How to predict the role of antivirals in reducing influenza transmission using modeling and simulation

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Predictive Modeling

19th September 2025

Why efficacious antiviral treatments are important

Joshua Lederberg's Famous Quote:

"The single biggest threat to man's continued dominance on this planet is the virus".

American molecular Nobel Prize in Medicine 1958

Agenda

- Introduction to flu and antiviral treatment
- Rational for transmission modeling
- Evaluation of the transmission in epidemiological context
- Validation using household contact trials
- Perspectives/Conclusion

Influenza represents a significant disease and socioeconomic burden that is often underestimated

Significant disease burden

Globally, annual epidemics result in:

- ***3 to 5** million cases of severe disease*
- *Up to **650,000** deaths*

*In the Northern Hemisphere, influenza affects **5–15%** of the population*

Large socioeconomic impact, with significant burden on the healthcare system

Lost workforce productivity

Over-stretched health services

Low awareness of risks and suboptimal management of influenza

Lack of awareness of risks posed by influenza

Patients present too late for intervention

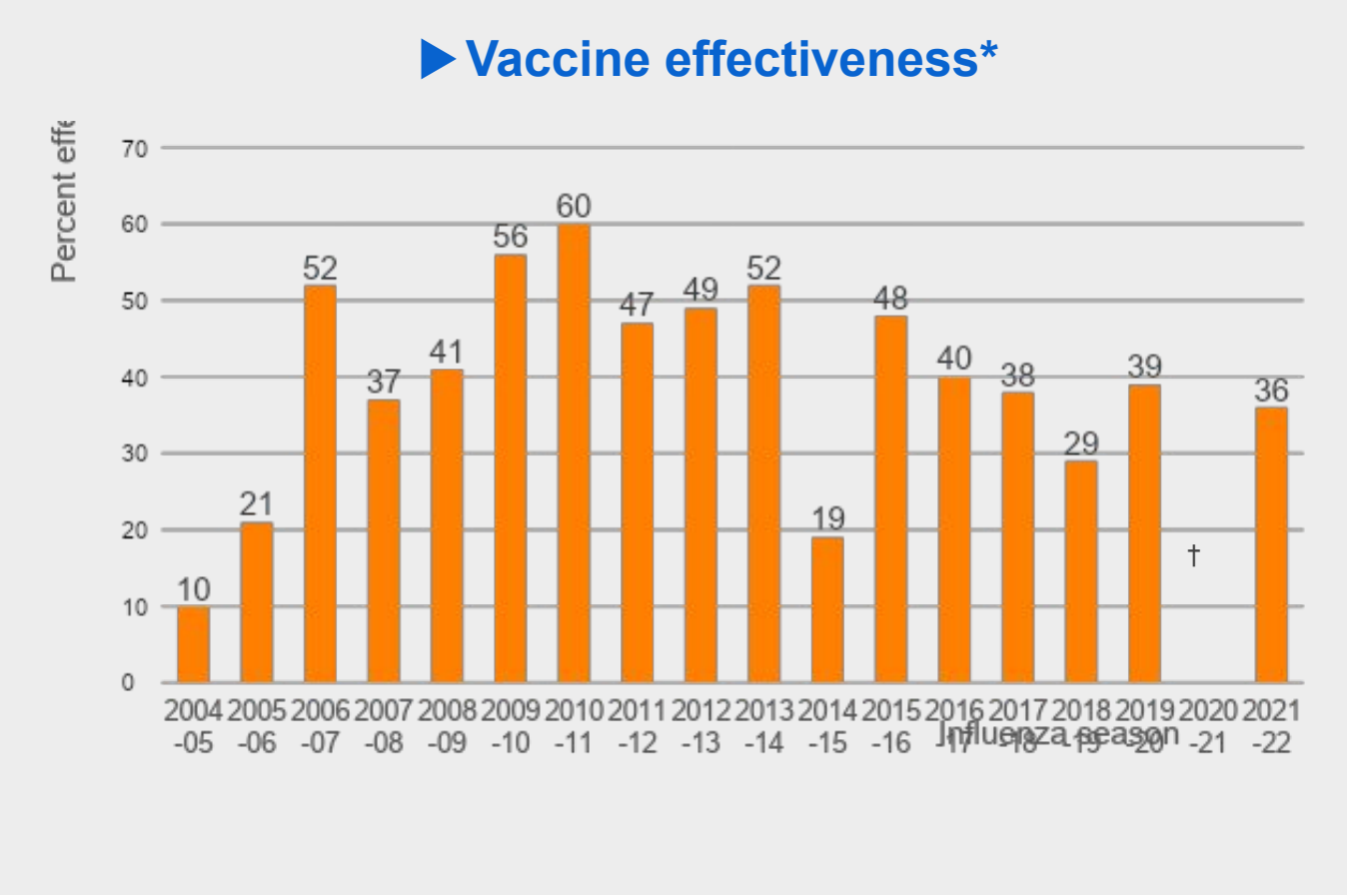
Value of antivirals under-appreciated; symptom relief is often the primary or only therapy

Baxter. Hum Vaccin Immunother 2016; Gaglia Jr. Clin Infect Dis 2007; Klepser. Drugs 2014
WHO 2017. Available at: http://www.who.int/mediacentre/news/releases/2017/seasonal-flu/en/
WHO 2023. Available at: http://www.who.int/mediacentre/factsheets/fs211/en/

The effectiveness of seasonal influenza vaccine is variable

- **Vaccination** is the cornerstone of prevention, but
  - **effectiveness can be variable** due to suboptimal uptake and mismatch between vaccine/circulating strains
  - **production takes ≥6 months** so would be **unavailable** during the first wave of a new pandemic

The need for antiviral agents remains high



*Vaccine effectiveness estimates are from the U.S. Flu Vaccine Effectiveness Network
†Vaccine effectiveness for 2020–21 was not estimated due to low influenza virus circulation

CDC 2017. Available at: https://www.cdc.gov/flu/vaccines-work/vaccineeffect.htm
CDC 2018. Available at: https://www.cdc.gov/flu/prevent/vaccine-selection.htm
CDC 2020. Available at: https://www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm
CDC 2022. Available at: https://www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm
WHO 2023. Available at: http://www.who.int/mediacentre/factsheets/fs211/en/

Antivirals are an important part of influenza clinical management

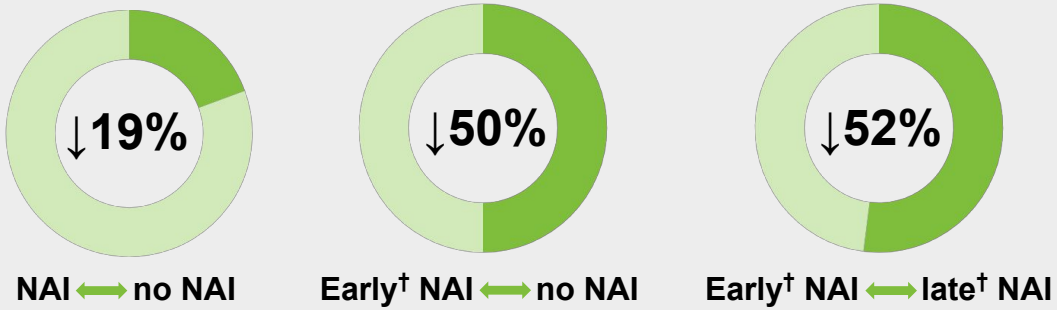
Three classes of antivirals are now approved for influenza treatment

M2 inhibitors (adamantanes)

NAIs (**oseltamivir**, peramivir, **zanamivir**, laninamivir)

Polymerase inhibitors (**baloxavir**, favipiravir)

Reduction of mortality risk with NAI treatment in a retrospective observational study



NAI ⟷ no NAI | **Early† NAI ⟷ no NAI** | **Early† NAI ⟷ late† NAI**

In hospitalised patients with severe influenza
The majority of NAI-treated patients received oseltamivir (92%)
†≤2 days after (early) or >2 days after (late) symptom onset

Antiviral agents

- The **adamantanes are now obsolete** due to widespread resistance in circulating influenza A strains
- Baloxavir is the **first widely available drug** in a **new class** of antiviral treatment options for influenza

Early antiviral treatment

- **Proven to reduce the risk of complications** and **mortality**
- **Recommended for hospitalised, high-risk and severely ill patients,** or within 48 hours of symptom onset for otherwise-healthy outpatients

CDC 2019. Available at: https://www.cdc.gov/flu/pandemic-resources/pandemic-timeline-1930-and-beyond.htm
CDC 2020. Available at: https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm
FDA 2018. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm624226.htm
Hussain. Infect Drug Resist 2017; Muthuri. Lancet Respir Med 2014; Myles. ESWI Science Policy Flu Summit 2015
Roche 2021. Available at: https://www.roche.com/investors/updates/inv-update-2021-01-11.htm

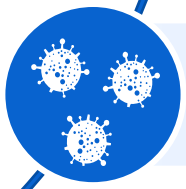
NAI: Neuroaminidase inhibitor

Baloxavir marboxil (Xofluza) is a new standard of care in influenza

Influenza is associated with considerable disease burden, and the need for effective antiviral drugs is high

A single dose of baloxavir is well tolerated and effective in most populations so far studied: otherwise-healthy patients (children, adolescent and adults), as well as in patients at high risk of complications

Baloxavir significantly reduces the duration of viral shedding versus placebo and oseltamivir in all populations examined

