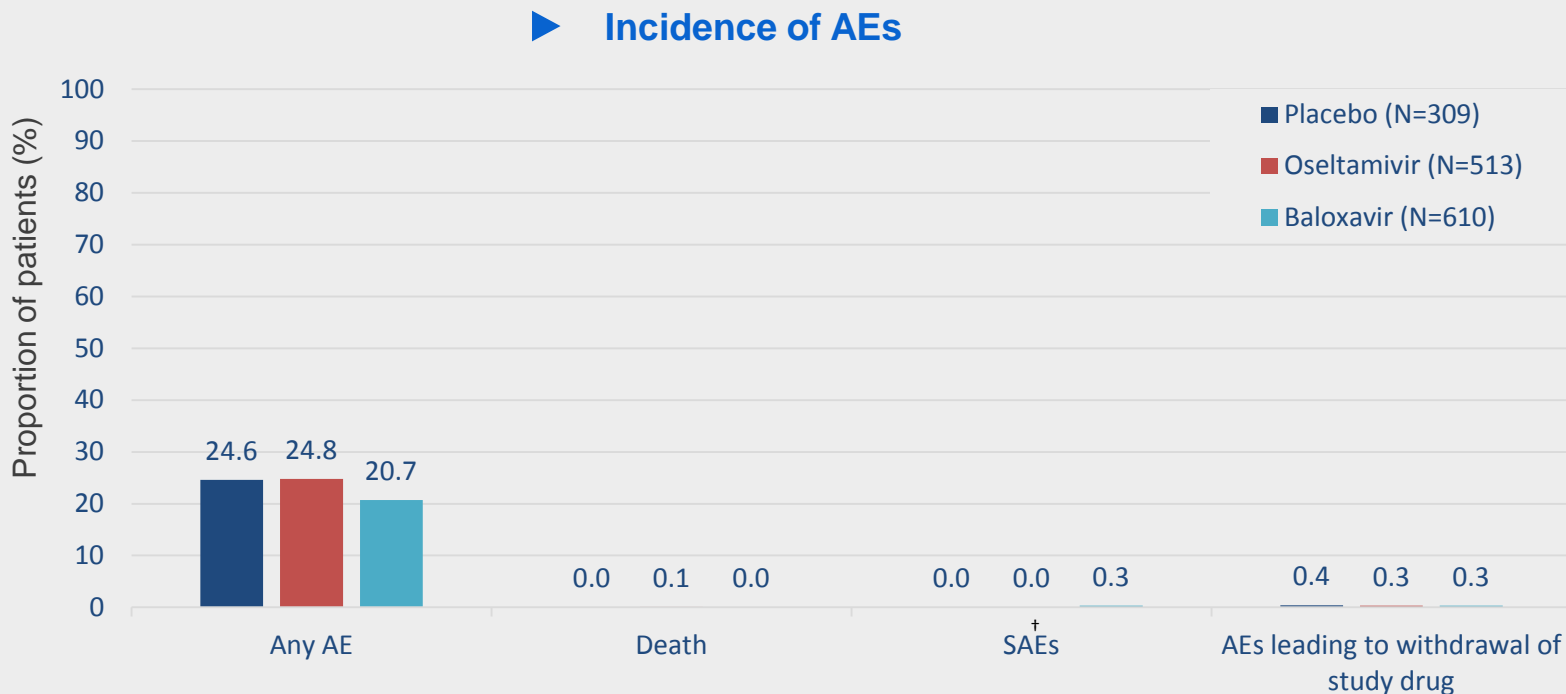
§Stratified generalised Wilcoxon test

One day was converted into 24 hours

Hayden et al. N Engl J Med 2018

Adapted from slide kindly provided by Zuzana Dobbie, Roche

Baloxavir was well tolerated, with numerically fewer AEs than oseltamivir



*No significant differences were noted between the groups except for pre-specified comparison of treatment-related AEs, which were more common with oseltamivir than baloxavir ($p=0.009$)

