



# 16<sup>th</sup> Residential Course on Clinical Pharmacology of Antiretrovirals

[www.fcarvturin.it](http://www.fcarvturin.it)

January  
13-15, 2021

COVID 19: THE CHALLENGING PATHWAY  
OF SARS-COV-2/COVID-19 MANAGEMENT

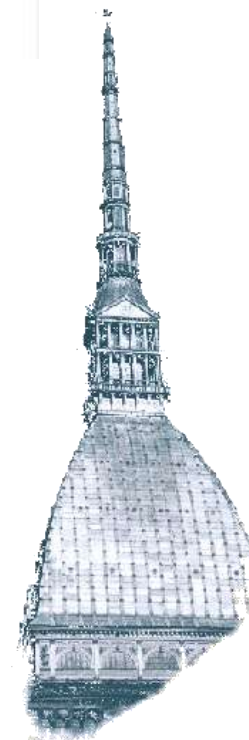
## Epidemiology

*Gianni Di Perri*

Clinica di Malattie Infettive  
Università degli Studi di Torino  
Ospedale Amedeo di Savoia



*Ospedale Amedeo di Savoia*



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- Abbvie
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- Janssen
- ViiV
- Pfizer
- Novartis
- Astellas
- Basilea
- Zambon
- Correvio
- Angelini

## ***Coronavirus sp.***

Fino al 2002 è stato ai margini dell'interesse scientifico, in quanto causa di episodi infettivi per lo più banali a carico delle vie aeree superiori (rinite o raffreddore).

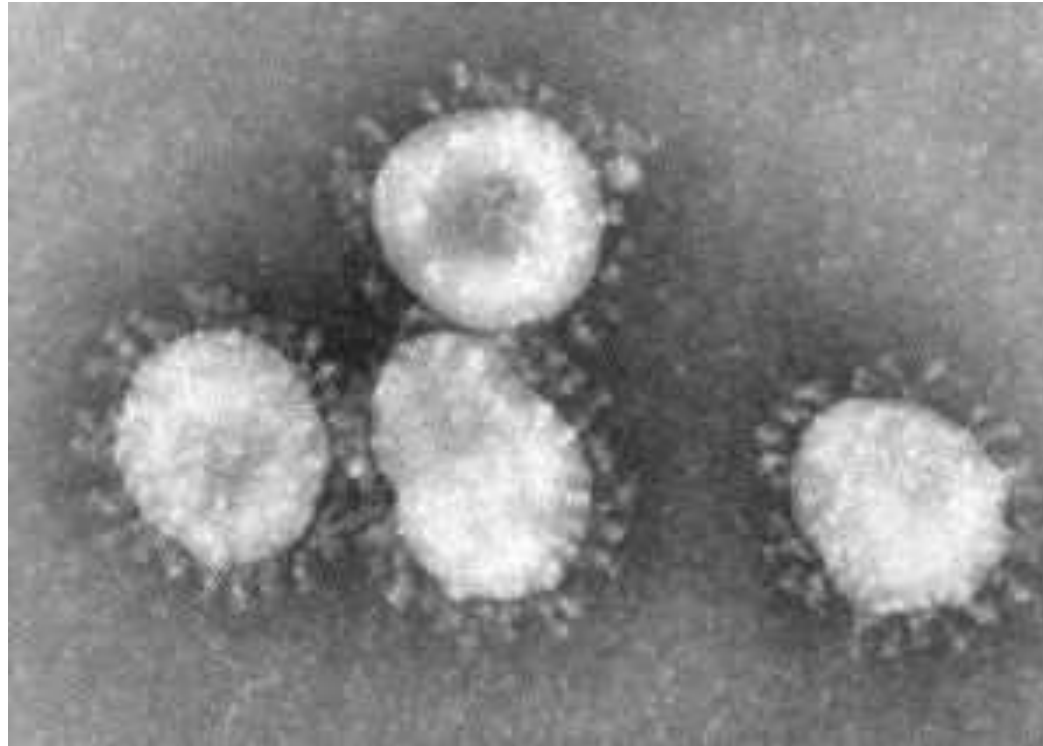
Ciononostante, per ragioni di ordine classificativo, ne erano stati caratterizzati 4 tipi su base molecolare:

**HCoV 229E**

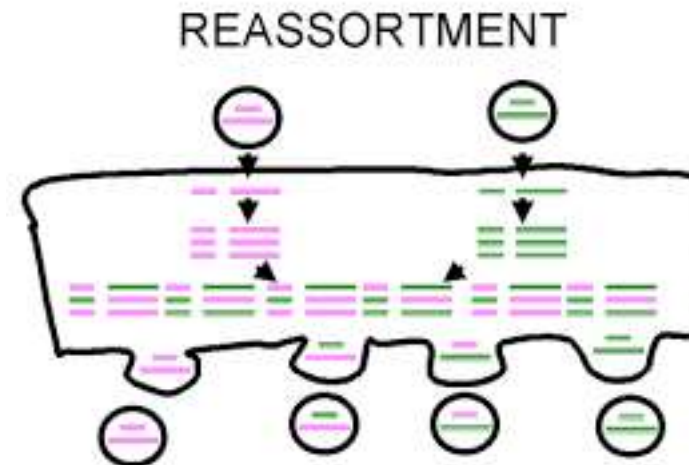
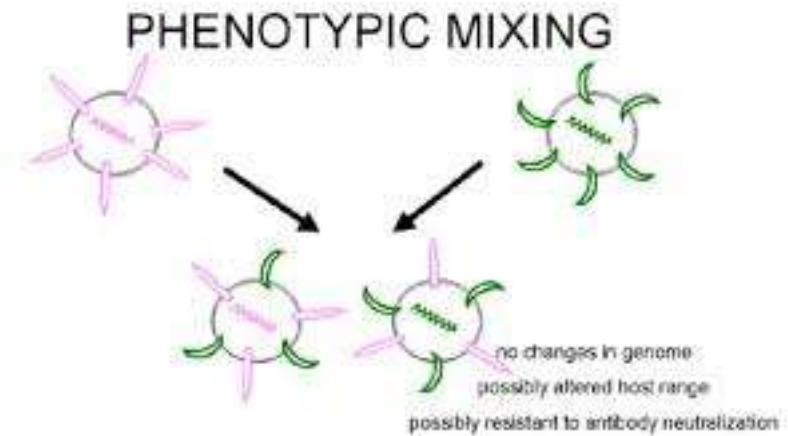
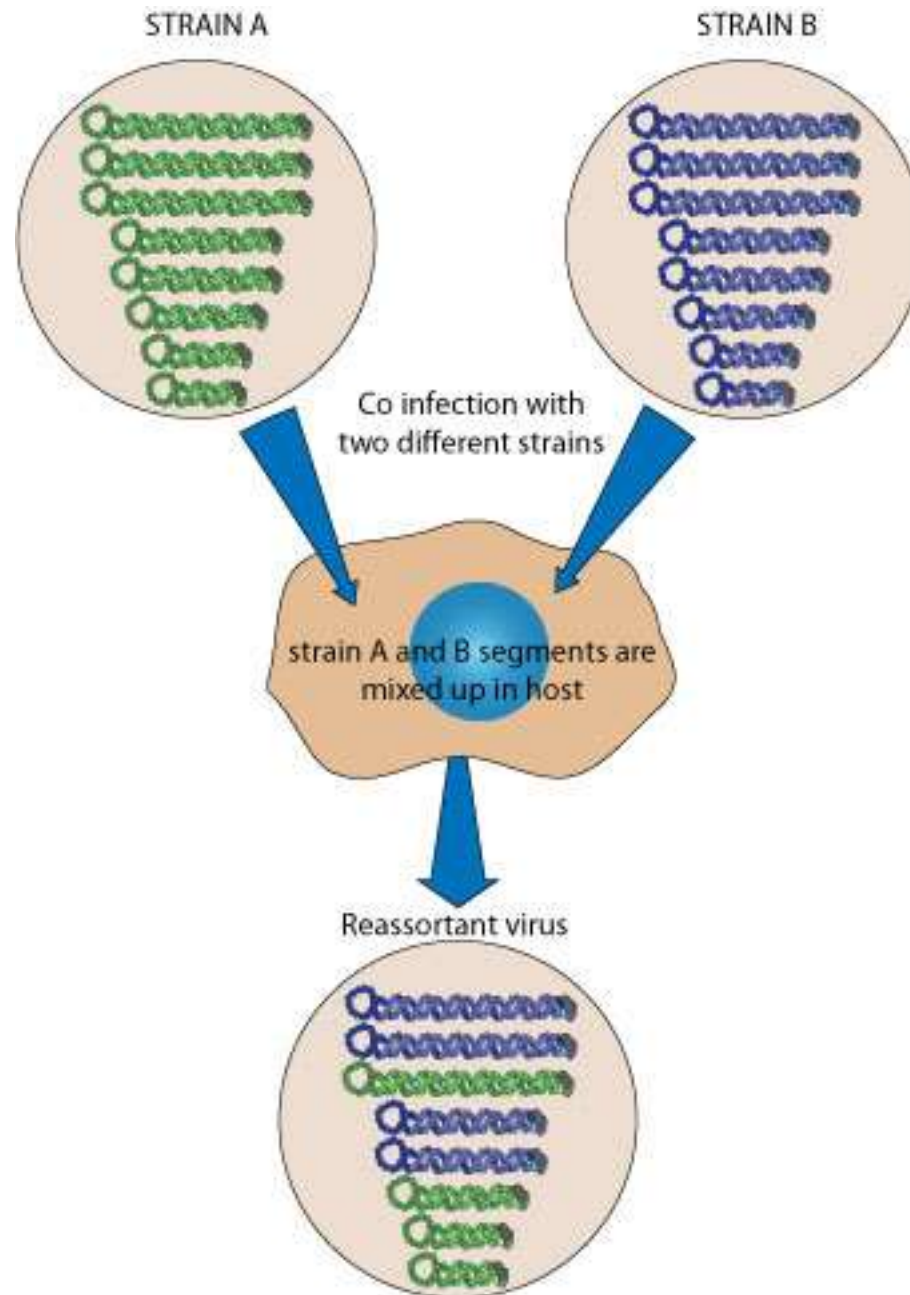
**HCoV OC43**

**HCoV NL63**

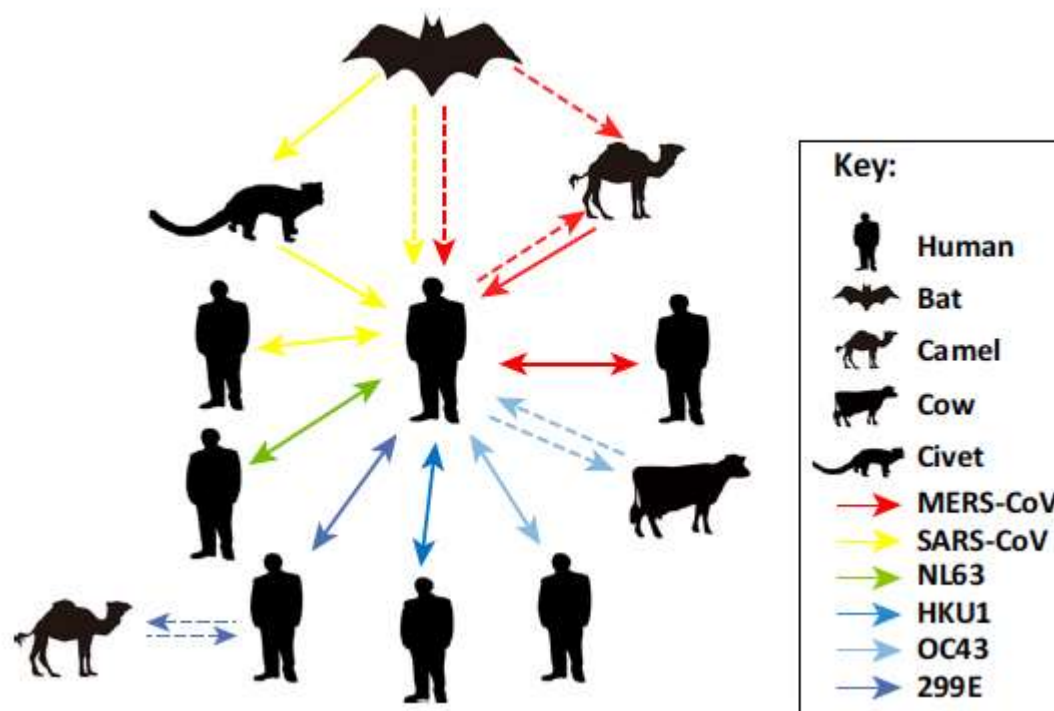
**HCoV HKU1**



## GENETIC RECOMBINATION AMONG DIFFERENT VIRAL STRAINS



**Intra- and Inter-Species Transmission of Human Corona-viruses.** Red, yellow, green, blue, brown, and purple arrows represent transmission of MERS-CoV, SARS-CoV, NL63, HKU1, OC43, and 229E, respectively, between bats, camels, cows, humans, and masked palm civets (shown in a legend on the side of the figure). Unbroken arrows represent confirmed transmission between the two species in question, and broken arrows represent suspected transmission.





# SARS-like WIV1-CoV poised for human emergence

Vineet D. Menachery<sup>a</sup>, Boyd L. Yount Jr.<sup>a</sup>, Amy C. Sims<sup>a</sup>, Kari Debbink<sup>a,b</sup>, Sudhakar S. Agnihothram<sup>c</sup>, Lisa E. Gralinski<sup>a</sup>, Rachel L. Graham<sup>a</sup>, Trevor Scobey<sup>a</sup>, Jessica A. Plante<sup>a</sup>, Scott R. Royal<sup>a</sup>, Jessica Swanstrom<sup>a</sup>, Timothy P. Sheahan<sup>a</sup>, Raymond J. Pickles<sup>c,d</sup>, Davide Corti<sup>e,f,g</sup>, Scott H. Randell<sup>d</sup>, Antonio Lanzavecchia<sup>e,f</sup>, Wayne A. Marasco<sup>h</sup>, and Ralph S. Baric<sup>a,c,1</sup>

3048–3053 | PNAS | March 15, 2016 | vol. 113 | no. 11

2016

## A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence

Vineet D Menachery<sup>1</sup>, Boyd L Yount Jr<sup>1</sup>, Kari Debbink<sup>1,2</sup>, Sudhakar Agnihothram<sup>3</sup>, Lisa E Gralinski<sup>1</sup>, Jessica A Plante<sup>1</sup>, Rachel L Graham<sup>1</sup>, Trevor Scobey<sup>1</sup>, Xing-Yi Ge<sup>4</sup>, Eric F Donaldson<sup>1</sup>, Scott H Randell<sup>5,6</sup>, Antonio Lanzavecchia<sup>7</sup>, Wayne A Marasco<sup>8,9</sup>, Zhengli-Li Shi<sup>4</sup> & Ralph S Baric<sup>1,2</sup>

VOLUME 21 | NUMBER 12 | DECEMBER 2015 **NATURE MEDICINE**

2015

## Coronavirus Diversity, Phylogeny and Interspecies Jumping

PATRICK C. Y. WOO<sup>\*,†,‡,1</sup> SUSANNA K. P. LAU<sup>\*,†,‡,1</sup> YI HUANG<sup>‡</sup>  
AND KWOK-YUNG YUEN<sup>\*,†,‡,2</sup>

Exp Biol Med (Maywood). 2009;234(10):1117–27.

2009

EDITORIAL

## The bright future of coronavirology

Journal of Feline Medicine and Surgery (2004) 6, 49–51

2004

Marian C. Horzinek  
Bilthoven  
Netherlands

# Fatal swine acute diarrhoea syndrome caused by an HKU2-related coronavirus of bat origin

Zhou P, et al 12 APRIL 2018 | VOL 556 | NATURE | 255

Here we provide virological, epidemiological, evolutionary and experimental evidence that a novel HKU2-related bat coronavirus, **swine acute diarrhoea syndrome coronavirus** (SADS-CoV), is the aetiological agent that was responsible for a large-scale outbreak of fatal disease in pigs in China that has caused the **death of 24,693 piglets** across four farms.

Furthermore, we identified SADS-related CoVs with 96–98% sequence identity in 9.8% (58 out of 591) of anal swabs collected from bats in Guangdong province during 2013–2016, predominantly in **horseshoe bats** (*Rhinolophus* spp.) that are known reservoirs of SARS-related CoVs.

We found that there were striking similarities between the SADS and SARS outbreaks in **geographical, temporal, ecological and aetiological settings**.