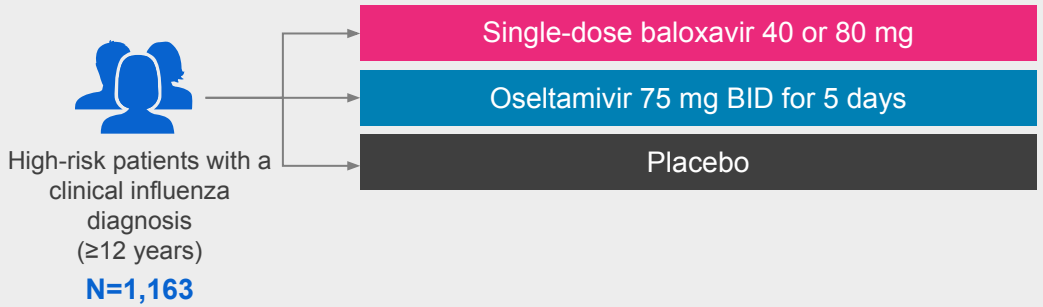


Baloxavir is effective and well tolerated for post-exposure prophylaxis of influenza

Baker. Pediatr Infect Dis J 2020; Hayden. N Engl J Med 2018
WHO 2017. Available at: http://www.who.int/mediacentre/news/releases/2017/seasonal-flu/en/
Ikematsu. N Engl J Med 2020; Ison. Lancet Infect Dis 2020

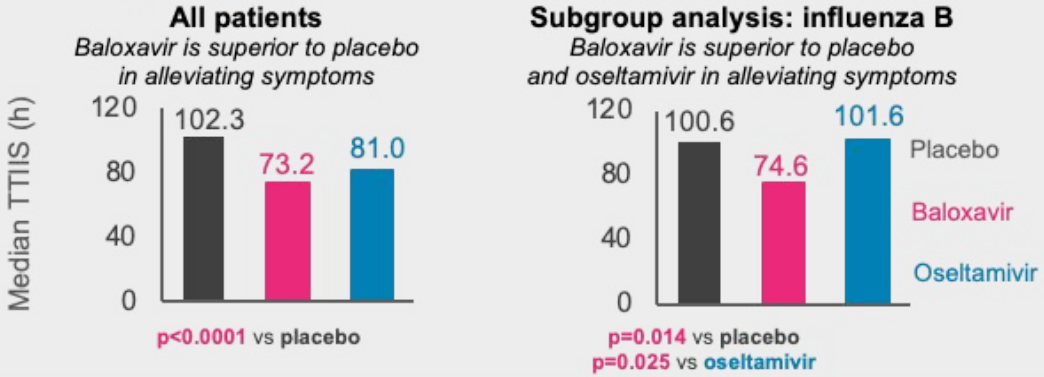
CAPSTONE-2: Phase III, randomised, double-blind study of baloxavir vs placebo or oseltamivir

Study design



Phase III trial conducted globally

Primary endpoint†

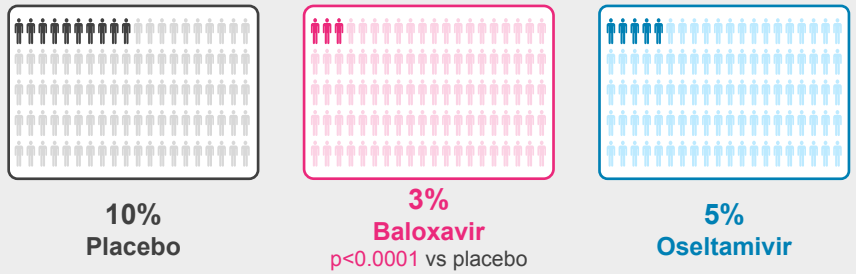


Secondary endpoint

Baloxavir results in more rapid cessation of viral shedding vs oseltamivir or placebo

Secondary endpoint

Baloxavir is associated with a significantly lower incidence of influenza-related complications than placebo



*To access the Baloxavir Clinical Development Programme slide deck, please copy and paste the following link into your browser:
https://medcin.roche.com/search?searchTerm=c7a58e02bdb9f3235753df6b33ab72b1&divisions=PHARMA

†Primary endpoint definitions vary slightly across clinical trials, so no direct comparisons can be made between trials

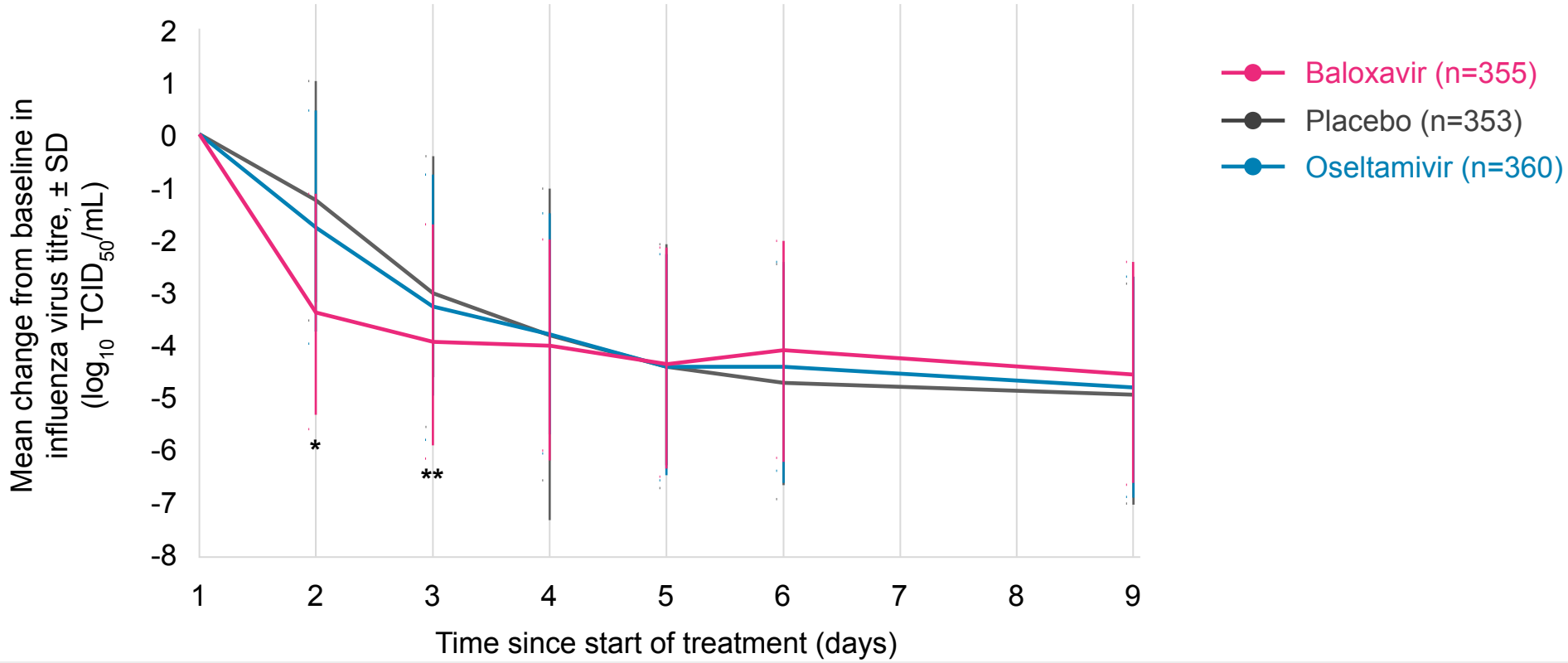
To view the clinical development programme for baloxavir, please visit MedCIN*

NCT02949011 (CAPSTONE-2)
Ison. Lancet Infect Dis 2020

CAPSTONE-2: Phase III, randomised, double-blind study of baloxavir vs placebo or oseltamivir

Baloxavir significantly reduced viral titres vs placebo and oseltamivir

Change in viral titre with baloxavir vs placebo and oseltamivir



*Day 2: p<0.0001 vs placebo, p<0.0001 vs oseltamivir; **Day 3: p<0.00001 vs placebo, p<0.0024 vs oseltamivir. Test: van Elteren
Stratification factors: region, composite symptom scores at baseline and pre-existing and worsened symptoms

Ison. Lancet Infect Dis 2020

Problem Statement:

Can we quantify the impact of reduction of Time of Viral Shedding via new antiviral on the transmission of influenza?

Literature review on the link between viral shedding & transmission

American Journal of Epidemiology

Vol. 167, No. 7
DOI: 10.1093/aje/kwm375
Advance Access publication January 29, 2008

Meta-Analysis

Time Lines of Infection and Disease in Human Influenza: A Review of Volunteer Challenge Studies

Fabrice Carrat[1,2,3], Elisabeta Vergu[1,2,4], Neil M. Ferguson[5], Magali Lemaitre[1,2], Simon Cauchemez[5], Steve Leach[6], and Alain-Jacques Valleron[1,2,3]

"Influenza infectiousness is usually equated to the presence of virus shedding"

"…profile of infectiousness over time that is remarkably consistent with viral shedding data from experimental infection studies"

Vol 437|8 September 2005|doi:10.1038/nature04017
nature

ARTICLES

Strategies for containing an emerging influenza pandemic in Southeast Asia

Neil M. Ferguson[1,2], Derek A.T. Cummings[3], Simon Cauchemez[4], Christophe Fraser[1], Steven Riley[5], Aronrag Meeyai[1], Sopon Iamsirithaworn[6] & Donald S. Burke[3]

Review > Trends Microbiol. 2016 Feb;24(2):123-133. doi: 10.1016/j.tim.2015.10.012. Epub 2015 Nov 21.

