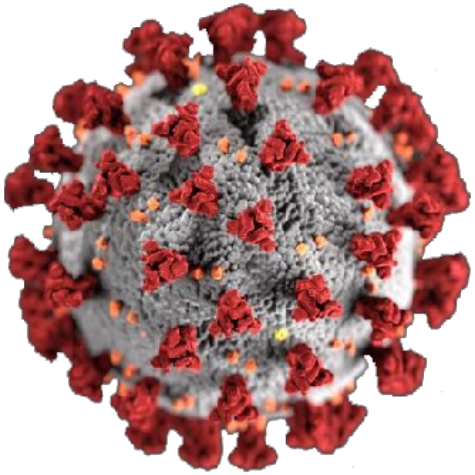
Understanding the 'Immunity Debt' to Common Infections During the COVID-19 Pandemic



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Disclosures

- No speaker's fees and no other funding received for this presentation

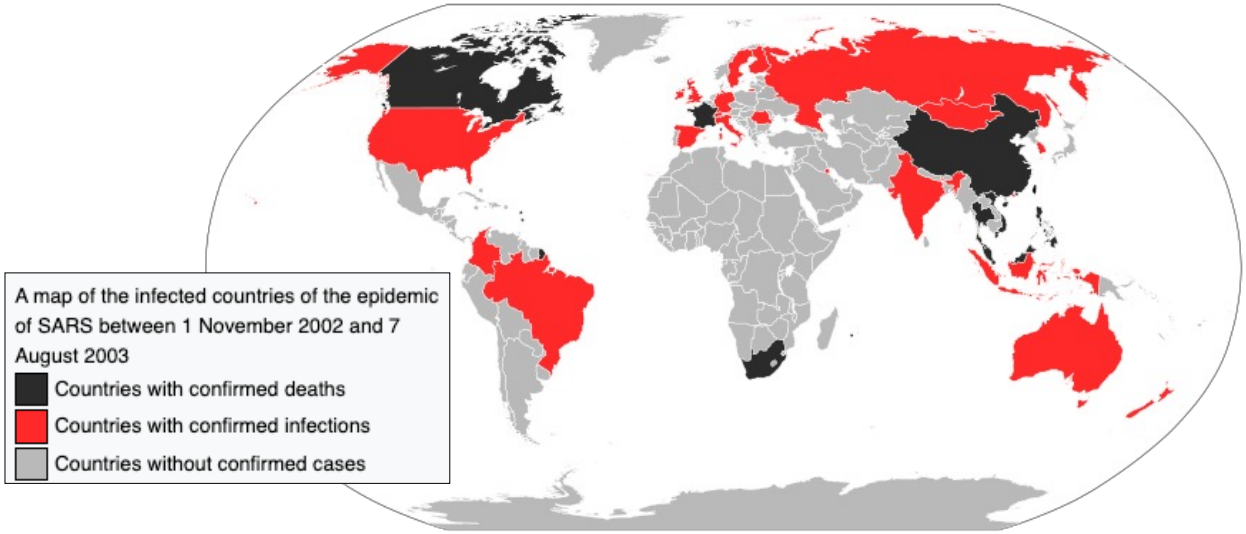
Background -- Singapore was hit quite badly by the 2003 SARS outbreak

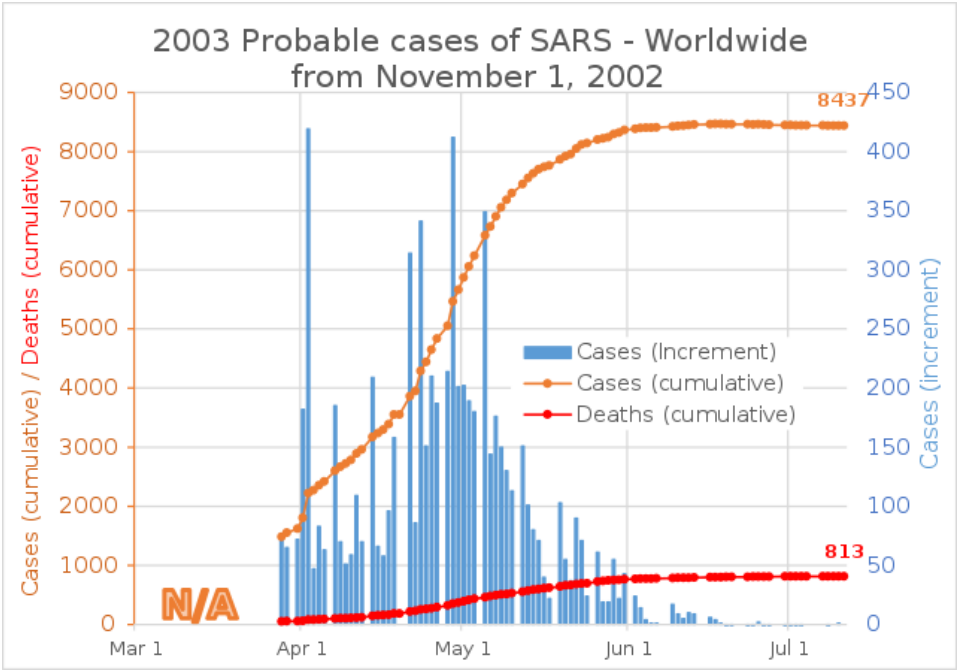
Probable cases of SARS by country and territory, 1 November 2002 – 31 July 2003[5]

Country or region	Cases	Deaths	Fatality (%)
Mainland China[a]	5,327	349	6.6
Hong Kong	1,755	299	17.0
Taiwan[b][6][7]	346	73	21.1
Canada	251	44	17.5
Singapore	238	33	13.9
Vietnam	63	5	7.9
Total excluding Mainland China	2,769	454	16.4
Total (29 territories)	**8,096**	**811**	**9.6**

a. ^ Figures for China exclude Hong Kong, Macau and Taiwan, which are reported separately by the WHO.
b. ^ After 11 July 2003, 325 Taiwanese cases were 'discarded'. Laboratory information was insufficient or incomplete for 135 of the discarded cases; 101 of these patients died.

Singapore also had 5 deaths among healthcare workers





Painful Lesson:

- Due to its exposed location as trade and travel hub, SG is extremely vulnerable to imported infections!

Images: Wikipedia

Singapore COVID-19 Overview

Singapore – tropical city-state with ~5.5 million population

MINISTRY OF HEALTH
SINGAPORE

COVID-19

COVID-19 Situation at a Glance →

As of 12 Feb 2023*

Total Cases
2,222,006

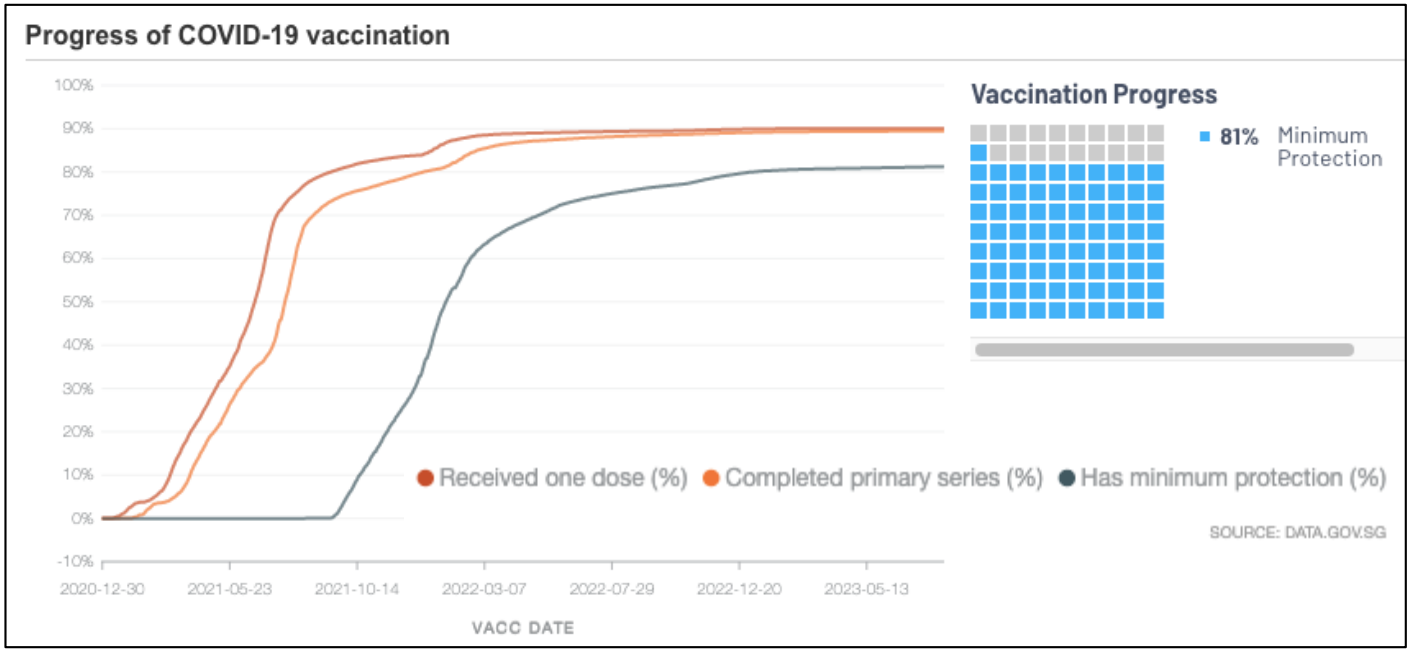
1722
Total Deaths

Rate 0.08%

*On 13 Feb 2023, daily reports were discontinued

As of 12 Feb 2023*

Active Cases	In ICU
1402	1



Sources: Ministry of Health; https://www.moh.gov.sg and Wikipedia

Pandemic Response Measures, Singapore

Year	Time	Phase	Key events or measures
2020	Feb	DORSCON Orange	• First restrictions (incl. travel restrictions)
	April	Circuit Breaker	• Complete Lockdown
	June	Phased Reopening	• Cautious reopening • Safe distancing measures remain in place • Masks outside of home remain compulsory
2021	Jan	Reopening Phase 3	• Loosening of measures • Mask-wearing & safe distancing measures remain in place
	May	Heightened Alert	• Tightening of measures after COVID clusters (Delta) • Routine Rostered Testing (RRT) of all healthcare staff • Subsequent (slight loosening of measures)
	Sep/Oct	Stabilisation phase	• Rise in COVID cases and deaths (Delta Wave) • Again, tightening of measures
2022	Jan	Transition Phase	• Continued from 2021 • Omicron Wave since Dec 2021/Jan 2022
	March	Transition Phase	• Further easing of measures • Outdoor mask-wearing no longer mandatory
	April	DORSCON Yellow	• Further relaxation of measures • No more requirement for TraceTogether and SafeEntry • Fully-vaccinated, well travellers can enter Singapore
	Oct	Transition Phase to Resilience	• Mandatory mask-wearing only healthcare facilities & publ. transport • Fully vacc. travellers may enter SG w/o testing or quarantine • Public life has returned to near-normal
2023	Feb	DORSCON Green	• Mask-wearing only mandatory in healthc. facilities w/ patient contact • All other restrictions are lifted

DORSCON, Disease Outbreak Response System Condition.

