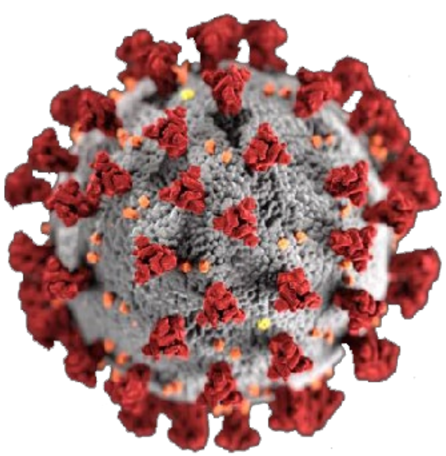
Health Watch USA Annual Conference, 29 Aug. 2025, Webinar

Unusual re-emergence of respiratory pathogens after lifting of COVID-19 restrictions in Singapore



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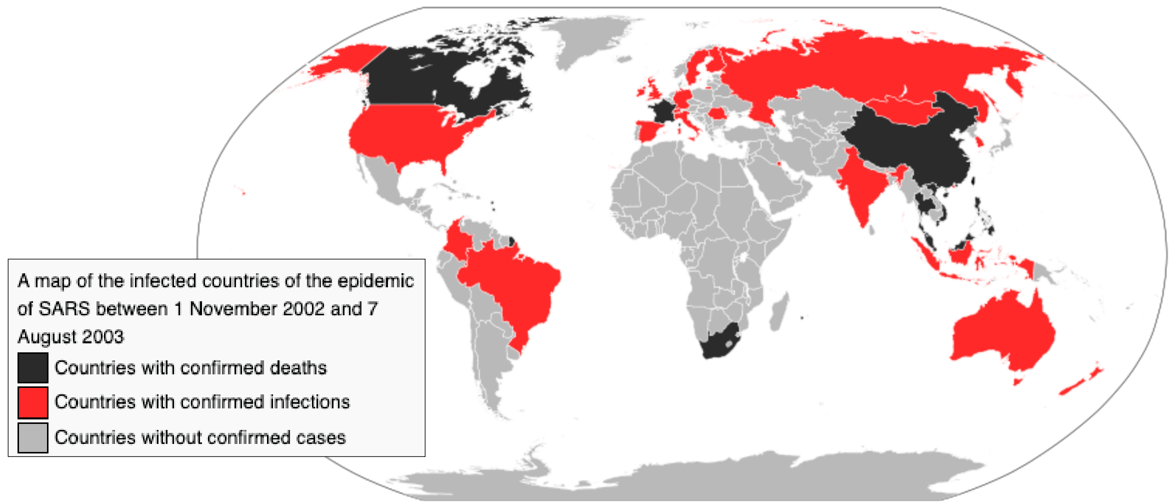
Background -- Singapore was hit quite badly by the 2003 SARS outbreak

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

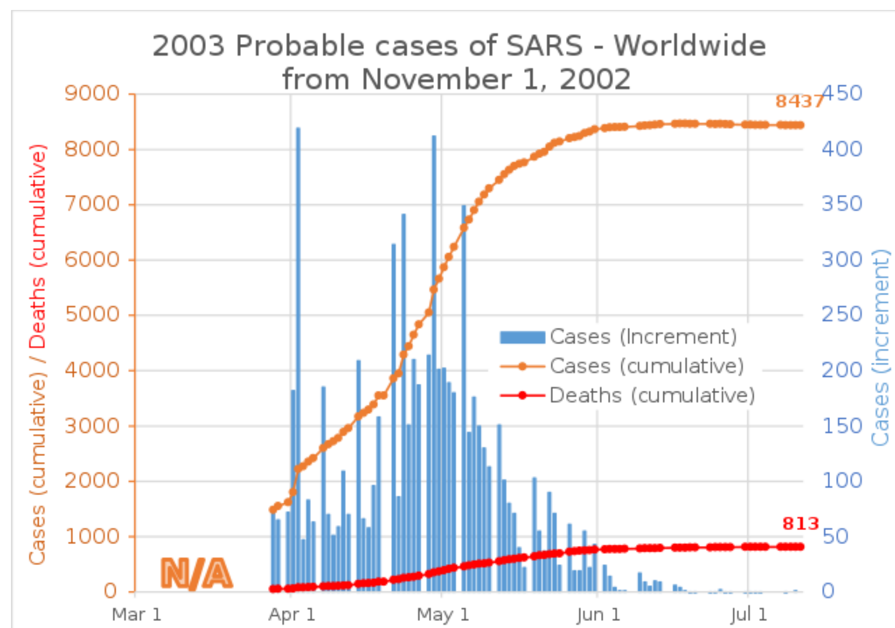
Country or region	Cases	Deaths	Fatality (%)
Mainland China[a]	5,327	349	6.6
Hong Kong	1,755	299	17.0
Taiwan[b][6][7]	346	73	21.1
Canada	251	44	17.5
Singapore	238	33	13.9
Vietnam	63	5	7.9
Total excluding Mainland China	2,769	454	16.4
Total (29 territories)	**8,096**	**811**	**9.6**

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

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	
	Jun	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	
	Mar	Transition Phase	• Further easing of measures • Outdoor mask-wearing no longer mandatory	
	Apr	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)

BioFire FilmArray RP 2.1 multiplex PCR

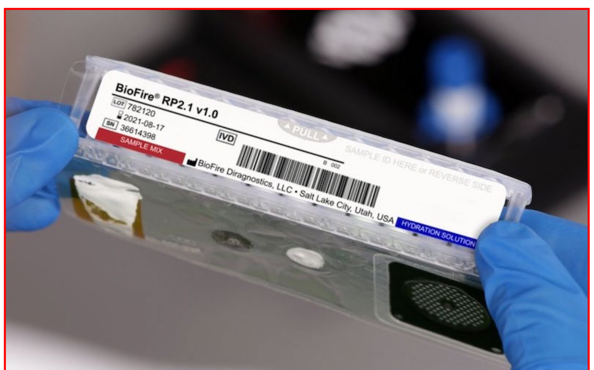
Rapid multiplex PCR with 19 respiratory pathogens & SARS-CoV-2 (~45 min)

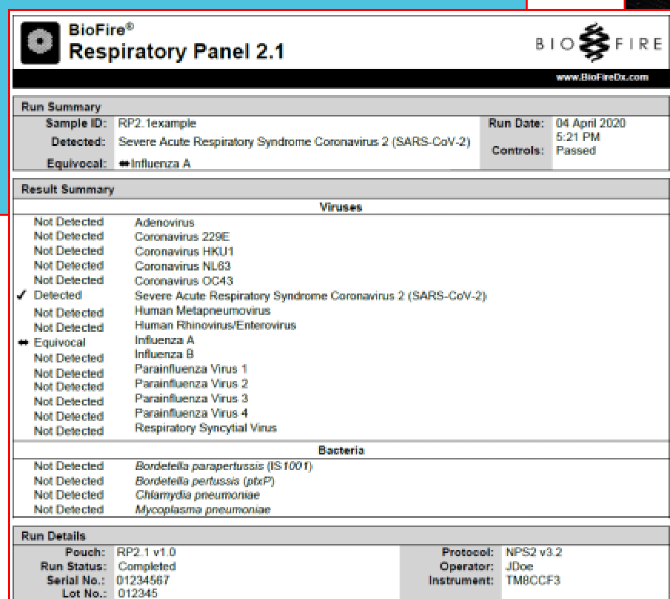
VIRUSES:

- 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

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 (IS1001)*
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		

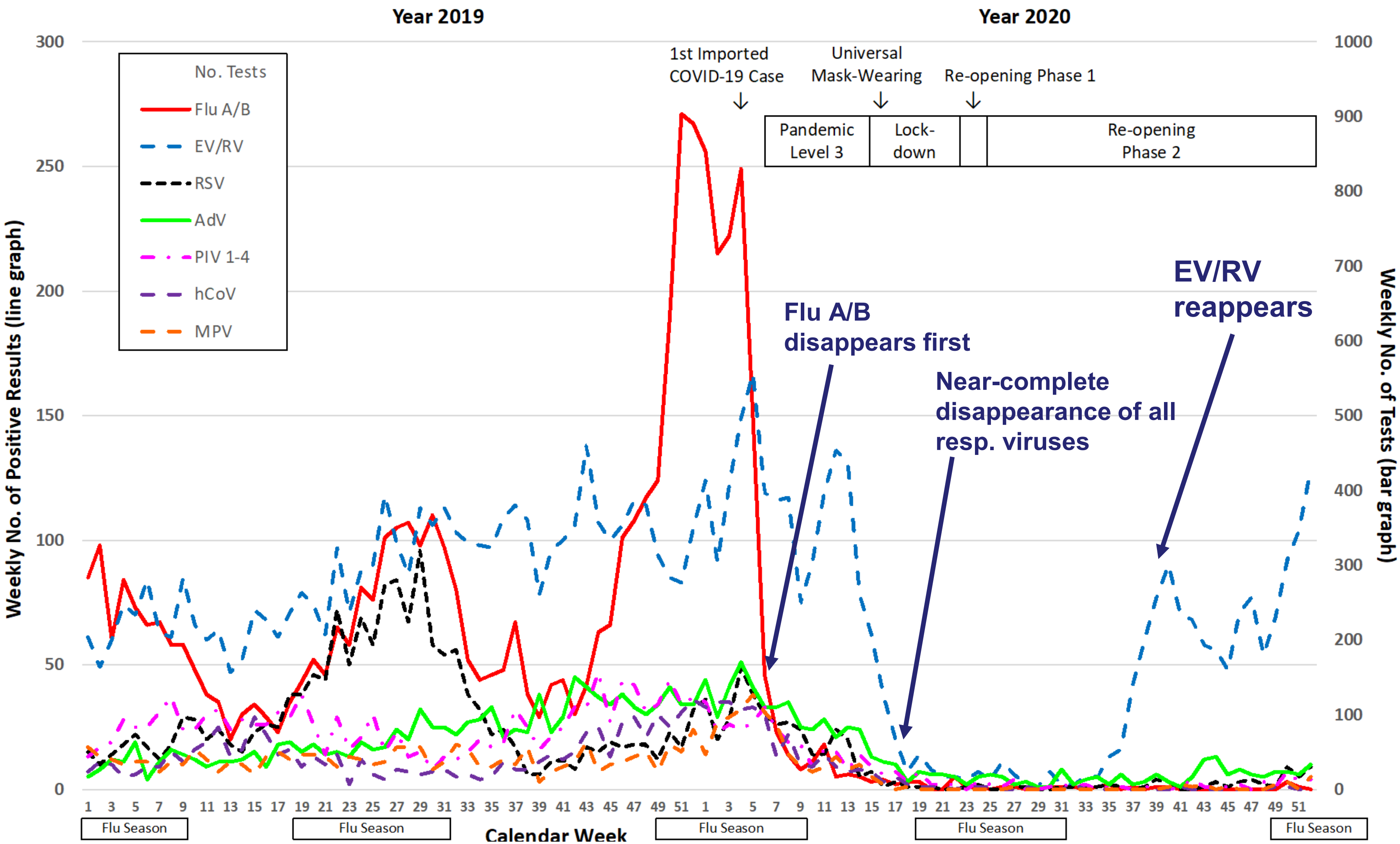
Images:
Manufacturer Websites; M. Maiwald

