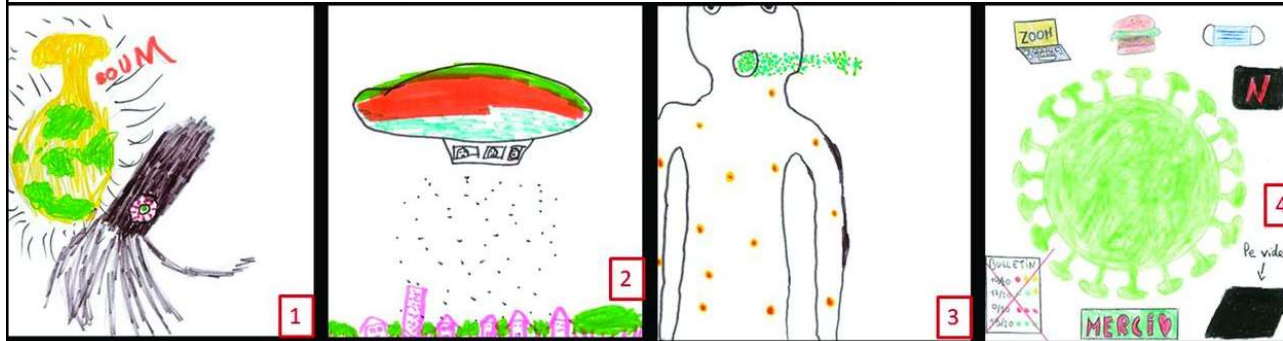


Respiratory viral infections in children: from diagnosis to immunisation

christoph.aebi@insel.ch



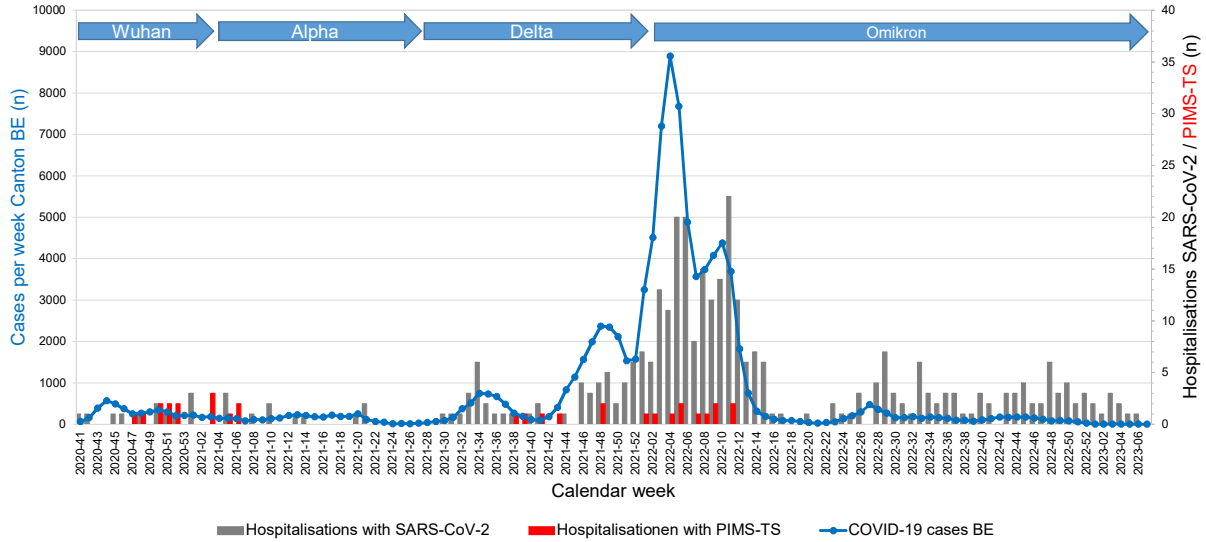
Martinerie L, Pediatrics 2021 Jun 1; <https://pediatrics.aappublications.org/content/early/2021/05/28/peds.2020-047621>