Household Transmission of Influenza Virus

Tim K Tsang [1], Lincoln L H Lau [2], Simon Cauchemez [3], Benjamin J Cowling [4]

Affiliations + expand

PMID: 26612500 PMCID: PMC4733423 DOI: 10.1016/j.tim.2015.10.012

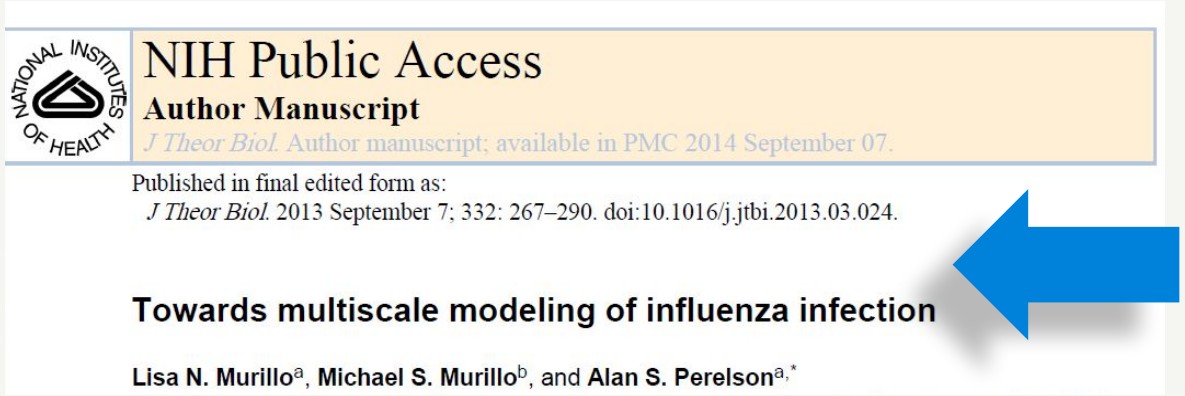
"Antiviral treatment of index cases was found to be associated with lower infectivity in a randomized controlled trial [58] and four observational studies [61,76,78,87]. It suggested that treatment could reduce onwards transmission"

Initial Modeling approach based on the Literature review

"Influenza infectiousness is usually equated to the presence of virus shedding"

- A patient with reduced Time of Viral Shedding (Tshed) should infect less people
- Proportion of infected patients with flu in a population would be reduced when increasing the number of treated patients with antiviral therapy

Investigate the impact of Tshed reduction on transmission



NIH Public Access
Author Manuscript
J Theor Biol. Author manuscript; available in PMC 2014 September 07.

Published in final edited form as:
J Theor Biol. 2013 September 7; 332: 267–290. doi:10.1016/j.jtbi.2013.03.024.

Towards multiscale modeling of influenza infection

Lisa N. Murillo[a], Michael S. Murillo[b], and Alan S. Perelson[a,*]

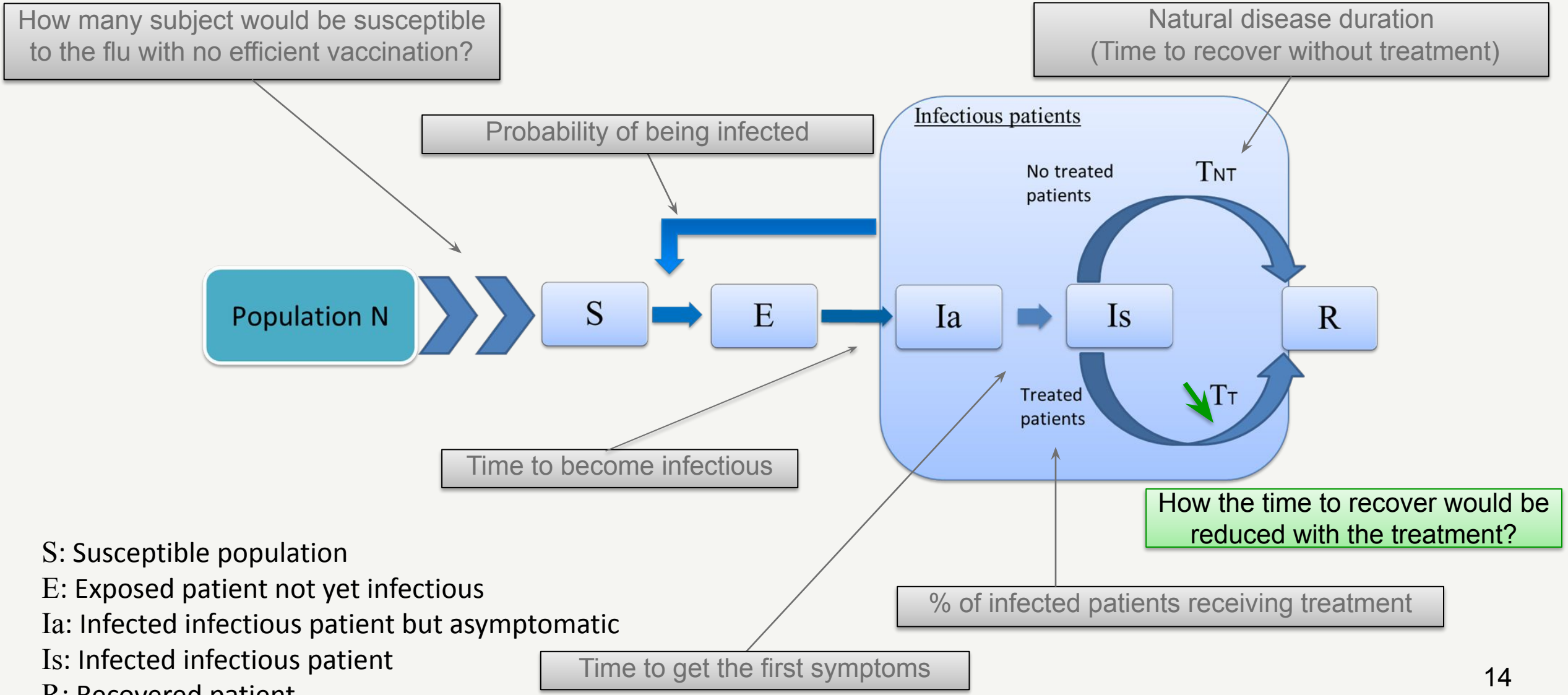
- *Many aspects of influenza epidemics can be modeled within the SIR framework, and several conclusions immediately follow.*
- *SIR model has proven quite useful for describing influenza outbreaks.*
- *An important application of the SIR framework is the study of antiviral use and the subsequent emergence of drug resistance*

using a SEIR model

Evaluation of the effect in epidemiological context

The model

Some elements specific to the flu and the social behavior
+ Some elements specific to the treatment



S: Susceptible population
E: Exposed patient not yet infectious
Ia: Infected infectious patient but asymptomatic
Is: Infected infectious patient
R: Recovered patient

Simulation scenarios:

Some differences between Pandemic and Seasonal flu

	Seasonal flu	Pandemic flu
% Susceptible population	30%	
% population with effective vaccination	20%	0%
Flu transmission	1.35 subjects infected by 1 patient over 5 days (β=0.27)	2.9 subjects infected by 1 patient over 6 days (β=0.48)
Exposed period not infectious	1 day	
Infectious period not treated	1 day	0 day
Infectious period without treatment	5 days	6 days
Tshed results from the Ph3 trial	Oseltamivir: 72 to 96 hours Baloxavir : 24 to 48 hours	

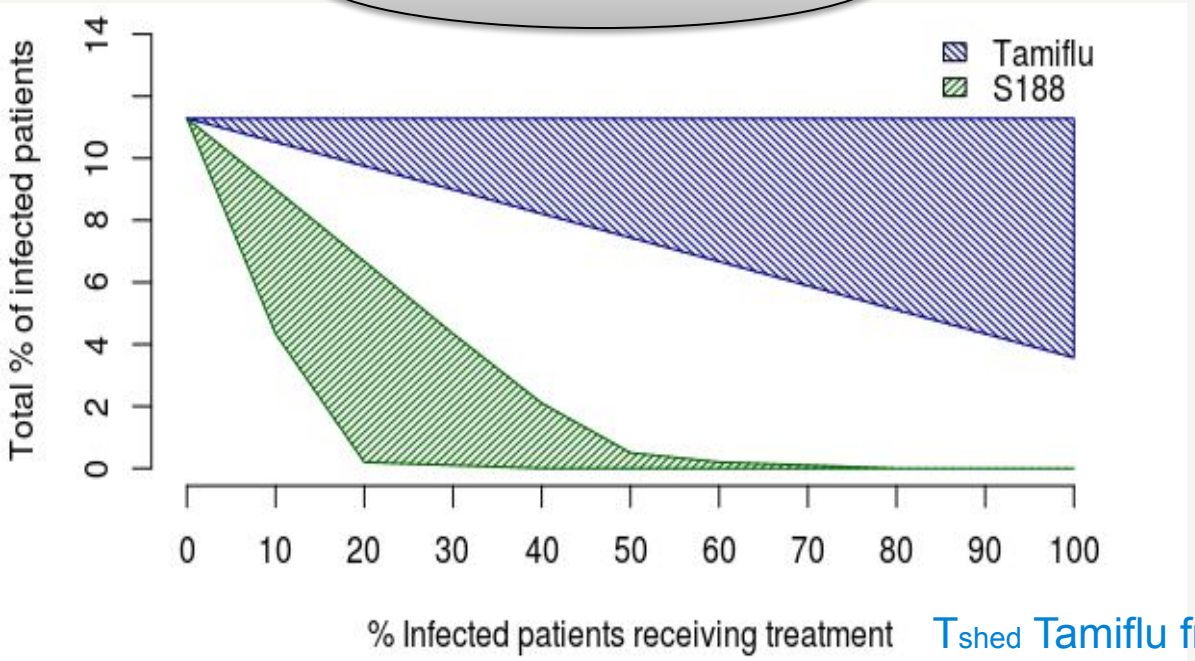
Pandemic flu could be assumed being characterized by:

- Efficient vaccination
- Flu transmission
- Infectious not-treated period as rapid medical intervention
- Total Infectious period

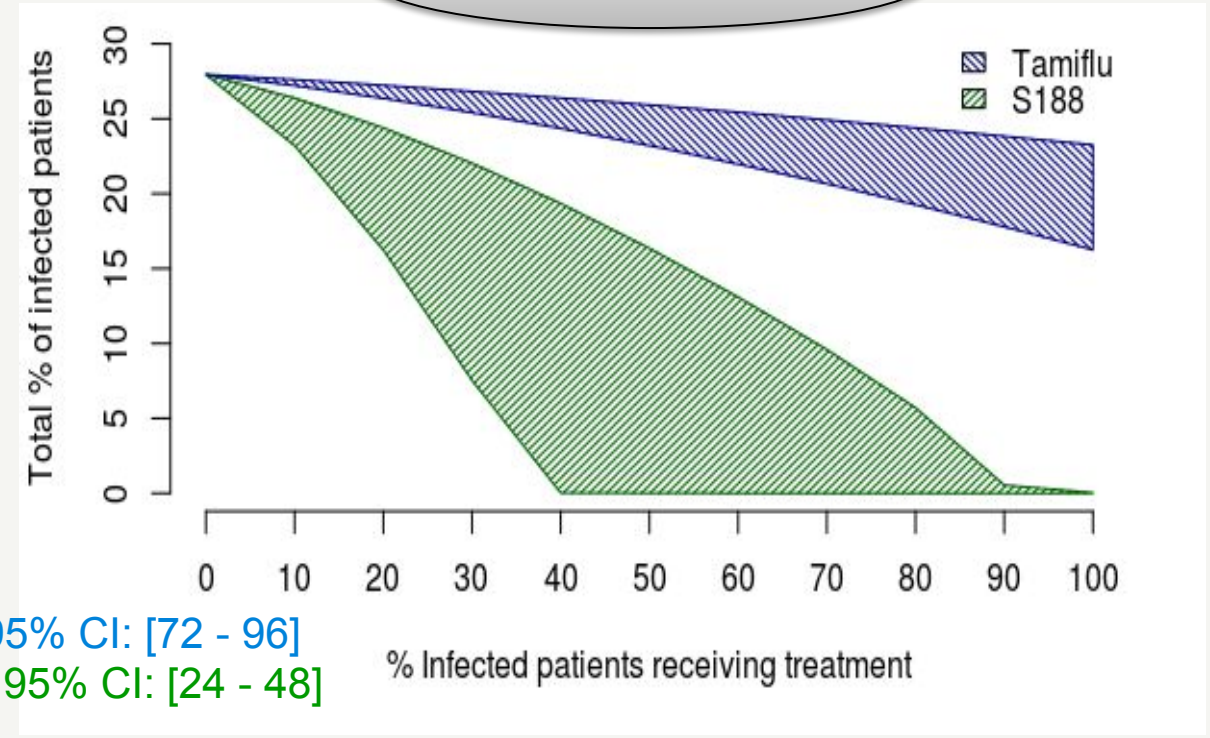
Simulation results with SEIR model:

% of infected patients with Xofluza significantly reduced as compared to Tamiflu in both seasonal and pandemic scenarios

Seasonal flu



Pandemic flu



T_{shed} Tamiflu from 95% CI: [72 - 96]

T_{shed} Xofluza from 95% CI: [24 - 48]

Assumptions:
- 1 day incubation+ 1 day infectious not treated
- 5 days infectious period without treatment
- Flu Transmission: 1.35 subjects infected by 1 patient over 5 days infectious period (β=0.27)
- 20% effective vaccination, 30 % susceptible population
- Tshed 24h for Baoxavir Marboxil, 72h for Oseltamivir

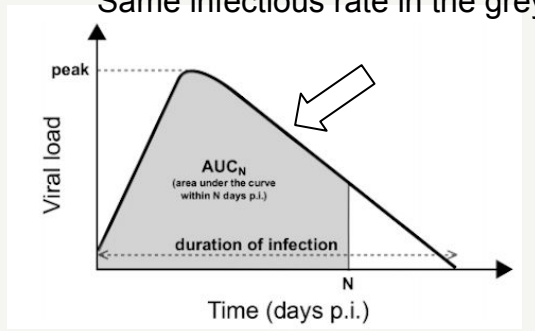
Assumptions:
- 1 day incubation
- 6 days infectious period without treatment
- Flu Transmission: 2.9 subjects infected by 1 patient over 6 days infectious period (β=0.48)
- No effective vaccination, 30 % susceptible population
- Tshed 24h for Baoxavir Marboxil, 72h for Oseltamivir

Initial modeling results from the SEIR model

Several approaches & assumptions used to explore the impact on results

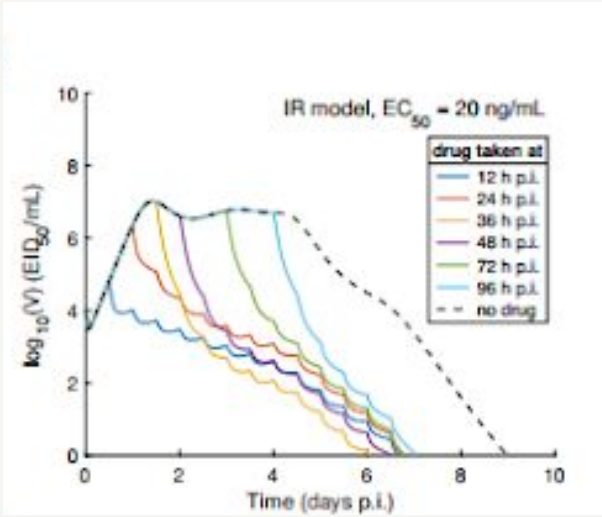
- **SEIR epidemiological model:**
  - Could show the potential impact of reduction of time of shedding on flu transmission
  - Limitation:
    - Model assuming same infectious rate and treatment effect in each patient
    - Model using a constant infectious rate over the infectious period
    - Results highly sensitive to the infectious rate and the time to treatment start

Same infectious rate in the grey area



- **How to improve the model:**
  - Adding between subject variability on the treatment effect
  - Varying the infectious rate with the viral titer level:
    - Infectious rate would depend on the treatment effect on viral titer

- **How to validate these results:**
  - Household Transmission trial with Index patients treated with Placebo or Xofluza



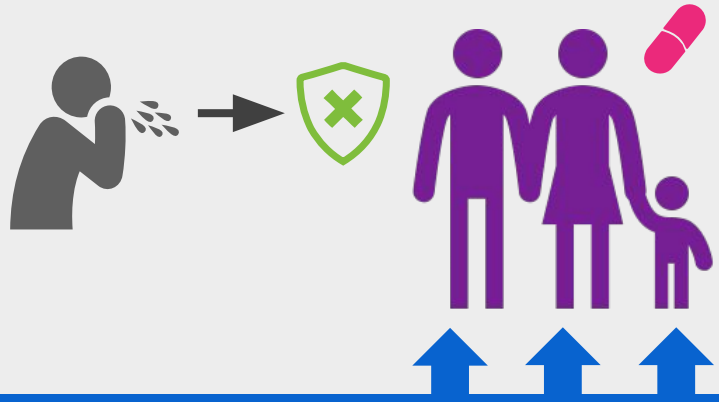
Illustrations from Cao & McCaw: Viruses 2017, 9(8), 197

Validation using household contact trials

Antivirals have the potential to limit the spread of influenza through two distinct approaches

PROPHYLAXIS

Prevent disease onset in healthy persons



Household contacts receive antiviral

BLOCKSTONE

TREATMENT OF INDEX PATIENT

Prevent disease transmission from an infected person

Infected patients receive antiviral

CENTERSTONE

ECDC 2017. Available at: https://ecdc.europa.eu/sites/portal/files/documents/Scientific-advice-neuraminidase-inhibitors-2017.pdf; Lowen. Infect Disord Drug Targets 2007 Hayden. Clin Infect Dis 2022

BLOCKSTONE: PhIII, randomised, placebo-controlled, post-exposure prophylaxis (PEP) study of baloxavir

Study design

Treatment (1 day) → *Observation (10 days)* → *Follow-up (5 days)*

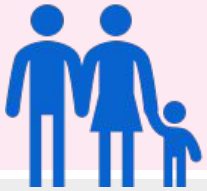
Index patient (IP)

- First in household with influenza in 18/19 season
- Tested positive for influenza by RIDT
- ≤48 hours from symptom onset

Healthy household contact (HHC)

- ≥48 hours living with the IP prior to consent
- No influenza virus infection

N=752



1 **Baloxavir**

1 **Placebo**

HHC

Visits will occur when:

- Axillary temp ≥37.5ºC
- Moderate or severe influenza symptoms

Days 11–15

Key exclusion criteria (HHCs)

- Prior diagnosis with influenza during the 18/19 season
- Inability to live with the IP until Day 10
- Patients with HHCs other than the IP diagnosed with, or suspected of having, influenza

Study primary endpoint

Proportion of HHCs who develop influenza, defined as:

- RT-PCR positive, **and**
- present with fever, **and**
- at least one respiratory symptom (Day 1 to Day 10)