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



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

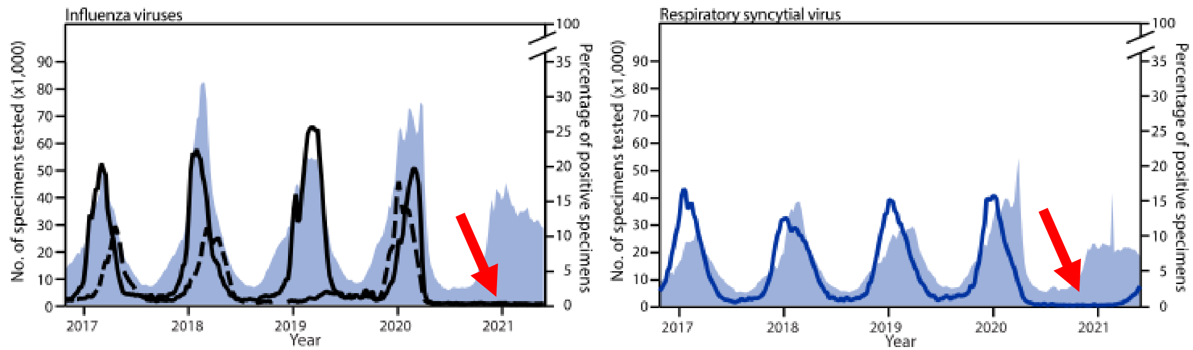
Our Australian hospital tested almost 22 000 symptomatic people over 11 weeks for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in a multiplex polymerase chain reaction (PCR) assay. Following travel bans and physical distancing, SARS-CoV-2 and other respiratory viruses diagnoses fell dramatically. 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

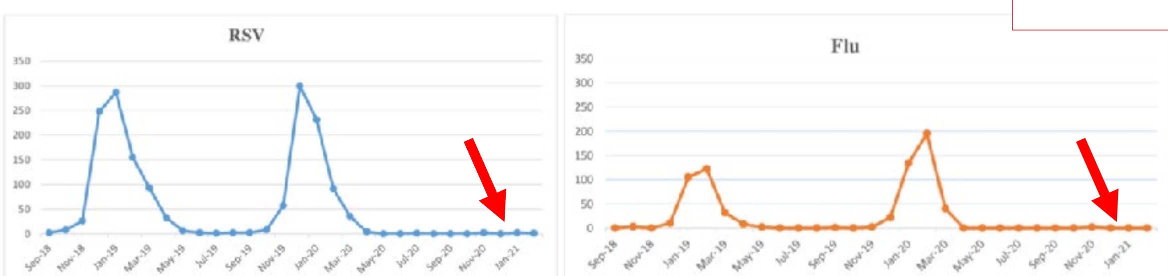
Pediatr. Pulmonol. 2020;55:2233-4

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*

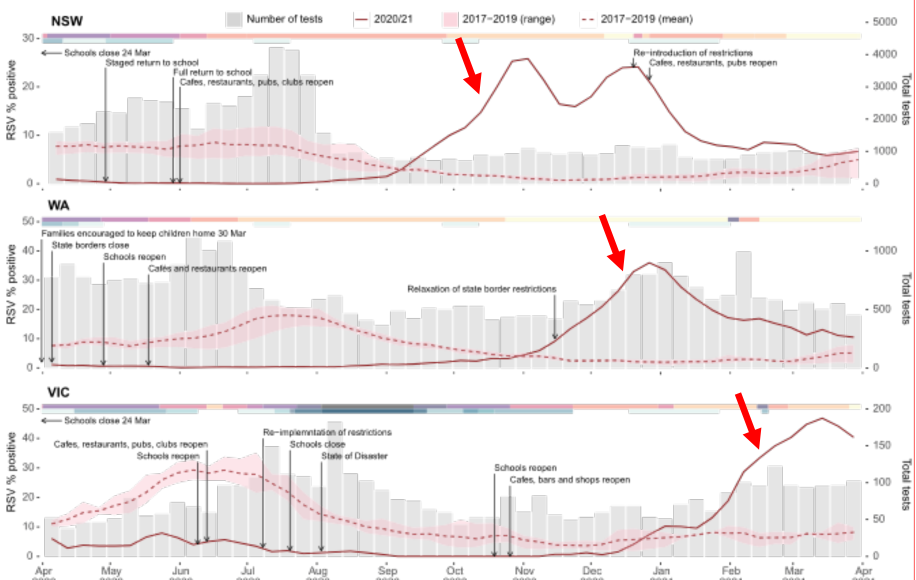
However, what happens thereafter?

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*

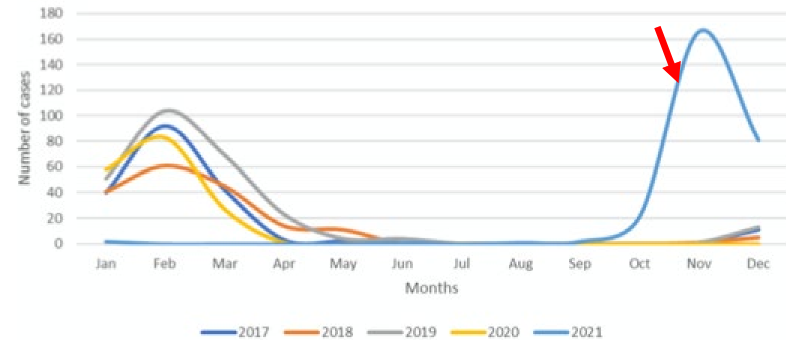


Article

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,*]



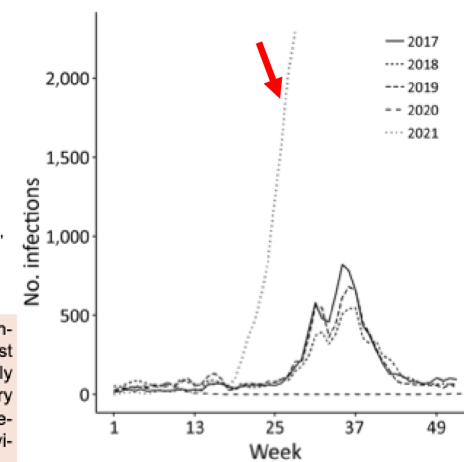
Resurgence of Respiratory Syncytial Virus Infections during COVID-19 Pandemic, Tokyo, Japan

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

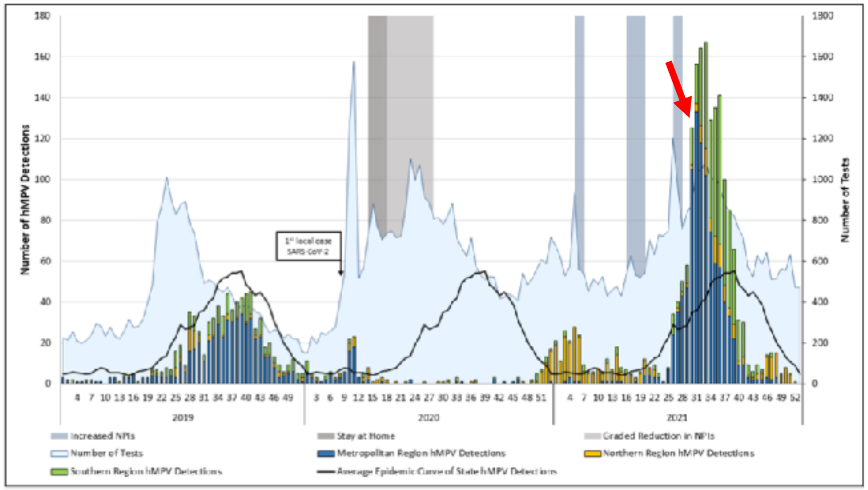
Thereafter (Continued)