Sources: Ministry of Health, Singapore, Wikipedia, Straits Times, Channel News Asia (CNA)

Disappearance and reappearance of respiratory viruses during COVID-19 response measures

- Routine Respiratory Pathogens (RP) multiplex PCR testing (BioFire)
- Around Dec 2019/Jan 2020 – Large proportion of positives – Mainly Flu A/B
- COVID restrictions set in –
  - DORSCON Orange in Feb ‘20; Hard Lockdown (“Circuit Breaker”) in Apr ‘20
  - Reopening Phase 1 in Jun ‘20; Phase 2 later in Jun ‘20; Phase 3 in Jan ‘21

Observations

- Around Apr ’20, noticed that <1/10 of RP PCRs had pathogens
- What is going on? All disappeared?
- About ~13 weeks after reopening, EV/RV reappeared; later AdV
- Into 2021, other viruses reappeared

EV = enterovirus
RV = rhinovirus
AdV = adenovirus

Wan WY, Thoon KC, Loo LH, Chan KS, Oon LLE, Ramasamy A, Maiwald M. Trends in respiratory virus infections during the COVID-19 pandemic in Singapore, 2020. JAMA Netw Open. 2021;4(6):e2115973. doi:10.1001/jamanetworkopen.2021.15973.

BioFire FilmArray RP 2.1 multiplex PCR

Rapid multiplex PCR with 19 respiratory pathogens & SARS-CoV-2 (~45 min)

VIRUSES:

- Adenovirus
- Coronavirus 229E
- Coronavirus HKU1
- Coronavirus NL63
- Coronavirus OC43
- **Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)**
- Human Metapneumovirus
- Human Rhinovirus/Enterovirus
- Influenza A virus
- Influenza A virus A/H1
- Influenza A virus A/H3
- Influenza A virus A/H1-2009
- Influenza B virus
- Parainfluenza virus 1
- Parainfluenza virus 2
- Parainfluenza virus 3
- Parainfluenza virus 4
- Respiratory syncytial virus

BACTERIA:

- *Bordetella parapertussis*
- *Bordetella pertussis*
- *Chlamydia pneumoniae*
- *Mycoplasma pneumoniae*

BioFire®
Respiratory Panel 2.1
BIOFIRE
www.BioFireDx.com

Run Summary

Sample ID:	RP2.1example	Run Date:	04 April 2020 5:21 PM
Detected:	Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)	Controls:	Passed
Equivocal:	Influenza A		

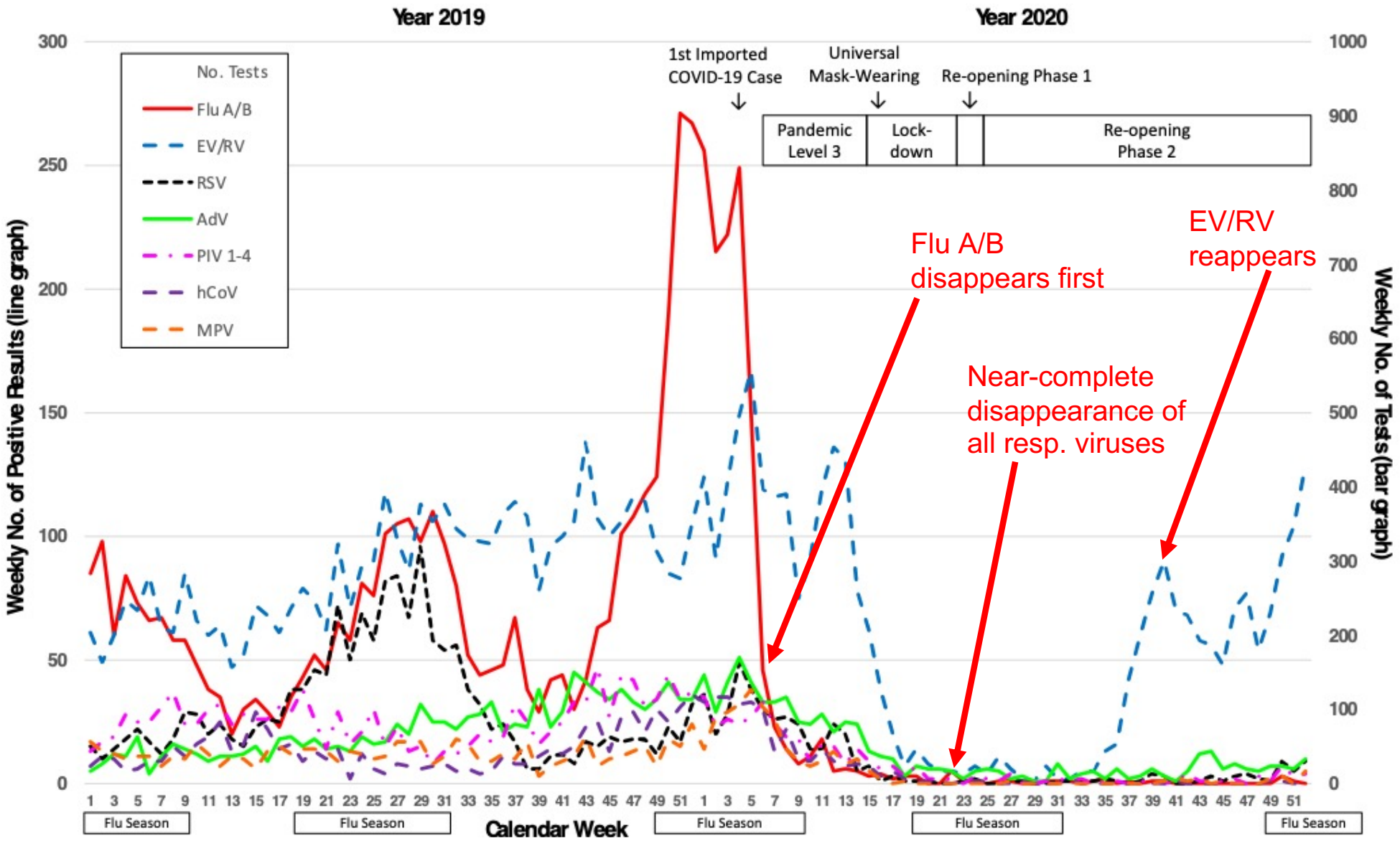
Result Summary

	Viruses
Not Detected	Adenovirus
Not Detected	Coronavirus 229E
Not Detected	Coronavirus HKU1
Not Detected	Coronavirus NL63
Not Detected	Coronavirus OC43
✓ Detected	Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
Not Detected	Human Metapneumovirus
Not Detected	Human Rhinovirus/Enterovirus
⬌ Equivocal	Influenza A
Not Detected	Influenza B
Not Detected	Parainfluenza Virus 1
Not Detected	Parainfluenza Virus 2
Not Detected	Parainfluenza Virus 3
Not Detected	Parainfluenza Virus 4
Not Detected	Respiratory Syncytial Virus
	Bacteria
Not Detected	*Bordetella parapertussis* (IS*1001*)
Not Detected	*Bordetella pertussis* (*ptxP*)
Not Detected	*Chlamydia pneumoniae*
Not Detected	*Mycoplasma pneumoniae*

Run Details

Pouch:	RP2.1 v1.0	Protocol:	NPS2 v3.2
Run Status:	Completed	Operator:	JDoe
Serial No.:	01234567	Instrument:	TM8CCF3
Lot No.:	012345		

Images:
Manufacturer Websites; M. Maiwald



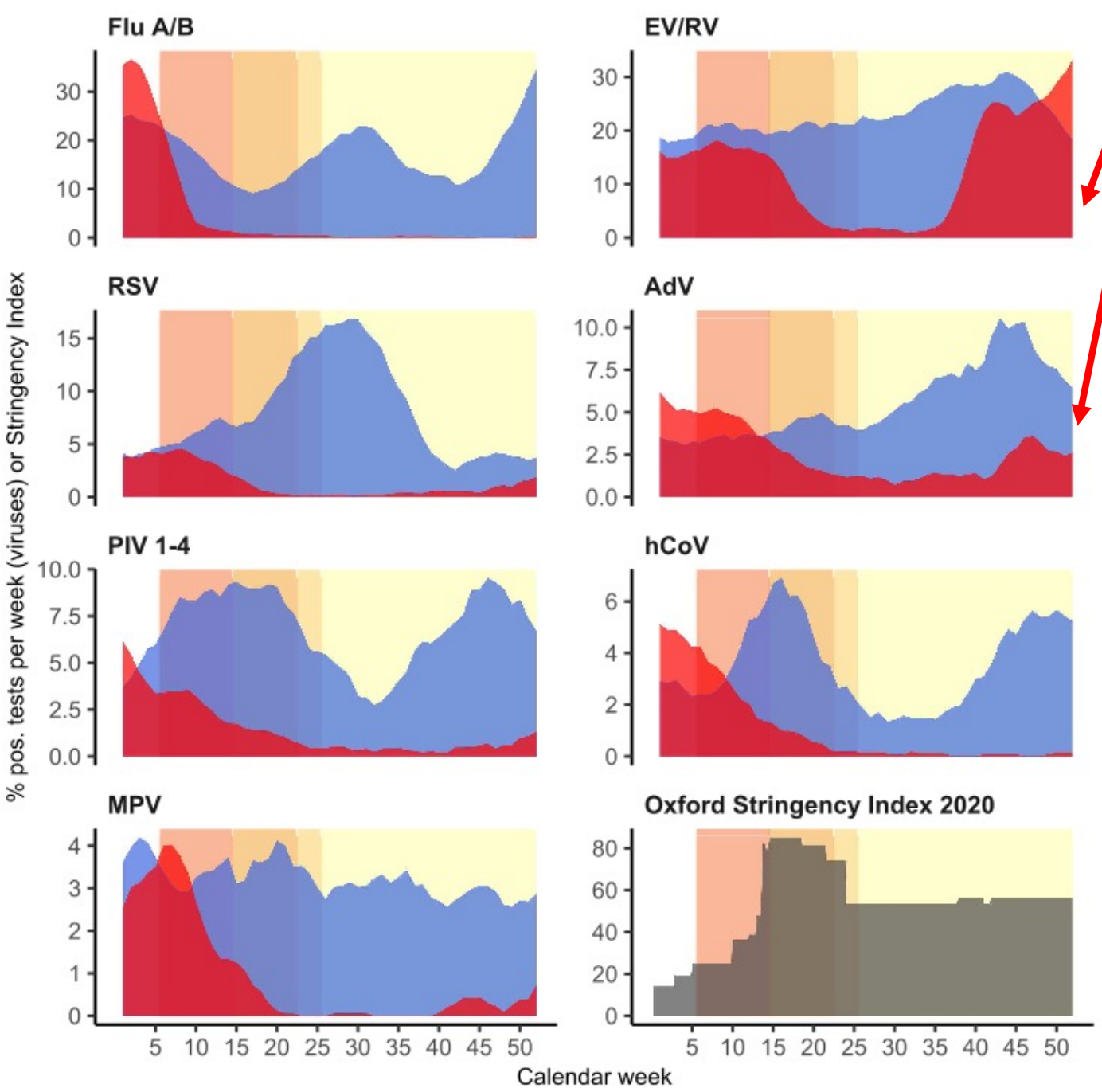
JAMA Network Open

Research Letter | Infectious Diseases

Trends in Respiratory Virus Infections During the COVID-19 Pandemic in Singapore, 2020