[†]Excluding death

See slide notes for AEs reported in at least 1% of patients in any treatment group

Hayden et al. N Engl J Med 2018

Adapted from slide kindly provided by Zuzana Dobbie, Roche

Summary: CAPSTONE 1 and 2

Lower Clinical Effectiveness of Oseltamivir against Influenza B Contrasted with Influenza A Infection in Children

Norio Sugaya,¹ Keiko Mitamura,³ Masahiko Yamazaki,⁷ Daisuke Tamura,¹ Masataka Ichikawa,⁸ Kazuhiro Kimura,⁸ Chiharu Kawakami,² Maki Kiso,^{4,9} Mutsumi Ito,⁴ Shuji Hatakeyama,^{4,6} and Yoshihiro Kawaoka^{4,5,9,10}

Clinical Infectious Diseases 2007;44:197–202

018)

al titres and

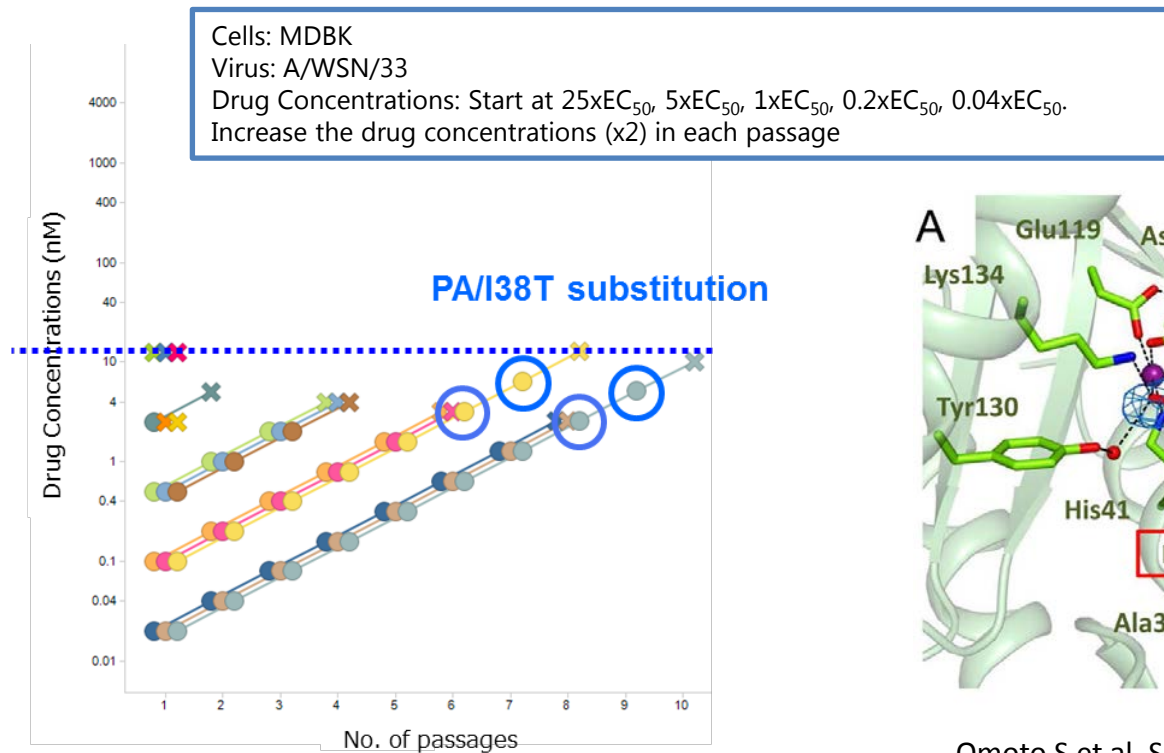
CAPSTONE-2: Phase III study in high-risk influenza patients of baloxavir vs placebo or oseltamivir (unpublished, Ison et al.ID Week, San Fran, 2018)