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

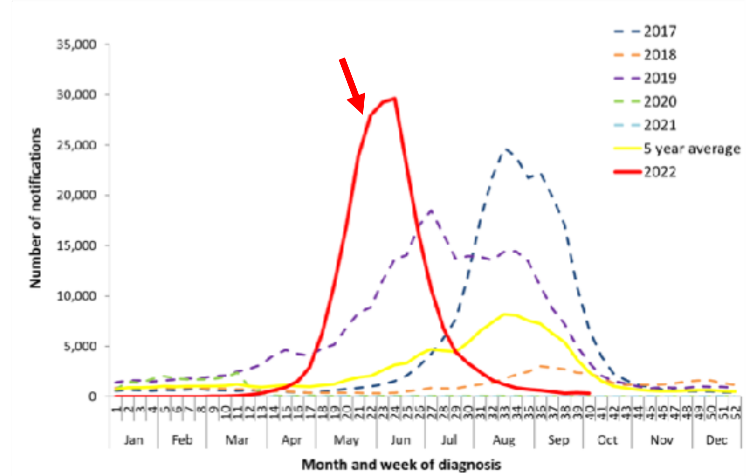
Department of Health and Aged Care

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 re-appearing

KKH Data, unpublished

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

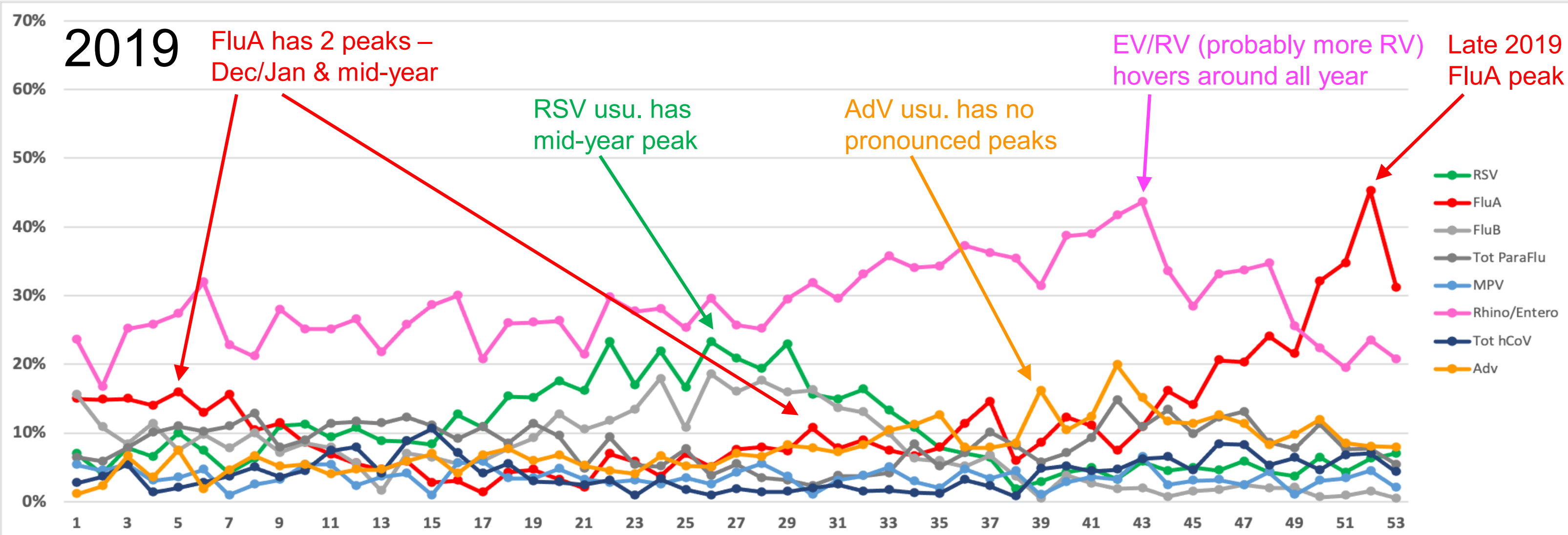
https://p.dw.com/p/47Mns

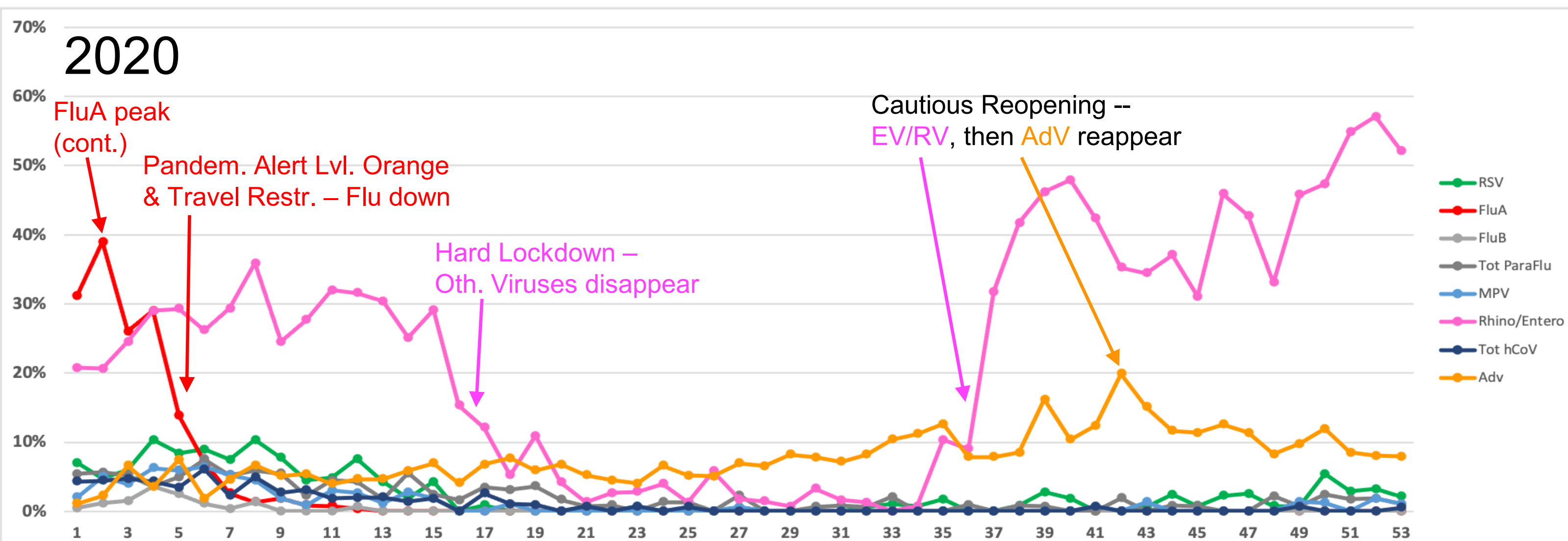
Although data indicate that the omicron variant has been less severe for children, they still face risks — including long COVID or inflammatory syndrome. Experts are urging prioritizing kids' well-being.

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

DEUTSCHE WELLE (Feb. 2022)

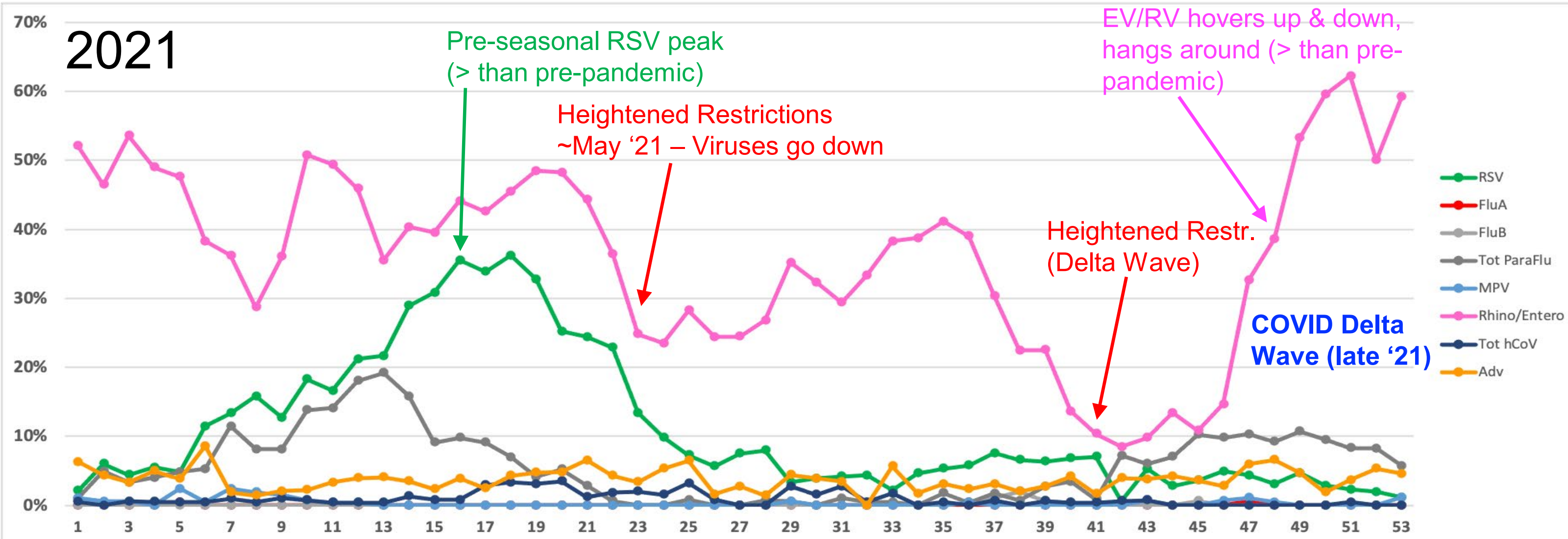
Percentages of respiratory viruses 2019-2020

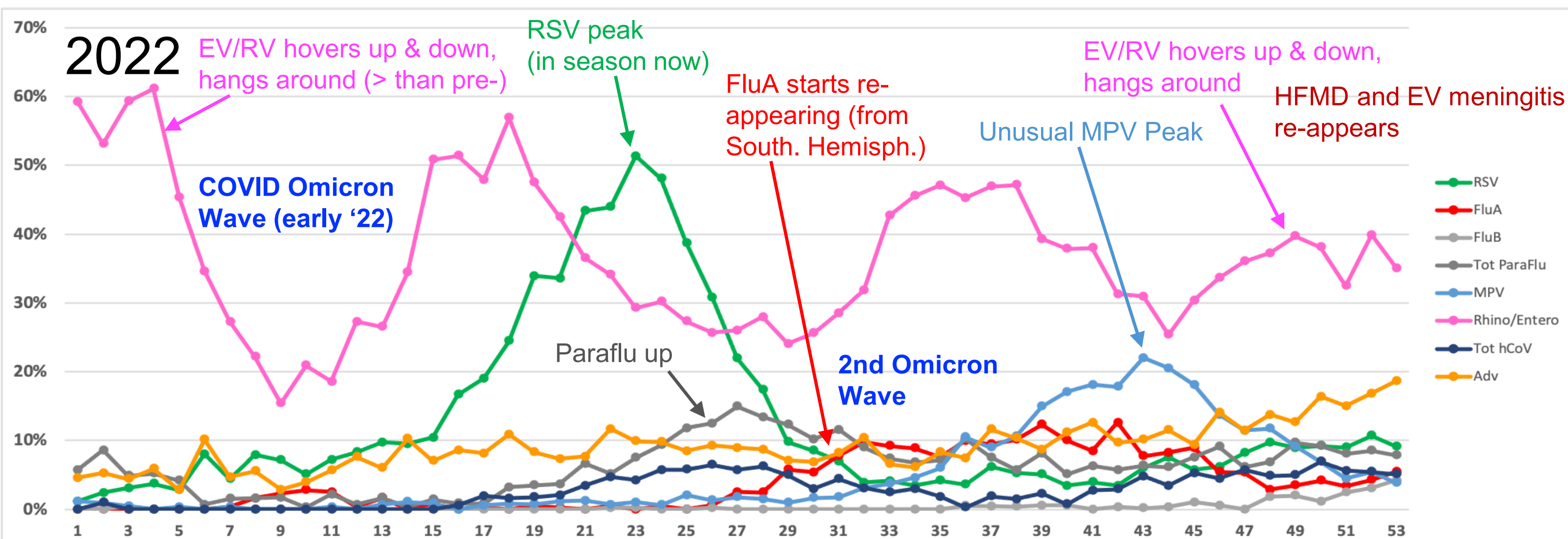




- EV/RV and AdV are non-enveloped viruses, i.e. more hardy in the environment
- Reopening still with mandatory mask-wearing, but increasing social contacts

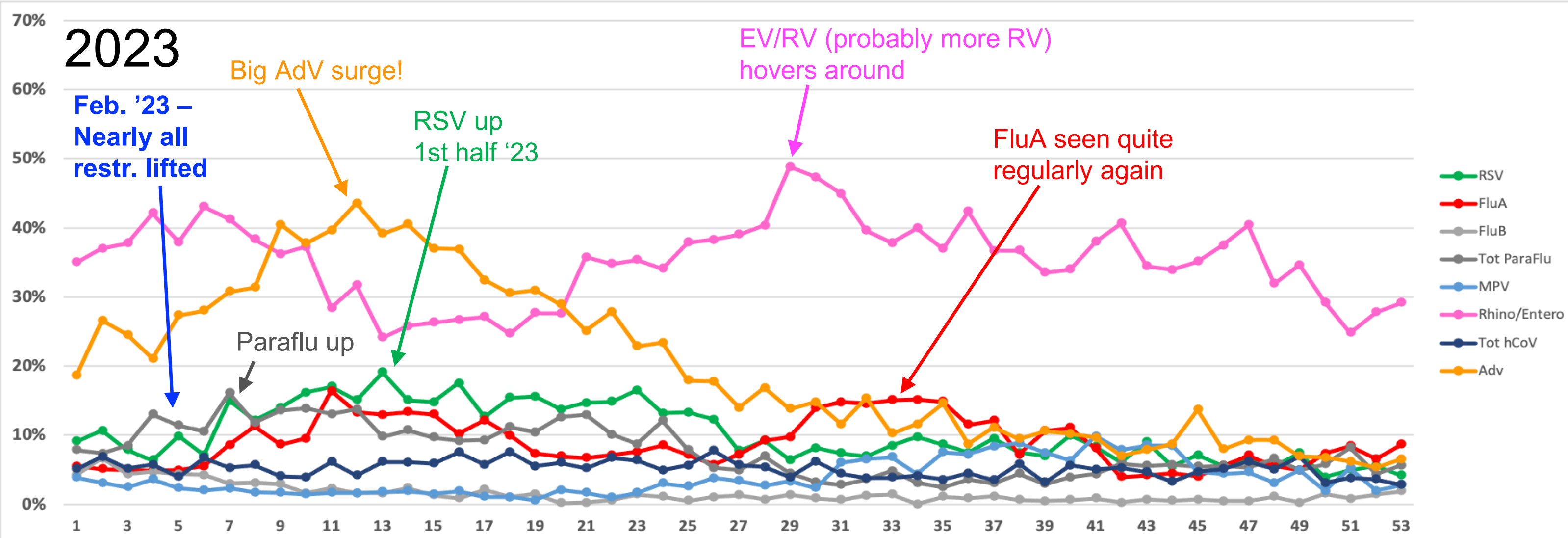
Percentages of respiratory viruses 2021-2022