Topics

- (1) COVID-19 in children
- (2) «entre parenthèses»
- (3) RSV - still greeting from the leader box
- (4) RSV seasons 2021/2022 and 2022/2023 – forecasting vs. reality
- (5) Influenza - more than meets our eyes
- (6) Other viruses
 - picornaviridae (rhinovirus/enterovirus) ... enterovirus D68
 - human metapneumovirus (hMPV)
 - parainfluenza, etc.
- (7) Virus-virus-interactions

Hospitalisations with a positive SARS-CoV-2 PCR and PIMS-TS at the Kinderklinik (0-16 y) and COVID-19 case numbers in the canton of BE (0-19 y) wk 41, 2020 to wk 07, 2023

Quellen: Meldedaten BAG <https://www.covid19.admin.ch/de/> and datafiles, Universitätsklinik für Kinderheilkunde, Inselspital Bern



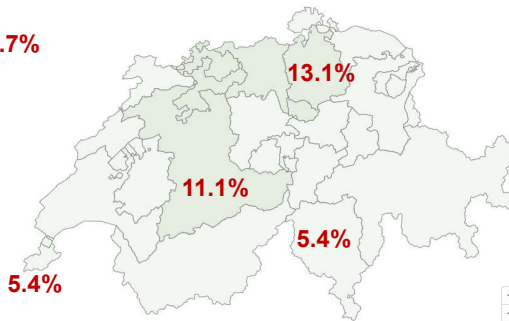
Data on file, Universitätsklinik für Kinderheilkunde, Inselspital Bern

COVID-19 immunization rates in the 5-15 y old

5-11 years

Schweiz und Liechtenstein	
5-11 Jahre, Stand: 02.10.2022	
Personen mit mind. 1 Impfdosis	53 458 8,66%
Mit Impfung in den letzten 6 Monaten	4069 0,66%

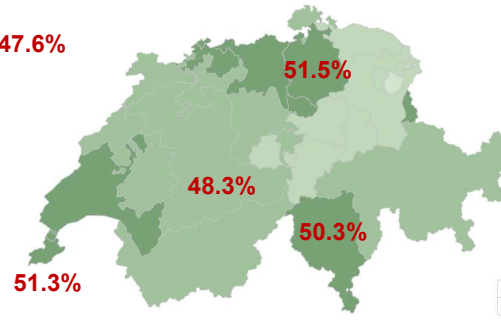
CH: 8.7%



12-15 years

Schweiz und Liechtenstein	
12-15 Jahre, Stand: 02.10.2022	
Personen mit mind. 1 Impfdosis	162 542 47,86%
Mit Impfung in den letzten 6 Monaten	11 000 3,26%

CH: 47.6%



seroprevalence 5-15 Jahre: > 90%

<https://www.ciao-corona.ch/>; 5. Testreihe 06/2022

COVID-19 – Impfpfehlungen EKIF/BAG 09.09.2022, CH

Spezielle Empfehlungssituation: Kinder und Jugendliche im Alter von 5-15 Jahren

Zielgruppe	Impfstatus	Anzahl Impfdosen gemäss Empfehlung Herbst 22 ⁷	Impfstoffe	
			Name	Dosierung
Jugendliche 12-15 Jahre	Geimpft	Keine Impfung	-	-
	Nicht geimpft	Keine Impfung Alternativ: 2 im Abstand von mind. 4 Wochen	Cominaty [®] # Nuvaxovid [®]	2 x 30 µg 2 x 5 µg
Kinder 5-11 Jahre	Geimpft	Keine Impfung	-	-
	Nicht geimpft	Keine Impfung Alternativ: 2 im Abstand von mind. 4 Wochen	Cominaty [®] #	2 x 10 µg
Jugendliche 12-15 Jahre mit chronischen Krankheiten	Geimpft	Keine Impfung	-	-
	Nicht geimpft	1 Alternativ: 2 im Abstand von mind. 4 Wochen	Cominaty [®] # Cominaty [®] # Nuvaxovid [®]	30 µg 2 x 30 µg 2 x 5 µg
Kinder 5-11 Jahre mit chronischen Krankheiten	Geimpft	Keine Impfung	-	-
	Nicht geimpft	1 Alternativ: 2 im Abstand von mind. 4 Wochen	Cominaty [®] # Cominaty [®] #	10 µg 2 x 10 µg

WHY NOT?