- Confirmed safety in this population
- Baloxavir was superior to placebo in improving influenza symptoms (29.1 hr)
 - For influenza B, baloxavir superior to placebo (by 26.0 hr) and oseltamivir (by 27.1 hr)
 - Baloxavir associated with significantly fewer influenza-related complications and reduced the requirement for antibiotics compared with placebo

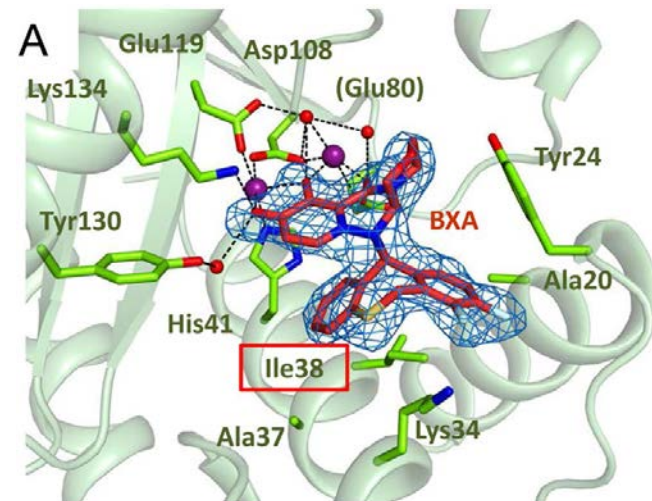
Frequency of resistance (or reduced susceptibility) to Baloxavir marboxil



Influenza A viral variants with reduced susceptibility to baloxavir have been characterised



Noshi T. et al. Antiviral Research 2018 (in press)



Omoto S et al. Scientific Reports 2018;8:9633

Viral variants conferring reduced susceptibility to baloxavir have been detected in clinical trials

Trials	Analysis Population (n=)	Predominant type/subtype	PA AA substitution detected and frequency	
			Fold change in susceptibility	
			<10 fold	>10 fold
Ph2 OwH in Japan	182	A(H1N1)pdm09	E23K (n=1)	I38T (n=2) I38F (n=2)
CAPSTONE-1 OwH	370	A(H3N2)	E23G (n=1) E23K (n=1) A37T (n=1)	I38T (n=33) I38T/M (n=2) I38M (n=1)
Pediatric study in Japan	77	A(H3N2)	A37T (n=1) E119G (n=1)	I38T (n=15) I38M (n=3)
CAPSTONE-2 HR	290	A(H3N2) and B	E23K (n=1)	I38T (n=13) I38M (n=1) I38N (n=1)

- PA/I38X viral variants not detected in placebo treated patients and occur very rarely among circulating viruses, PA/I38T not detected

Incidence of treatment-emergent PA/I38X varied across baloxavir clinical trials

Proportion of I38X variant emergence (patients with I38X/total patients)	Total*	Type/subtype**		
		A/H1N1pdm	A/H3	B
Ph2 OwH in Japan	2.2% (4/182)	3.6% (4/112)	0% (0/14)	0% (0/56)
CAPSTONE-1 OwH	9.7% (36/370)	0% (0/4)	10.9% (36/330)	2.7% (1/37)
Pediatric study in Japan	23.4% (18/77)	0% (0/2)	25.7% (18/70)	0% (0/6)
CAPSTONE-2 HR	5.2% (15/290)	5.6% (1/18)	9.2% (13/141)	0.8% (1/131)

*Patients with mixed infection were counted once in total number of patients.

**Patients with mixed infection with paired sequencing data were counted once by each virus type/subtype category.

- Substantially higher rates of resistance in children (<11 years)
- Rates of resistance in **H3N2** > H1N1pdm09 > B

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How does that compare to oseltamivir-resistance in treated patients?