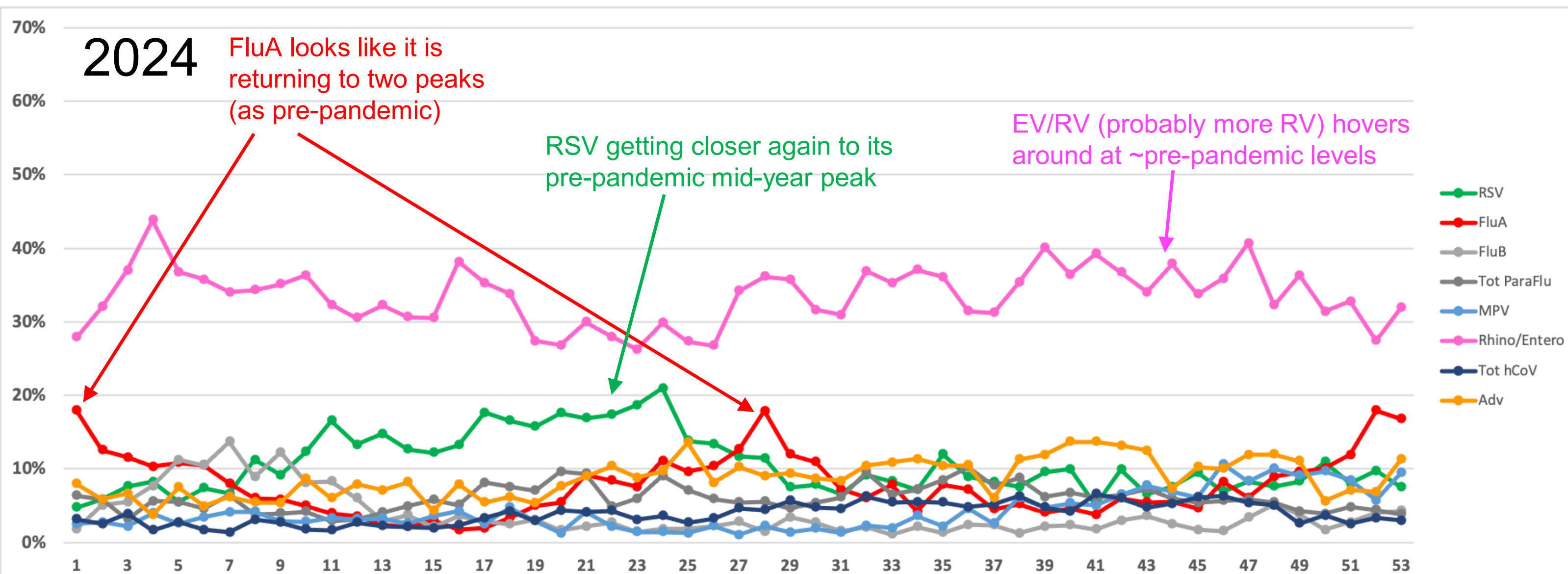




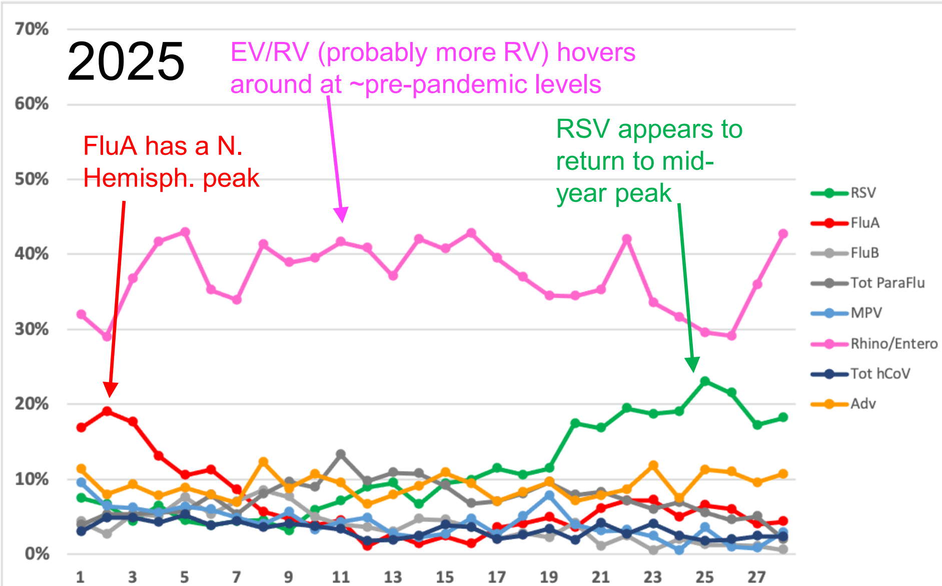
- 2021 had a pre-seasonal RSV peak, higher than pre-pandemic RSV peaks
- FluA re-appears 2nd half 2022; EV/RV higher than pre-pandemic; HFMD & EV men. re-appears

Percentages of respiratory viruses 2023-2024





Percentages of respiratory viruses 2025

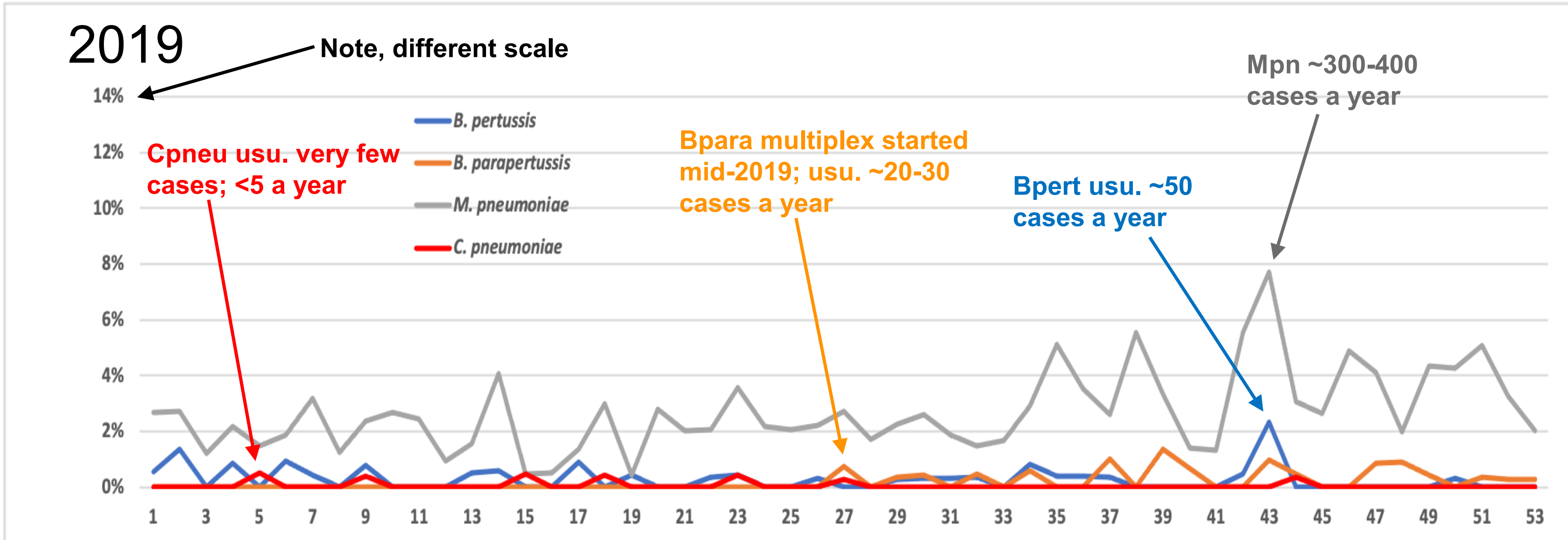


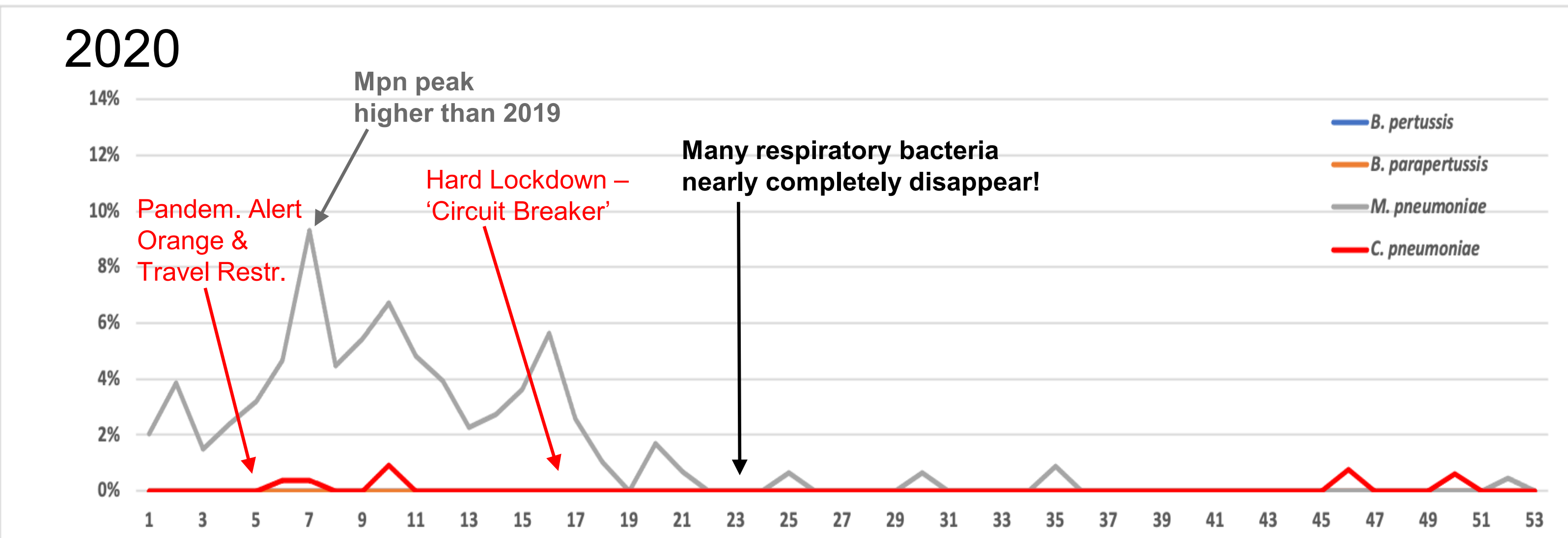
- Virus patterns in 2025 appear to be returning to near pre-pandemic levels
- Includes FluA Northern Hemisphere Winter peak
- Includes RSV mid-year peak

Summary of respiratory viruses 2019-2025

- In total, >120,000 samples tested btw. 2019-6/2025 (~90% paeds. pats.)
- Resp. viruses follow COVID-related restrictions, but not all in the same way
- EV/RV and AdV returned first – both non-enveloped viruses – at increasing social contacts with still mandatory mask-wearing – suggests partial role of contact transmission
- Subsequent heightened (e.g. Omicron wave) and/or lowered restrictions – viruses go up and down accordingly
- Some countries had RSV peaks that strained children's hospitals in late 2020; SG in early 2021
- Several viruses (AdV, MPV) had unusual phases of high activity; much higher than pre-pandemic
- FluA returned only 2nd half of 2022; probably from Southern Hemisphere
- EV/RV overall commonest virus; keeps hovering up and down, 2021-2023 at greater than pre-pandemic levels, 2024 & 2025 near pre-pandemic levels