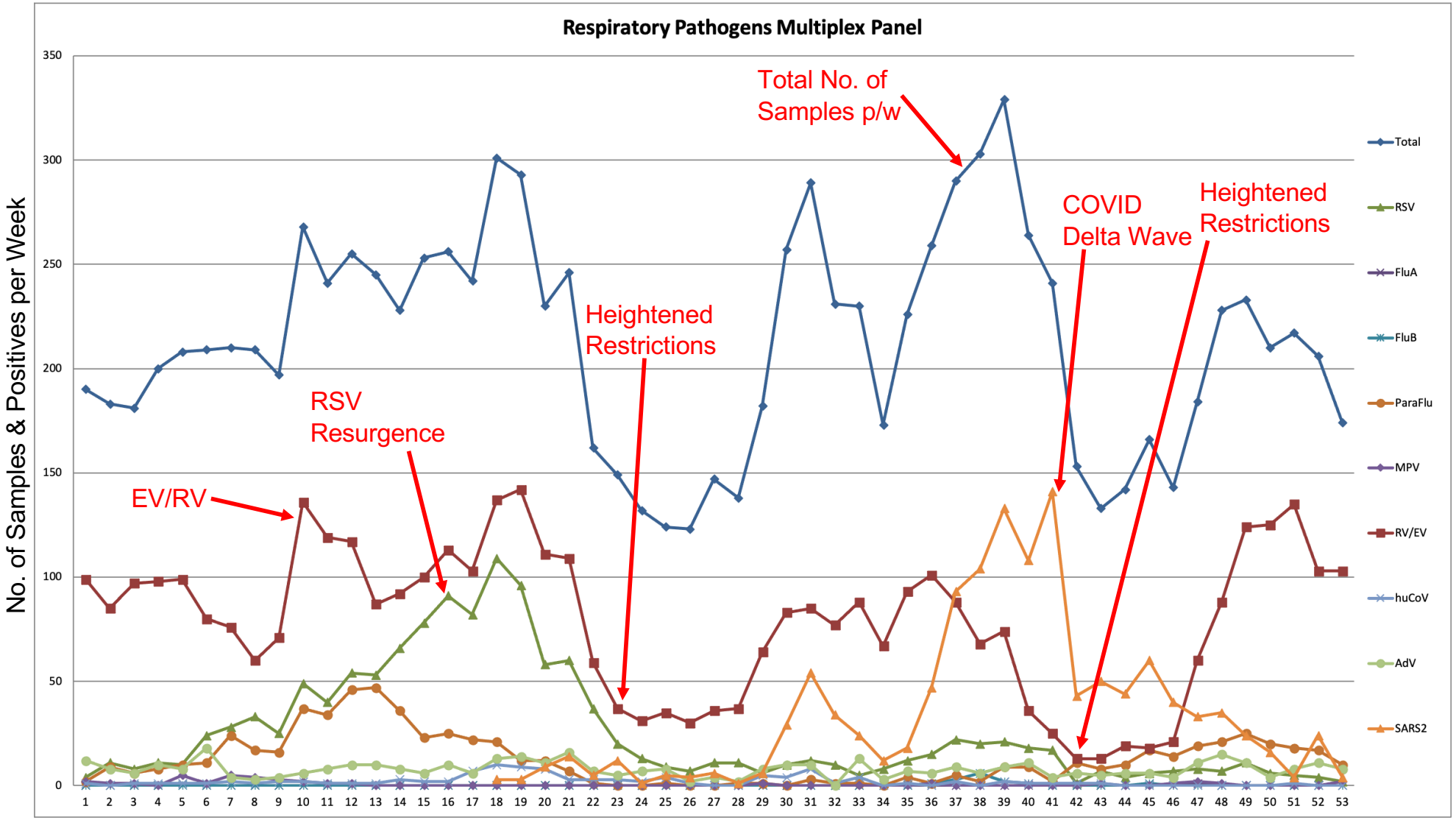
Wei Yee Wan, MD; Koh Cheng Thoon, MD; Liat Hui Loo, PhD; Kian Sing Chan, MD; Lynette L. E. Oon, MD; Adaikalavan Ramasamy, PhD; Matthias Maiwald, MD

JAMA Network Open. 2021;4(6):e2115973. doi:10.1001/jamanetworkopen.2021.15973



Wan WY, et al. JAMA Netw Open. 2021;4(6):e2115973. doi:10.1001/jamanetworkopen.2021.15973.

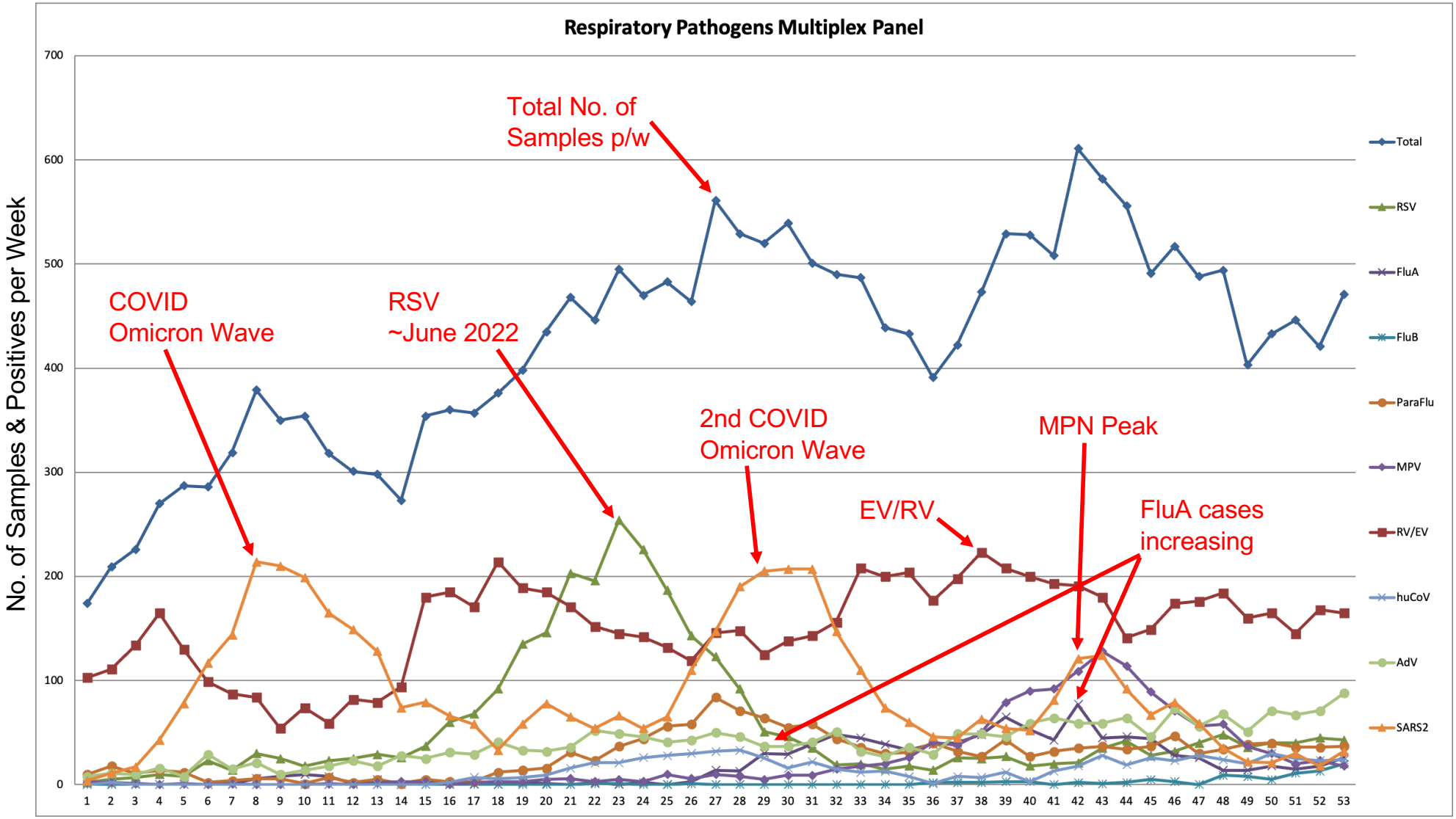
Singapore Resp. Virus Data 2021 (KKH)



- EV/RV hangs around and hovers up and down
- RSV has big resurgence ~April 2021
- Resp. virus up/down follows restrictions
- No Influenza A/B

KKH Molecular Microbiology Laboratory (unpubl. data)