- IRIS study, n=1162 oseltamivir treated patients

Age group	Influenza A viruses
1-5	11.8 % (30/253)
> 5	1.4 % (13/909)

(Lina et al., IRV,
12:267-278, 2018)

- Substantially higher rates of oseltamivir resistance in young children (<5 years)

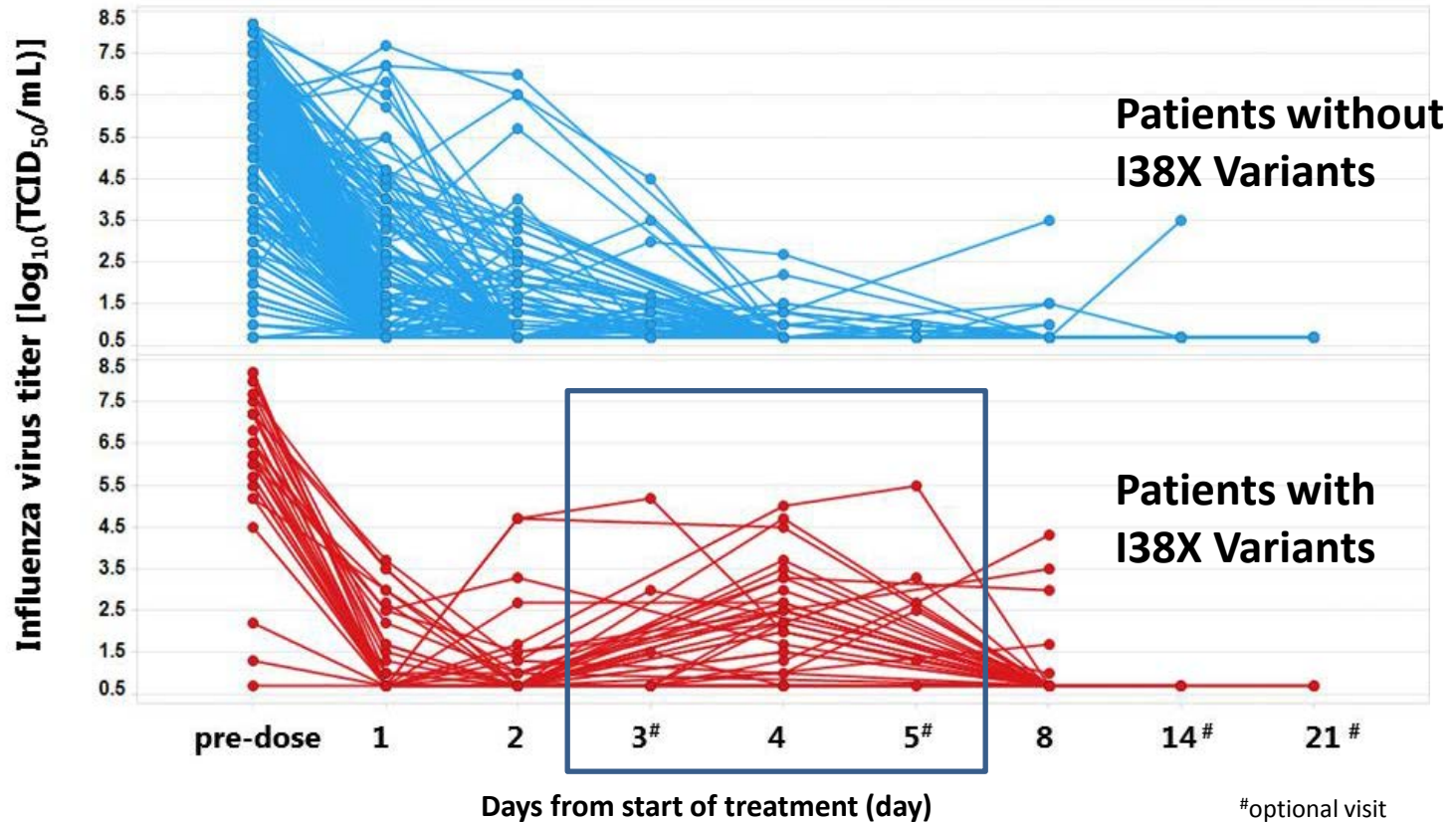
Age group	H1N1pdm09	H3N2
1-5	16.1 % (20/124)	7.7 % (10/129)
> 5	1.7 % (7/403)	1.2 % (6/506)
All	5.1 % (27/527)	2.5 % (16/635)