Spezielle Empfehlungssituation: Schwer immundefiziente Personen

Zielgruppe	Impfstatus	Anzahl Impfdosen gemäss Empfehlung Herbst 22 ⁷	Impfstoffe	
			Name	Dosierung
Schwer immundefiziente Personen ≥12 Jahre	Geimpft ²	1	Cominaty [®] # Spikevax [®] 10 Spikevax Bivalent Original/Omicron [®]	30 µg 100 µg 100 µg ¹¹
	Nicht geimpft	3 + 1	Cominaty [®] # Spikevax [®] 10 Spikevax Bivalent Original/Omicron [®]	Je 30 µg Je 100 µg Je 100 µg ¹¹
Schwer immundefiziente Kinder 5-11 Jahre	Geimpft	Keine Impfung	-	-
	Nicht geimpft	2 + Serologie. Wenn keine Antikörper, 3. Dosis zur Grundimmunisierung	Cominaty [®] #	Je 10 µg

[Tabellarische Übersicht der Impfpfehlungen Herbst 2022.pdf \(mcusercontent.com\)](#)

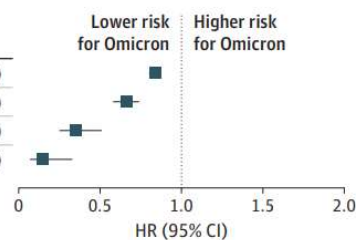
Clinical outcome of Omicron vs. Delta in children under 5

- previously uninfected children < 5.
- incidence of Omicron infections 6-8x greater than Delta.
- Omicron associated with a **significantly lower risk** for ED visit, hospitalization, ICU admission and mechanical ventilation.

Figure. Comparison of Risks of Clinical Outcomes of SARS-CoV-2 Infection in Children Younger Than 5 Years

A Omicron vs Delta cohorts

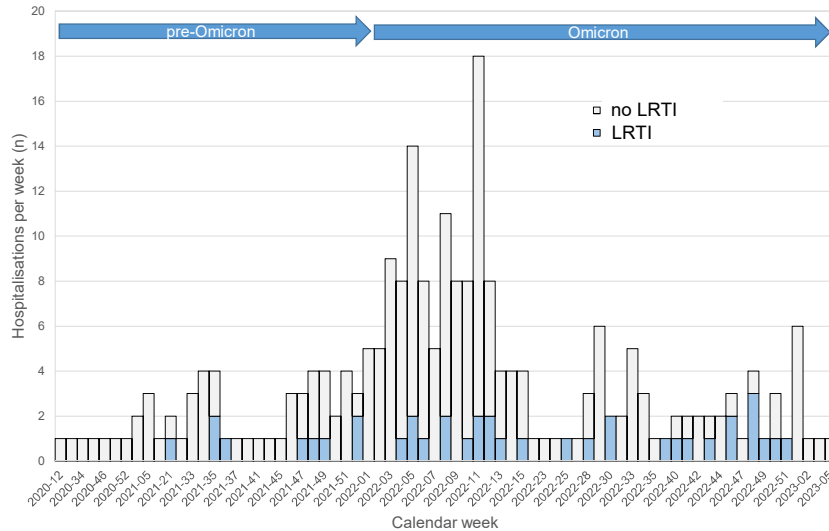
Outcome	Matched Omicron cohort, No. (%)	Matched Delta cohort, No. (%)	HR (95% CI)
ED visits	4637 (20.36)	5602 (24.60)	0.84 (0.80-0.87)
Hospitalizations	401 (1.76)	741 (3.25)	0.66 (0.58-0.74)
ICU admissions	38 (0.17)	115 (0.51)	0.35 (0.25-0.51)
Mechanical ventilation	10 (0.04)	51 (0.22)	0.15 (0.07-0.33)



Wang L et al. JAMA Pediatr 2022, <https://doi.org/10.1001/jamapediatrics.2022.0945>