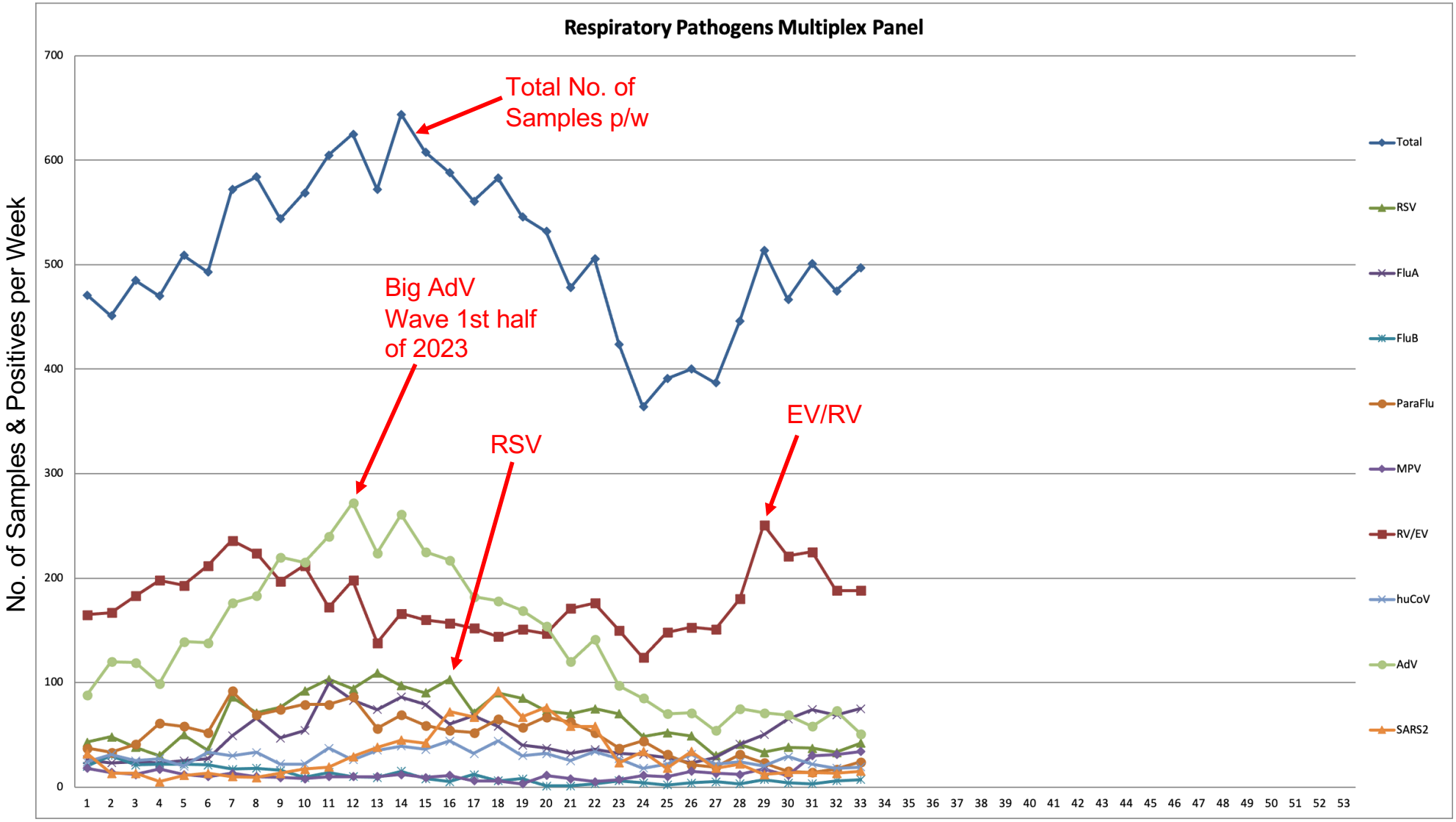
Singapore Resp. Virus Data 2022 (KKH)



- EV/RV hangs around and hovers up and down
- RSV has big resurgence ~June 2022; MPN has peak around October 2022
- Influenza A/B is coming back 2nd half of year (South. Hemi. Flu Season)
- HFMD (EV) is coming back Oct/Nov 2022 (not shown)

KKH Molecular Microbiology Laboratory (unpubl. data)

Singapore Resp. Virus Data 2023 (KKH)



- AdV has big wave 1st half of 2023
- EV/RV hangs around and hovers up and down; cases of EV & PeV meningitis come back
- RSV has small wave 1st half of 2023
- SARS-CoV-2 is getting less

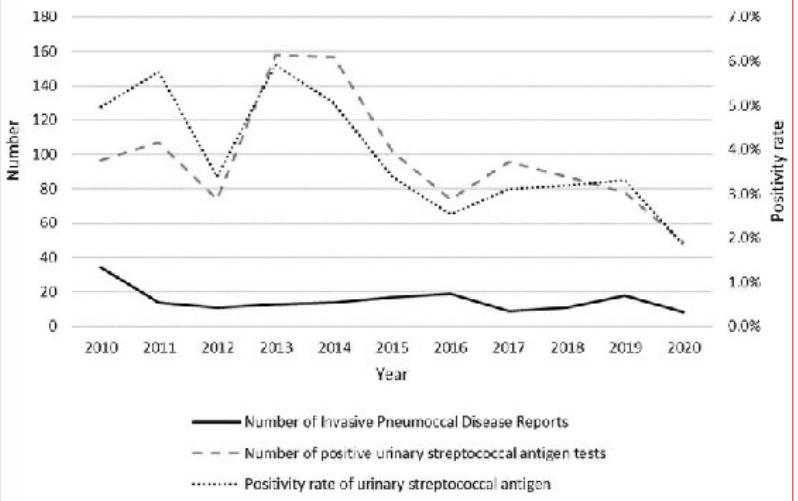
KKH Molecular Microbiology Laboratory (unpubl. data)

Similar Trends for Bacterial Illnesses

Decline in pneumococcal disease incidence in the time of COVID-19 in Singapore

Rachel HF Lim
Angela Chow
Hanley J Ho*
Department of Clinical Epidemiology, Office of Clinical Epidemiology, Analytics, and Knowledge, Tan Tock Seng Hospital, Singapore
*Corresponding author. Tel.: +65-63577477; Fax: +65-63577465.
E-mail address: hanleyho@gmail.com (H.J. Ho)

Journal of Infection 81 (2020) e19–e21



Bordetella pertussis
- KKH in pre-pandemic years >50 cases per year
- Last case seen March 2020
- Zero cases since (>2.5 years)

Bordetella parapertussis
- Came back 2023

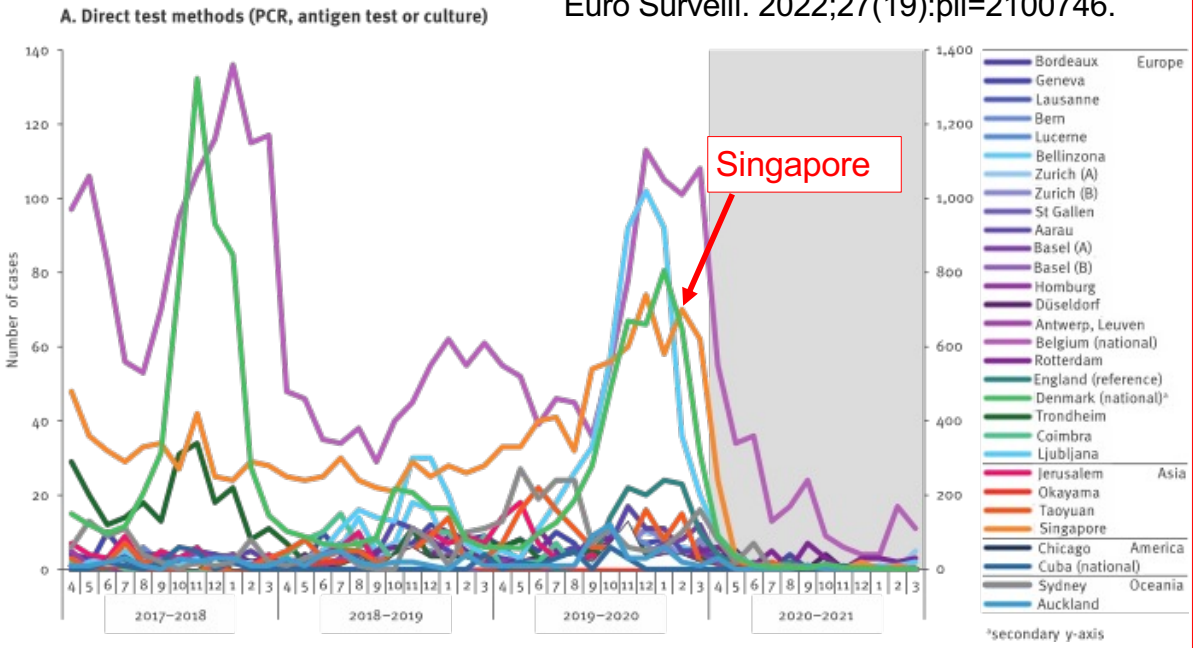
KKH Data, unpublished

RESEARCH

Mycoplasma pneumoniae detections before and during the COVID-19 pandemic: results of a global survey, 2017 to 2021

Patrick M Meyer Sauteur[1], Michael L Beeton[2], Søren A Uldum[3], Nathalie Bossuyt[4], Melissa Vermeulen[4], Katherine Loens[5], Sabine Pereyre[6], Cécile Bébéar[6], Darja Keše[7], Jessica Day[8], Baharak Afshar[8], Victoria J Chalker[8], Gilbert Greub[9], Ran Nir-Paz[10,11], Roger Dumke[12], ESGMAC–MyCOVID Study Team[13]

Euro Surveill. 2022;27(19):pii=2100746.



Mycoplasma pneumoniae beyond the COVID-19 pandemic: where is it?