- Higher rates of oseltamivir resistance in **H1N1pdm09** than H3N2
- At this stage, rates of resistance in treated patients appear higher following baloxavir treatment compared to oseltamivir

Clinical impact of PA/I38X variants



CAPSTONE-1: transient increases in viral titers observed in patients with PA/I38X variants



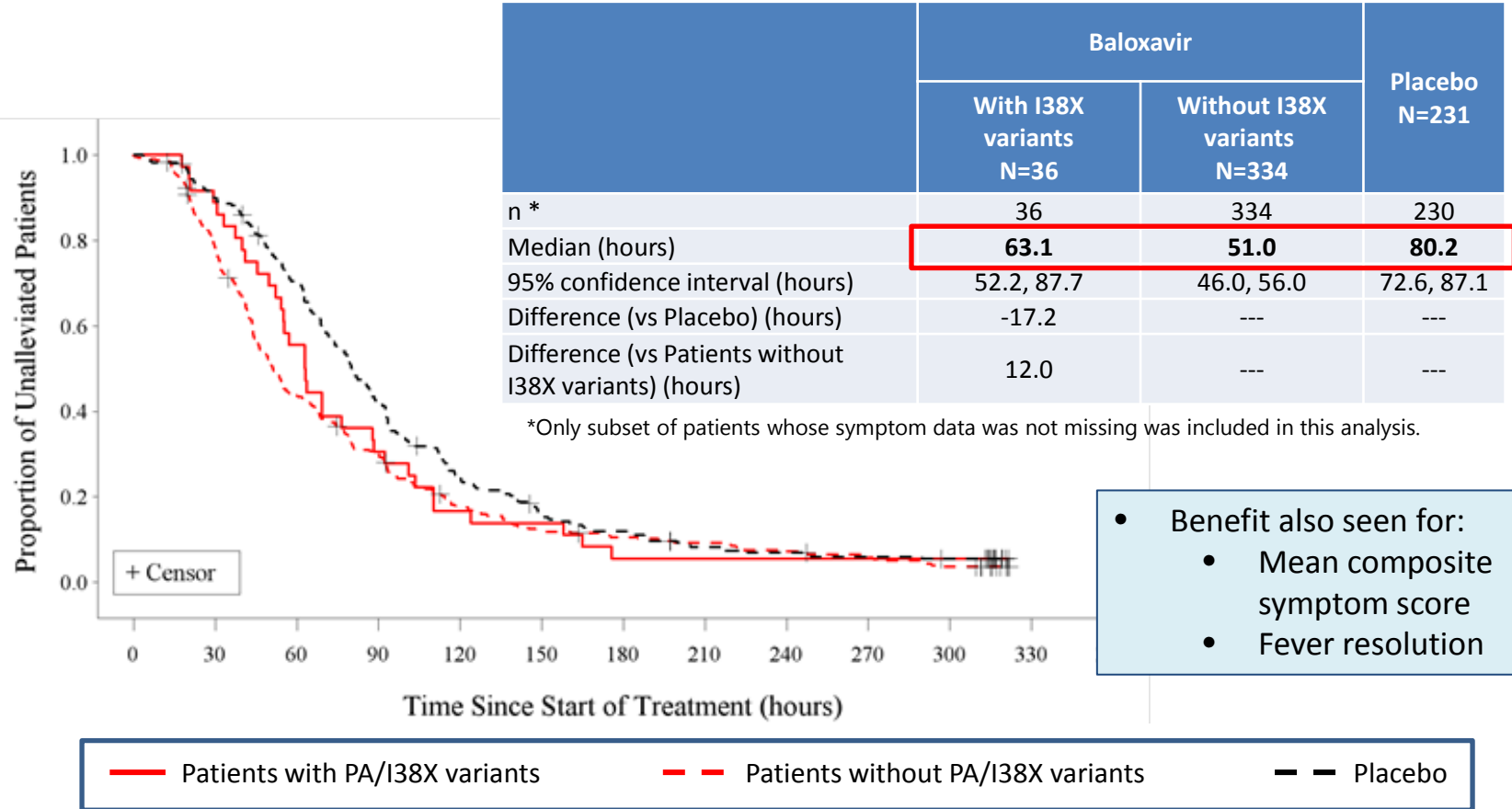
Clinical and Viral Shedding Implications of PA/I38X Variant Viruses