LRTI associated with pre-Omicron vs. Omicron variant disease

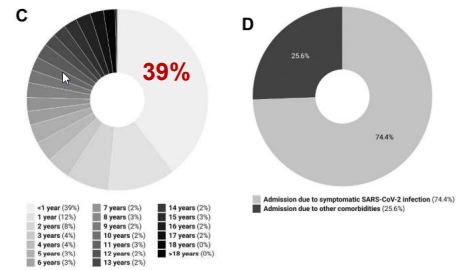
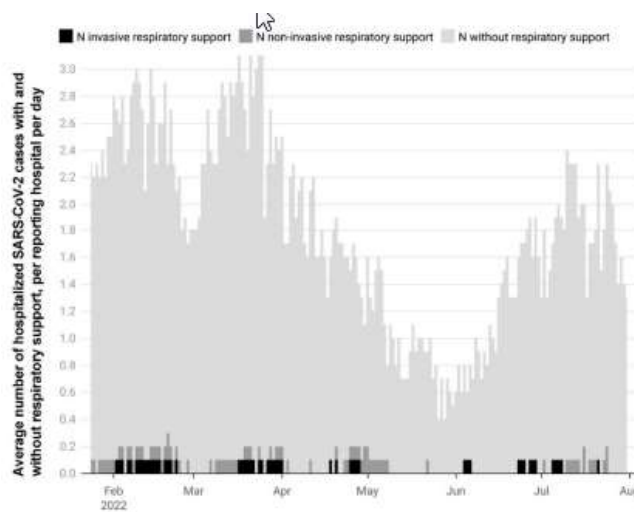
[Bern 2020-2023]



- hospitalised patients **without** comorbidity (n=235; 66%).
- LRTI (n=37) defined as
 - . laryngotracheitis and/or
 - . wheezy bronchitis and/or
 - . bronchiolitis and/or
 - . pneumonia
- 67/235 (30%) with co-infection by another respiratory virus.
- ICU admissions 11/235 (5%).
- permanent sequelae 0.
- case fatality 0.

Data on file, Universitätsklinik für Kinderheilkunde, Inselspital Bern

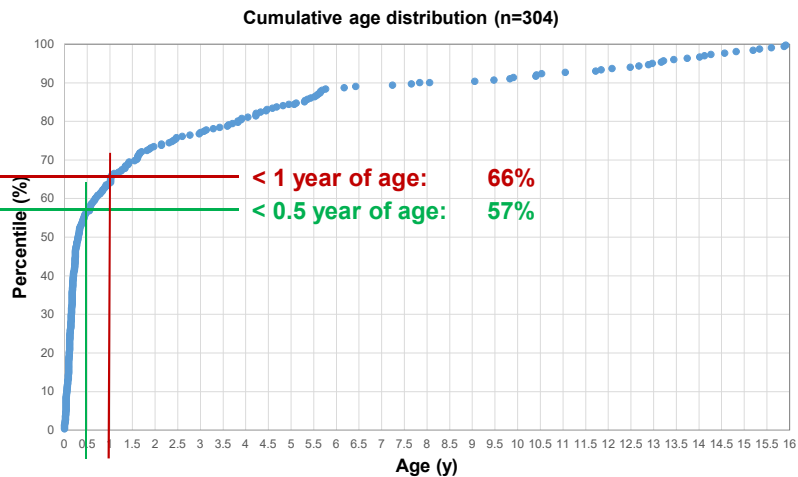
Burden of Pediatric SARS-CoV-2 Hospitalizations during the Omicron Wave in Germany (CLRS/DGPI)



“Despite the high incidence rates documented in connection with the Omicron variant in early 2022, the number of pediatric hospital admissions, and especially the number of cases with the need for intensive care treatment and respiratory support due to symptomatic SARS-CoV-2 infection, remained relatively low. **Higher Omicron incidence rates had only a modest impact on SARS-CoV-2-related admissions and hospitalization in German children’s hospitals.**”