*Patrick M Meyer Sauteur, Victoria J Chalker, Christoph Berger, Ran Nir-Paz, Michael L Beeton, on behalf of the ESGMAC and the ESGMAC–MyCOVID study group
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The Lancet Microbe 2022
Published Online
August 11, 2022
https://doi.org/10.1016/S2666-5247(22)00190-2

- *M. pneumoniae* remained largely absent from most countries until March 2022

Similar Trends in Other Countries

Concomitant Marked Decline in Prevalence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Other Respiratory Viruses Among Symptomatic Patients Following Public Health Interventions in Australia: Data from St Vincent's Hospital and Associated Screening Clinics, Sydney, NSW

Deborah Marriott,[1] Rohan Beresford,[2] Feras Mirdad,[1] Damien Stark,[1] Allan Glanville,[1] Scott Chapman,[1] Jock Harkness,[1] Gregory J. Dore,[1,3] David Andresen,[1,a] and Gail V. Matthews[1,3,a]

[1]Department of Infectious Diseases, St Vincent's Hospital, Sydney, Australia, [2]Concord Hospital, Sydney, Australia, [3]Kirby Institute, University of New South Wales Sydney, Sydney, Australia

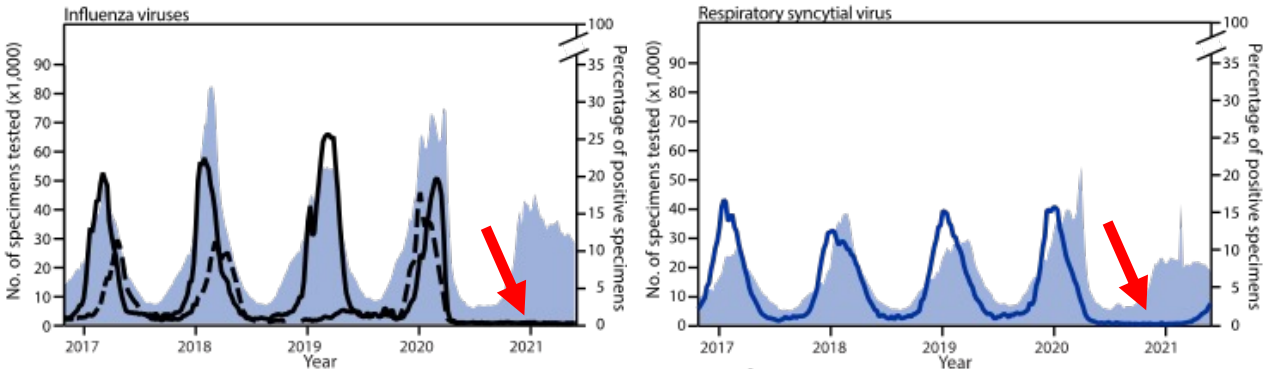
Our Australian hospital tested almost 22 000 symptomatic people over 11 weeks for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in a multiplex polymerase chain reaction (PCR) assay. Following travel bans and physical distancing, SARS-CoV-2 and other respiratory viruses diagnoses fell dramatically. Increasing rhinovirus diagnoses as social control measures were relaxed may indirectly indicate an elevated risk of coronavirus disease 2019 (COVID-19) resurgence.

Clin. Infect. Dis. 2021;72(10):e649–51

Morbidity and Mortality Weekly Report — July 23, 2021

Changes in Influenza and Other Respiratory Virus Activity During the COVID-19 Pandemic — United States, 2020–2021

Sonja J. Olsen, PhD[1]; Amber K. Winn, MPH[2]; Alicia P. Budd, MPH[1]; Mila M. Prill, MSPH[2]; John Steel, PhD[1]; Claire M. Midgley, PhD[2]; Krista Kniss, MPH[1]; Erin Burns[1]; Thomas Rowe, MS[1]; Angela Foust[1]; Gabriela Jasso[1]; Angiezel Merced-Morales, MPH[1]; C. Todd Davis, PhD[1]; Yunho Jang, PhD[1]; Joyce Jones, MS[1]; Peter Daly, MPH[1]; Larisa Gubareva, PhD[1]; John Barnes, PhD[1]; Rebecca Kondor, PhD[1]; Wendy Sessions, MPH[1]; Catherine Smith, MS[1]; David E. Wentworth, PhD[1]; Shikha Garg, MD[1]; Fiona P. Havers, MD[2]; Alicia M. Fry, MD[1]; Aron J. Hall, DVM[2]; Lynnette Brammer, MPH[1]; Benjamin J. Silk, PhD[2]



Dramatic decrease of laboratory-confirmed influenza A after school closure in response to COVID-19

Andres Perez-Lopez MD, PhD[1,2] | Mohammad Hasan PhD[1,2] | Muhammad Iqbal MSc[1] | Mohammed Janahi MD[2,3] | Diane Roscoe MD[1] | Patrick Tang MD, PhD[1,2]

[1]Department of Pathology and Laboratory Medicine, Division of Microbiology, Sidra Medicine, Qatar Foundation, Doha, Qatar
[2]Weill Cornell Medical College, Doha, Qatar
[3]Division of Paediatric Infectious Diseases, Sidra Medicine, Qatar Foundation, Doha, Qatar

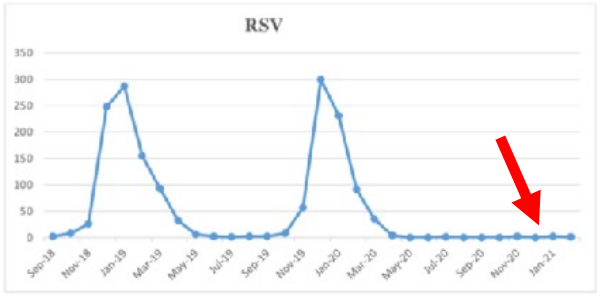
Pediatr. Pulmonol. 2020;55:2233-4

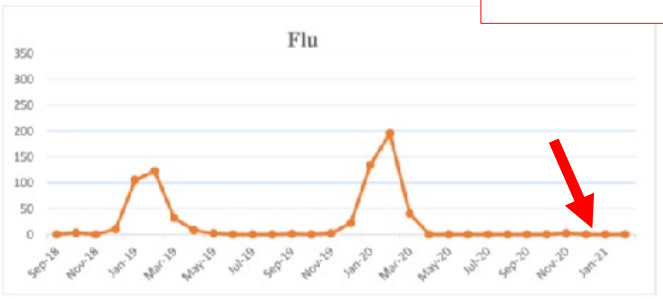
Article

The Disappearance of Respiratory Viruses in Children during the COVID-19 Pandemic

Int. J. Environ. Res. Public Health **2021**, *18*, 9550.

Anna Chiara Vittucci [1,*], Livia Piccioni [2], Luana Coltella [2], Claudia Ciarlitto [1], Livia Antilici [1], Elena Bozzola [1], Fabio Midulla [3], Paolo Palma [4], Carlo Federico Perno [2] and Alberto Villani [1]





International Journal of *Environmental Research and Public Health*

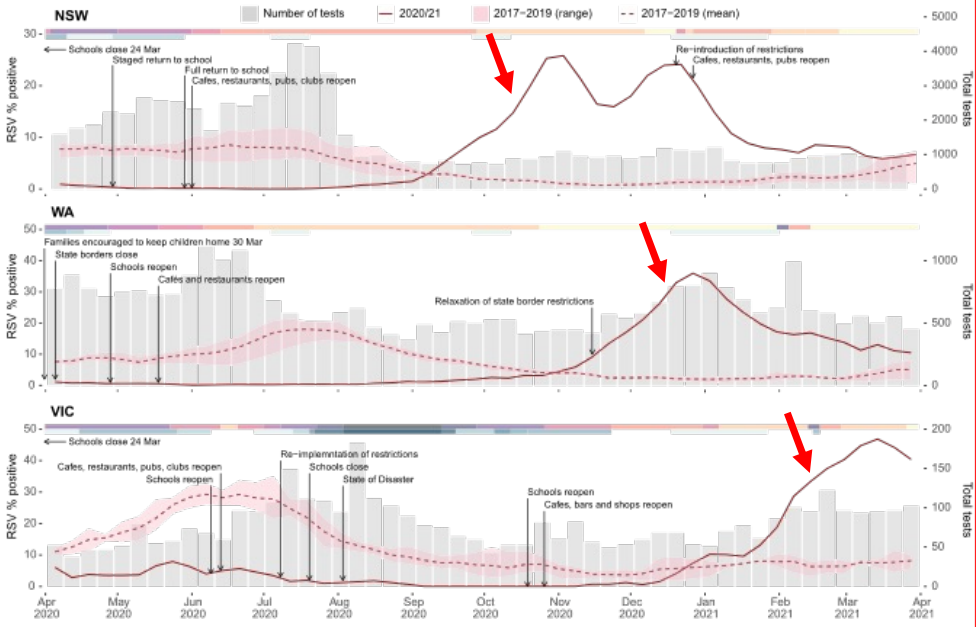
However, what happens thereafter?

nature COMMUNICATIONS

Nat Commun. 2022; 13(1): 2884

Off-season RSV epidemics in Australia after easing of COVID-19 restrictions

John-Sebastian Eden[1,2,20], Chisha Sikazwe[3,4,20], Ruopeng Xie[5,6,20], Yi-Mo Deng[7,8], Sheena G. Sullivan[7,9], Alice Michie[4], Avram Levy[3], Elena Cutmore[1,2], Christopher C. Blyth[3,10,11,12], Philip N. Britton[2,13], Nigel Crawford[14,15,16], Xiaomin Dong[7,8], Dominic E. Dwyer[2,17], Kimberly M. Edwards[5,6], Bethany A. Horsburgh[1,2], David Foley[3], Karina Kennedy[18], Cara Minney-Smith[3], David Speers[3,19], Rachel L. Tulloch[1,2], Edward C. Holmes[2], Vijaykrishna Dhanasekaran[5,6,21✉], David W. Smith[3,10,21✉], Jen Kok[17,21✉], Ian G. Barr[7,8,21✉] & the Australian RSV study group*

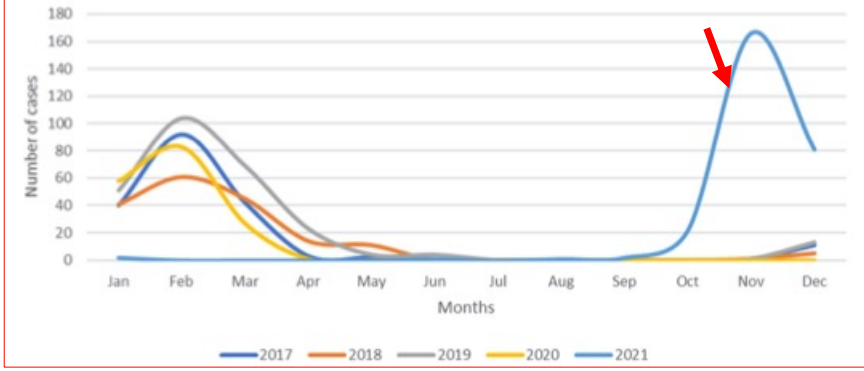


Article

Out-of-Season Epidemic of Respiratory Syncytial Virus during the COVID-19 Pandemic: The High Burden of Child Hospitalization in an Academic Hospital in Southern Italy in 2021

Children 2022, 9, 848

Daniela Loconsole [1], Francesca Centrone [1], Caterina Rizzo [2], Désirée Caselli [3], Azzurra Orlandi [3], Fabio Cardinale [4], Cristina Serio [4], Paola Giordano [5], Giuseppe Lassandro [5], Leonardo Milella [6], Maria Teresa Ficarella [6], Maria Elisabetta Baldassarre [7], Nicola Laforgia [8] and Maria Chironna [1,*]



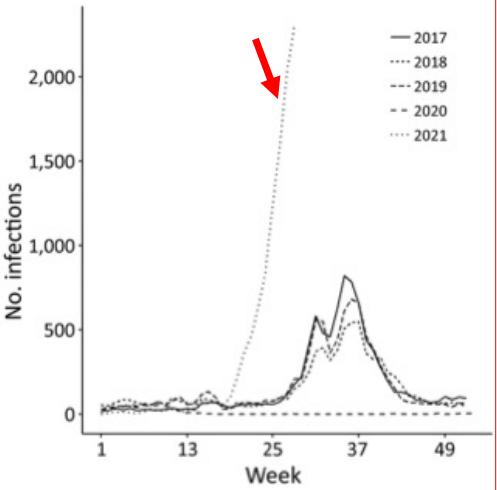
Resurgence of Respiratory Syncytial Virus Infections during COVID-19 Pandemic, Tokyo, Japan

Mugen Ujiie, Shinya Tsuzuki, Takato Nakamoto, Noriko Iwamoto

Author affiliation: National Center for Global Health and Medicine, Tokyo, Japan

DOI: https://doi.org/10.3201/eid2711.211565

More than a year into the coronavirus-19 pandemic, intensified infection control measures have controlled most viral respiratory infections in Tokyo, Japan. As of July 2021, however, an unusually high number of respiratory syncytial virus infections were reported in Tokyo. This resurgence may have resulted from restarting social activities for children.



Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 27, No. 11, November 2021

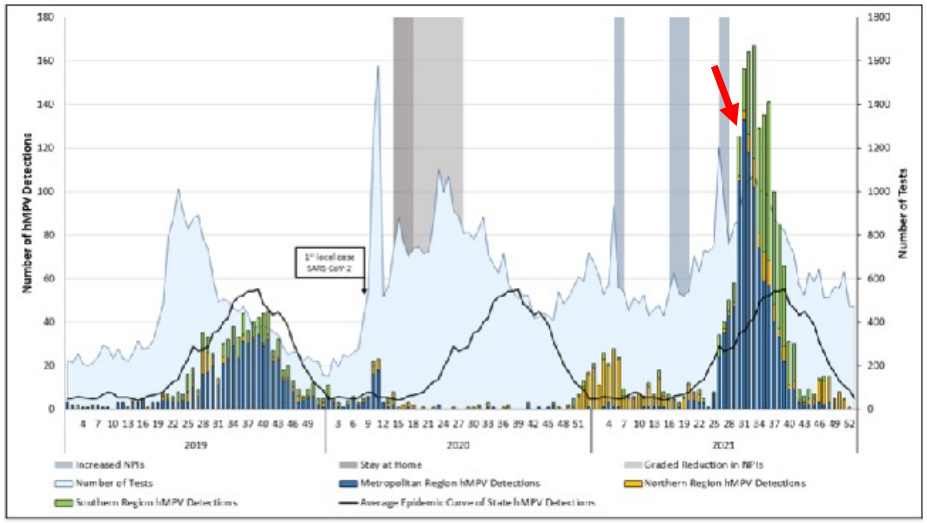
Thereafter (Continued)

viruses Viruses 2022; 14: 2135 MDPI

Article

An Unusual Resurgence of Human Metapneumovirus in Western Australia Following the Reduction of Non-Pharmaceutical Interventions to Prevent SARS-CoV-2 Transmission

David Anthony Foley [1,2,3,*], Chisha T. Sikazwe [1,4], Cara A. Minney-Smith [1], Timo Ernst [4], Hannah C. Moore [2,5], Mark P. Nicol [4], David W. Smith [1,3], Avram Levy [1,4] and Christopher C. Blyth [1,2,3,6]



Australian Government

Department of Health and Aged Care

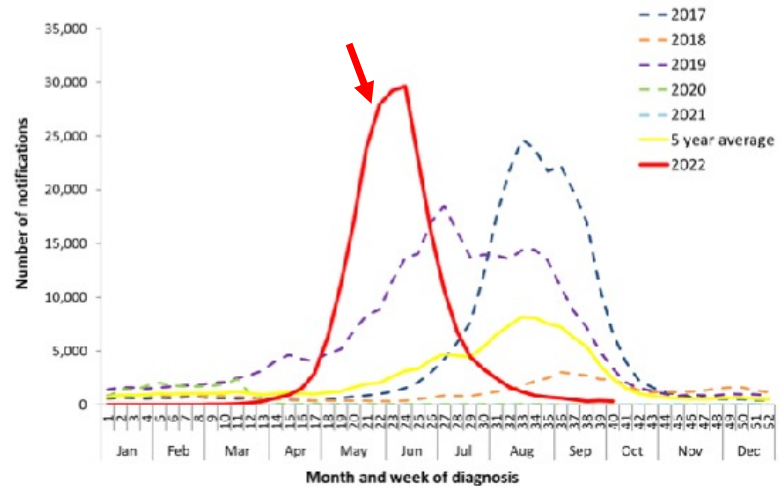
AUSTRALIAN INFLUENZA SURVEILLANCE REPORT

http://www.health.gov.au/flureport

No. 14, 2022

Reporting fortnight: 26 September to 09 October 2022

Figure 4. Notifications of laboratory-confirmed influenza, Australia, 01 January 2017 to 09 October 2022, by month and week of diagnosis*



Singapore 2022:

- FluA/B cases rising since mid-year
- RSV surged early/mid 2021 & 2022
- HFMD (EV) case clusters on the rise
- EV meningitis cases increasing

KKH Data, unpublished

How have children fared in Germany in the latest wave of the COVID pandemic?

https://p.dw.com/p/47Mns

Although data indicate that the omicron variant has been less severe for children, they still face risks — including long COVID or inflammatory syndrome. Experts are urging prioritizing kids' well-being.

- RSV rose sharply from Oct. 2021
- Children hospitalized with RSV about 6-8 x higher than those with COVID-19

DEUTSCHE WELLE (Feb. 2022)

Mycoplasma pneumoniae – Further Developments

Mycoplasma pneumoniae beyond the COVID-19 pandemic: where is it?

Patrick M Meyer Sauteur, Victoria J Chalker, Christoph Berger, Ran Nir-Paz, Michael L Beeton, on behalf of the ESGMAC and the ESGMAC–MyCOVID study group *
patrick.meyersauteur@kispi.uzh.ch

Division of Infectious Diseases and Hospital Epidemiology, University Children's Hospital Zurich, Zurich 8032, Switzerland (PMMS, CB); United Kingdom Health Security Agency, London, UK (VJC); Department of Clinical Microbiology and Infectious Diseases, Hadassah Hebrew University Medical Center, Jerusalem, Israel (RN-P); Microbiology and Infection Research Group, Department of Biomedical Sciences, Cardiff Metropolitan University, Cardiff, UK (MLB)

*KKH, Singapore, as a study site

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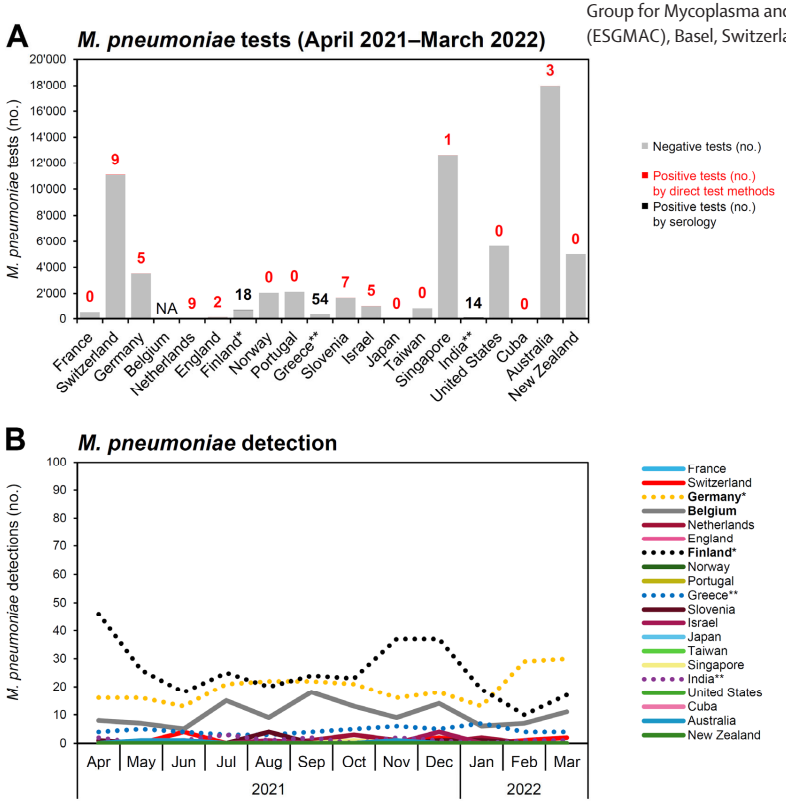
www.thelancet.com/microbe **Vol 3 December 2022**



Mycoplasma pneumoniae: gone forever?

Patrick M Meyer Sauteur, Michael L Beeton, †on behalf of the ESGMAC and the ESGMAC MAPS study group
patrick.meyersauteur@kispi.uzh.ch

Division of Infectious Diseases and Hospital Epidemiology, University Children's Hospital Zurich, Zurich 8032, Switzerland (PMMS); Microbiology and Infection Research Group, Department of Biomedical Sciences, Cardiff Metropolitan University, Cardiff , UK (MLB); European Society of Clinical Microbiology and Infectious Diseases Study Group for Mycoplasma and Chlamydia Infections (ESGMAC), Basel, Switzerland