This study highlights the importance of identifying coronavirus diversity and distribution in bats to mitigate future outbreaks that could threaten livestock, public health and economic growth.



## Concluding Remarks

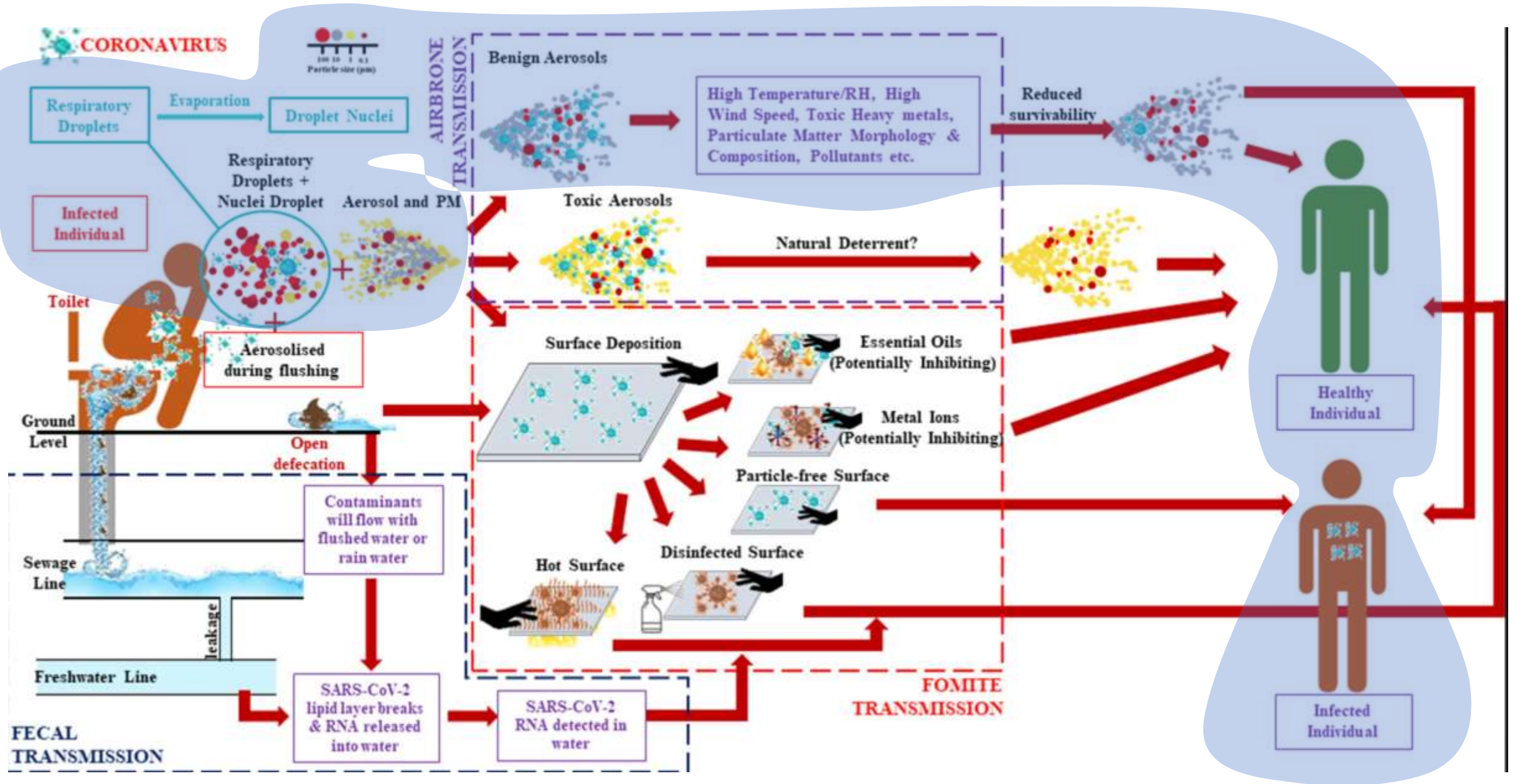
.....it is likely not a matter of **if**, but  
**when**, the next recombinant CoV will  
emerge and cause another outbreak in  
the human population.....





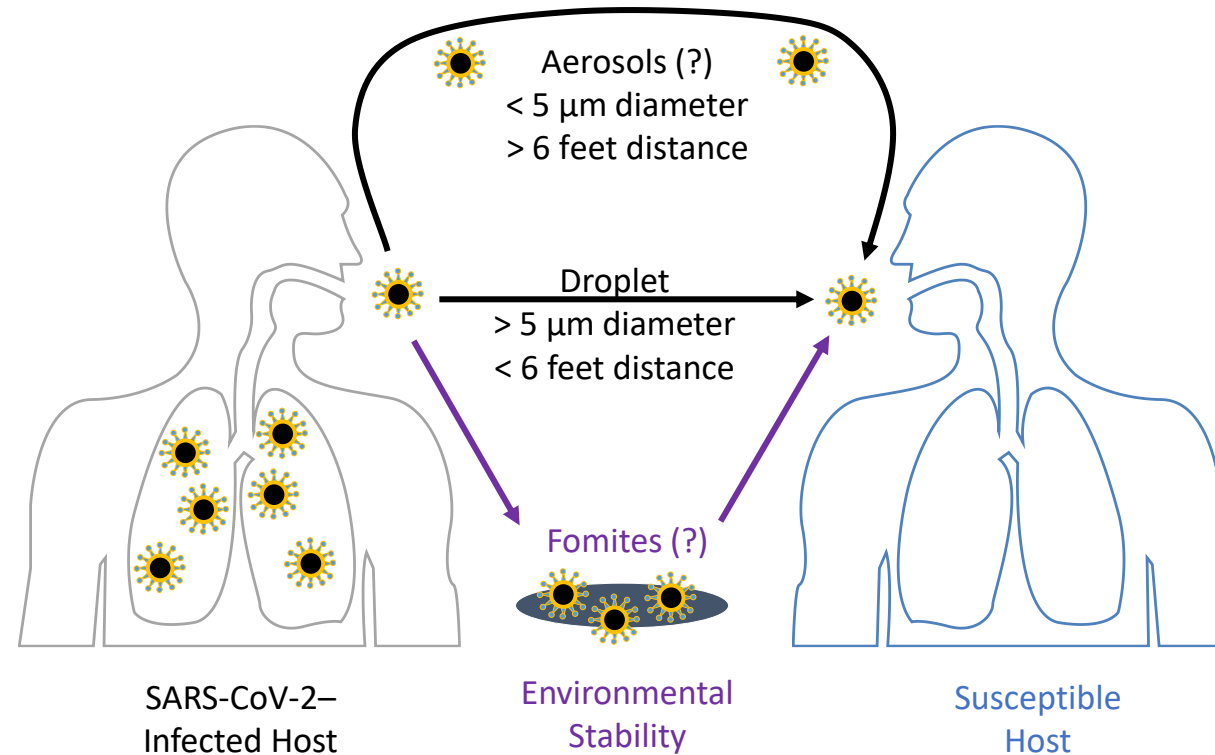
## Images of the Wuhan Market from the Web







# Proposed Routes of SARS-CoV-2 Transmission

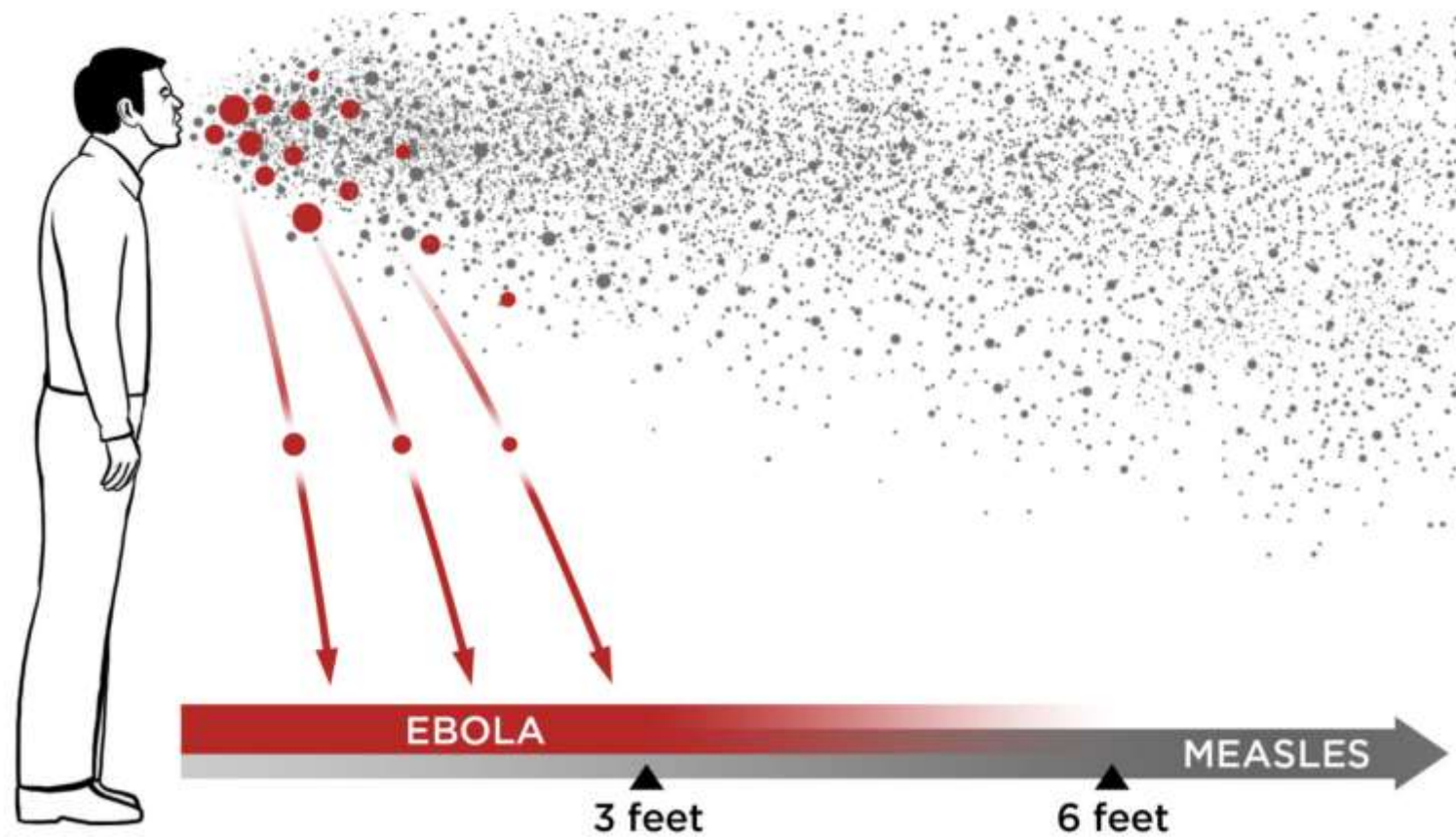


# COMMUNITY ACQUIRED INFECTIONS

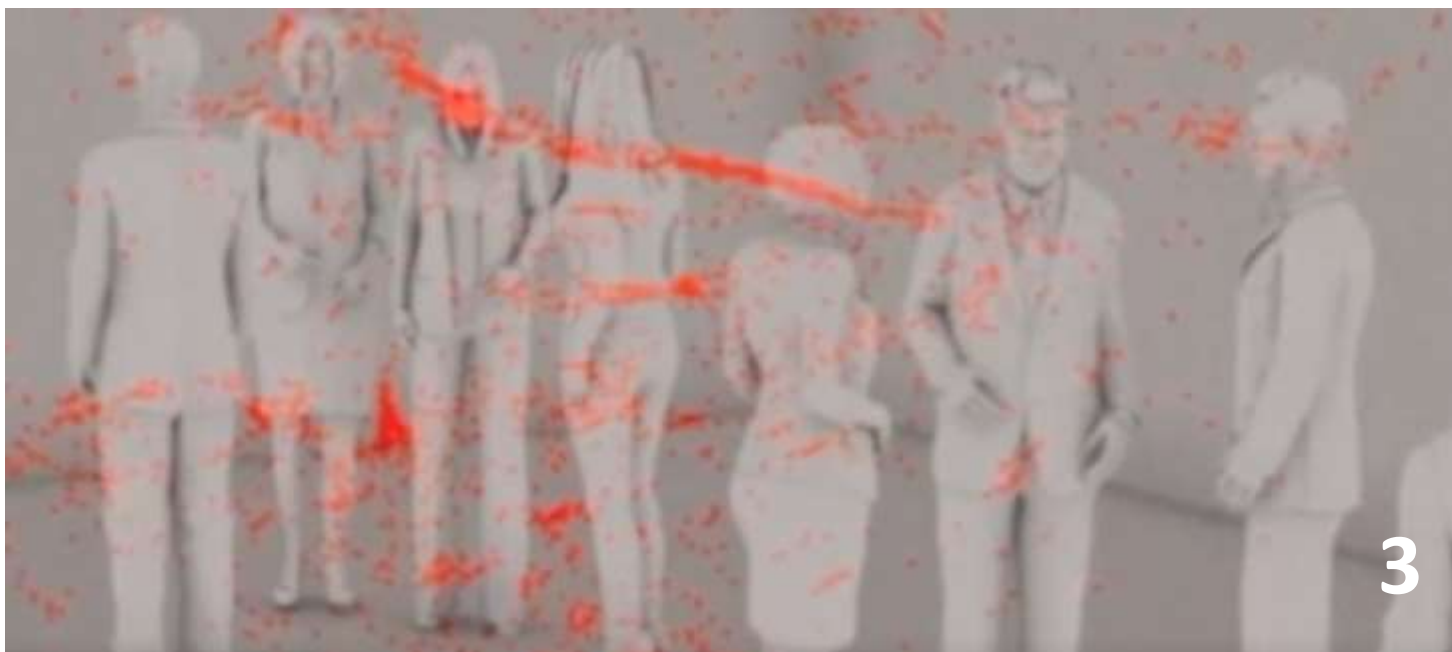
## RESPIRATORY TRACT INFECTIONS

- Upper RTI-mostly viral  
(Adenovirus, Rhinovirus, Coronavirus etc.)
- Lower RTI-mostly bacterial  
(*Strep pneumoniae*,  
*Haemophilus influenzae*,  
*Mycoplasma pneumoniae*,  
*Legionella pneumophila*  
etc.)
- Acquired from other patients through droplet infection
- *Strep pneumoniae*-from oropharynx





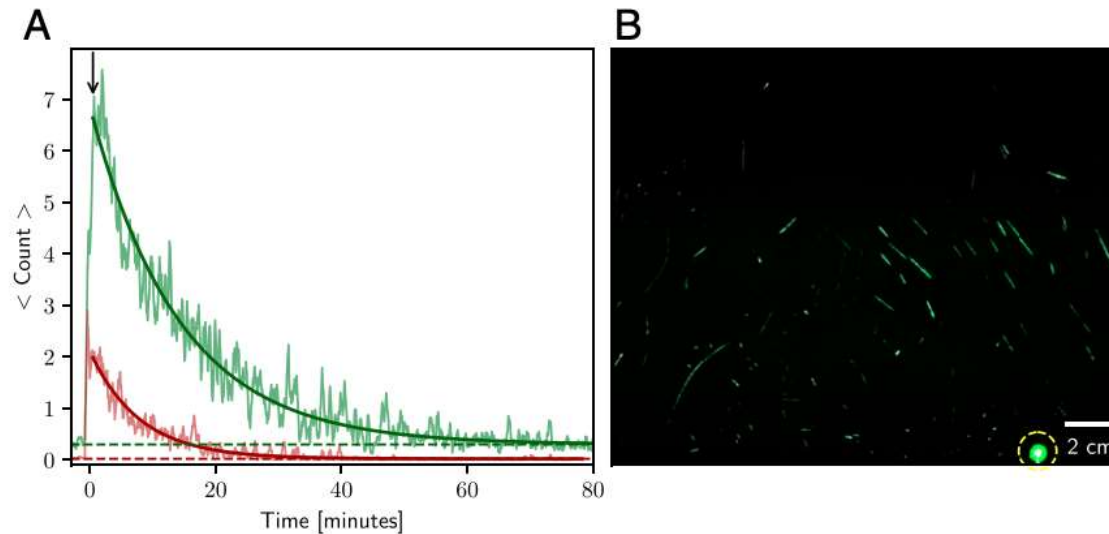




# The airborne lifetime of small speech droplets and their potential importance in SARS-CoV-2 transmission

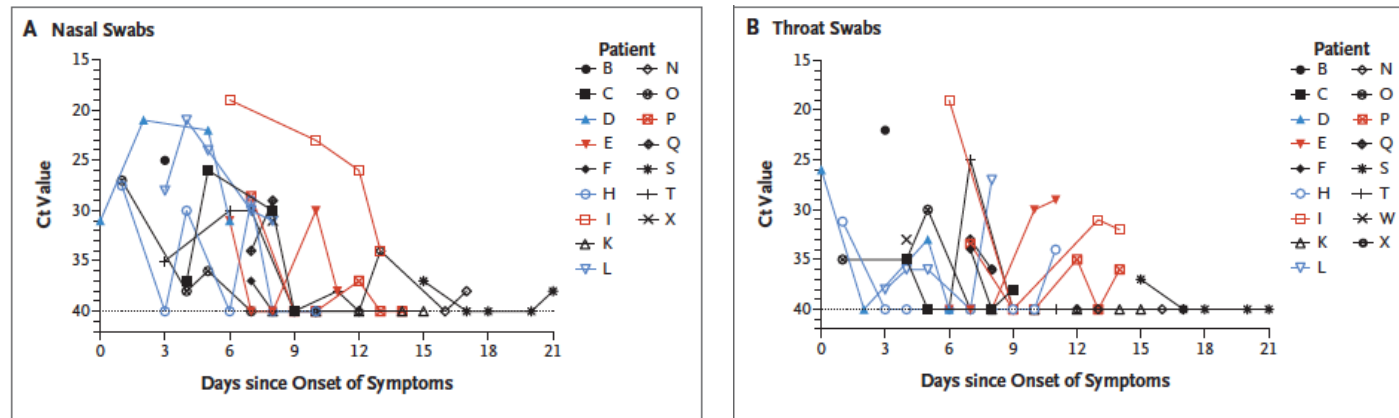
Valentyn Stadnytskyi<sup>a</sup>, Christina E. Bax<sup>b</sup>, Adriaan Bax<sup>a,1</sup>, and Philip Anfinrud<sup>a,1</sup>