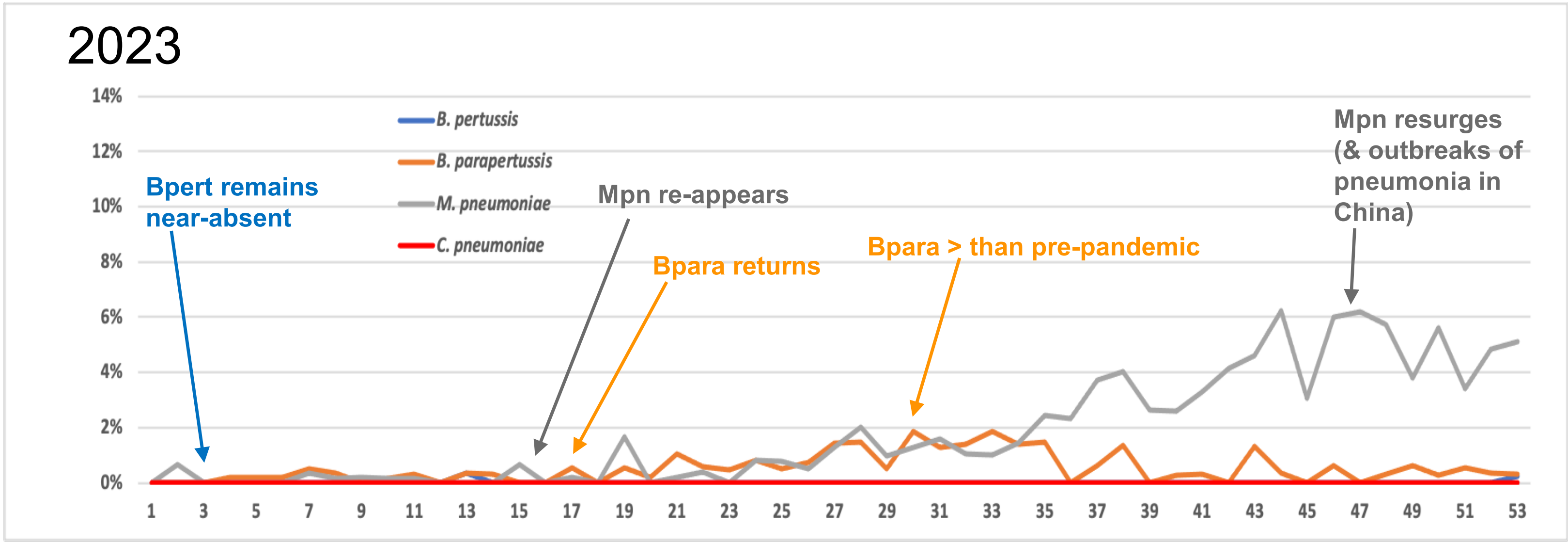
Percentages of respiratory bacteria 2019-2020

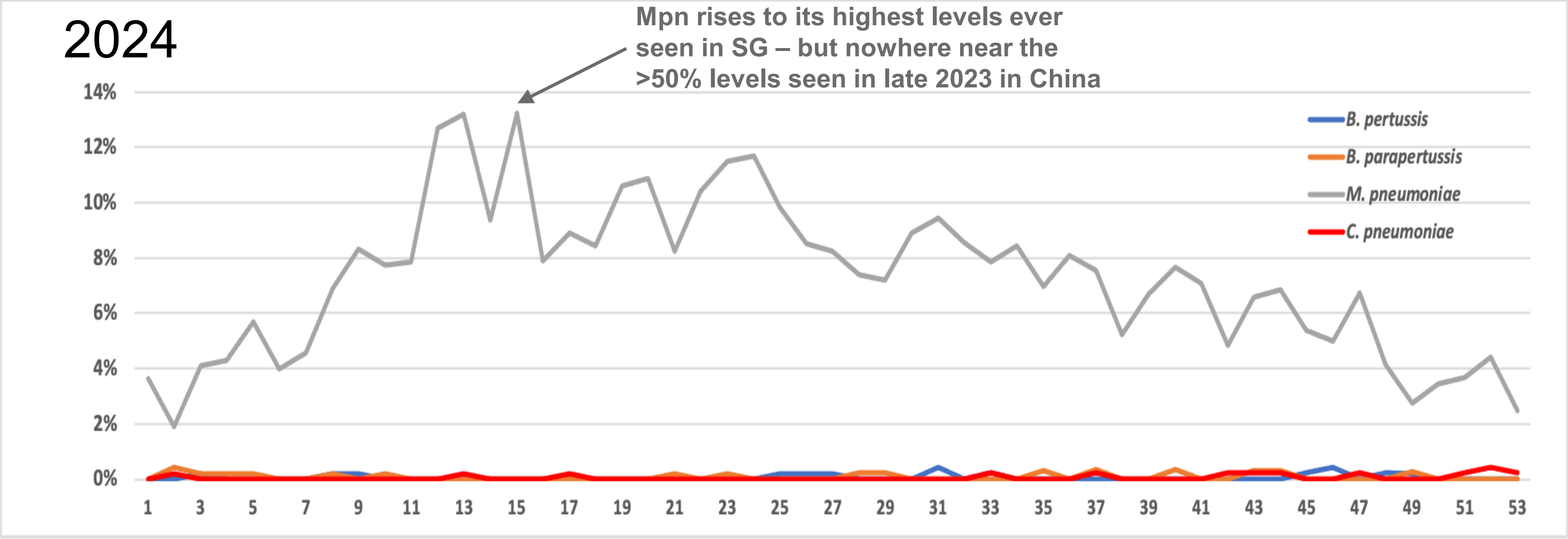




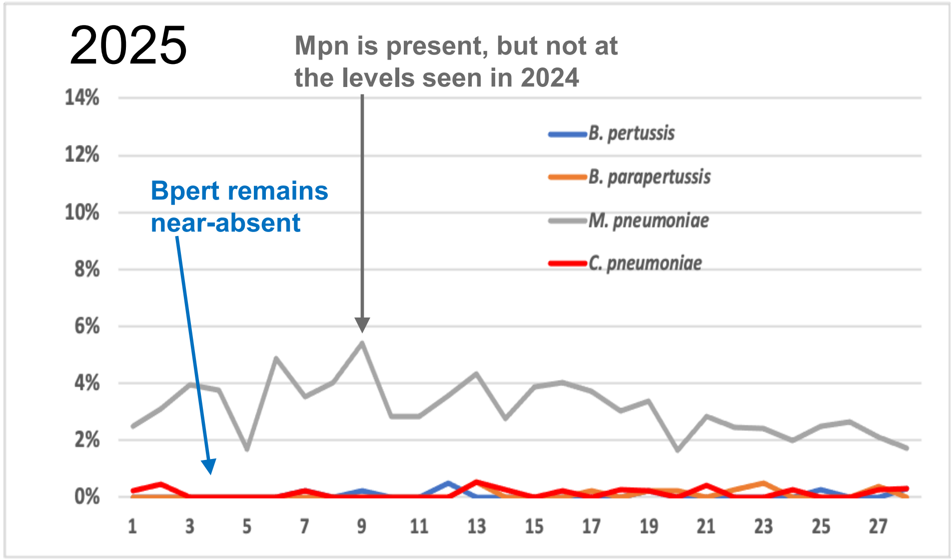
Then -- 2021 & 2022 – near-absence of resp. bacteria (not shown)

Percentages of respiratory bacteria 2023-2024





Percentages of respiratory bacteria 2025



- *Mycoplasma pneumoniae* hovers around at near pre-pandemic levels
- *B. pertussis*, *B. parapertussis* & *C. pneumoniae* remain near-absent
- *B. parapertussis* prevalence from 2023 is NOT repeated

Summary of respiratory bacteria 2019-2025

- Resp. bacteria disappeared similarly to viruses in early pandemic
- 2021 & 2022 – near-absence of resp. bacteria (not shown)
- Mpn remained near-absent until Apr. 2023 (same in many countries)
- Late 2023 saw a big Mpn resurgence – also huge case numbers in China (>50% of all specimens pos. for Mpn and >90% genotypic macrolide res.)
- Bpert remained near-absent throughout, only 5 cases btw. 2020-23; slow return of 14 cases in 2024, a few cases in 2025
- Bpara returned around Mar. 2023; greater numbers than pre-pandemic (>100 cases in 2023) – but trend did not continue in 2024 & 2025
- Cpneu had very few cases pre- and post-pandemic – no change
- Slight uptick in invasive pneumococcal disease in late 2024 (anecdotal; data not shown/analysed)

Similar Trends for Bacterial Illnesses

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

Journal of Infection 81 (2020) e19–e21

Rachel HF Lim
Angela Chow
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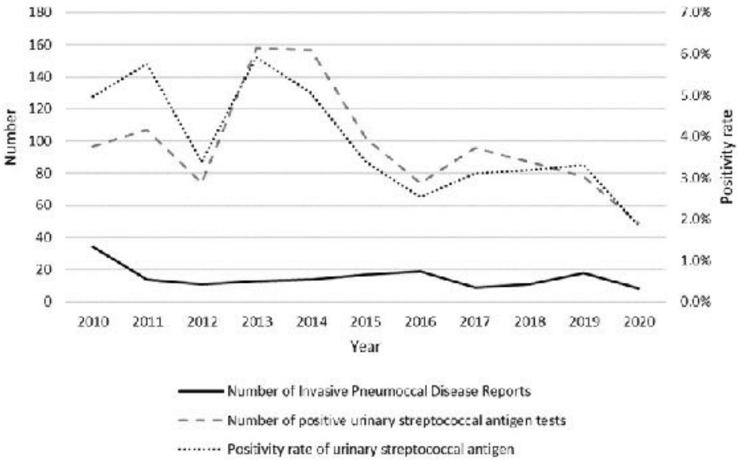
E-mail address: hanleyho@gmail.com (H.J. Ho)



Bordetella pertussis

- KKH in pre-pandemic years >50 cases per year
- Last case seen March 2020
- 5 cases until 2023; 14 in 2024