Study conducted in Japan

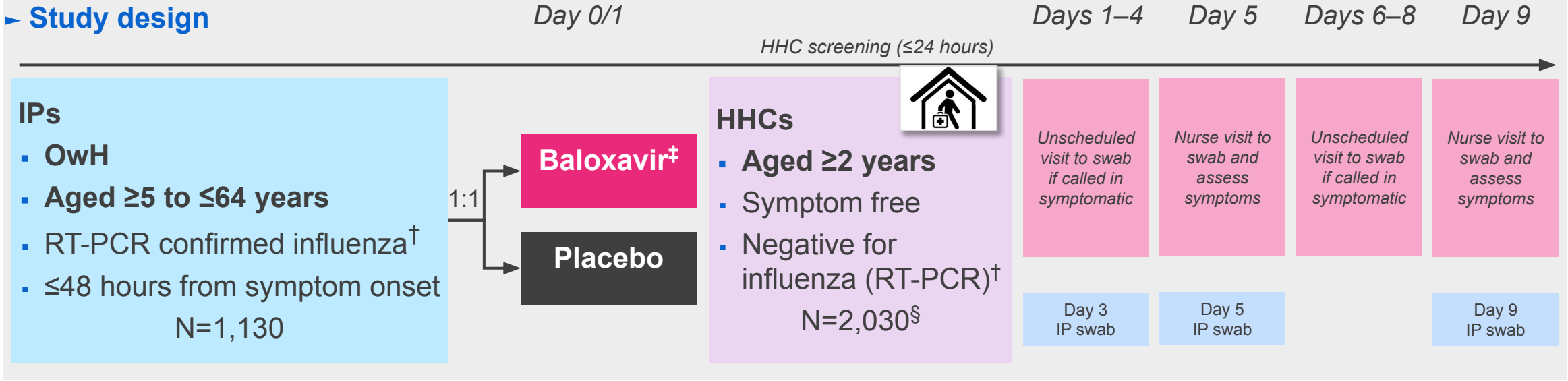
*To access the Baloxavir Clinical Development Programme slide deck, please copy and paste the following link into your browser:
https://medcin.roche.com/search?searchTerm=c7a58e02bdb9f3235753df6b33ab72b1&divisions=PHARMA

To view the clinical development programme for baloxavir, please visit MedCIN*

Ikematsu. New Engl J Med 2020

CENTERSTONE: Phase III, randomised, placebo-controlled transmission trial in OwH patients

Study design



Key exclusion criteria (IPs)

- Severe influenza virus infection requiring hospitalisation
- SARS-CoV-2 infection
- Pregnant or breastfeeding
- Lives with any HHCs who meet HHC exclusion criteria

Key exclusion criteria (HHCs)

- Immunocompromised
- SARS-CoV-2 infection
- Pregnant or within 2 weeks post-partum

*To access the Baloxavir Clinical Development Programme slide deck, please copy and paste the following link into your browser: https://medcin.roche.com/search?searchTerm=c7a58e02bdb9f3235753df6b33ab72b1&divisions=PHARMA; †PCR testing for influenza A or B; ‡Single dose. ≥12 years: 40 mg for body weight <80 kg, 80 mg for body weight ≥80 kg; <12 years: 2 mg/kg for body weight <20 kg, 40 mg for body weight ≥20 kg; §Primary analysis population (PAS-HHC), defined as all full trial unvaccinated HHCs associated with an IP who was RT-PCR–positive for influenza and received trial drug, with all HHCs in the household RT-PCR–negative for influenza at baseline

To view the clinical development programme for baloxavir, please visit MedCIN*

Kuhlbusch. OPTIONS X 2019
NCT03969212 (CENTERSTONE)

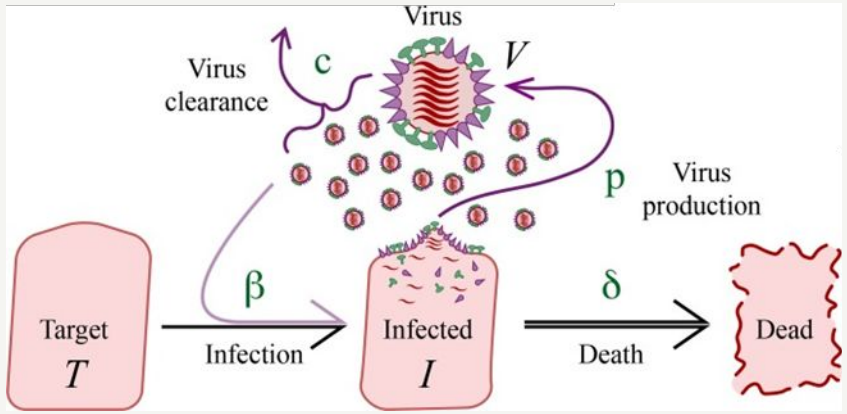
Step 1: Development of the transmission tool

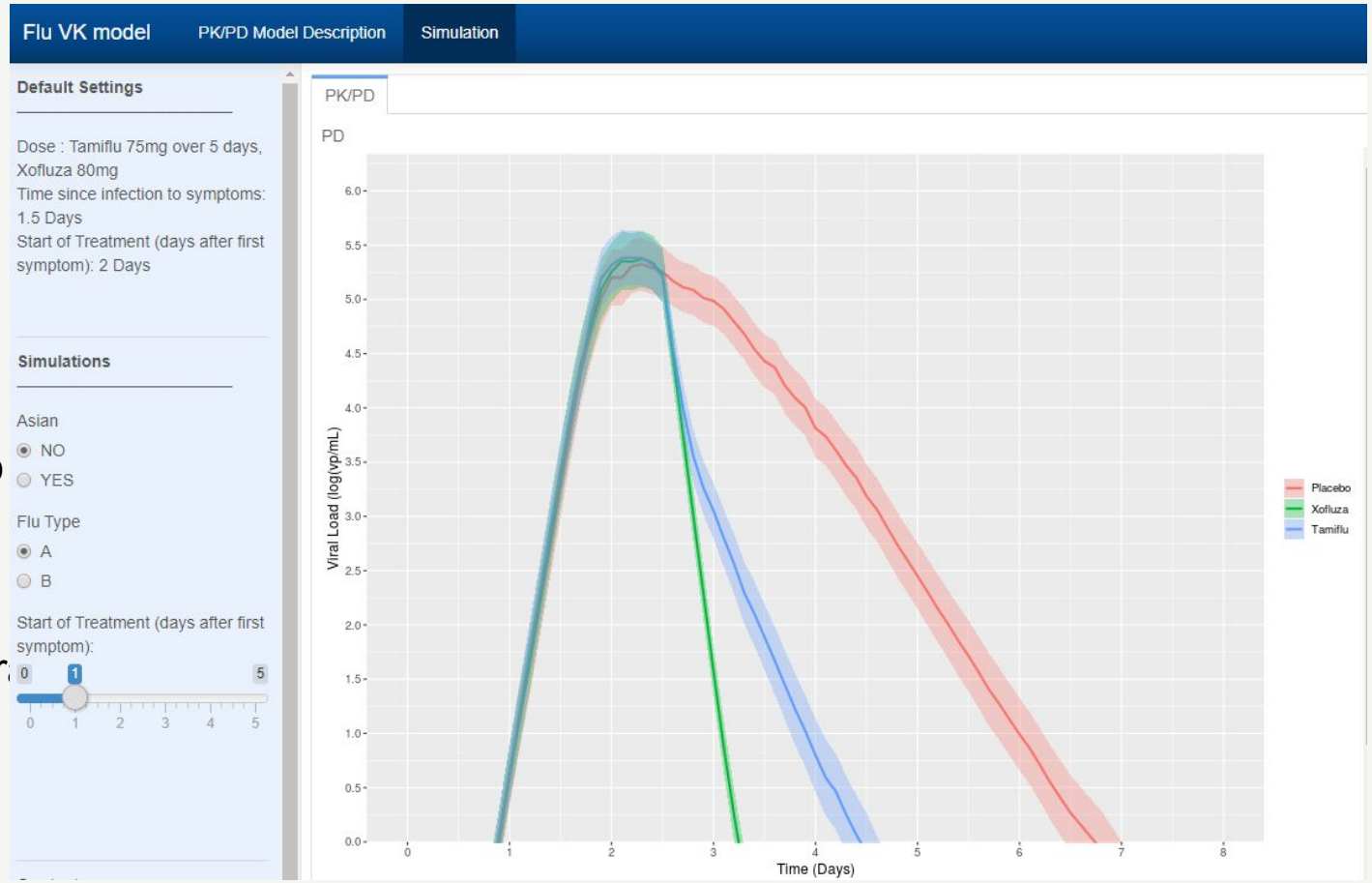
Objective: Evaluate the effect when treating IPs to prevent flu spreading in non-treated HHC

Method:

- For each category (age, flu type, Race) and each treatment (Placebo/Baloxavir)
  - Select randomly Index Patients (IP) among the observed individuals pooling all trials data
  - Use the viral kinetic model to generate individual daily viral titer levels over the 5 days post treatment using observed viral titer data
  - Simulate the expected number of infected household contact (HHC) for each IP
  - For a range of coefficient of infectiousness:
    - Simulate an infected status for each of the HHC
    - Compute the percentage of transmission for each treatment

Characterize the time course of viral titer using a Viral Kinetic model





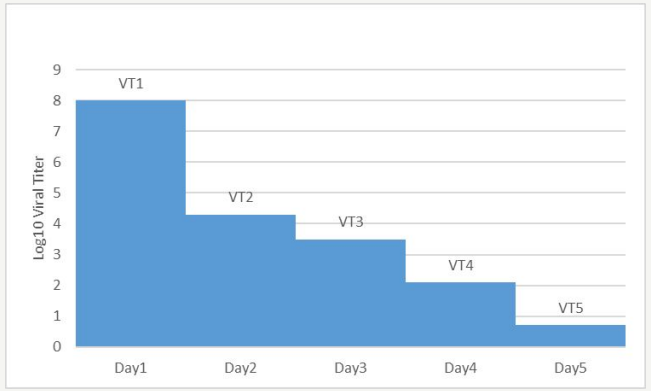
Key findings:

- Differences in the disease parameters related to the immune system between Asian and Non-Asian
- The individual PK exposure is driving the anti-vir effect via inhibition of the virus production
- Different inhibition between Type A and Type B

How to generate the infected status of each HHC

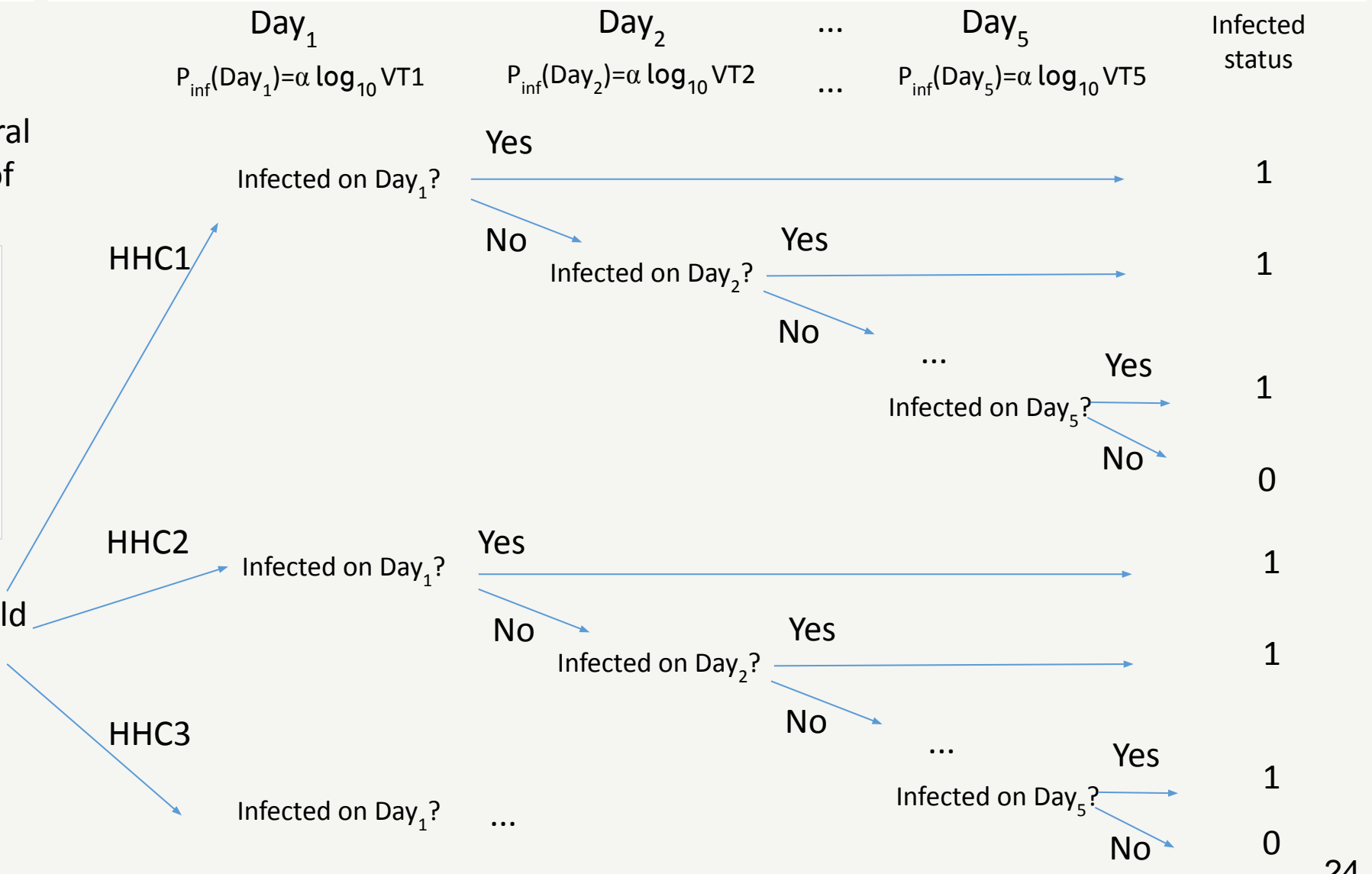
IP	HHC

1. Select randomly an observed patient
2. Compute the individual daily viral titer level over the first 5 days of treatment



Example of Viral titer time course

3. Generate a number of household contact (normal distribution of mean 1.8, sd 0.5)
4. Report for each HHC the final infected status (1 or 0)



Step 2: Calibration for the simulation of the effect

- Need to determine the α to match the observed probability of infection
  - Use the results from Blockstone
    - ✔ HHC: no treatment
    - ✔ IP: treated with NAI (assuming Oseltamivir treatment)
  - Determine the α for each age category that would allow to match the observation with the simulation outcome

- Simulation outcome validating the calibration

Exploratory analysis result: Inhibitory effect of the intrahousehold infection by age of IPs

Age of IPs	Proportion of HHCs with influenza virus infection, fever and at least one respiratory symptom (%) (RT-PCR positive and negative at baseline for HHC)	
	Baloxavir Marboxil	NAI
< 6 years	27.6% (8/29)	20.7% (17/82)
6 to <12 years	10.6% (9/85)	14.1% (10/71)
≥ 12 years	5.3% (4/75)	14.3% (3/21)
Total	11.1% (21/189)	17.2% (30/174)

Age of IPs	Proportion of HHCs with influenza virus infection, fever and at least one respiratory symptom (%) (RT-PCR negative at baseline for HHC)	
	Baloxavir Marboxil	NAI
< 6 years	16.7% (4/24)	21.7% (15/69)
6 to <12 years	8.9% (7/79)	10.4% (7/67)
≥ 12 years	5.7% (4/70)	10.5% (2/19)
Total	8.7% (15/173)	15.5% (24/155)

Baloxavir Marboxil

Age of IP	% Infected HHC	PI95%
<5	21.63	[17.0 ; 27.1]
>=5 and <12	10.38	[6.5 ; 14.2]
>=12	10.67	[6.9 ; 14.9]

Simulation of the Baloxavir effect using the α from the calibration

Age of IP	% Infected HHC	PI95%
<5	16.7	[12.0 ; 20.9]
>=5 and <12	7.7	[4.8 ; 11.3]
>=12	7.4	[4.3 ; 10.7]

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Baloxavir Marboxil

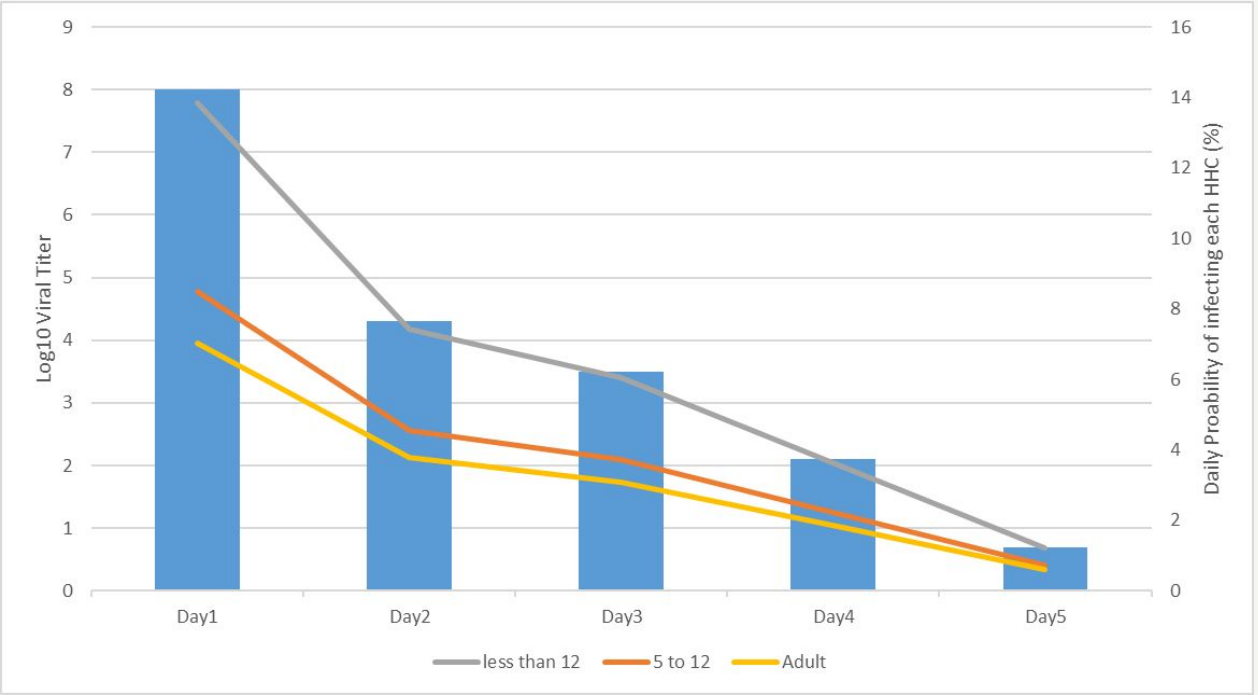
Using

The daily infectious rate proportional to the daily viral titer + The coefficient of infectiousness α calibrated for each age category would allow to describe both the Oseltamivir (from calibration) and Baloxavir effect