Proportion of patients shedding virus in different groups (CAPSTONE-1)

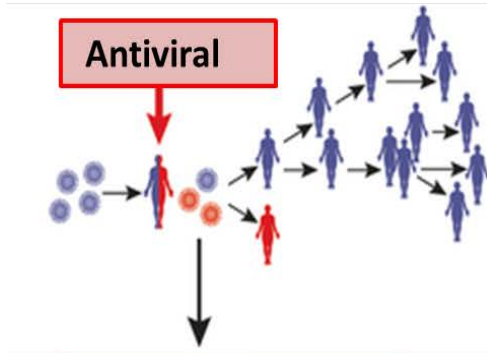
	Placebo	Baloxavir Treated (WT Viruses)	Baloxavir Treated (PA/I38X Variant Viruses)
Day 5	31.0%	7.5%	90.6%
Day 9	5.6%	1.7%	16.7%

- Resulted in prolonged viral shedding beyond that seen in the placebo treated patients

CAPSTONE-1: clinical benefit in TTAS observed in baloxavir group regardless of PA/I38 status



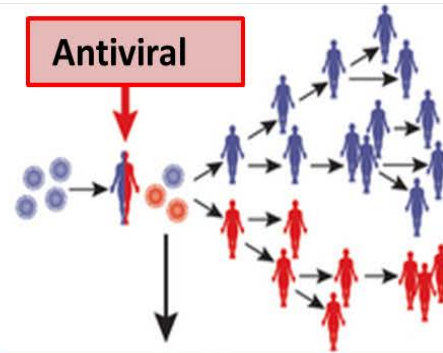
The fitness of a resistant virus matters!



Low viral fitness

Little or no spread to the community

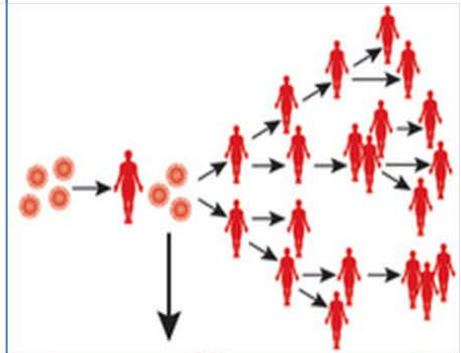
The antiviral remains appropriate for treating subsequent cases