Bordetella parapertussis

- Came back 2023

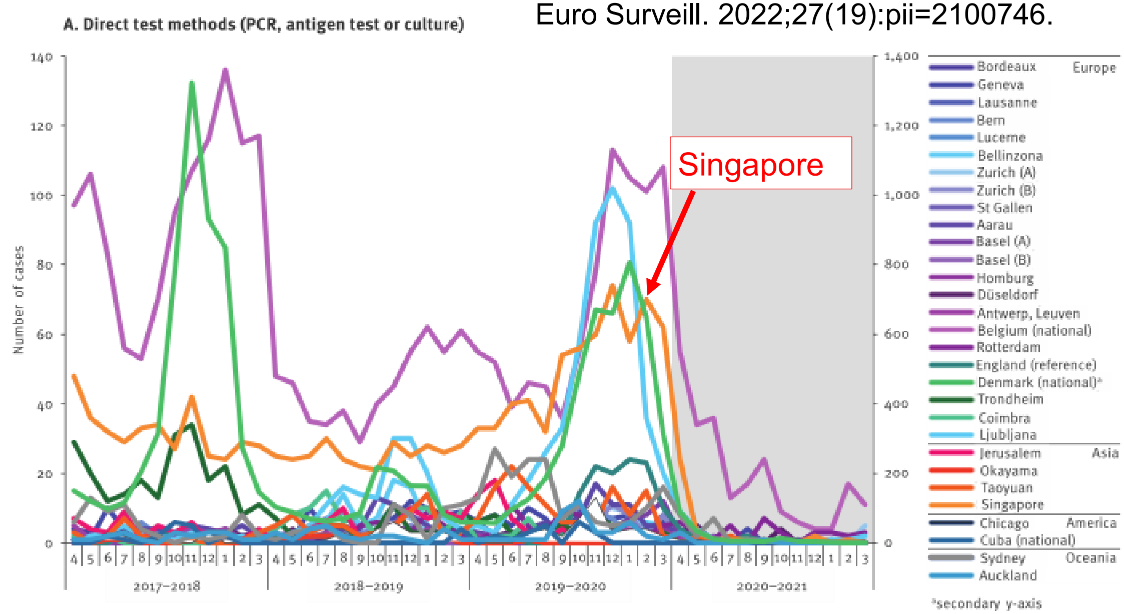
KKH Data, unpublished

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
patrick.meyersauteur@kispi.uzh.ch

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

Mycoplasma pneumoniae

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

*KKH, Singapore, as a study site

*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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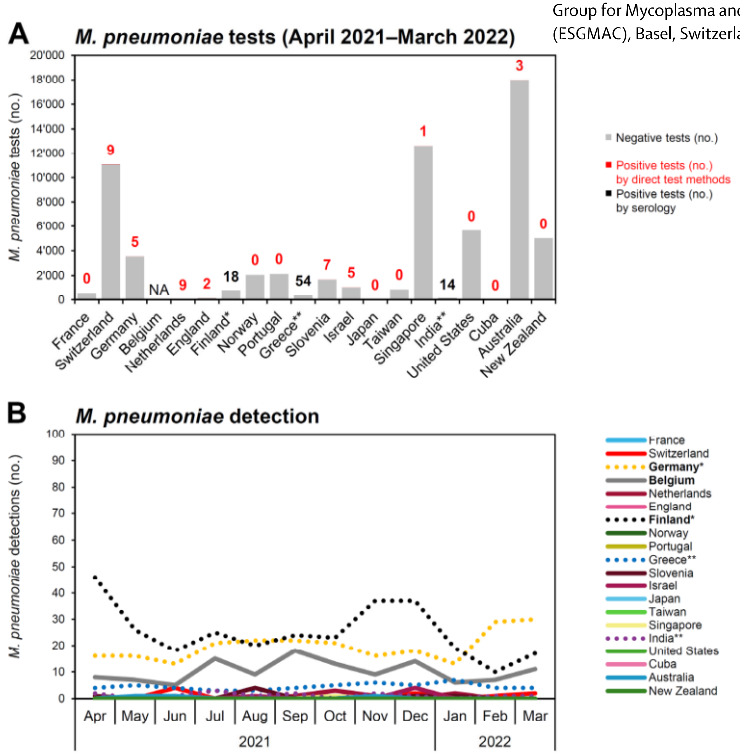
Published Online
August 11, 2022
https://doi.org/10.1016/S2666-5247(22)00190-2

www.thelancet.com/microbe Vol 3 December 2022



***Mycoplasma pneumoniae*: gone forever?**

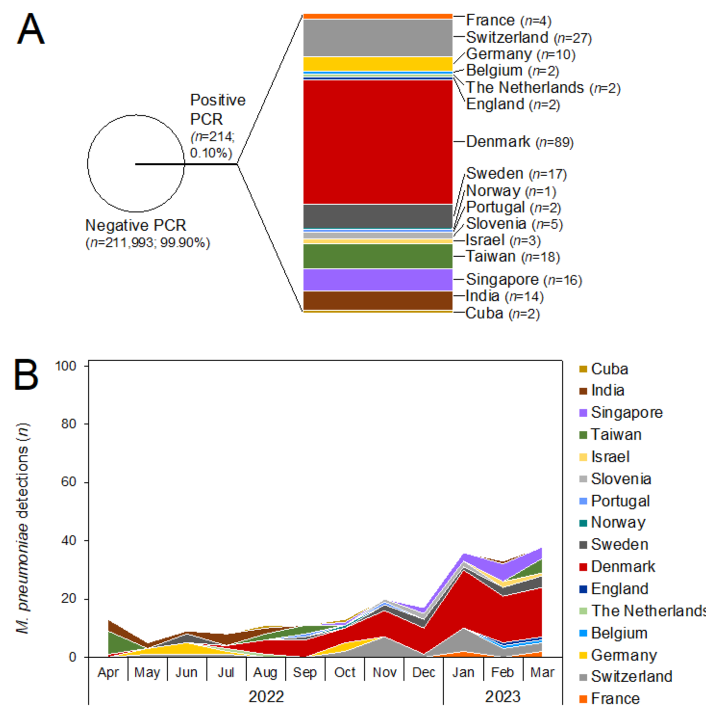
*KKH, Singapore, as a study site

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

Lancet Microbe 2023
Published Online
June 29, 2023
https://doi.org/10.1016/S2666-5247(23)00182-9

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



Mycoplasma pneumoniae

Mycoplasma pneumoniae: delayed re-emergence after COVID-19 pandemic restrictions

Patrick M Meyer Sauteur, Michael L Beeton, on behalf of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Mycoplasma and Chlamydia Infections (ESGMAC), and the ESGMAC Mycoplasma pneumoniae Surveillance (MAPS) study group†
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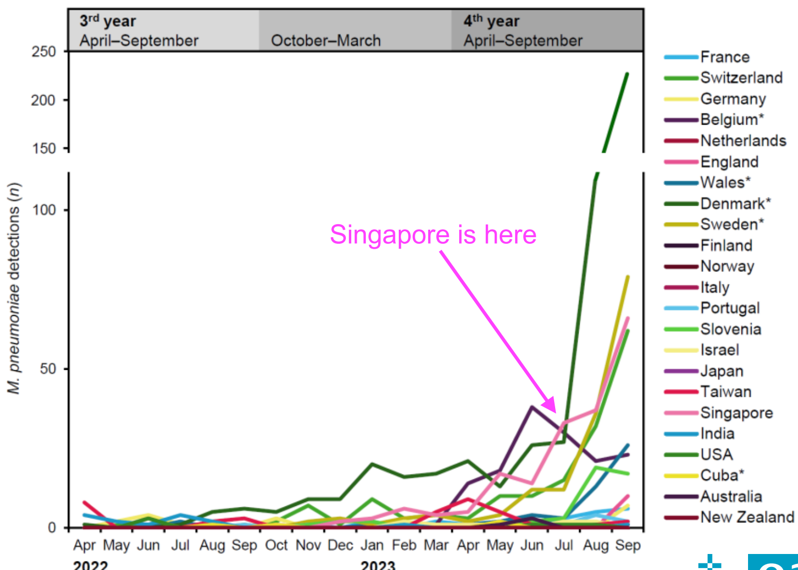
*KKH, Singapore, as a study site



Lancet Microbe 2024

Published Online
https://doi.org/10.1016/S2666-5247(23)00405-6

Pneumonia outbreaks due to re-emergence of *Mycoplasma pneumoniae*

Patrick M Meyer Sauteur, Michael L Beeton, on behalf of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Mycoplasma and Chlamydia Infections (ESGMAC), and the ESGMAC Mycoplasma pneumoniae Surveillance (MAPS) study group†
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Lancet Microbe 2024

Published Online
https://doi.org/10.1016/S2666-5247(23)00406-8

*KKH, Singapore, as a study site

Inclusion of late 2023 data from China!

Resurgence of *Mycoplasma pneumonia* by macrolide-resistant epidemic clones in China

*Heng Li, Shengkai Li, Huajiang Yang, *Zhengrong Chen, *Zhemin Zhou*
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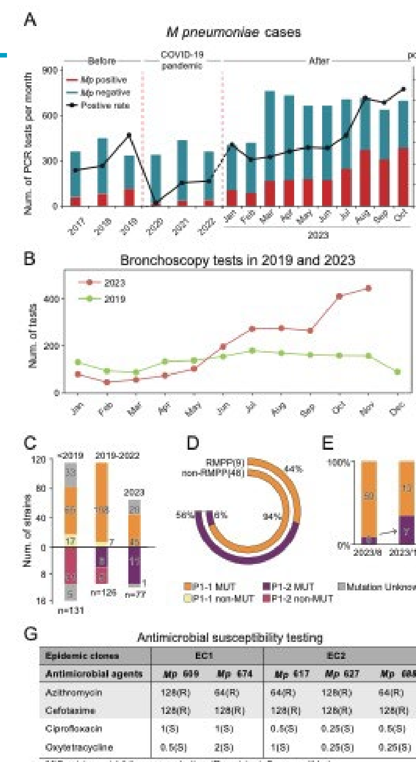
Key Laboratory of Alkene-Carbon Fibers-Based Technology & Application for Detection of Major Infectious Diseases, Pasteurien College, Suzhou Medical College, Soochow University, Suzhou 215123, China (HL, SL, HY, ZZ); Department of Respiratory Disease, Children's Hospital of Soochow University, Suzhou, China (ZC); MOE Key Laboratory of Geriatric Diseases and Immunology, Suzhou Key Laboratory of Pathogen Bioscience and Anti-infective Medicine, Suzhou Medical College, Soochow University, Suzhou, China (HL, SL, HY, ZZ); National Key Laboratory of Intelligent Tracking and Forecasting for Infectious Diseases, National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China (ZZ)



>50% of all tests pos.!!!

Few epi-demic clones!

High % of macrolide resistance!

Mycoplasma pneumoniae – Situation in China 2023

NEWS EXPLAINER | 27 November 2023

What's behind China's mysterious wave of childhood pneumonia?

Scientists expected a surge in respiratory disease, but what is happening in China is unusual.