More about the coefficient of infectiousness α

What did we learn from the calibration with BLOCKSTONE

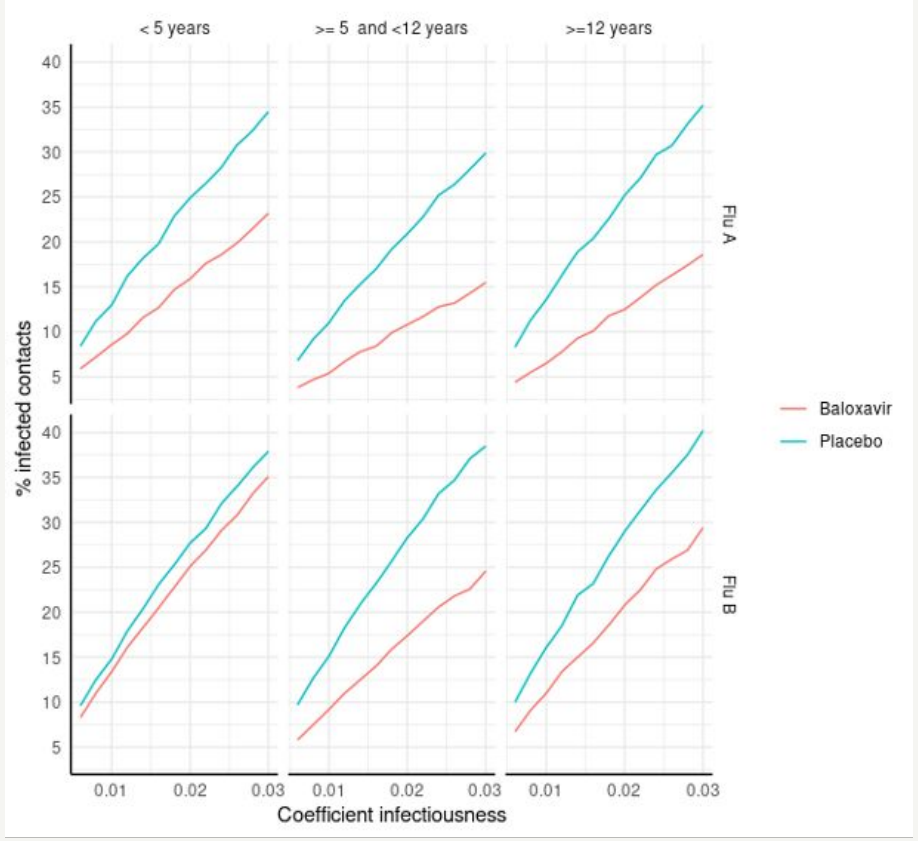
- It is possible to find an α that would allow to describe the % of infected HHC in each treatment group, this coefficient being independent of the treatment
- This coefficient would be higher in pediatric population
  - At a similar viral titer level, and independently of the treatment
    - A pediatric from 5 to 12 years would be 20% more infectious than an adult
    - A young pediatric below 5 years would be 2 times more infectious than an adult



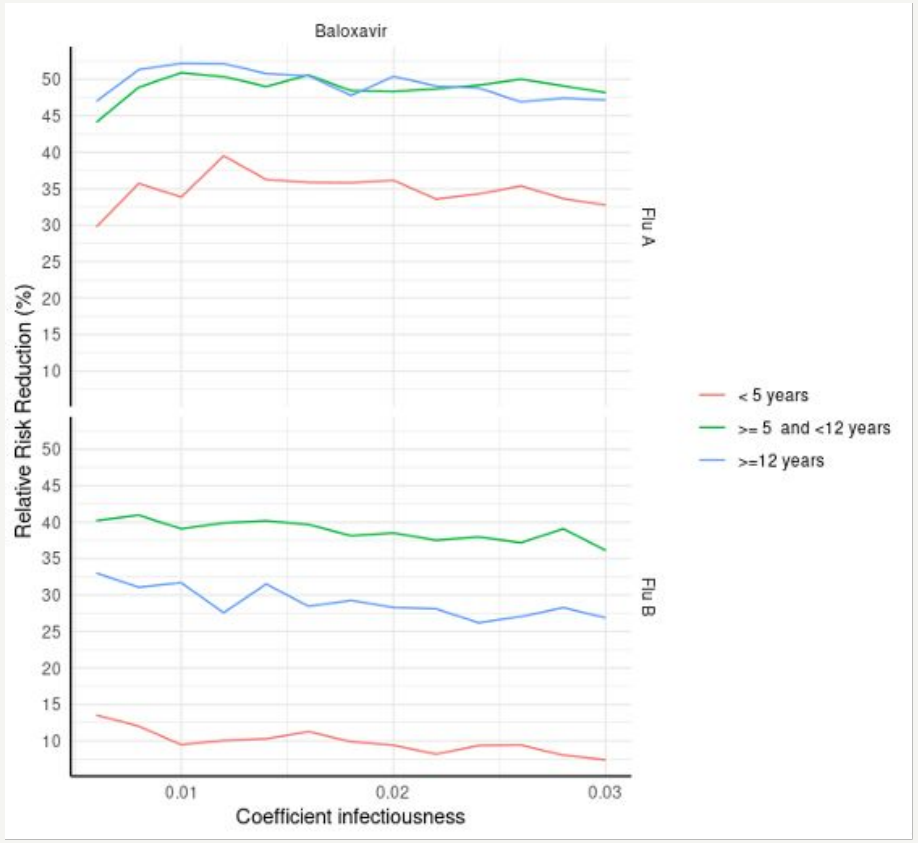
More about the coefficient of infectiousness α

Varying this coefficient would impact on the % of infected contacts, with differences between age and flu categories... However, the relative risk reduction of baloxavir versus placebo would remain rather constant for each category

Percentage of Infected Contacts over 5 Days depending on Coefficient of Infectiousness for Flu A and B (Virtual Transmission Trial)



Relative risk reduction (RRR) Baloxavir versus Placebo by age category for flu A and flu B



RRR= (% Infected from Placebo IPs - % Infected from Baloxavir IPs)/(% Infected from Placebo IPs)

Step 3: Extend the Simulation to a larger transmission trial

Objective: Validation of the transmission tool

Could we

- Simulate the effect size observed in Centerstone for each category
- Estimate for each category a unique coefficient of infectiousness for Placebo and Baloxavir, which provides percentages of transmission matching the percentages of transmission observed in Centerstone

Observed percentages of transmission in Centerstone

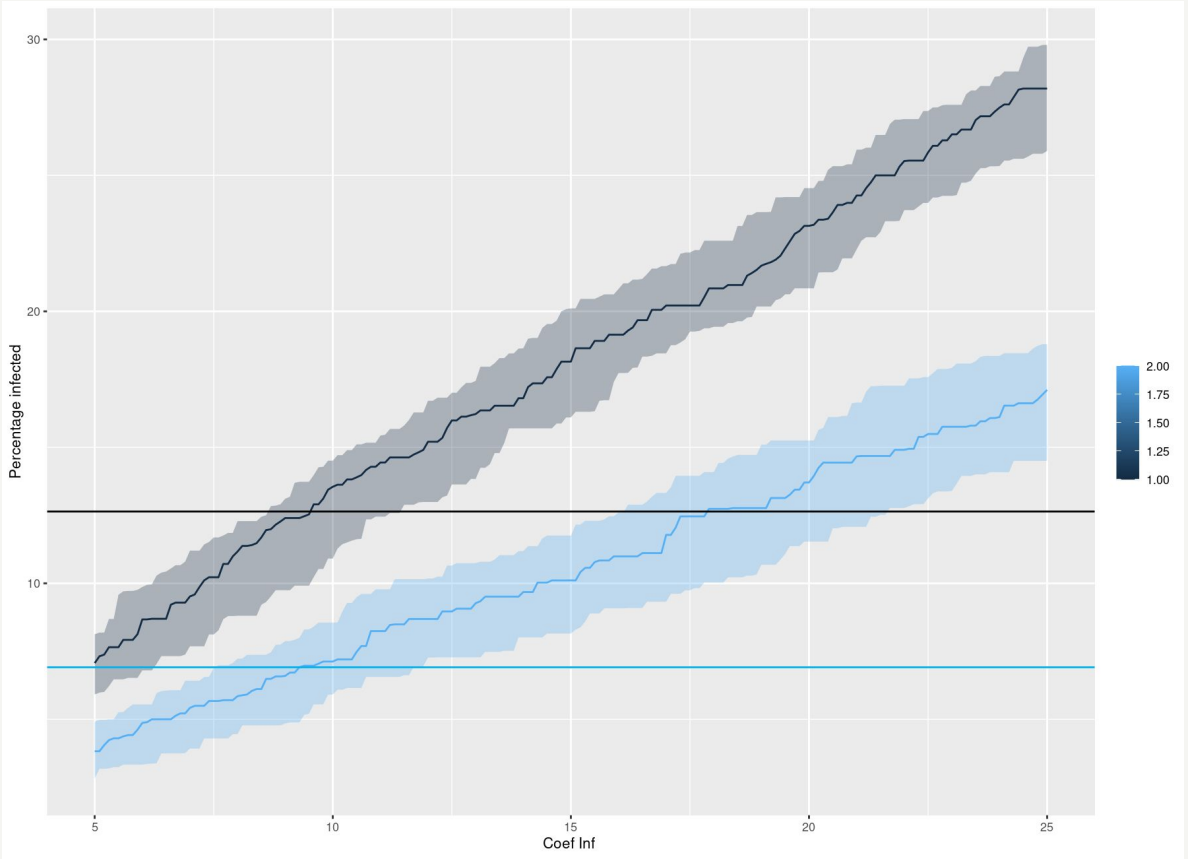
Roche

Presented by age categories, flu types and race

	Placebo		Xofluza		Effect size
	Number IP	% HHC infected	Number IP	% HHC infected	
All	544	13.42	548	9.50	29.21
≥5 and <12	46	12.65	44	6.91	45.38
≥12	498	12.25	504	8.96	26.86
≥18	417	12.94	417	8.48	34.47
Flu A	451	13.09	450	8.70	33.54
Flu B	91	7.63	93	5.71	25.16
Non-Asian	403	10.95	410	8.10	26.03
Asian	141	15.34	138	9.52	37.94