PNAS | June 2, 2020 | vol. 117 | no. 22 | 11875–11877



Light scattering observation of airborne speech droplet nuclei, generated by a 25-s burst of repeatedly speaking the phrase “stay healthy” in a loud voice (maximum 85 dB at a distance of 30 cm; average 59 dB). (A) Chart of particle count per frame versus time (smoothed with a 24-s moving average), with the red curve representing the top 25% in scattering brightness and the green curve representing the rest. The bright fraction (red) decays with a time constant of 8 min, and the **dimmer fraction (green) decays with a time constant of 14 min.**

## SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients



Higher viral loads (inversely related to Ct value) were detected soon after symptom onset, with higher viral loads detected in the **nose** than in the **throat**.

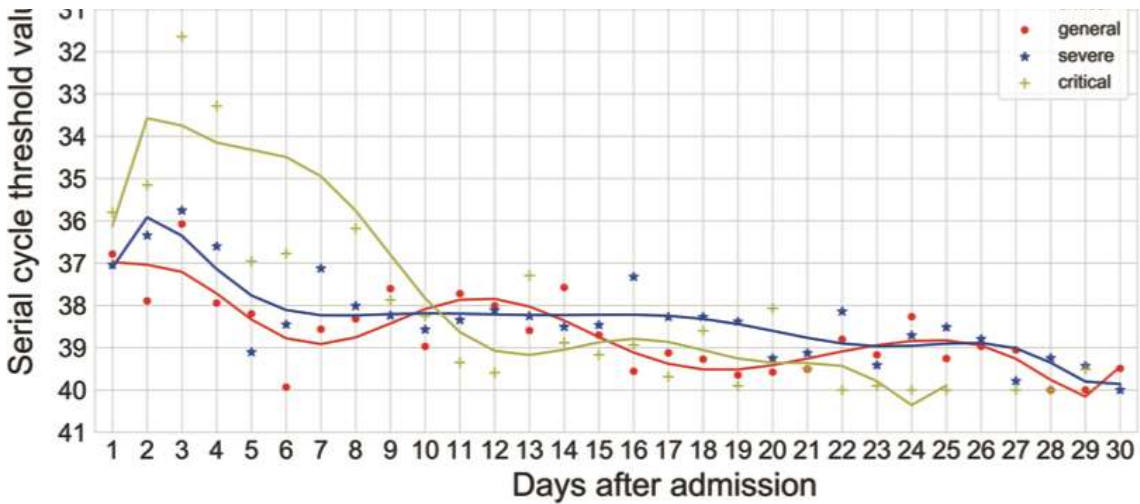
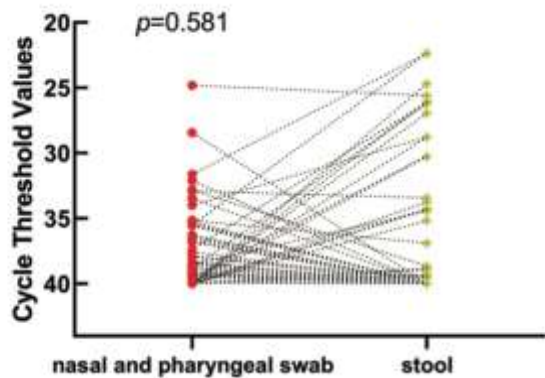
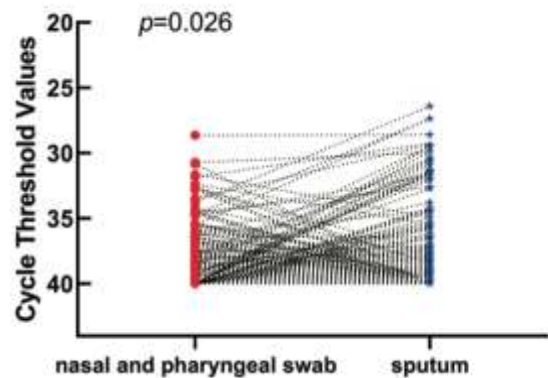
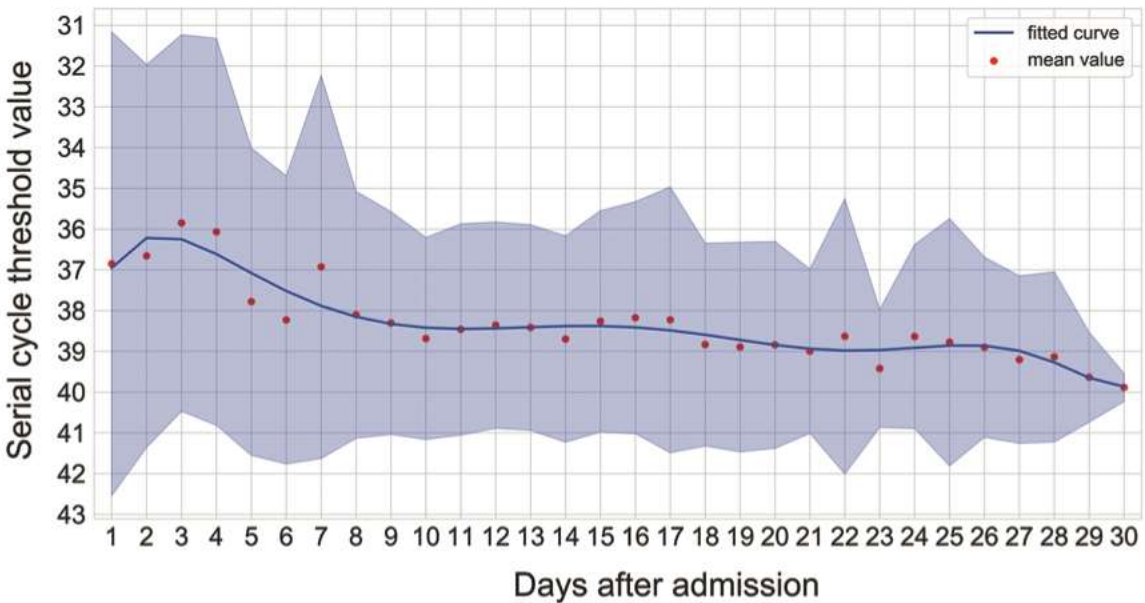
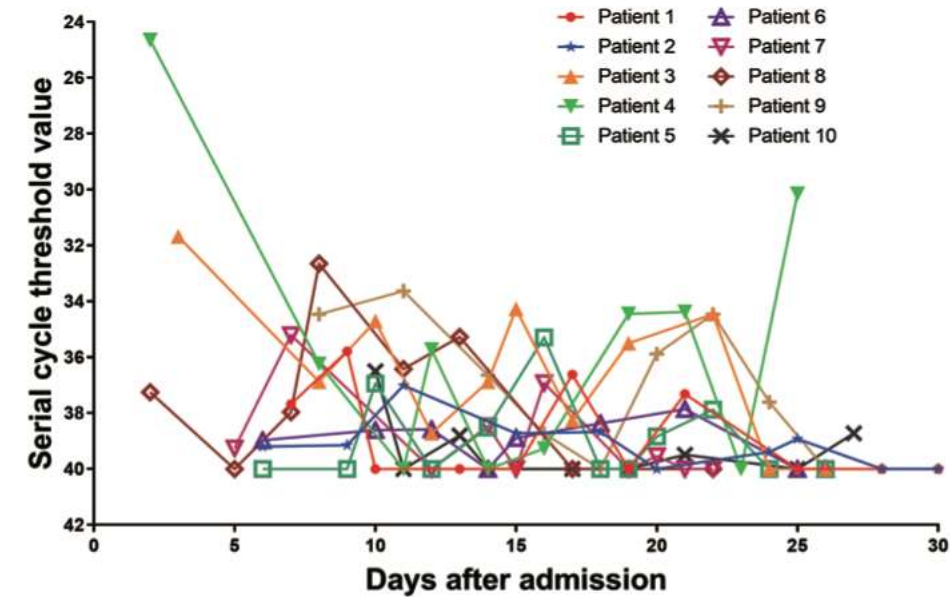
The viral load that was detected in the **asymptomatic patient** was similar to that in the **symptomatic patients**, which suggests the transmission potential of asymptomatic or minimally symptomatic patients. These findings are in concordance with reports that **transmission may occur early in the course of infection** and suggest that case detection and isolation may require strategies different from those required for the control of SARS-CoV.

# Chronological Changes of Viral Shedding in Adult Inpatients With COVID-19 in Wuhan, China

Jing-Tao Huang,<sup>1,a</sup> Ruo-Xi Ran,<sup>2,a</sup> Zhi-Hua Lv,<sup>1</sup> Li-Na Feng,<sup>1</sup> Chen-Yang Ran,<sup>2</sup> Yong-Qing Tong,<sup>1</sup> Dong Li,<sup>1</sup> Han-Wen Su,<sup>1</sup> Cheng-Liang Zhu,<sup>1</sup> Shi-Li Qiu,<sup>1</sup> Jie Yang,<sup>1</sup> Meng-Yao Xiao,<sup>2</sup> Ming-Jun Liu,<sup>2</sup> Yu-Ting Yang,<sup>4</sup> Song-Mei Liu,<sup>2,b</sup> and Yan Li<sup>1,3</sup>

Clinical Infectious Diseases®

2020;71(16):2158–66



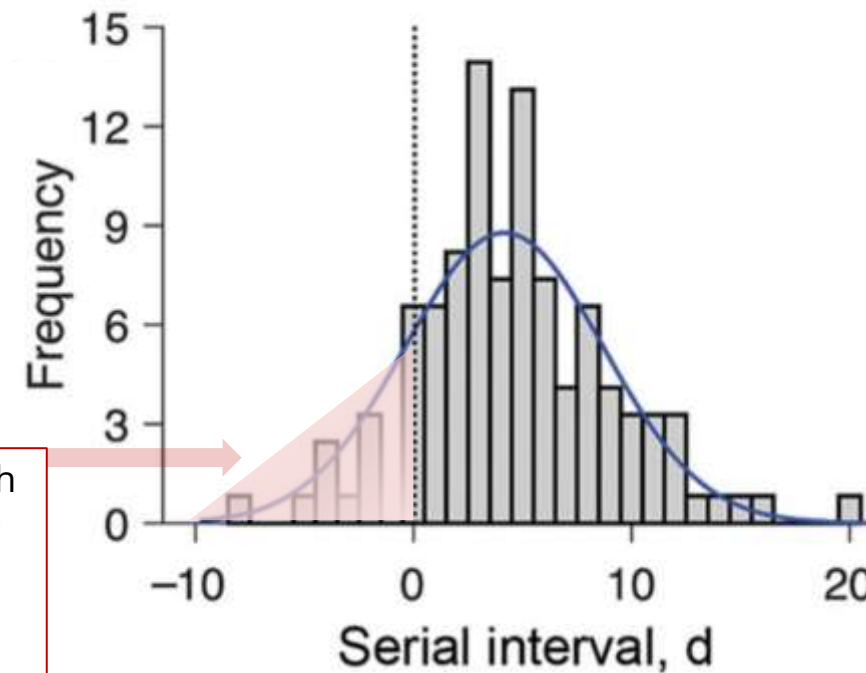


The **serial interval** of COVID-19 is defined as the time duration between a primary case-patient (**infector**) having symptom onset and a secondary case-patient (**infectee**) having symptom onset.

We estimate a mean serial interval for COVID-19 of **3.96** (95% CI 3.53–4.39) days, with an SD of 4.75 (95% CI 4.46–5.07) days, which is considerably lower than reported mean serial intervals of **8.4 days** for severe acute respiratory syndrome to **14.6 days** for Middle East respiratory syndrome.

Fifty-nine of the 468 reports indicate that the infectee had symptoms earlier than the infector. Thus, **presymptomatic transmission** might be occurring.

Gray bars indicate the number of infection events with specified serial interval, and blue lines indicate fitted normal distributions. Negative serial intervals (left of the vertical dotted lines) suggest the possibility of COVID-19 transmission from asymptomatic or mildly symptomatic case-patients.





# Household secondary attack rate of COVID-19 and associated determinants in Guangzhou, China: a retrospective cohort study

Qin-Long Jing\*, Ming-jin Liu\*, Zhou-Bin Zhang\*, Li-Qun Fang\*, Jun Yuan\*, An-Ran Zhang, Natalie E Dean, Lei Luo, Meng-Meng Ma, Ira Longini, Eben Kenah, Ying Lu, Yu Ma, Neda Jalali, Zhi-Cong Yang, Yang Yang

Lancet Infect Dis 2020

Published Online

June 17, 2020

[https://doi.org/10.1016/](https://doi.org/10.1016/S1473-3099(20)30471-0)

S1473-3099(20)30471-0

## ATTACK RATES:

< 20 years: 5.2%

20 – 59 years: 14.8%

≥ 60 years: 18.4%

Compared with the oldest age group (≥60 years; OR 1.00), the risk of household infection was

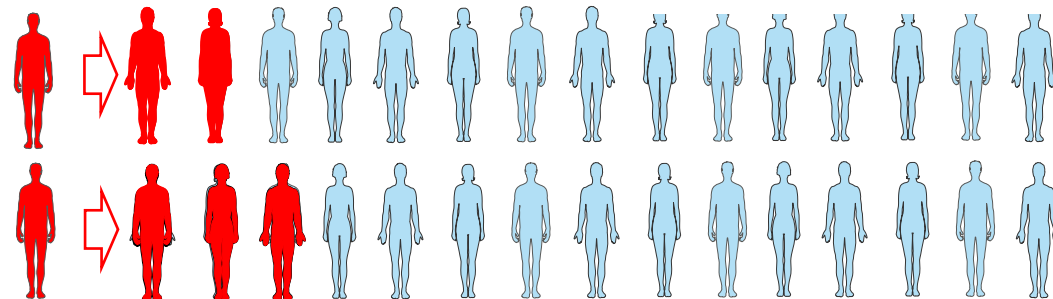
- lower in the youngest age group (<20 years; odds ratio [OR] 0.23 [95% CI 0.11–0.46])
- and among adults aged 20–59 years (OR 0.64 [95% CI 0.43–0.97]).