By Gemma Conroy

nature

Parents wait for their children to be treated for respiratory disease in Chongqing, China. Credit: Costfoto/NurPhoto via Getty

Current *Mycoplasma pneumoniae* epidemic among children in Shanghai: unusual pneumonia caused by usual pathogen

Xiao-Bo Zhang[1] · Wen He[1] · Yong-Hao Gui[2] · Quan Lu[3] · Yong Yin[4] · Jian-Hua Zhang[5] · Xiao-Yan Dong[3] · Ying-Wen Wang[6] · Ying-Zi Ye[7] · Hong Xu[8] · Jia-Yu Wang[9] · Bing Shen[10] · Dan-Ping Gu[11] · Li-Bo Wang[1] · Yi Wang[12]

Received: 7 November 2023 / Accepted: 21 December 2023 / Published online: 17 January 2024

World Journal of Pediatrics (2024) 20:5–10
https://doi.org/10.1007/s12519-023-00793-9

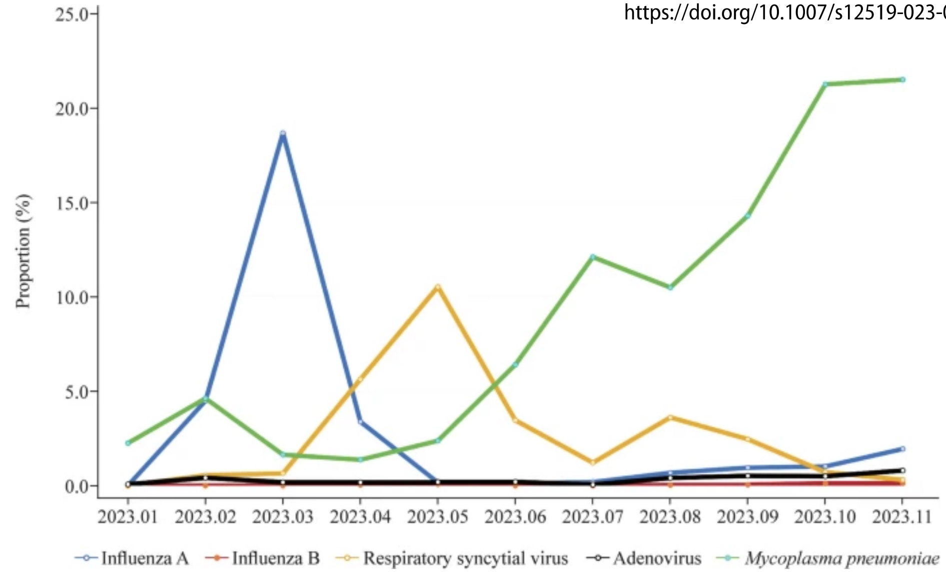


Chart of trends in the prevalence of influenza A, influenza B, respiratory syncytial virus, adenovirus and *Mycoplasma pneumoniae* among children with pneumonia in Shanghai between January 2023 and November 2023. The data were collected from children's specialized hospital in Shanghai

In 2023, through an ongoing respiratory pathogen surveillance system, we observed from mid-September onwards, an increase of respiratory illness among children aged ≤15 years presenting at hospital outpatient clinics in Beijing, China. Data indicated that illness was caused by multiple pathogens, predominantly *Mycoplasma pneumoniae*. Seasonality, periodicity and high prevalence of resistance to macrolide (30 of 30 strains sequenced with the A2063G mutation) were important characteristics of the *M. pneumoniae* epidemic, which resulted in a rise in consultations at specialised paediatric hospitals.

RAPID COMMUNICATION

Increase of respiratory illnesses among children in Beijing, China, during the autumn and winter of 2023

Cheng Gong[1,2,3] , Fang Huang[1,2,3] , Luodan Suo[1,2] , Xuejiao Guan[1] , Lu Kang[1,2] , Hui Xie[1] , Geng Hu[1] , Peng Yang[1,2] , Quanyi Wang[1,2]
1. Beijing Center for Disease Prevention and Control, Beijing, People's Republic of China
2. Beijing Research Center for Respiratory Infectious Diseases, Beijing, People's Republic of China
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Correspondence: Quanyi Wang (wangqy@bjcdc.org), Peng Yang (yangpengcdc@163.com)

Euro Surveill. 2024;29(2):pii=2300704. https://doi.org/10.2807/1560-7917.ES.2024.29.2.2300704

Mycoplasma pneumoniae & *Bordetella pertussis*

Mycoplasma pneumoniae: re-emergence and beyond

oa OPEN ACCESS

Lancet Microbe 2025
Published Online
https://doi.org/10.1016/j.lanmic.2025.101191

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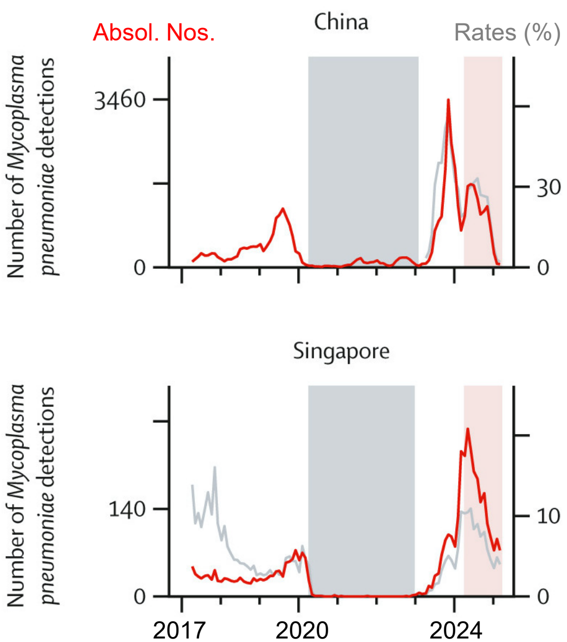
patrick.meyersauteur@kispi.uzh.ch



Resurgence of *Mycoplasma pneumoniae* infections in children: emerging challenges and opportunities

Ruben C.A. de Groot[a], *Bianca M.M. Streng*[b], *Louis J. Bont*[b], *Patrick M. Meyer Sauteur*[c] *and Annemarie M.C. van Rossum*[d]

Correspondence to Ruben C.A. de Groot, MD, PhD, Wytemaweg 80, 3000 CA Rotterdam, The Netherlands. Tel: +31 10 70 407 04;
e-mail: r.degroot@erasmusmc.nl

Curr Opin Infect Dis 2025, 38:000–000
DOI:10.1097/QCO.0000000000001126

KEY POINTS

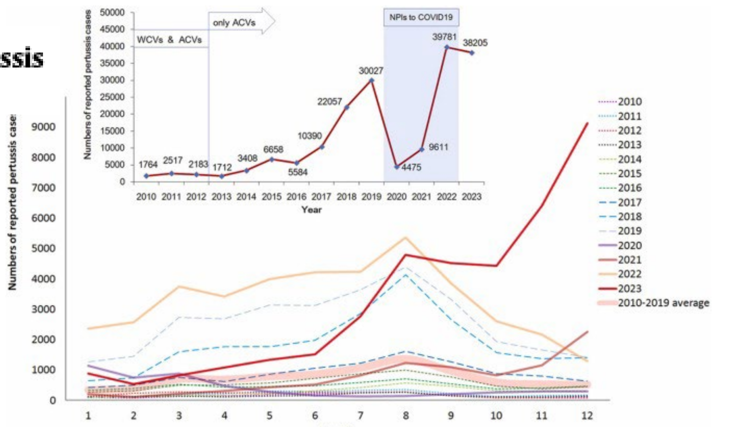
- *M. pneumoniae* infections have resurged globally in 2023–2024 after a period of exceptionally low *M. pneumoniae* prevalence related to COVID-19 nonpharmaceutical interventions.
- Tetracyclines or fluoroquinolones provide well tolerated and effective alternatives to macrolides, since resistance to macrolide antibiotics remains problematic, especially in East-Asia.
- While most *M. pneumoniae* infections remain mild, severe complications, including mucocutaneous manifestations, were frequently reported during the 2023–2024 resurgence, in particular in young adults.

Resurgence and atypical patterns of pertussis in China

Guo Mengyang, Hu Yahong,
Meng Qinghong, Shi Wei, Yao Kaihu

Journal of Infection 88 (2024) 106140

*Correspondence to: Beijing Children's Hospital, Capital Medical University, No. 56 Nanlishi Road, Xicheng District, Beijing.
E-mail address: yaokaihu@bch.com.cn *(Y. Kaihu).*



Summary of Observed Phenomena

- COVID-19 pandemic restrictions (travel bans, mask-wearing, lockdowns, social distancing, etc.) were associated with a broad decline of many resp. 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.)
- **<u>Flu B/Yamagata</u>** lineage likely went **<u>extinct</u>** (B/Victoria & FluA returned)
- Several viruses (RV/EV, RSV, AdV) returned to > than pre-pandemic levels
- Pertussis remains near-absent; parapertussis had a > pre-pandemic surge
- *Mycoplasma pneumoniae* returned after long hiatus – big surge in China

An ‘Immunity Debt’ may have arisen

Disponible en ligne sur
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EM|consulte
www.em-consulte.com

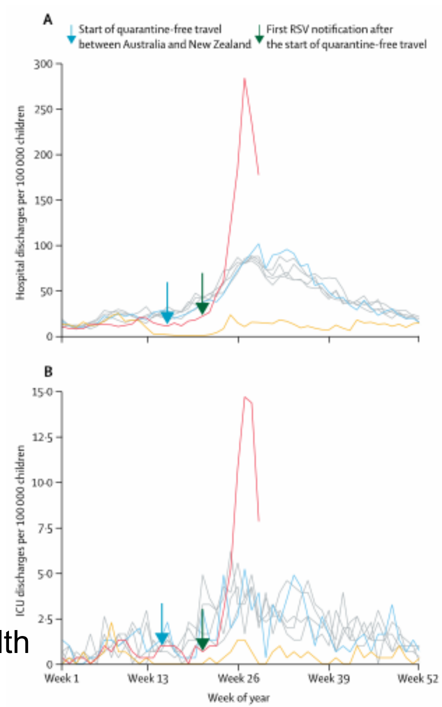
Review Infect Dis Now. 2021; 51(5): 418-23

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
- Children are now non-immune to many pathogens
- Consequence – More frequent infections & infections at older than usual age

Clinical Infectious Diseases

VIEWPOINTS

https://doi.org/10.1093/cid/ciae493

Cycles of Susceptibility: Immunity Debt Explains Altered Infectious Disease Dynamics Post-Pandemic

Alasdair P. S. Munro[1,2] and Thomas House[3]

[1]NIHR Southampton Clinical Research Facility and Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom; [2]Clinical and Experimental Sciences, University of Southampton, Southampton, United Kingdom; and [3]Department of Mathematics, University of Manchester, Manchester, United Kingdom

Scepticism also expressed . . .

The Guardian Aus

Immunity debt: does it really exist?

Philip Ball

Sun 15 Jan 2023 03.00 AEDT

Some claim the rise in winter infections has been caused by the reduction of seasonal bugs during lockdowns. But experts are sceptical about these oversimplified explanations