Exemple of a simulation

Simulation settings:
Use historical predicted VT, age from 5 to 12y, 100 IP, 30 replicates, Comparing to 12.65% infection with Placebo, and 6.91% with Xofluza

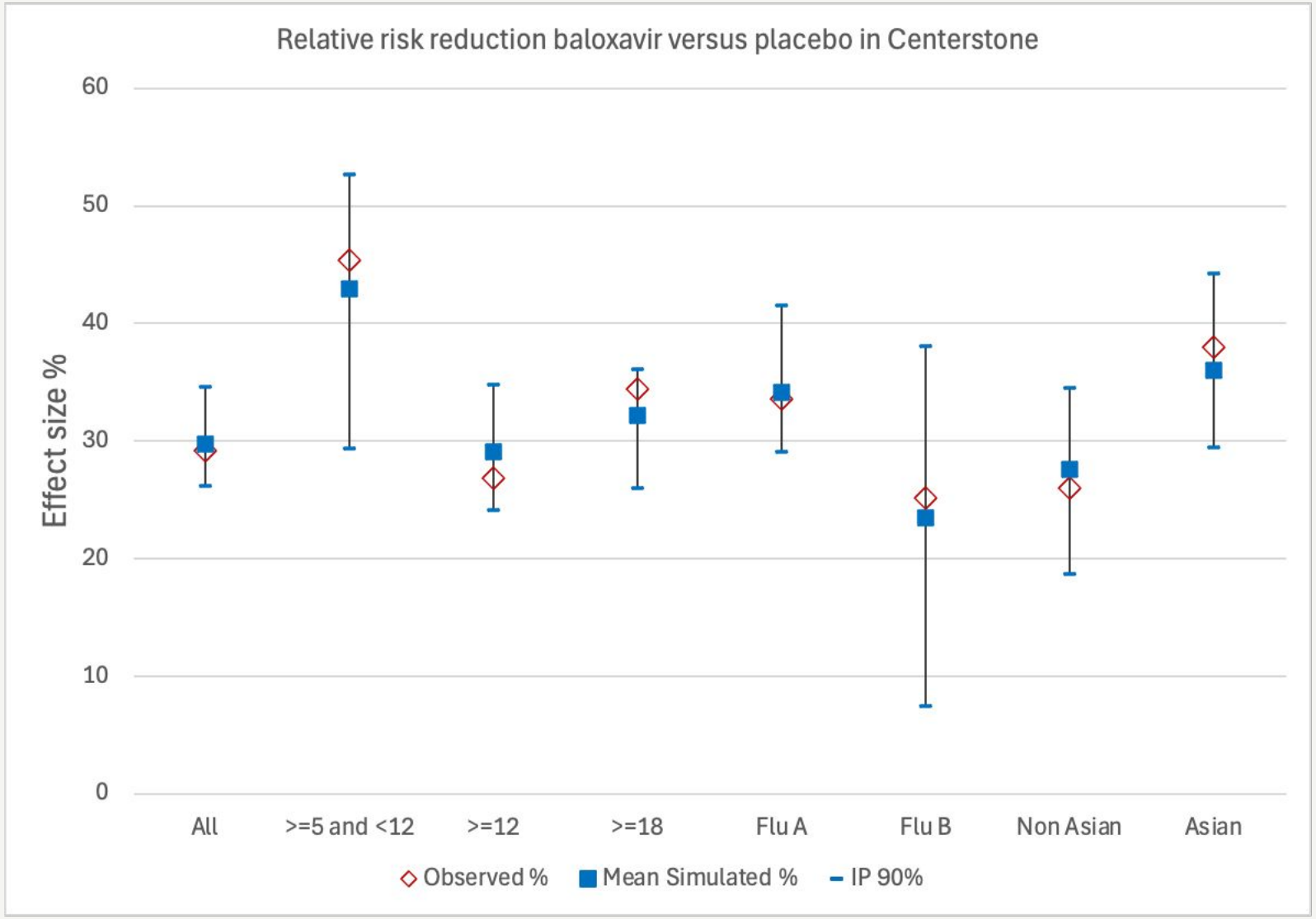


Coefficient of Infectiousness= 9.2 [8.6 ; 10.3]
Percentage infection from Placebo IP= 12.67 [11.45 ; 13.29]
Percentage infection from Xofluza IP= 7.01 [6.56 ; 7.37]
Effect size (%)= 45.25 [37.33 ; 52.75]

https://rsconnect.roche.com/connect/#/apps/07e6318b-1fa4-4f0c-9be2-2bd2cc04dd6a/access

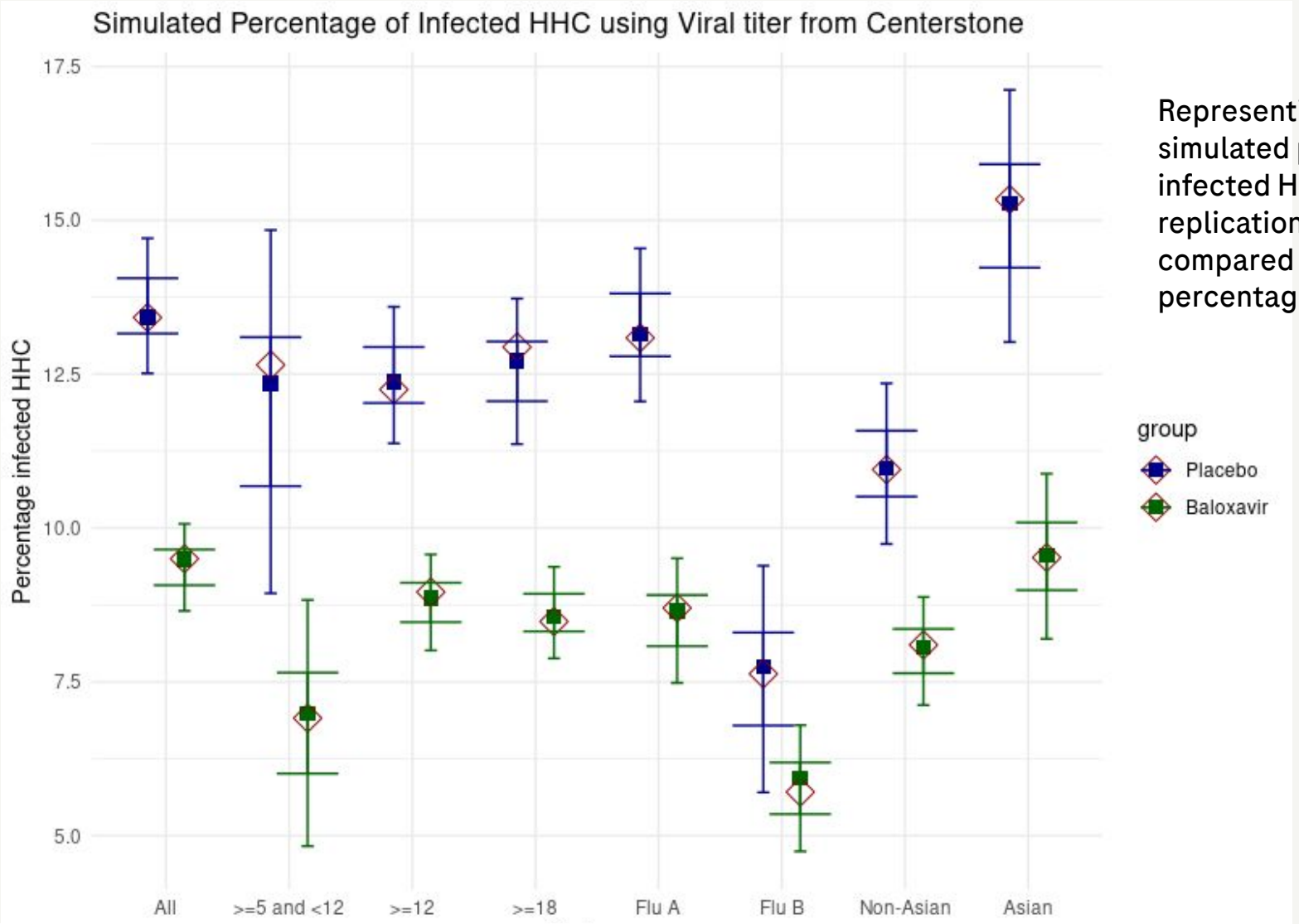
Results of the Validation with Centerstone (1/2)

- The simulation tool can properly estimate the effect size observed in Centerstone for each category



Results of the Validation with Centerstone (2/2)

- The simulation tool can properly estimate for each category (age, flu type, Race) a unique coefficient of infectiousness for Placebo and Baloxavir, which provides similar percentages of transmission as the ones observed in Centerstone



Representing the mean simulated percentage of infected HHC from 100 replications, IP50% and IP90%, compared to the observed percentage (in red)

- The estimated coefficient of infectiousness can differ between each categories

Number of IPSs	545	45	500	400	450	90	400	140
Coefficient of infectiousness $x10^{-3}$	22.1	16.1	20.1	21.3	21.0	9.1	19.5	18.5

Perspectives/Conclusion

How to predict the role of antivirals in reducing influenza transmission using modeling and simulation

Perspectives/Conclusion

- Epidemiological model could show a potential effect on reducing flu transmission with reduced time to cessation of viral shedding
- Accounting for individual viral titer level and relationship with infectiousness, a transmission tool has been developed successfully validated using the Centerstone study.
- Such modelling approach would allow:
  - To show the societal impact for a drug like Xofluza to reduce overall transmission of influenza
  - To support the interactions with Health Authorities with regards to transmission label for Xofluza
  - To further extrapolate impact of transmission in younger age category for the pediatric filling

Doing now what patients need next