## UNDISCLOSED FACTORS

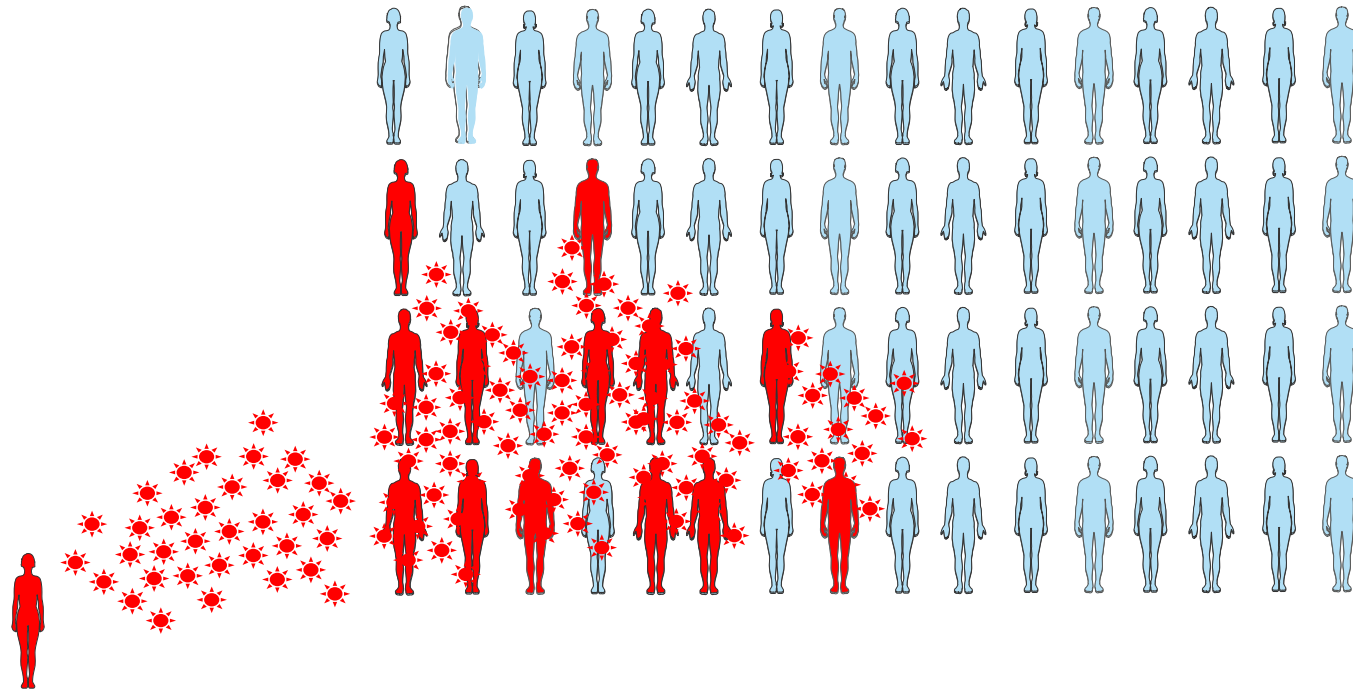
- Heterogeneity in individual exposure history,
  - The possibility of transmission among contacts themselves,
- The infection risks from untraced contacts or fomites.

The estimated secondary attack rate among household contacts was 12.4% (95% CI 9.8–15.4) when household contacts were defined on the basis of close relatives

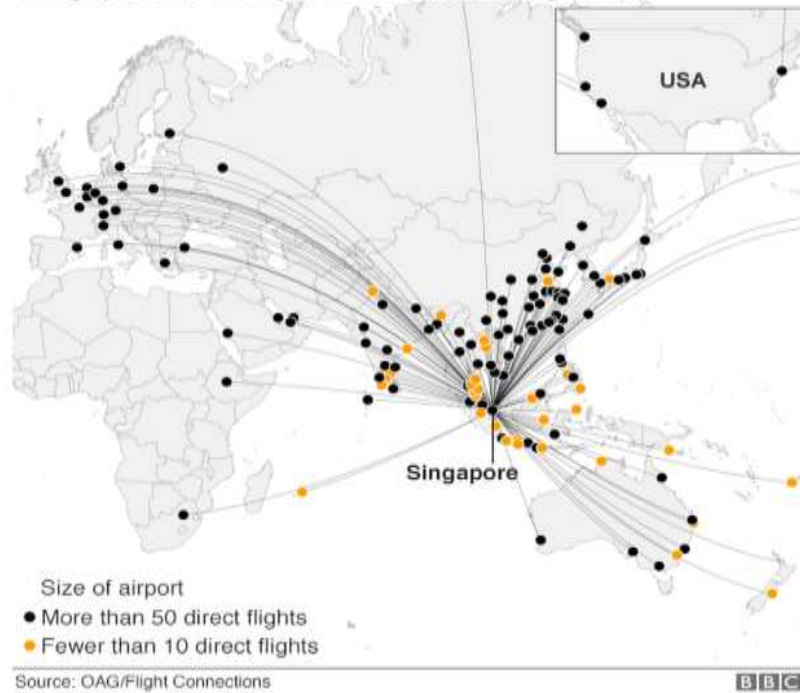
and 17.1% (13.3–21.8) when household contacts were defined on the basis of residential address.



# Few infectious subjects might account for the majority secondary cases



## Singapore is a major international flight hub

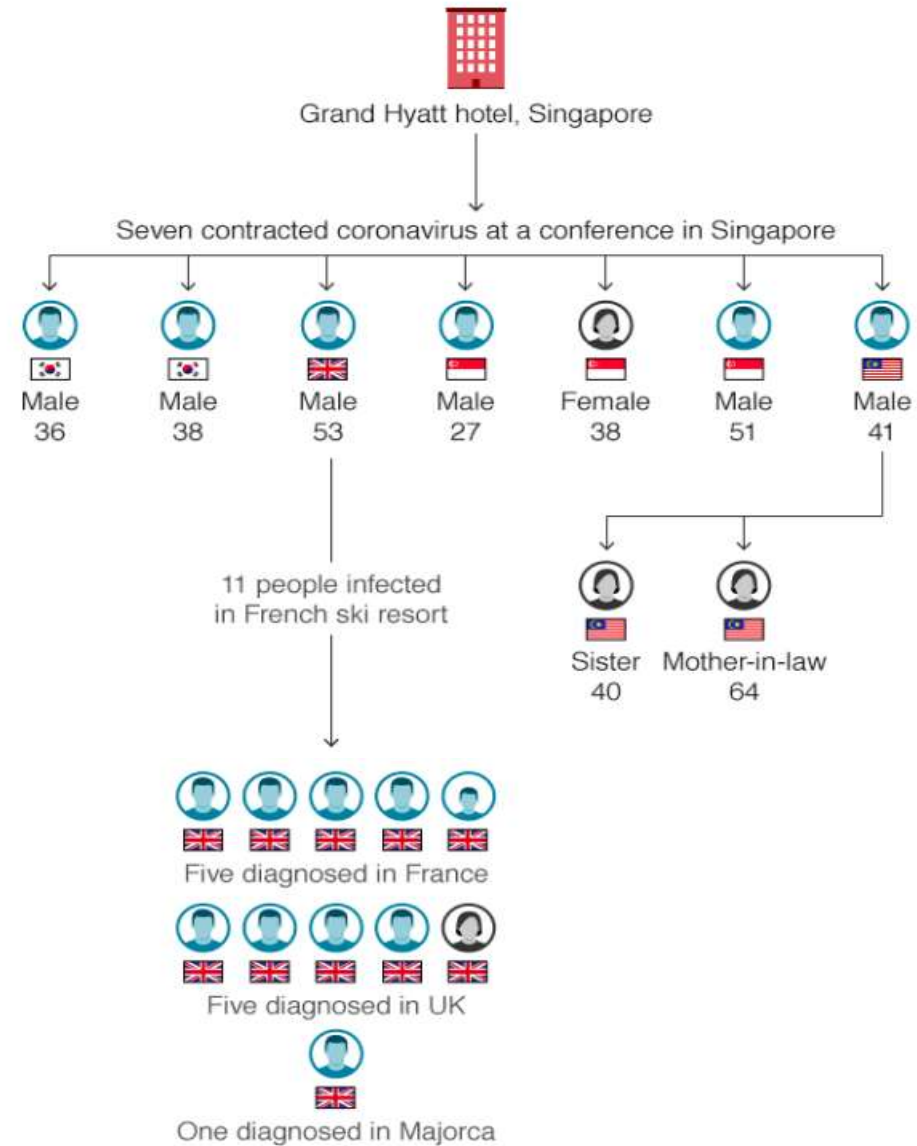


## The meeting that infected the world

One meeting held in a luxury hotel in mid-January spawned several coronavirus cases around the world.

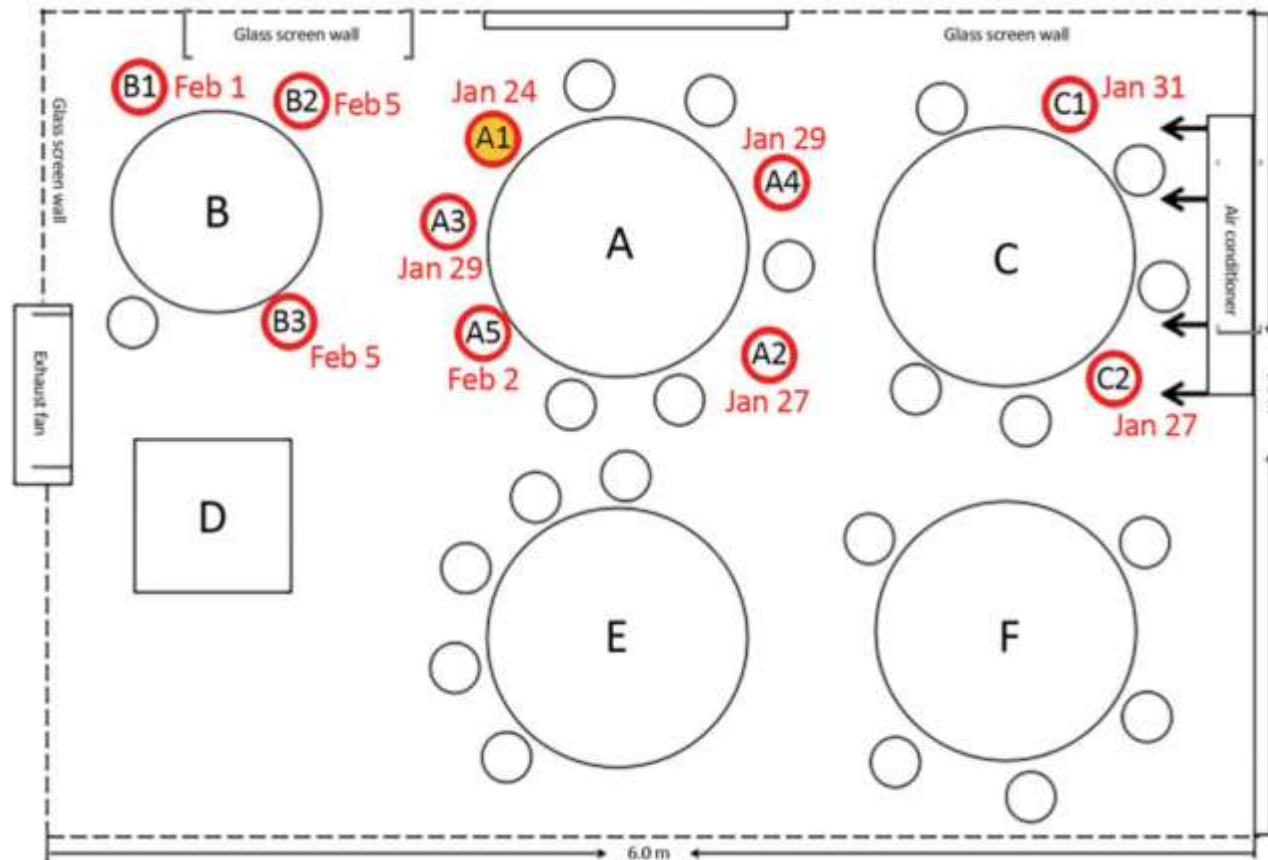
More than 100 people attended the sales conference, including some from China.

## How virus spread from Singapore hotel



Source: Singapore, Malaysian, South Korean and UK health ministries

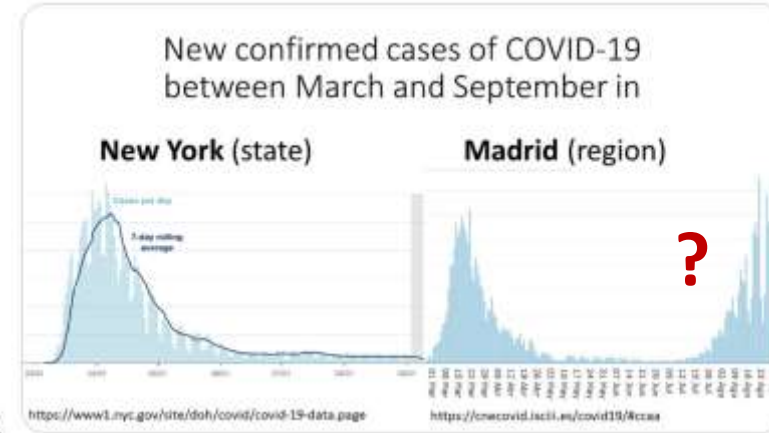
## Un esempio di contagio da SARS-CoV-2: Ristorante in Cina



CASO INDICE

Asintomatico, malattia  
conclamatasi in serata

CASI SECONDARI



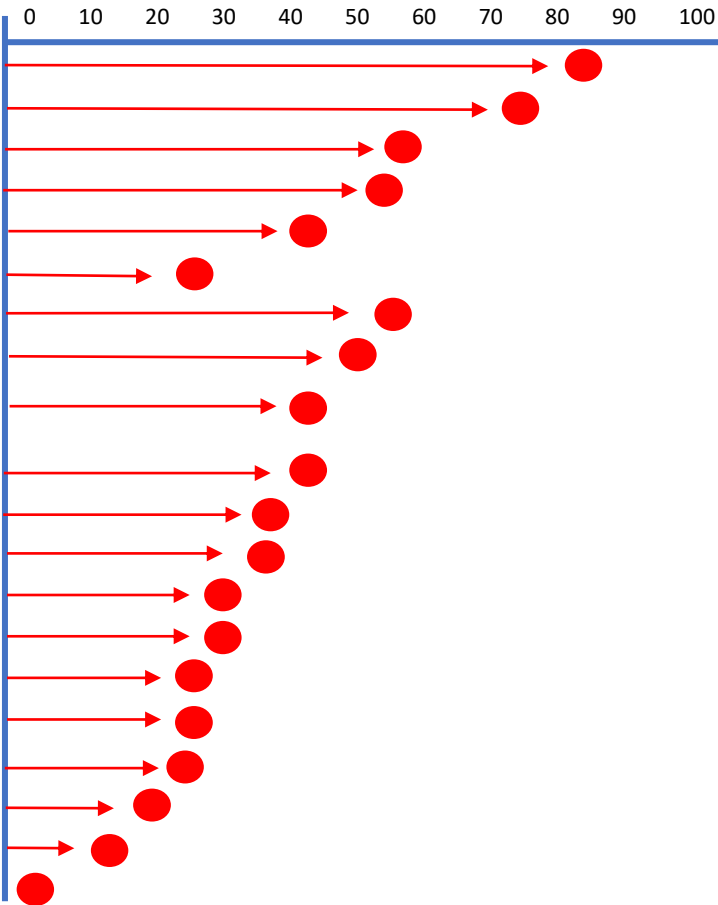
In **New York**, indoor dining is **CLOSED**. Indoor dining in **Madrid was OPEN at 60%** capacity in June. Bar service opened too. Protocols weren't aggressively enforced. Since June it has been easy to find crowded bars and tables. The contrast with NY was striking as anyone spending time in both places can tell you.