*KKH, Singapore, as a study site

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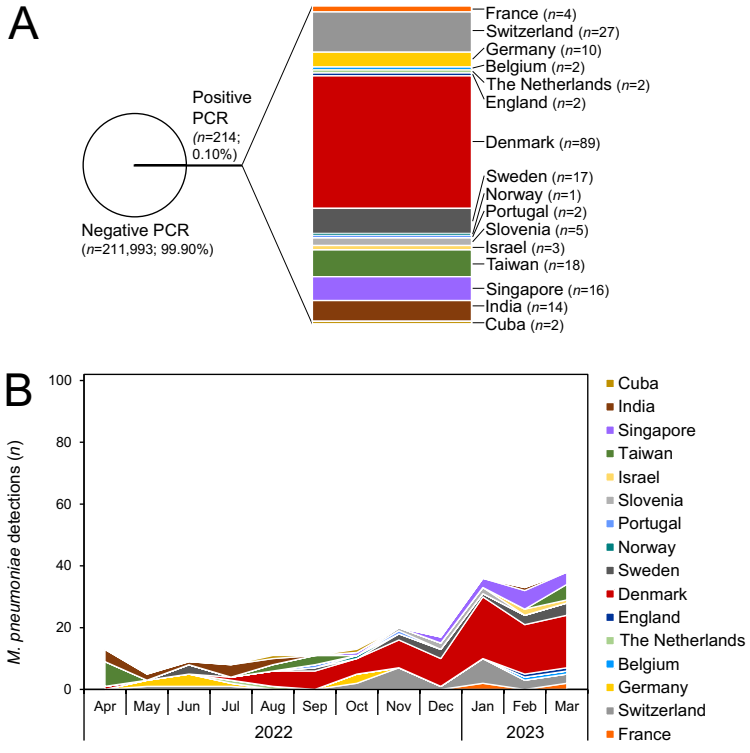
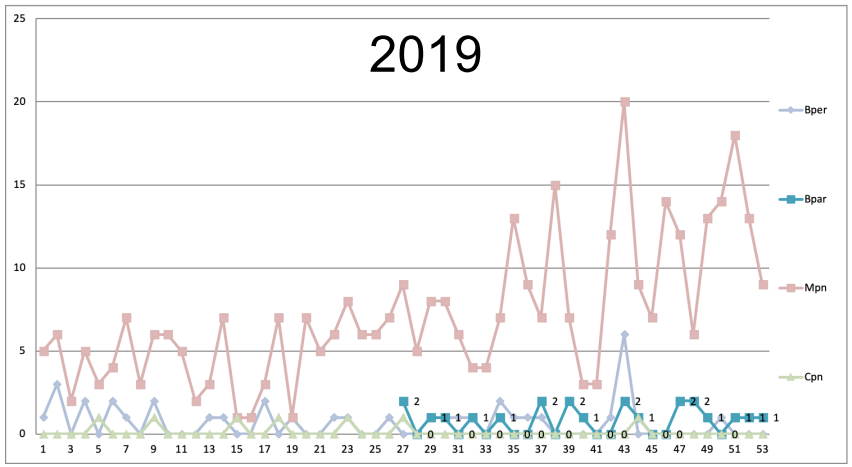
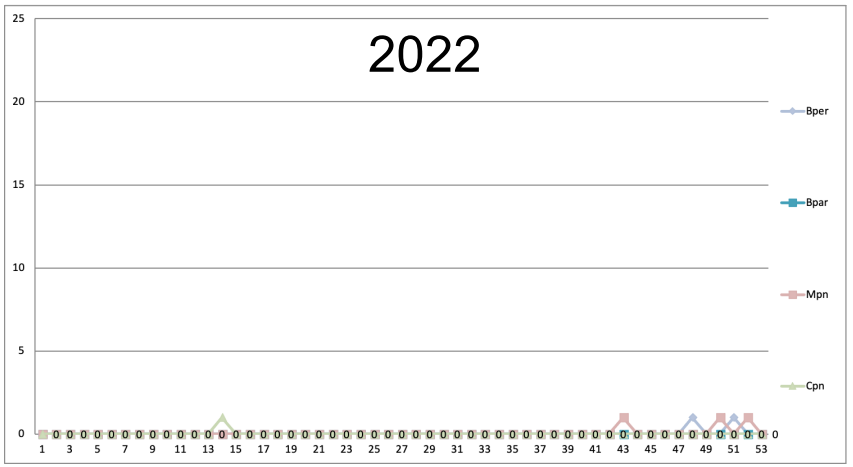
https://doi.org/10.1016/S2666-5247(23)00182-9

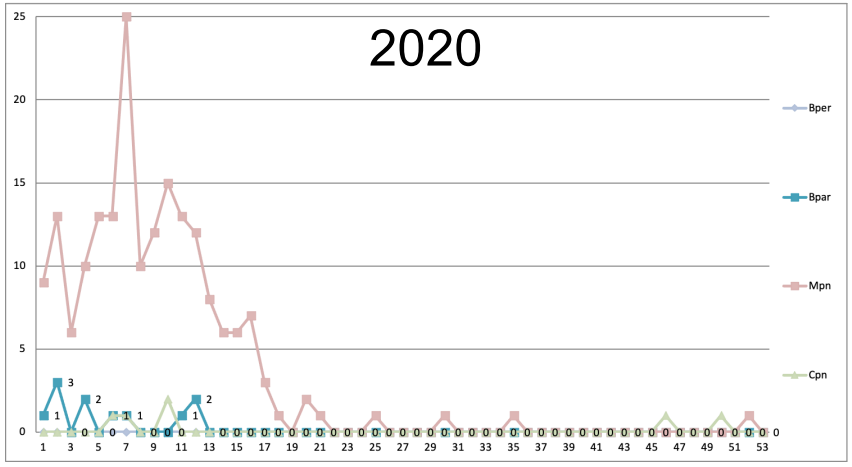
www.thelancet.com/microbe **Published online June 29, 2023**

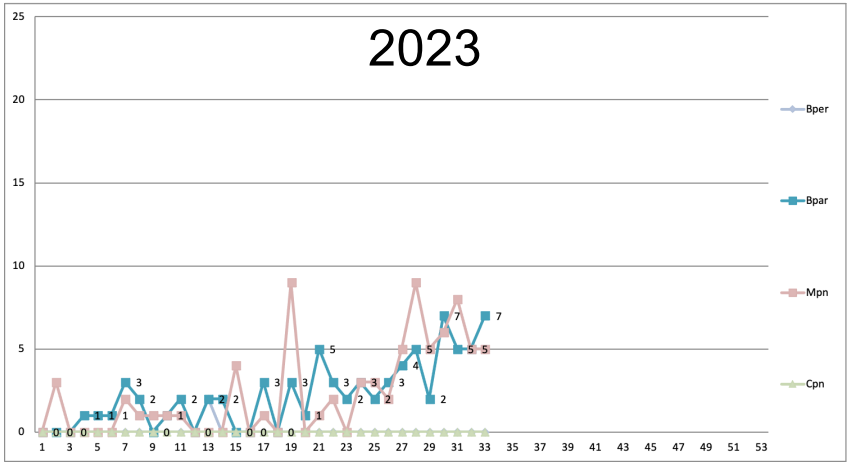


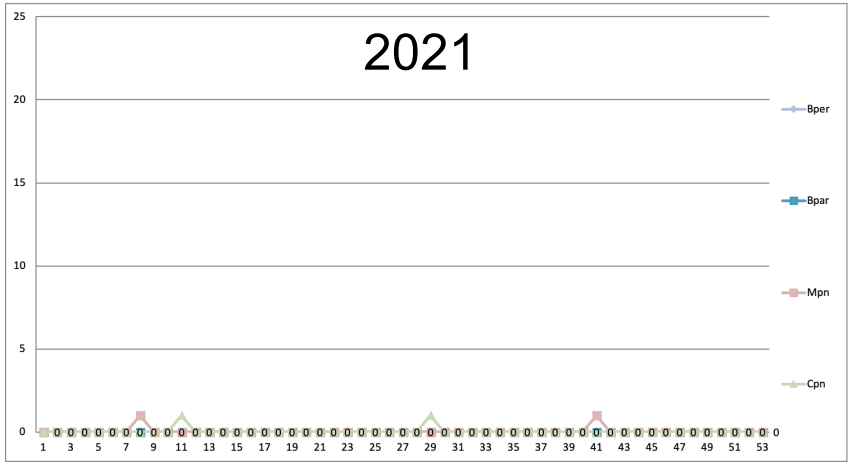
Respiratory Bacteria – Further Developments











Bper – *Bordetella pertussis*
Bpar – *Bordetella parapertussis*
Mpn – *Mycoplasma pneumoniae*
Cpn – *Chlamydophila pneumoniae*

- Pertussis remains absent
- *Mycoplasma* returns slowly after >2.5 y near-absence
- Parapertussis returns to > than pre-pandemic levels
- *Chlamydophila* very few cases pre- and post-pandemic

KKH Data, unpublished

COMMENTARY

Bordetella parapertussis Re-emerges as a Cause of Respiratory Illness in Children

Kristina A. Bryant, MD

DISCLOSURES | June 22, 2023

Medscape

A 4-year-old male presented to an urgent care center with a 2-week history of runny nose and cough. The treating clinician suspected a postviral cough, but the child's mother was unconvinced. Testing for SARS-CoV-2, influenza, and respiratory syncytial virus performed earlier in the week at the pediatrician's office was negative. At the mother's insistence, an expanded respiratory panel was ordered and revealed a surprising result: *Bordetella parapertussis*.

Just like *B. pertussis*, *B. parapertussis* can cause a prolonged cough illness characterized by coughing paroxysms, whoop, and posttussive emesis. Testing is the only way to reliably distinguish between the two infections. In general, disease due to *B. parapertussis* tends to be milder than typical pertussis and symptoms usually don't last as long. In one study, 40% of people with *B. parapertussis* had no symptoms. *B. parapertussis* does not produce pertussis toxin and this may affect disease severity. Rarely, children can be coinfected with both *B. pertussis* and *B. parapertussis*.

Kristina A. Bryant, MD

The burden of *B. parapertussis* in the United States is not well described because only pertussis cases caused by *B. pertussis* are reportable to the Centers for Disease Control and Prevention. Nevertheless, some states include cases in public reporting and outbreaks have been reported. Historically, disease has been cyclical, with peaks in cases every 4 years and no seasonality.

Summary of Observed Phenomena

- COVID-19 pandemic restrictions (travel bans, mask-wearing, lockdowns, social distancing, etc.) were associated with a broad decline of many other respiratory pathogens
- Loosening/lifting of restrictions is/was associated with pathogen return
- Effects of control measures and relaxation varied btw. pathogens and phases
- However, pathogens did not return all at once
- Non-enveloped viruses (RV/EV, AdV) returned first
- RSV had early out-of-season peaks – straining children's hospitals
- Influenza A returned late – probably travel-associated (South. Hemisph.)
- Several viruses (RV/EV, RSV, AdV) returned to > than pre-pandemic levels
- Pertussis remains absent; parapertussis has a surge; Mpn starts returning

An ‘Immunity Debt’ may have arisen

Disponible en ligne sur
ScienceDirect
www.sciencedirect.com
Elsevier Masson France
EM|consulte
www.em-consulte.com

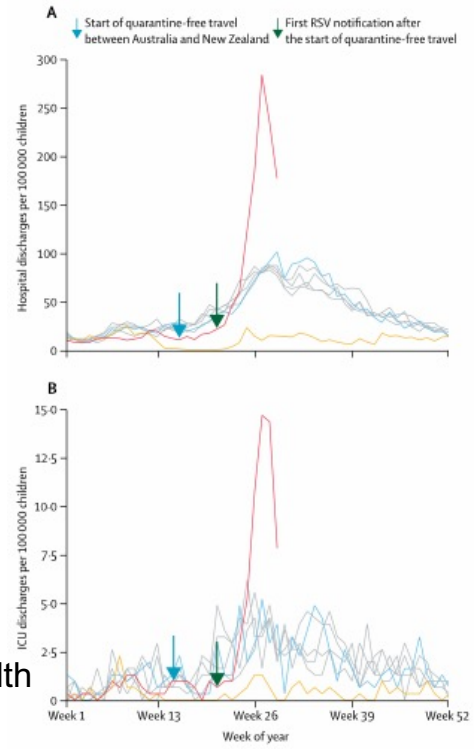
Review Infect Dis Now. 2021; 51(5): 418-23

Pediatric Infectious Disease Group (GPIP) position paper on the immune debt of the COVID-19 pandemic in childhood, how can we fill the immunity gap?