Moderate viral fitness

Cluster of resistant cases in the community

Alternative antivirals are required for treating the cluster of cases



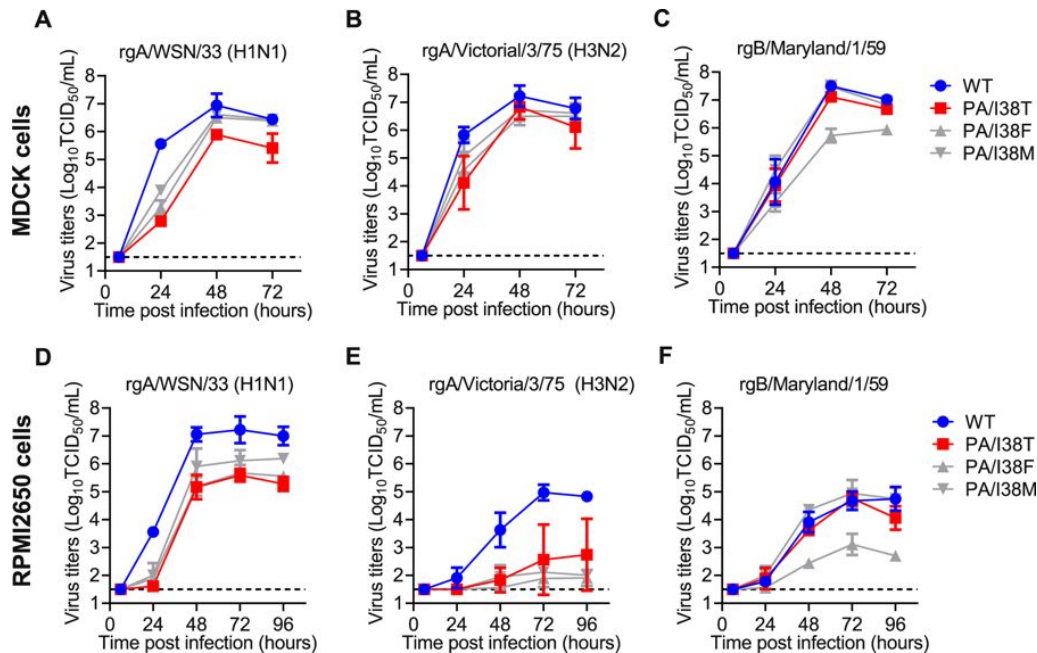
High viral fitness

Widespread resistance

The antiviral is no longer suitable for treatment of all cases in the community

Fitness of I38X Variant Viruses

- I38X variant viruses show some reduced replicative fitness *in vitro* and reduced endonuclease activity
- Understanding transmissibility of these variant viruses is important. Ferret studies planned, including the potential for compensatory mutations to improve fitness.
- Surveillance for PA/I38X variants in patients NOT being treated with baloxavir would indicate fitness of the variant



Final thoughts....

- Roche filing for licensure for OwH and HR indications in Australia in April 2019
- Globally, further baloxavir studies in progress or planned
 - Hospitalised, paediatric, prophylaxis, effect of treatment on transmission
- Data in hospitalised patients will be very useful
 - 2-3 doses of baloxavir + SOC (NAI) vs placebo + SOC (NAI)
 - How might the superior effect on viral load translate in hospitalised patients who typically present/ get treated late
 - RCT data is lacking in this group of patients (Cochrane debate)
 - Implications for pandemic planning / stockpiles
- Rates of resistance are concerning, close monitoring is necessary
- The advancement of new compounds with different action to the NAIs opens up many opportunities for improved treatment, including combination that will hopefully improve efficacy and reduced resistance

Thank you

The Melbourne WHO Collaborating Centre for Reference and Research on Influenza is supported by the Australian Government Department of Health.

PATRIOTIC DRIVE AGAINST THE "FLU"

An onion car arrived today,
Labelled red, white and blue,
"Eat onions, plenty, every day,
And keep away the 'Flu'."

Cabbage, too, they vend down
there,
At the Bessemer Transfer track,
Solid heads, three cents the
pound,
Enough to supply the town.

So take a trip out Kittinging St.
And see what you can buy,
With what is left from Liberty
Bonds,
Lay in your winter supply.

Eat More ONIONS

**One of the Best Preventatives
for Influenza.**

Car Load of Onions will be on sale
on siding at Bessemer Freight
Station

**TODAY and TOMORROW
Will Be Sold Direct from Car**
Bring Your Own Sacks or Baskets if Possible
THE PRICES ARE RIGHT
J. W. GARDOCKY, Grower

A U.S. government booth set up to treat flu patients.