# Ranking the effectiveness of worldwide COVID-19 government interventions

Nils Haug, et al. Nat Hum Behav 2020  
<https://doi.org/10.1038/s41562-020-01009-0>

Score (%)




**Table 1 | Comparison of effectiveness rankings on L2**

L2 category	Score (%)	Consensus	$\Delta R_t^{CC}$	$\Delta R_t^{LASSO}$	Importance (RF)	$\Delta R_t^{TF}$
Small gathering cancellation	83	4	-0.35 (2)	-0.22 (5)	0.020 (2)	-0.327 (3)
Closure of educational institutions	73	4	-0.16 (2)	-0.21 (4)	0.028 (2)	-0.146 (2)
Border restriction	56	4	-0.23 (2)	-0.12 (2)	0.017 (2)	-0.057 (2)
Increased availability of PPE	51	4	-0.11 (2)	-0.13 (2)	0.012 (1)	-0.062 (2)
Individual movement restrictions	42	4	-0.13 (2)	-0.08 (3)	0.017 (2)	-0.121 (2)
National lockdown	25	4	-0.14 (3)	-0.09 (2)	0.0020 (9)	-0.008 (3)
Mass gathering cancellation	53	3	-0.33 (2)	0	0.012 (1)	-0.127 (2)
Educate and actively communicate with the public	48	3	-0.18 (4)	0	0.018 (2)	-0.276 (2)
The government provides assistance to vulnerable populations	41	3	-0.17 (3)	-0.18 (4)	0.009 (1)	0.090 (3)
Actively communicate with managers	40	3	-0.15 (2)	-0.20 (4)	0.004 (2)	-0.050 (2)
Measures for special populations	37	3	-0.19 (2)	0	0.008 (1)	-0.100 (2)
Increase healthcare workforce	35	3	-0.17 (20)	-0.13 (3)	0.030 (8)	0.011 (2)
Quarantine	30	3	-0.28 (2)	-0.2 (1)	0.0023 (9)	0.023 (2)
Activate or establish emergency response	29	3	-0.13 (2)	0	0.0037 (9)	-0.121 (2)
Enhance detection system	25	3	-0.19 (3)	0	0.0032 (9)	-0.106 (2)
Increase in medical supplies and equipment	25	3	-0.13 (3)	-0.004 (3)	0.003 (2)	-0.200 (3)
Police and army interventions	23	3	-0.16 (2)	0	0.003 (2)	-0.091 (2)
Travel alert and warning	20	3	-0.13 (3)	0.0 (1)	0.002 (1)	-0.159 (3)
Public transport restriction	13	3	0.020 (4)	-0.01 (7)	0.004 (1)	-0.023 (3)
Actively communicate with healthcare professionals	11	3	0	-0.08 (4)	0.003 (1)	-0.003 (2)

Out of the 46 NPI categories, all four methods show significant results for six NPIs (consensus 4) while three methods agree on 14 further NPIs (consensus 3). We report the average normalized score, the observed reduction in  $R_t$  for the various methods and NPI importance for RF. Numbers in parentheses denote half of the amount by which the last digit of the corresponding number outside the parentheses fluctuates within the 95% confidence interval.

# Italy: Piedmont Region



- Comparison between the 1st and the 2nd wave of COVID – 19 (SARS-CoV-2 infection):  


The diagram shows a horizontal timeline. A red line segment starts at a red dot labeled 'Feb 29' and ends at a red dot labeled 'May 23'. A green line segment starts at a green dot labeled 'Sept 12' and ends at a green dot labeled 'Dec 5'.
- Hospital records only: only symptomatic subjects were screened in the 1st wave
- Patients classified as conventional hospitalization, ICU admission and death

*To be considered:*

- a. In the 1st wave, the adoption of non-invasive ventilatory support (oxygen delivery, Venturi's mask, CPAP) was progressively introduced into conventional wards and the allocation of patients requiring hospitalization varied accordingly.
- b. In the first half of the 2nd wave most infected persons were younger than the general population (and much younger than in the 1st wave) and this might contribute to explain the low mortality recorded.



1° Gennaio 2019

	♂	♀	Totale	%	% su Pop. Straniera	Variaz. Anno Prec.
1. Lombardia	34.182	34.930	69.112	23,1%	5,85%	+3,7%
2. Toscana	28.467	27.617	56.084	18,7%	13,44%	+7,5%
3. Veneto	17.831	17.883	35.714	11,9%	7,13%	+3,1%
4. Emilia-Romagna	15.132	15.024	30.156	10,1%	5,51%	+1,8%
5. Lazio	12.503	12.741	25.244	8,4%	3,69%	+1,8%
6. Piemonte <b>78.9%</b>	10.053	10.038	20.091	6,7%	4,70%	+0,8%
7. Campania	7.455	6.360	13.815	4,6%	5,21%	-1,9%
8. Marche	4.839	4.674	9.513	3,2%	6,95%	-0,3%
9. Sicilia	3.788	3.618	7.406	2,5%	3,70%	-0,5%
10. Puglia	3.139	2.969	6.108	2,0%	4,40%	+3,9%
11. Liguria	2.684	2.724	5.408	1,8%	3,70%	+8,5%
12. Abruzzo	2.217	2.160	4.377	1,5%	4,90%	+1,6%
13. Friuli Venezia Giulia	1.903	1.958	3.861	1,3%	3,50%	+2,6%
14. Sardegna	1.779	1.658	3.437	1,1%	6,15%	+1,9%
15. Calabria	1.556	1.472	3.028	1,0%	2,68%	-3,8%
16. Umbria	1.281	1.311	2.592	0,9%	2,66%	-0,1%
17. Trentino-Alto Adige	1.220	1.186	2.406	0,8%	2,46%	+0,5%
18. Basilicata	476	430	906	0,3%	3,90%	+9,7%
19. Valle d'Aosta	154	160	314	0,1%	3,79%	+2,3%
20. Molise	130	121	251	0,1%	1,81%	- 0,8%

**Cinesi in Italia:**

**299.823**

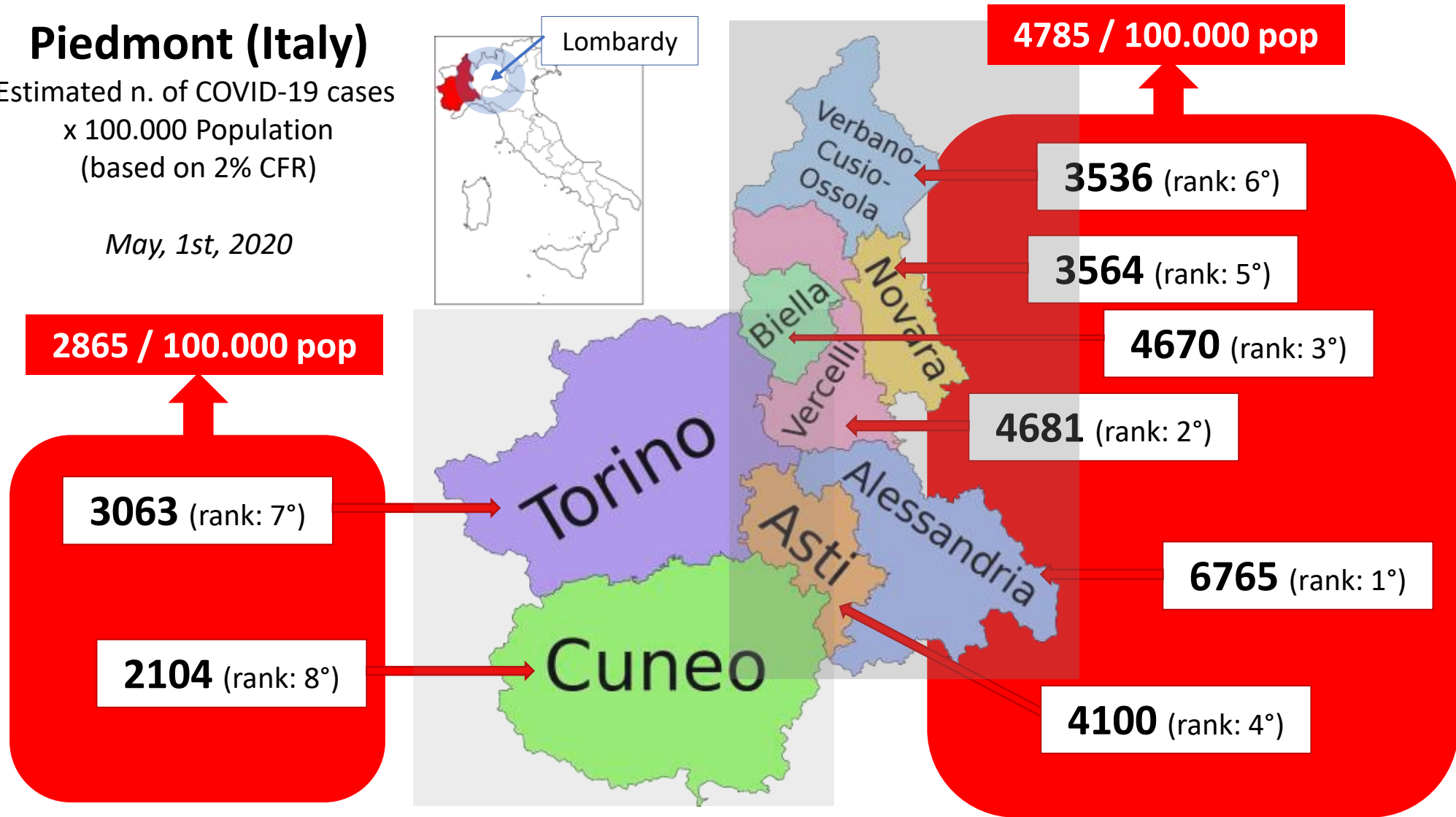
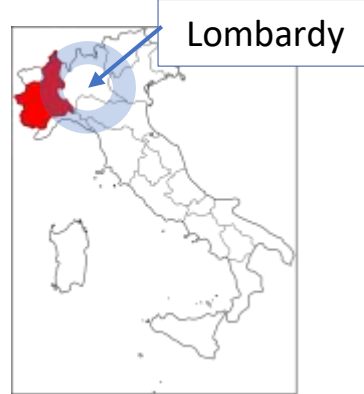
**su 5.255.503 stranieri in Italia (5,7%)**



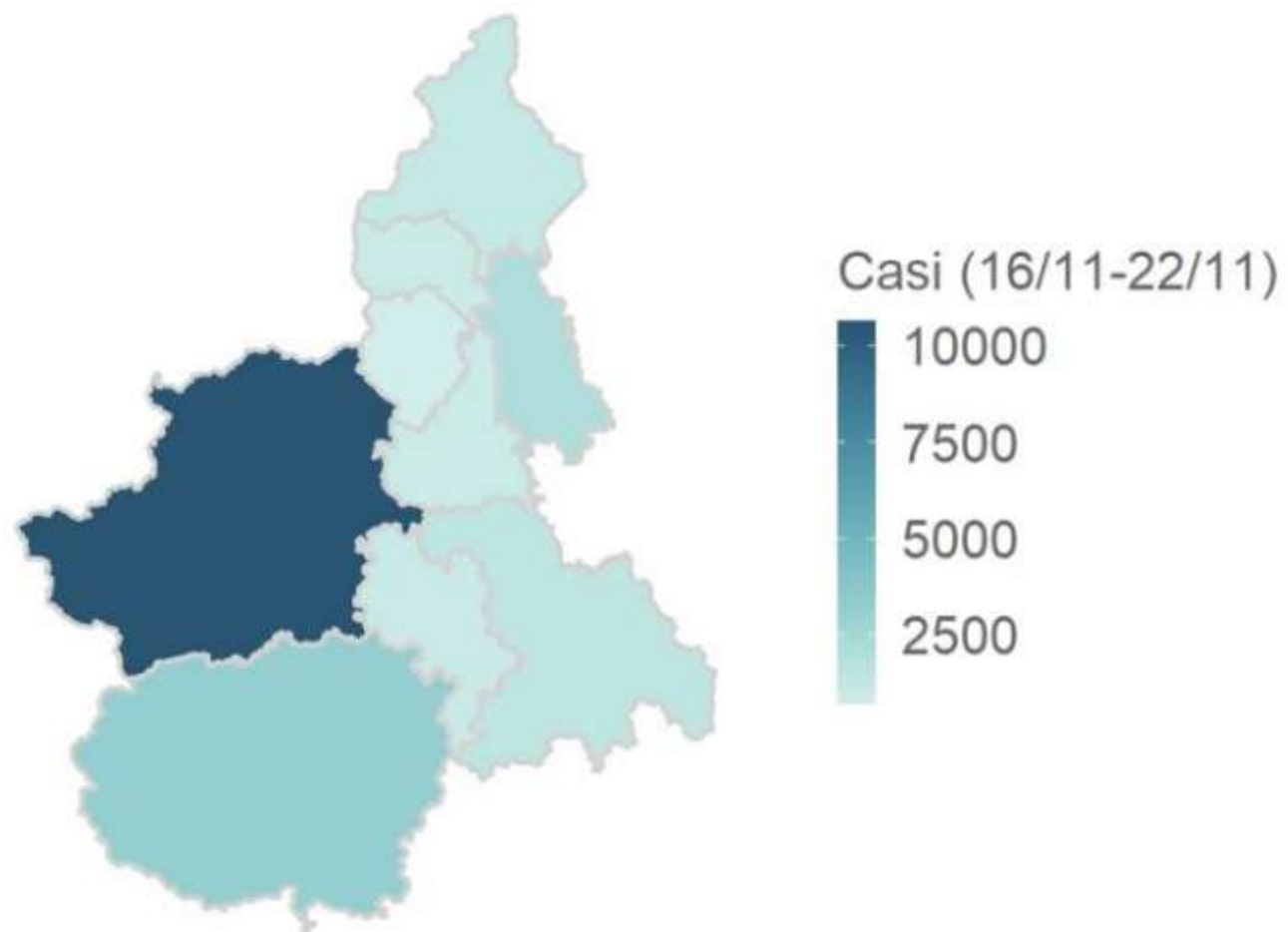
## Piedmont (Italy)

Estimated n. of COVID-19 cases  
x 100.000 Population  
(based on 2% CFR)

May, 1st, 2020







Piemonte 21024 casi





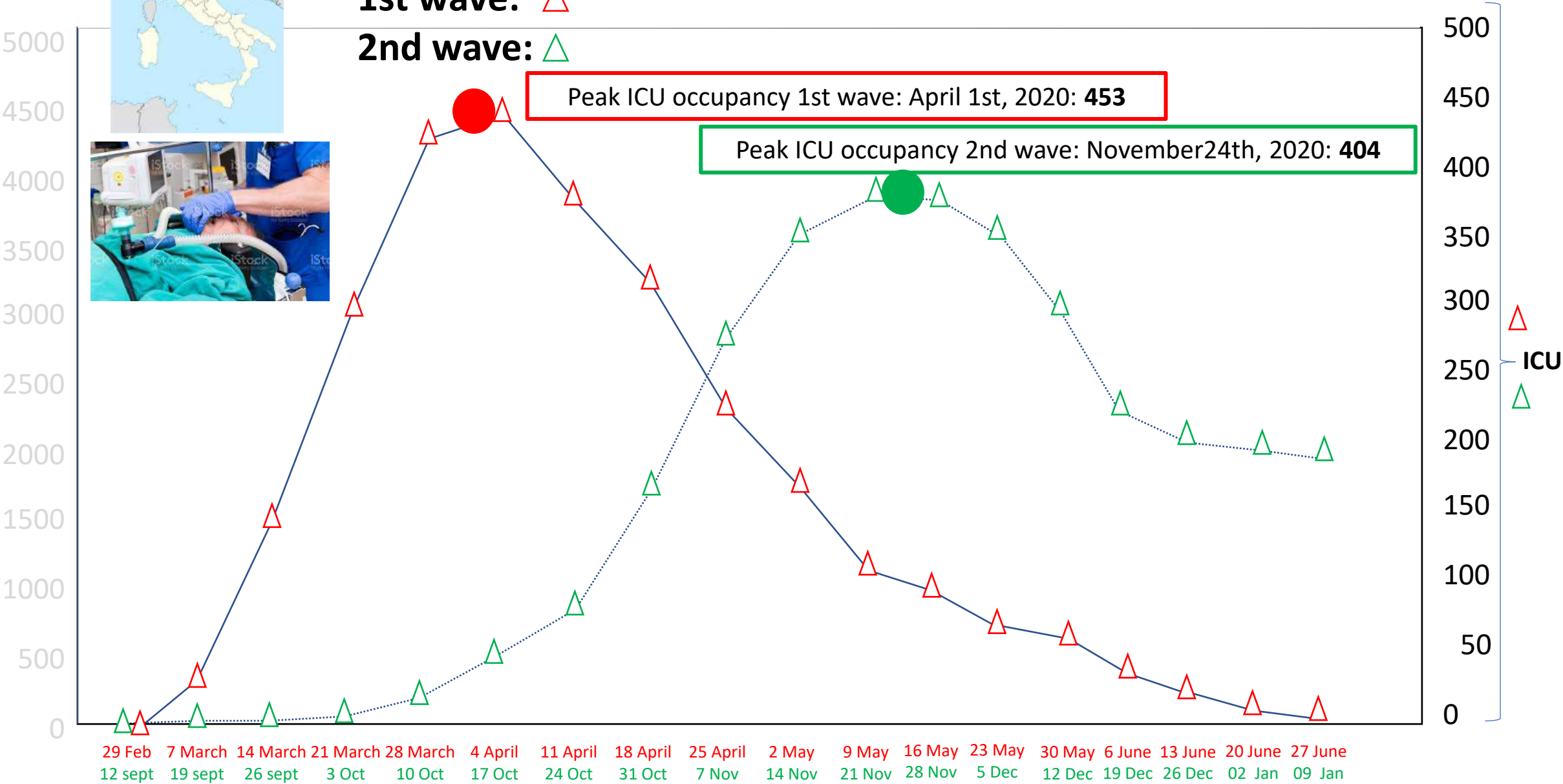
# Piedmont: COVID – 19 ICU Admissions

1st wave:

2nd wave:

Peak ICU occupancy 1st wave: April 1st, 2020: **453**

Peak ICU occupancy 2nd wave: November24th, 2020: **404**

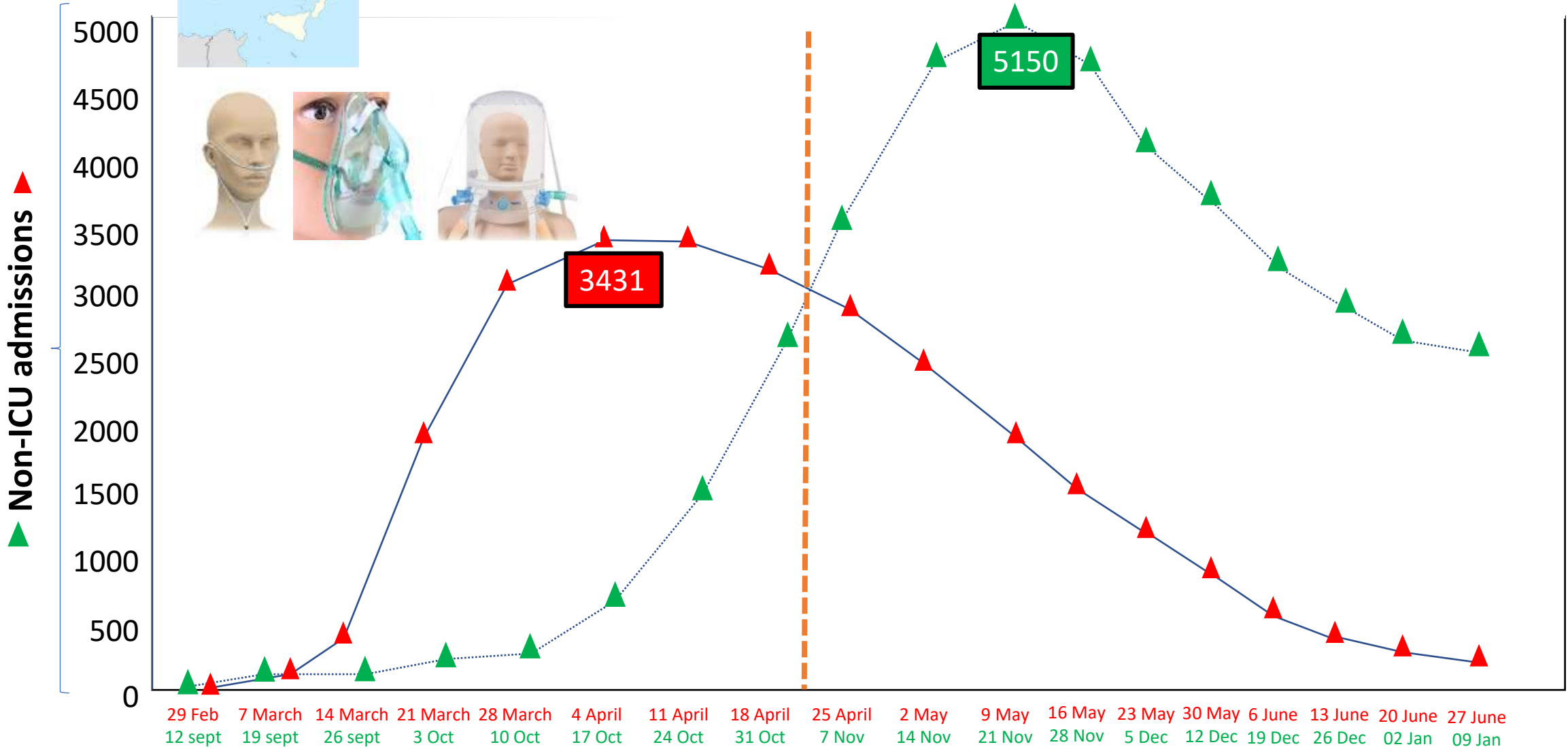




# Piedmont: COVID – 19 non-ICU Admissions

1st wave: ▲

2nd wave: ▲







# Piedmont: COVID – 19 cumulative deaths

1st wave: ▲

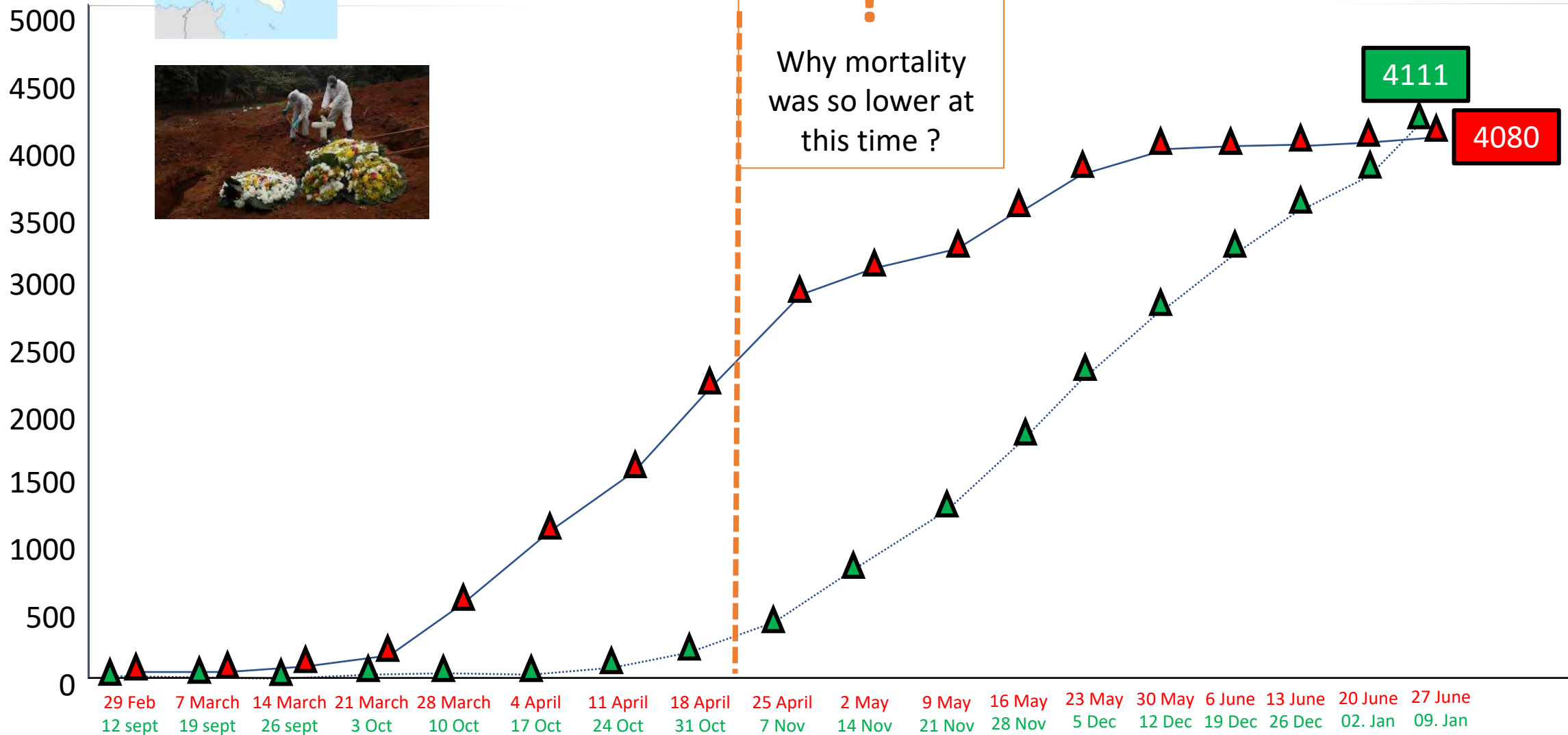
2nd wave: ▲



?

Why mortality was so lower at this time ?

Cumulative deaths ▲



**80.9%** of infections are **mild** (half described as **asymptomatic**)

**13.8%** severe

**4.7%** critical

**Men** are more likely to die (2.8%) than **women** (1.7%).

**Ranking of death risk according to comorbidity:**

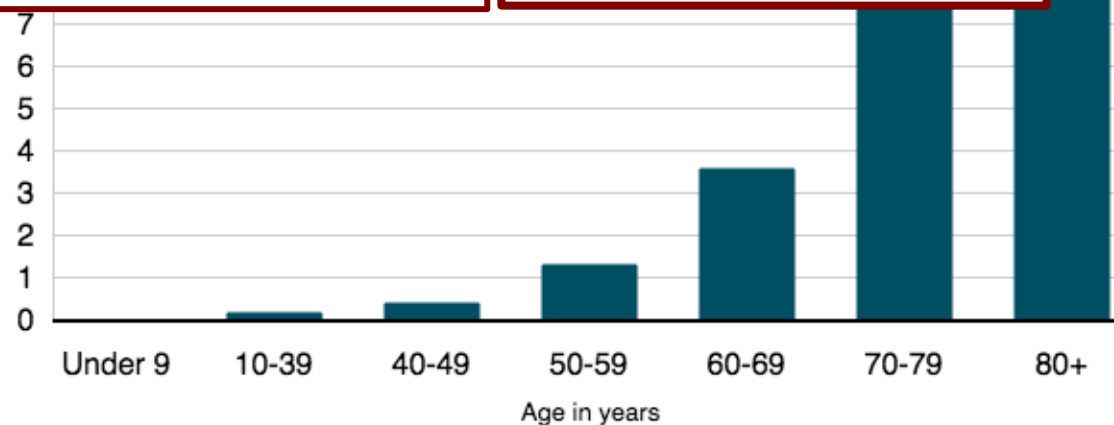
1. cardiovascular disease,
2. diabetes,
3. chronic respiratory disease,
4. hypertension.

**1716 HCWs infected:**

5 died by Feb 11

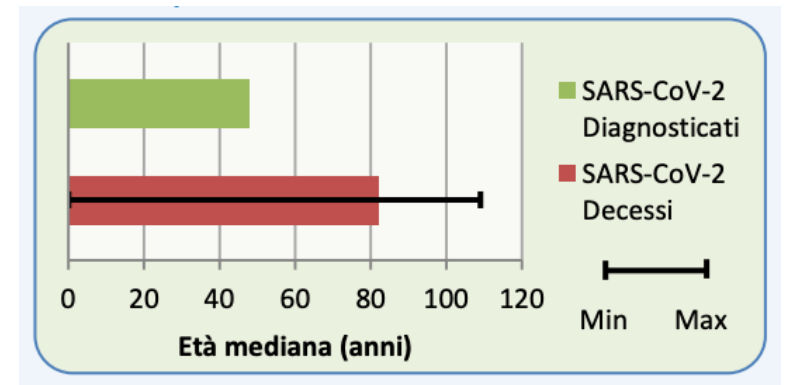
## Rate in China

PRE-EXISTING CONDITION	DEATH RATE*
Cardiovascular disease	10.5%
Diabetes	7.3%
Chronic respiratory disease	6.3%
Hypertension	6.0%
Cancer	5.6%
no pre-existing conditions	0.9%



Source: Chinese Centre for Disease Control

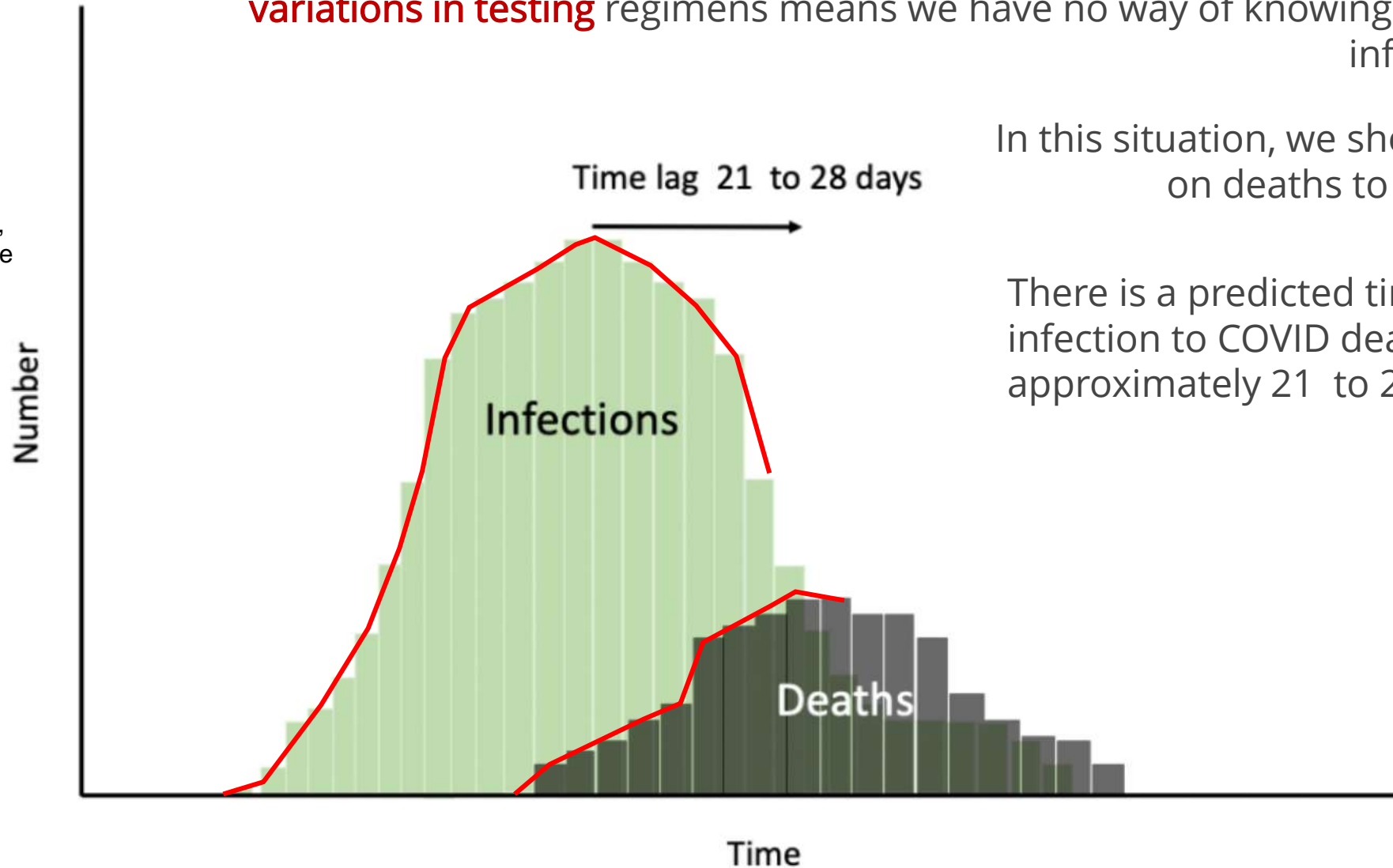
BBC





**William Farr** (30 November 1807 – 14 April 1883) was a British epidemiologist, regarded as one of the founders of medical statistics.

Farr shows us that once peak infection has been reached then it will roughly follow the same symmetrical pattern on the downward slope. However, **under testing and variations in testing** regimens means we have no way of knowing when the peak of infections occurred.