Competing Hypotheses

Hypothesis 1 – Simple lack of exposure; lack of specific immunity

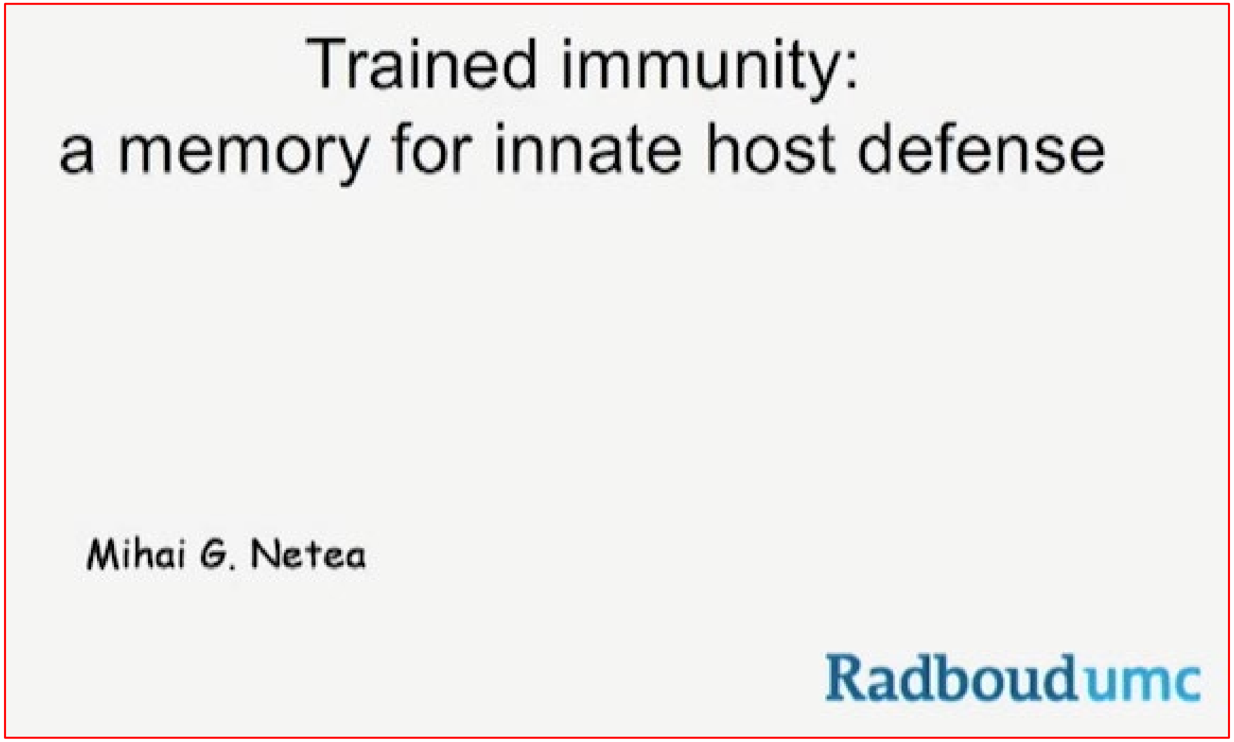
- Example: 1846 Faroe Islands measles outbreak – Measles had not been seen for >60 years, and no one <60 y/o had immunity – Over ~5 mo, 6100/7900 inhabitants fell ill, >100 died (https://time.com/5800558/coronavirus-human-civilization)

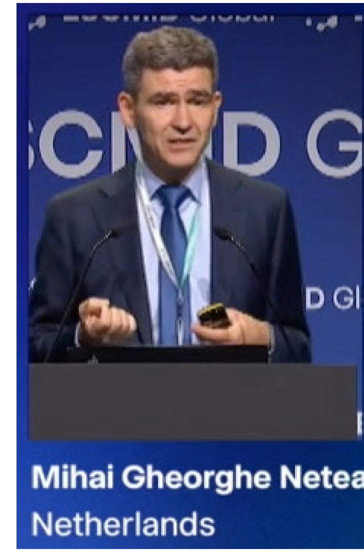
Hypothesis 2 – Lack of training of (innate) immune system

- Trained innate immunity – partial cross-protection against unrelated pathogens
- Possible overlap with ‘Hygiene Hypothesis’ (exposure to dirt is beneficial)

Hypothesis 3 – COVID-19-induced immune dysregulation

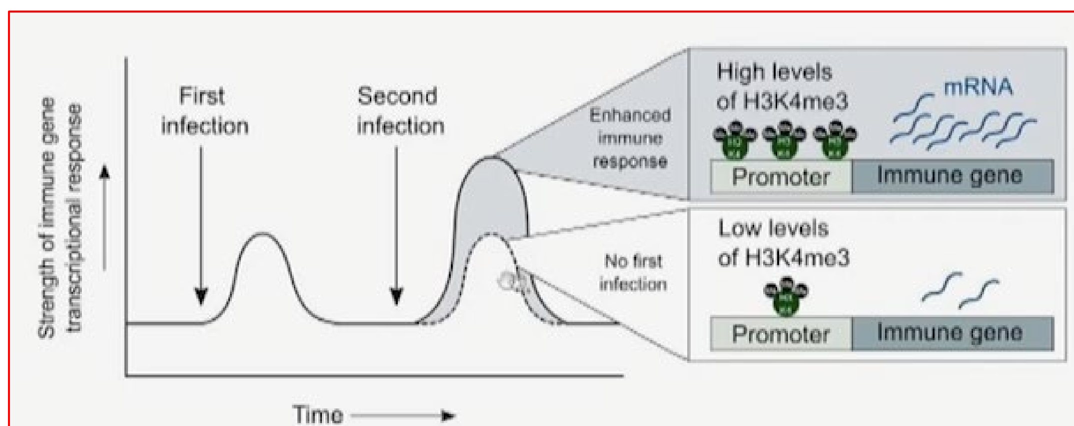
- Some other viruses known to cause (mostly temp.) immune deficiency
- Some countries that had very little measures had big RSV surges
- Some measured immune parameters are different after COVID





Fascinating talk at ESCMID Global (ECCMID) Barcelona 2024

- Epigenetic reprogramming of myeloid cells can lead to faster & more effective innate (!) immune response against unrelated pathogens



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

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.

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.

Further on COVID-19-related Immune Dysregulation

Cheong et al., 2023, Cell *186*, 3882–3902
August 31, 2023 © 2023 Elsevier Inc.
https://doi.org/10.1016/j.cell.2023.07.019

Cell

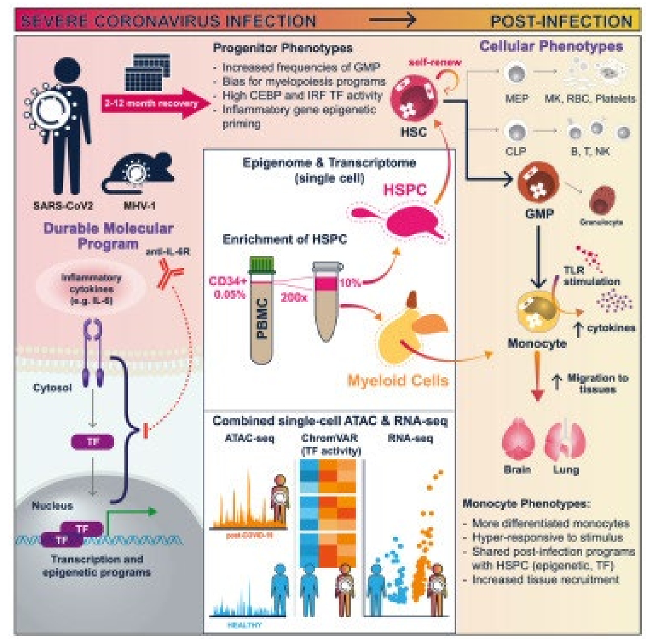
Article

Epigenetic memory of coronavirus infection in innate immune cells and their progenitors

Jin-Gyu Cheong,[1,2] Arjun Ravishankar,[1,22] Siddhartha Sharma,[3,22] Christopher N. Parkhurst,[5,22] Simon A. Grassmann,[6] Claire K. Wingert,[6] Paoline Laurent,[7] Sai Ma,[8,9] Lucinda Paddock,[1] Isabella C. Miranda,[5] Emin Onur Karakaslar,[3,21] Djamel Nehar-Belaid,[3] Asa Thibodeau,[3] Michael J. Bale,[1,2] Vinay K. Kartha,[8,9] Jim K. Yee,[1] Minh Y. Mays,[1] Chenyang Jiang,[1] Andrew W. Daman,[1,2] Alexia Martinez de Paz,[1] Dughan Ahimovic,[1,2] Victor Ramos,[10] Alexander Lercher,[10] Erik Nielsen,[1,5] Sergio Alvarez-Mulett,[5] Ling Zheng,[1] Andrew Earl,[8,9] Alisha Yallowitz,[1] Lexi Robbins,[1] Elyse LaFond,[11] Karissa L. Weidman,[5] Sabrina Racine-Brzostek,[1] He S. Yang,[1] David R. Price,[5] Louise Leyre,[2] André F. Rendeiro,[12,13,14] Hiranmayi Ravichandran,[13,15] Junbum Kim,[12] Alain C. Borczuk,[1,16] Charles M. Rice,[10] R. Brad Jones,[17,18] Edward J. Schenck,[5] Robert J. Kaner,[19] Amy Chadburn,[1] Zhen Zhao,[1] Virginia Pascual,[20] Olivier Elemento,[12,13] Robert E. Schwartz,[5] Jason D. Buenrostro,[8,9] Rachel E. Niec,[5,10] Franck J. Barrat,[2,7,18] Lindsay Lief,[5] Joseph C. Sun,[6] Duygu Ucar,[3,4,*] and Steven Z. Josefowicz[1,2,23,24,*]

In brief

Severe COVID-19 can reprogram hematopoiesis and establish epigenetic memory in hematopoietic stem and progenitor cells (HSPC) and progeny myeloid cells for up to 1 year. These durable alterations, which could affect post-infection immune responses and equilibrium, are controlled in part by the activity of IL-6 during acute disease.

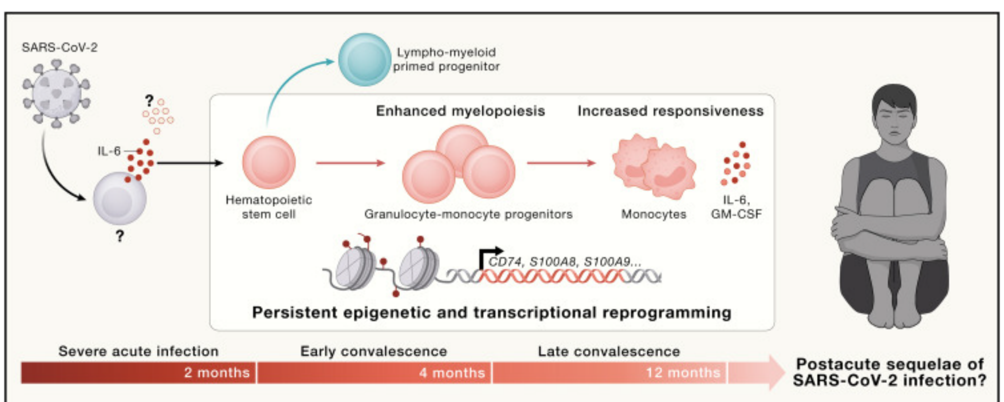


Previews

Haunting innate immune memories of COVID-19

Birgit Sawitzki[1,*]
[1]Translational Immunology, Berlin Institute of Health at Charité - Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany
*Correspondence: birgit.sawitzki@bih-charite.de
https://doi.org/10.1016/j.cell.2023.07.033

In addition to acute hyperinflammatory responses, SARS-CoV-2 infections can have long-term effects on our immune system leading to, for example, post-acute sequelae of COVID-19 (PASC). In this issue of *Cell*, Cheong et al. show that severe infections via IL-6 induce persistent epigenetic signatures in hemopoietic stem cells and their myeloid progenitors associated with increased inflammatory potential.



Competing Hypotheses

Hypothesis 4 – Virus interference with SARS-CoV-2

- Viruses interfere with each other
- SARS-CoV-2 was dominant circulating virus early in pandemic
- May explain downturn, but not irregular return of other pathogens

Hypothesis 5 – Psychological factors

- Before pandemic, people ignored ‘trivial’ infections; now seek diagnosis
- May explain increased numbers, but not severe infections

Hypothesis 6 – Multifactorial causation

- My opinion – likely multifactorial
- Complex interplay – not yet fully understood

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 applies is unclear
- Likely combination of factors, i.e. multifactorial
- Situation is very complicated – Need for ongoing research & observations

Acknowledgements

- Team of the Molecular Microbiology Laboratory, KK Hospital (KKH) Singapore
- Dr. Liat Hui Loo, Molecular Microbiology, KKH Singapore
- Mr. Han Yang Soong, Molecular Microbiology, KKH Singapore
- Dr. Wei Yee Wan, Virology Section, Singapore General Hospital (SGH)