Robert Cohen[a,b,c,d,e], Marion Ashman[a,f], Muhamed-Kheir Taha[g], Emmanuelle Varon[h], François Angoulvant[e,i,j], Corinne Levy[a,b,c,d,e,*], Alexis Rybak[a,d,e], Naim Ouldali[a,d,e,j,k], Nicole Guiso[l], Emmanuel Grimprel[e,m]

Respiratory syncytial virus: paying the immunity debt with interest

*Lee Hatter, Allie Eathorne, Thomas Hills, Pepa Bruce, Richard Beasley
lee.hatter@mrinz.ac.nz
Medical Research Institute of New Zealand, New Zealand (LH, AE, TH, PB, RB); Auckland District Health Board, New Zealand (TH); Capital and Coast District Health Board, New Zealand (RB)



Lancet Child Adolesc Health 2021 Dec; 5(12): e44-e45

The Guardian

Tess McClure *in Christchurch*
@tessairini

Thu 8 Jul 2021 05.50 BST

New Zealand children falling ill in high numbers due to Covid ‘immunity debt’

Doctors say children haven’t been exposed to range of bugs due to lockdowns, distancing and sanitiser and their immune systems are suffering

The Wellington hospital in New Zealand. The city has 46 children hospitalised with respiratory illnesses. Photograph: Dave Lintott/REX/Shutterstock

WORLD

Post-Covid-19, World Risks Having to Pay Off ‘Immunity Debt’

Many people had little exposure to common viruses during social distancing, meaning bugs could spread more quickly once countries reopen

By Miho Inada Follow

THE WALL STREET JOURNAL.
June 28, 2021 5:30 am ET

Concept of 'Immunity Debt'

- Children who were born, and/or raised from young, were not exposed to many pathogens during COVID-19 pandemic restrictions
- There are many different resp. viruses & bacteria (e.g. Rhinovirus >100 types)
- Similar for gastrointestinal pathogens
- Children are now non-immune to many pathogens
- Children who were not much exposed during restrictions are now exposed to returning pathogens
- Consequence – More frequent infections & infections at older than usual age

Possible Relationship to the 'Hygiene Hypothesis'

- Exposure to dirt and less harmful pathogens helps train immune system
- May also have preventative function against allergies

Why Old McDonald had a farm but no allergies: genes, environments, and the hygiene hypothesis

Michael Kabesch*,[1] and Roger P. Lauener†

*University Children's Hospital Munich, Germany; and †Division of Immunology, University Children's Hospital Zurich, Switzerland

Journal of Leukocyte Biology Volume 75, March 2004 **383**

Competing Hypotheses

Hypothesis 1 – Simple lack of exposure

- People not exposed to specific pathogens – lack of specific immunity
- Example: 1846 Faroe Islands measles outbreak – Measles had not been seen for >60 years, and no one <60 y/o had immunity – Over ~5 mo, 6100/7900 inhabitants fell ill, >100 died (https://time.com/5800558/coronavirus-human-civilization)

Hypothesis 2 – Lack of training of immune system

- See Hygiene Hypothesis – earlier slide
- Biologically very plausible, but concrete support is missing

Hypothesis 3 – COVID-19-induced immune dysregulation

- Some other viruses known to cause (mostly temp.) immune deficiency
- Some countries that had very little measures had big RSV surges
- Some measured immune parameters are different after COVID

Examples of Papers discussing Long COVID and Immune Dysregulation

JANUARY 20, 2023 | Editors' notes

Examining COVID-19's long-term effects on the innate immune system

by Karin Söderlund Leifler, Linköping University

Marie Larsson, Professor of virology at Linköping University. Credit: Cecilia Säfström/Linköpi...

The more severe the COVID-19 infection, the slower the recovery of immune cells, such as the dendritic cells, which are necessary for the activation of the immune system. This is shown by researchers at Linköping University in Sweden in a new study published in *Frontiers in Immunology*. Six months after severe COVID-19, a negative impact on several types of immune cells can still be seen.

https://medicalxpress.com/news/2023-01-covid-long-term-effects-innate-immune.html

Letter | Published: 13 January 2022

Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection

Chansavath Phetsouphanh, David R. Darley, Daniel B. Wilson, Annett Howe, C. Mee Ling Munier, Sheila K. Patel, Jennifer A. Juno, Louise M. Burrell, Stephen J. Kent, Gregory J. Dore, Anthony D. Kelleher & Gail V. Matthews

Nature Immunology **23**, 210–216 (2022) | Cite this article

Abstract

A proportion of patients surviving acute coronavirus disease 2019 (COVID-19) infection develop post-acute COVID syndrome (long COVID (LC)) lasting longer than 12 weeks. Here, we studied individuals with LC compared to age- and gender-matched recovered individuals without LC, unexposed donors and individuals infected with other coronaviruses. Patients with LC had highly activated innate immune cells, lacked naive T and B cells and showed elevated expression of type I IFN (IFN-β) and type III IFN (IFN-λ1) that remained persistently high at 8 months after infection. Using a log-linear classification model, we defined an optimal set of analytes that had the strongest association with LC among the 28 analytes measured. Combinations of the inflammatory mediators IFN-β, PTX3, IFN-γ, IFN-λ2/3 and IL-6 associated with LC with 78.5–81.6% accuracy. This work defines immunological parameters associated with LC and suggests future opportunities for prevention and treatment.

Article | Open Access | Published: 11 March 2022

ACE2-independent infection of T lymphocytes by SARS-CoV-2

Xu-Rui Shen, Rong Geng, Qian Li, Ying Chen, Shu-Fen Li, Qi Wang, Juan Min, Yong Yang, Bei Li, Ren-Di Jiang, Xi Wang, Xiao-Shuang Zheng, Yan Zhu, Jing-Kun Jia, Xing-Lou Yang, Mei-Qin Liu, Qian-Chun Gong, Yu-Lan Zhang, Zhen-Qiong Guan, Hui-Ling Li, Zhen-Hua Zheng, Zheng-Li Shi, Hui-Lan Zhang, Ke Peng & Peng Zhou

Signal Transduction and Targeted Therapy **7**, Article number: 83 (2022) | Cite this article

Abstract

SARS-CoV-2 induced marked lymphopenia in severe patients with COVID-19. However, whether lymphocytes are targets of viral infection is yet to be determined, although SARS-CoV-2 RNA or antigen has been identified in T cells from patients. Here, we confirmed that SARS-CoV-2 viral antigen could be detected in patient peripheral blood cells (PBCs) or postmortem lung T cells, and the infectious virus could also be detected from viral antigen-positive PBCs. We next prove that SARS-CoV-2 infects T lymphocytes, preferably activated CD4 + T cells in vitro. Upon infection, viral RNA, subgenomic RNA, viral protein or viral particle can be detected in the T cells. Furthermore, we show that the infection is spike-ACE2/TMPRSS2-independent through using ACE2 knockdown or receptor blocking experiments. Next, we demonstrate that viral antigen-positive T cells from patient undergone pronounced apoptosis. In vitro infection of T cells induced cell death that is likely in mitochondria ROS-HIF-1a-dependent pathways. Finally, we demonstrated that LFA-1, the protein exclusively expresses in multiple leukocytes, is more likely the entry molecule that mediated SARS-CoV-2 infection in T cells, compared to a list of other known receptors. Collectively, this work confirmed a SARS-CoV-2 infection of T cells, in a spike-ACE2-independent manner, which shed novel insights into the underlying mechanisms of SARS-CoV-2-induced lymphopenia in COVID-19 patients.

Conclusions

- Many pathogens disappeared during pandemic restrictions & are now reappearing
- Pathogen absence is an unusual state, not their presence
- COVID-19 pandemic created a ‘human experiment’ unprecedented in history
- Pathogen return is part of return to ‘normality’
- Reappearance is not homogeneous – we see irregular and out-of-season return of pathogens after pandemic ‘bottleneck’
- We also seem to see more serious presentations, esp. in young children, and older than usual age at presentation
- Which of the **hypotheses** exactly apply is currently unclear – possibly combination
- Situation is very complicated – Need for ongoing research

www.webbertraining.com/schedulep1.php

August 24, 2023	**ARE THERE OTHER POSSIBLE SOLUTIONS FOR CONTROLLING THE SPREAD OF CPE?** Speaker: **Dr. Jean–Ralph Zahar**, French-Muslim Hospital, Bobigny, France
September 13, 2023	*(South Pacific Teleclass)* **HUMAN AMR SURVEILLANCE - WHERE ARE WE NOW AND WHERE SHOULD WE BE HEADING?** Speaker: **Prof. Paul Turner**, Oxford University Centre for Tropical Medicine and Global Health, Thailand
September 21, 2023	**FACTORS INFLUENCING OPPORTUNISTIC PREMISE PLUMBING PATHOGENS** Speaker: **Prof. Joseph O. Falkinham III**, Virginia Tech University
September 26, 2023	*(FREE European Teleclass)* **DATA QUALITY INDICATORS IN NATIONAL TB INFECTION CONTROL PROGRAMS: READING BETWEEN THE LINES** Speaker: **Dr. Eltony Mugomeri**, Africa University, Zimbabwe
September 28, 2023	*(FREE Teleclass)* **MENTAL HEALTH, HEALTHY LIFESTYLE BEHAVIORS AND ORGANIZATIONAL WELLNESS SUPPORT DURING THE COVID-19 PANDEMIC IN INFECTION PREVENTION PROFESSIONALS: IMPLICATIONS FOR ACTION** Speaker: **Bernadette Mazurek Melnyk**, The Ohio University
October 12, 2023	**MANAGEMENT PRACTICES TO SUPPORT INFECTION PREVENTION** Speaker: **Ann Scheck McAlearney**, Ohio State University College of Medicine

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