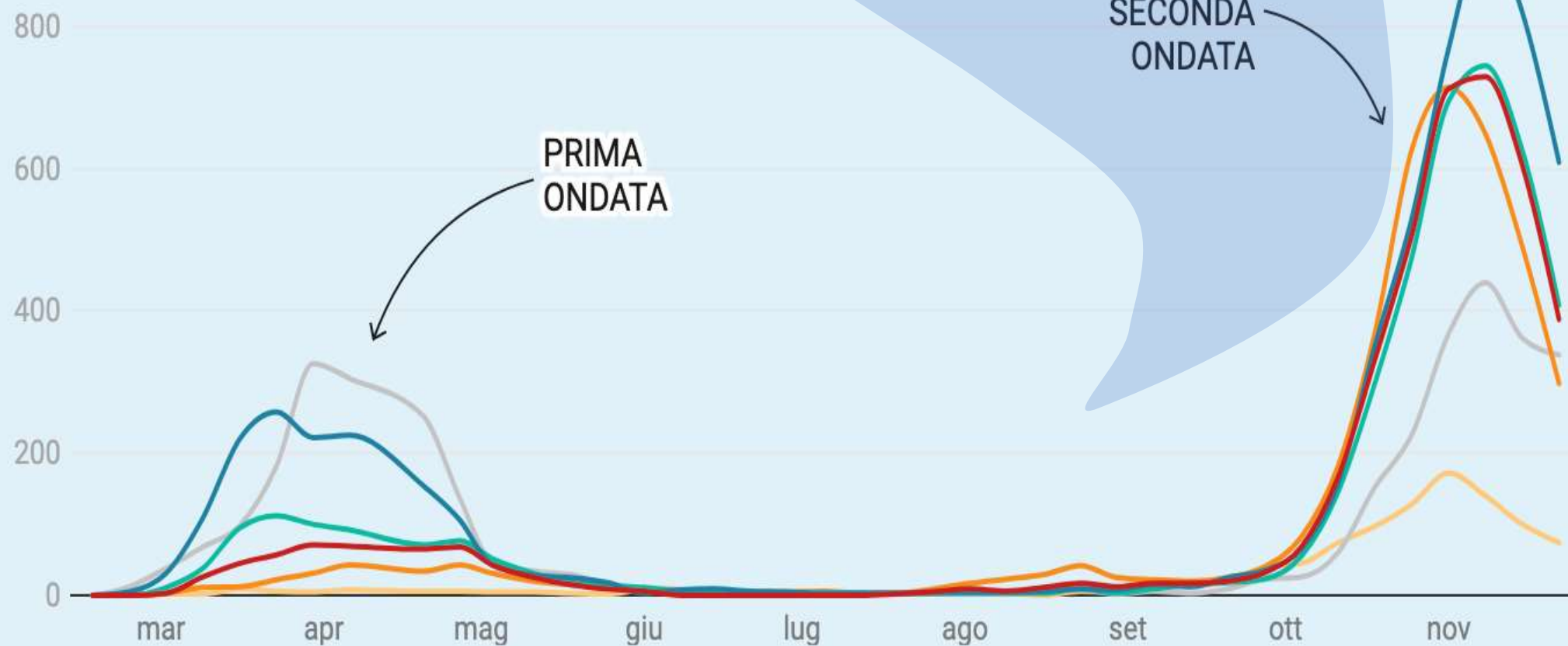


In this situation, we should use the data on deaths to predict the peak.

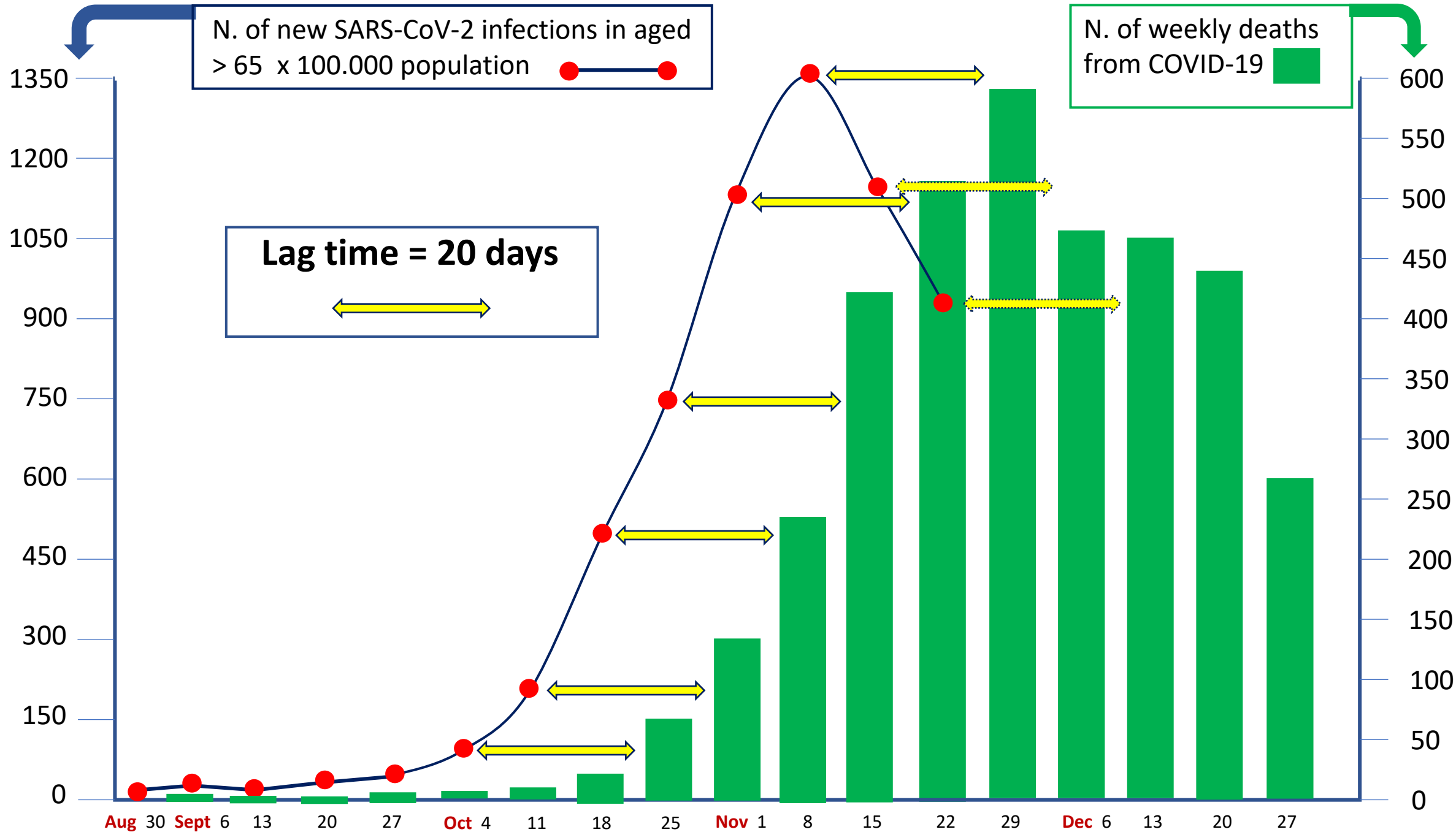
There is a predicted time lag from infection to COVID deaths of approximately 21 to 28 days.

## Tassi per 100.000 per fasce d'età

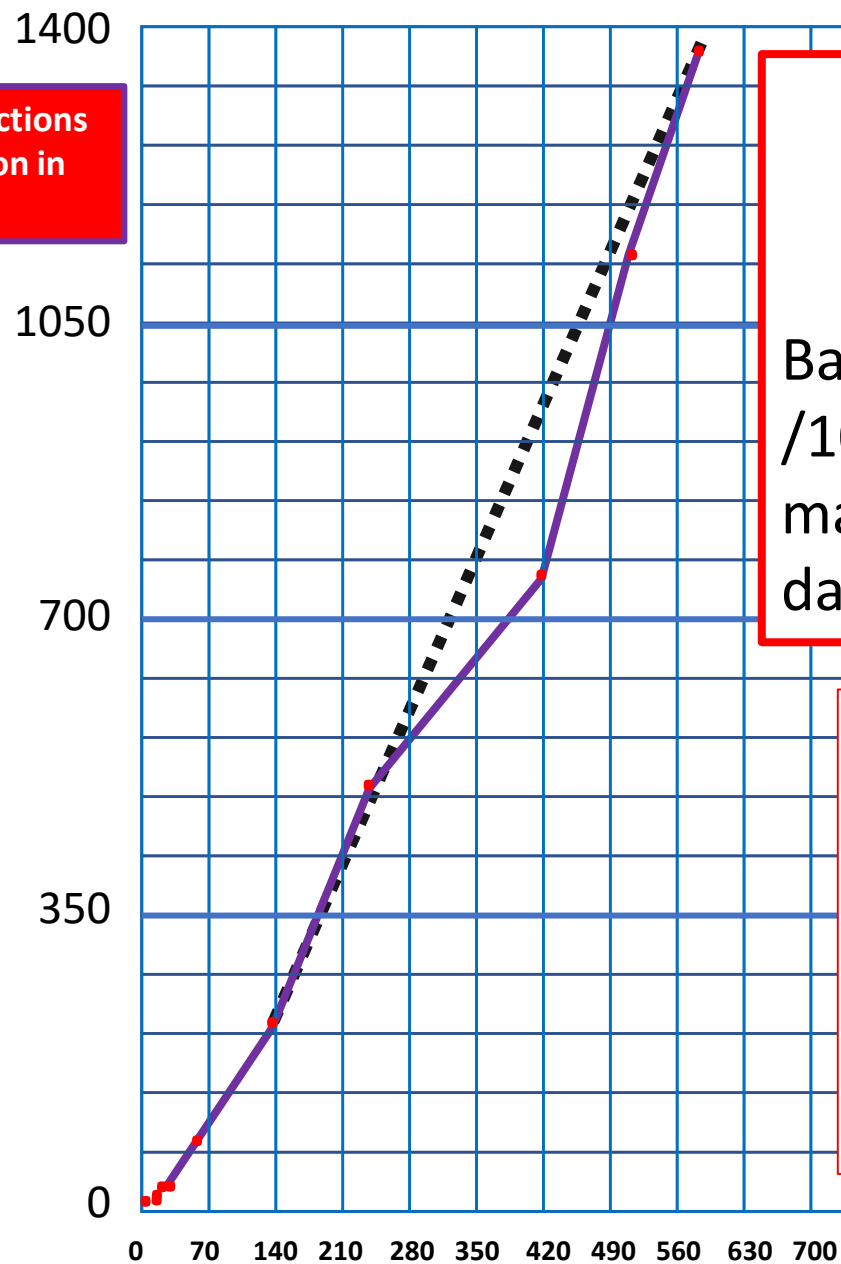
0-5 anni 19-24 anni 25-44 anni 45-64 anni 65-84 anni Oltre 85 anni







New SARS-CoV-2 infections  
per 100.000 population in  
people aged > 65 yrs



$$y = 2.54 x - 127$$

$$x = y + 127 / 2.54$$

Based on y (n. of new SARS-CoV-2 infections /100.000 population in those aged > 65 yrs), we may predict the n. of weekly deaths occurring 20 days later

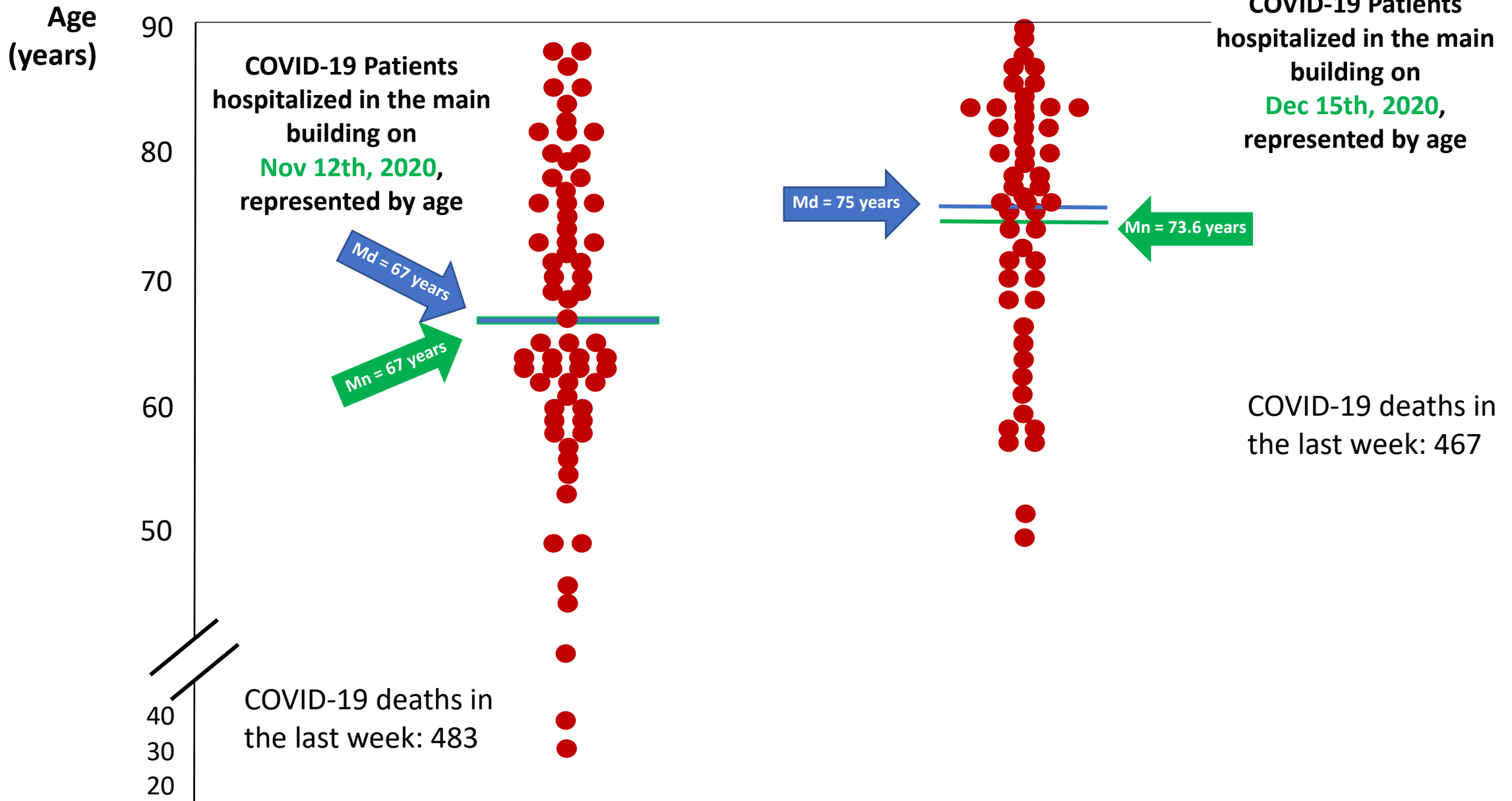
If 350 new infections/100.000 are diagnosed in people aged > 65 yrs, 187 weekly deaths are to be expected 20 days later

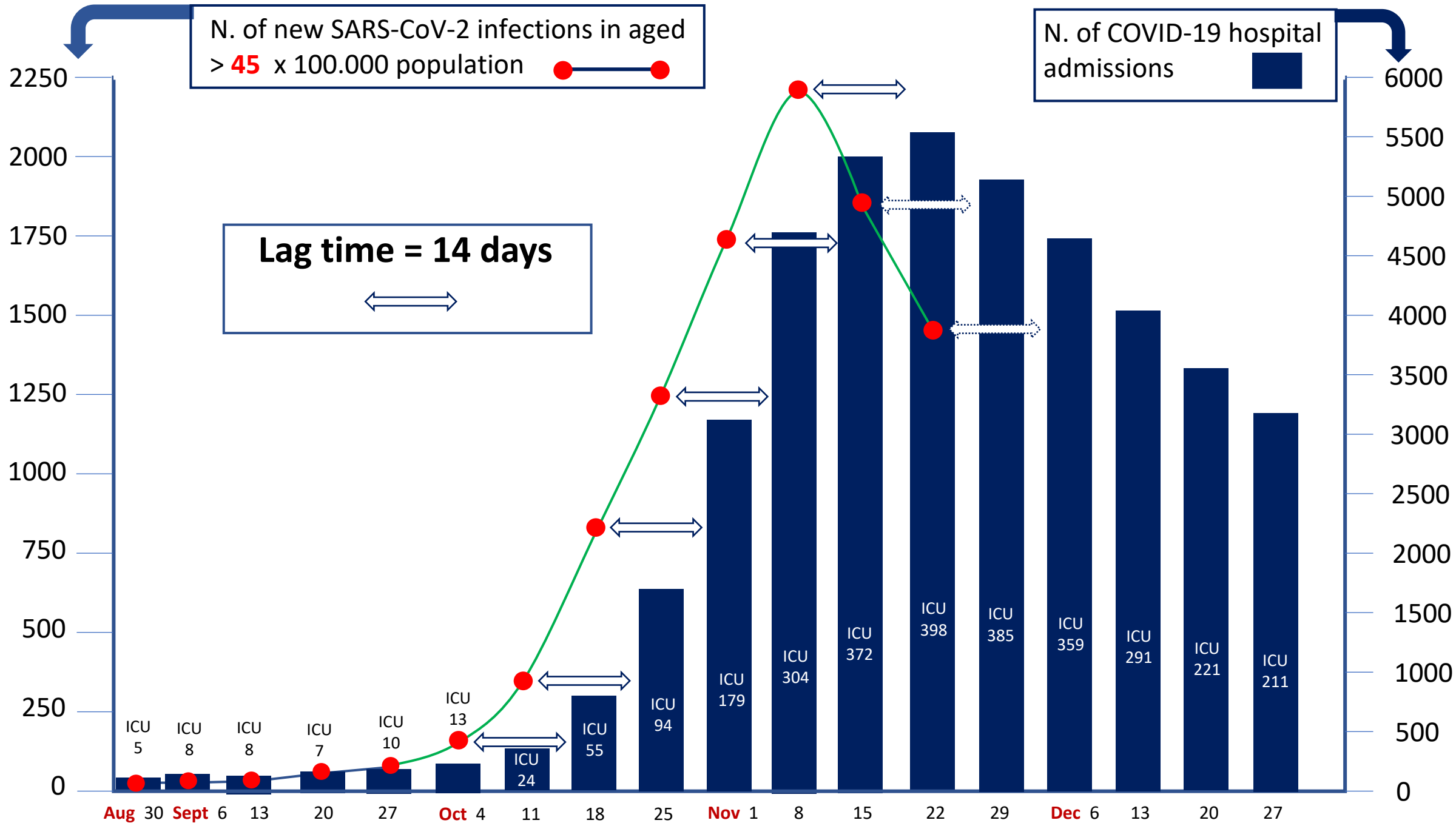
If 217 new infections/100.000 are diagnosed in people aged > 65 yrs, 135 weekly deaths are predicted 20 days later

If 1374 new infections/100.000 are diagnosed in people aged > 65 yrs, 589 weekly deaths are predicted 20 days later

N. of weekly deaths in COVID-19 patients recorded 20 days after the diagnosis of new SARS-CoV-2 infections in people aged > 65 yrs

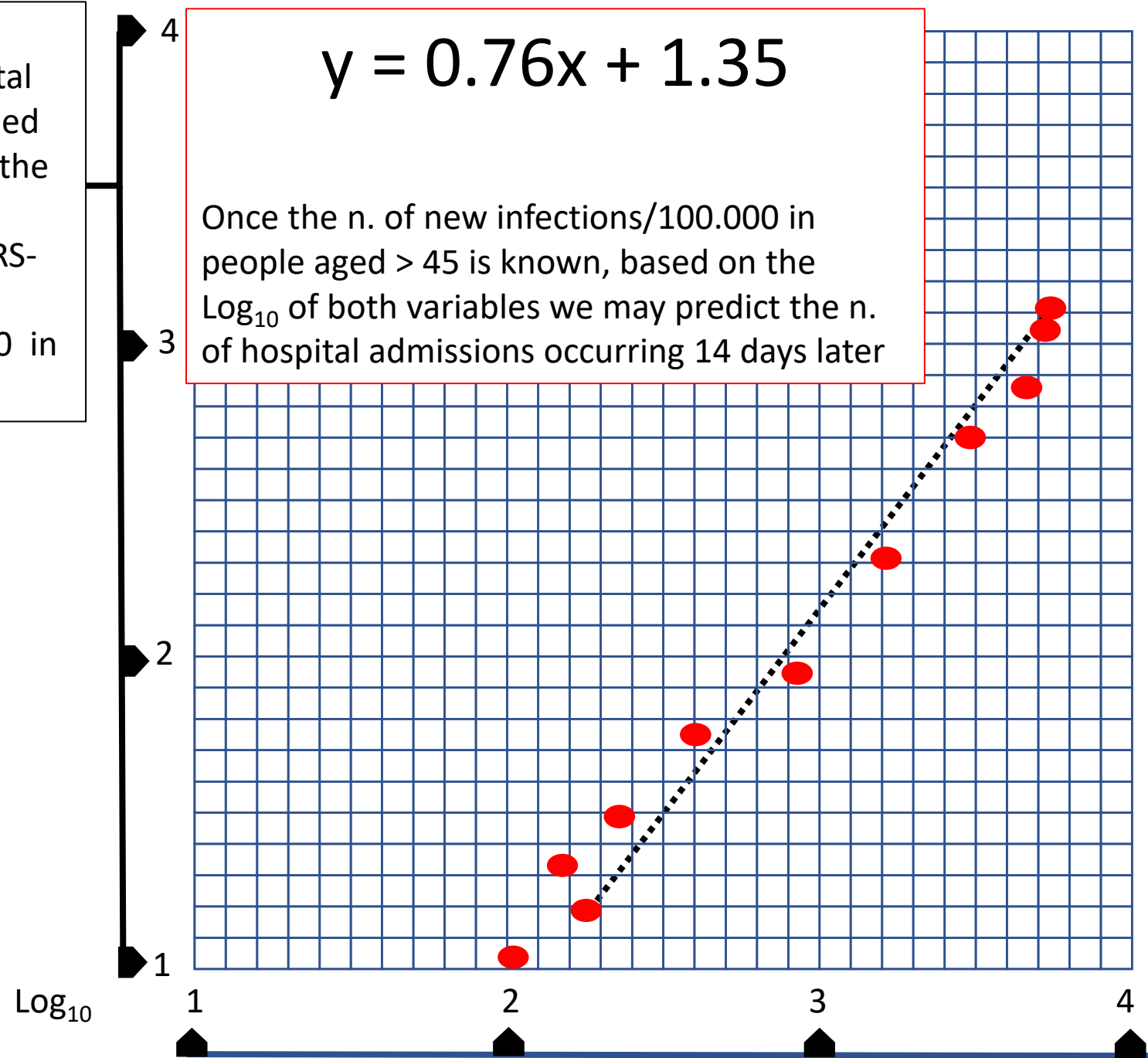
# Amedeo di Savoia Hospital





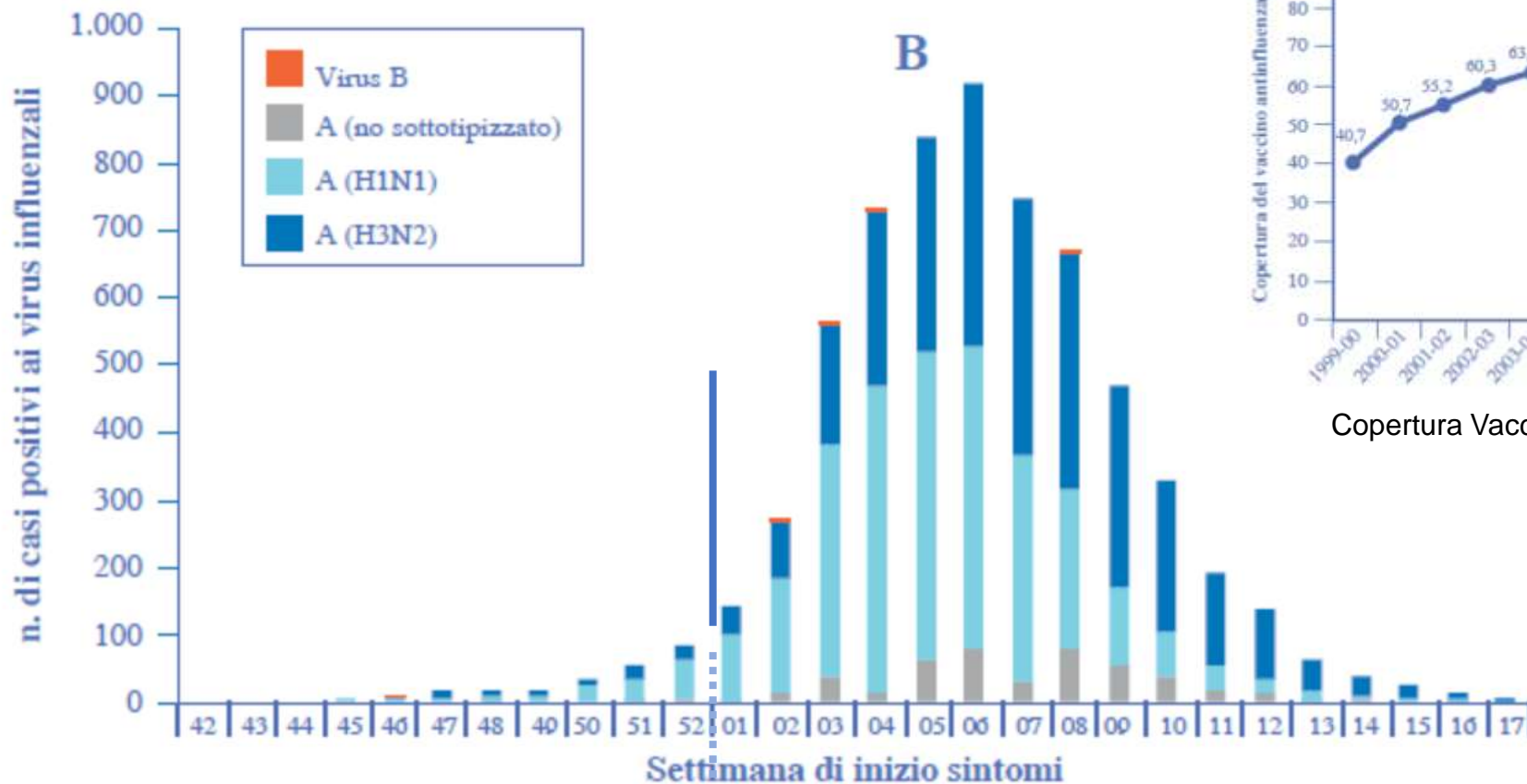


Log<sub>10</sub> of the n. of cumulative hospital admissions recorded 14 days following the corresponding n. (Log<sub>10</sub>) of new SARS-CoV-2 infections/100.000 in people aged > 45



Log<sub>10</sub> of the n. of new SARS-CoV-2 infections per 100.000 population in people aged > 45 recorded at consecutive weekly intervals in the ascending part of the 2nd COVID-19 wave (September – November 2020)

# INFLUENZA



Capodanno



Copertura Vaccinale della popolazione anziana in Italia: 1999 - 2019

Every year for decades, hundreds of labs throughout the world have sent flu samples to the World Health Organization's Global Influenza Surveillance Network. They are all analysed using a venerable test for similarity called haemagglutinin inhibition.

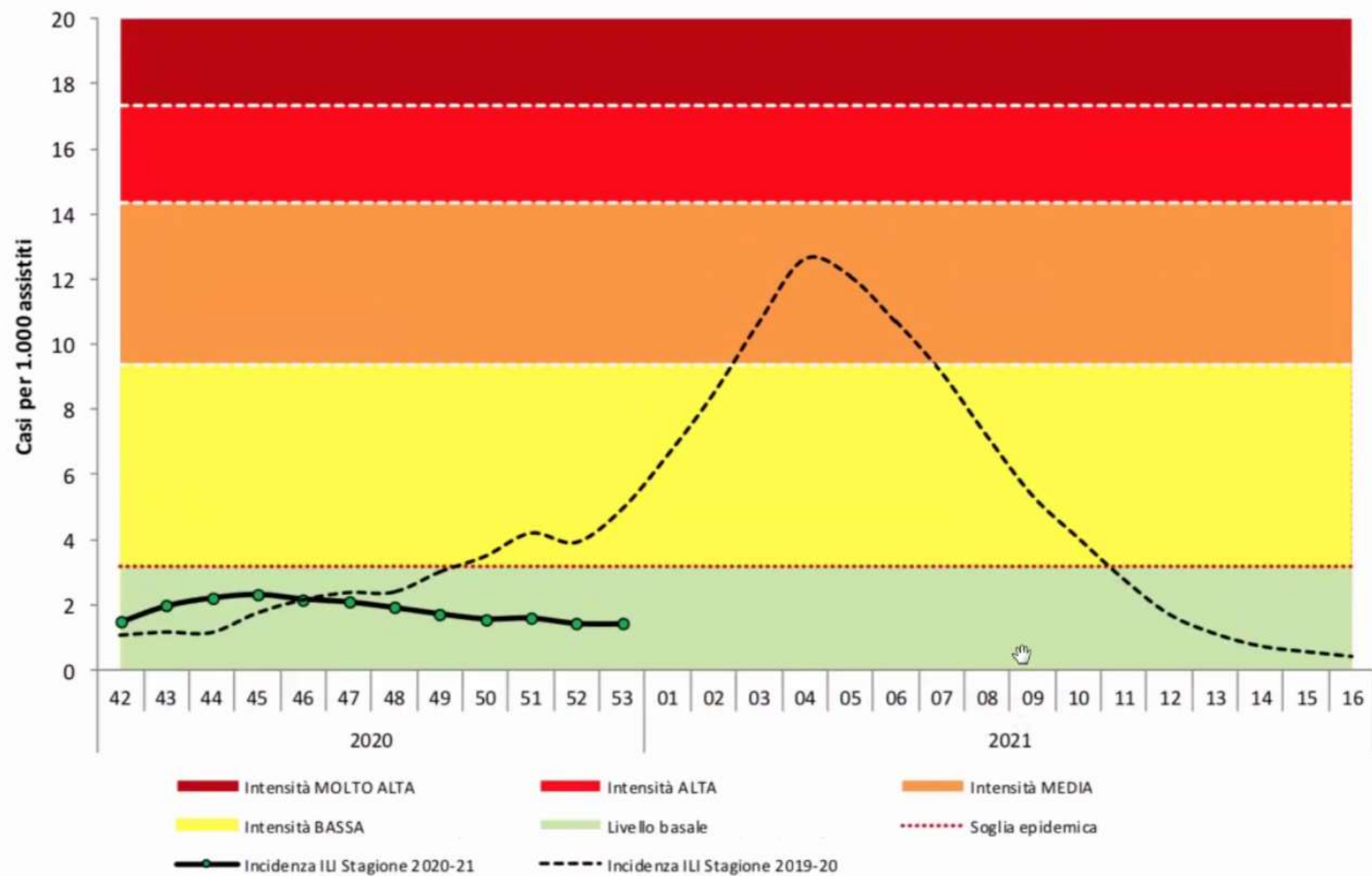
The data showed that new viruses appeared in eastern and southeast Asia 6 to 9 months before they showed up anywhere else, and took another 6 to 9 months to reach Latin America

Outbreaks follow the cooler temperatures of the rainy seasons, which are staggered in time across the region because of complex geography and air movements.



<https://www.newscientist.com/article/dn13724-revealed-the-asian-source-of-the-annual-flu-epidemic/>

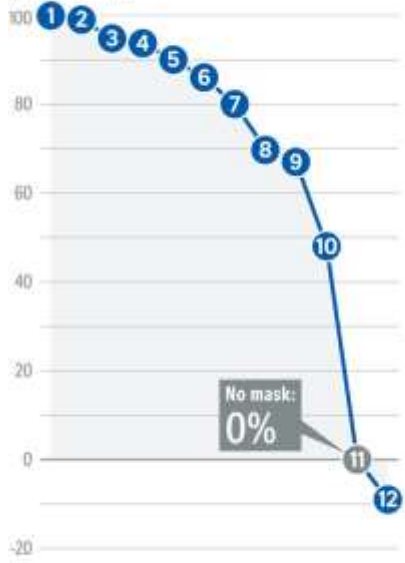
Then when the climatic conditions are right in the northern or southern temperate zones, they strike a spark and seed the next winter epidemic. That then goes to Europe, Oceania and North America first, probably because of **frequent travel between those regions**, then finally gets to less-connected Latin America.





## Effectiveness of different types of masks

% of protection



NOTE: This is a low-level test to show relative effectiveness, and results should not be taken to be conclusive.  
\*The neck gaiter, made of 92% polyester and 8% spandex, broke the droplets up into smaller particles which stayed in the air for longer.



## **TORINO:**

Stefano Bonora  
Francesco G. De Rosa  
Andrea Calcagno  
Antonio D'Avolio  
Mauro Sciandra  
Marco Siccardi  
Cristina Tettoni  
Sabrina Audagnotto  
Letizia Marinaro  
Jessica Cusato  
Laura Trentini  
Marco Simiele  
Amedeo De Nicolò  
Anna Lucchini  
Filippo Lipani  
Roberto Bertucci  
Chiara Montrucchio  
Chiara Alcantarini  
Marino Bonasso  
Ilaria De Benedetto  
Stefano Biffi  
Paolo Tiralongo



Micol Ferrara  
Alice Trentalange  
Lucio Boglione  
Pino Cariti  
Ilaria Motta  
Silvia Corcione  
Ambra Barco  
Tommaso Lupia  
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