Doenhardt M et al. Viruses 2022, <https://doi.org/10.3390/v14102102>

Age distribution of children hospitalized with a positive SARS-CoV-2 PCR [Bern wk 09/2020-wk 38/2022]

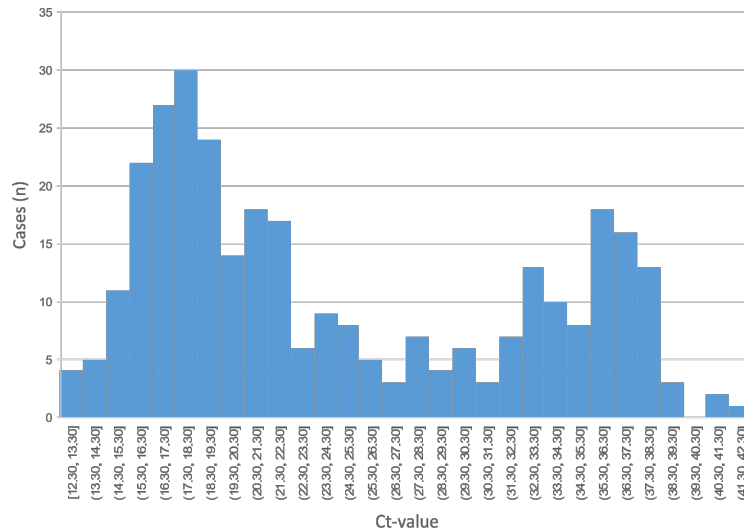


Data on file, Universitätsklinik für Kinderheilkunde, Inselspital Bern
Doenhardt M et al. Viruses 2022, <https://doi.org/10.3390/v14102102>

Case – Oleg, 16 days (term 39/2; healthy, parents with URTI)

day 1 02.00	Poor feeding, T 39.2°C.	
day 1 06.00 ER	Physical examination: HR 182, RR 38, SaO ₂ 98%; T 38.9° . Moderately ill, alert, recap 2". Mild rhinorrhea . Remainder of physical examination WNL. Test feed: drinks 55 ml (usually 120-150 ml per feeding). <ul style="list-style-type: none"> admission, 24/7 SaO₂ monitoring. NG tube feeding 150 ml/kg/d. i.v. amoxicillin 50 mg/kg q8 + amikacin 15 mg/kg q24. 	<ul style="list-style-type: none"> ► Sepsis w/u • WBC 13.0; CRP < 3. • U-Flow WNL. • CXR: not done. • LP 13 Mono; Protein 0.62. • NPA pending. • Blood, urine, CSF cultures pending.
day 2	T max 38.5°C; drinks ~70 ml/kg/d per feeding	CRP < 3. NPA: <ul style="list-style-type: none"> • SARS-CoV-2 Ct 16.82. • Picornavirus positiv.
day 3	<ul style="list-style-type: none"> T max 38.0°C; well-appearing; drings 110 ml/kg/d. antibiotics discontinued. discharge home. 	blood, urine, CSF cultures: no growth.

SARS-CoV-2 PCR Ct-values on admission (Bern, 2020-2023)

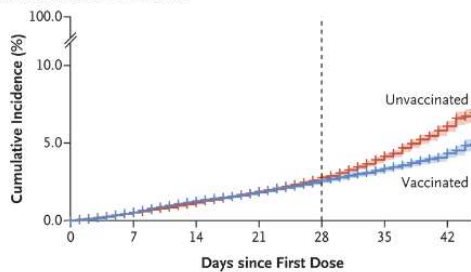


Data on file, Universitätsklinik für Kinderheilkunde, Inselspital Bern

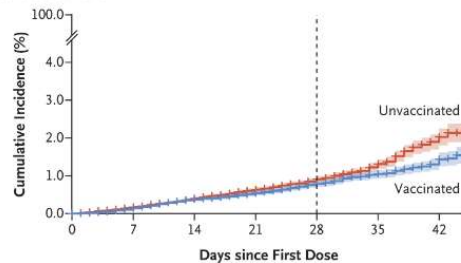
BNT162b2 Vaccine Effectiveness against Omicron in Children 5-11

- Israel.
- vaccinated from 23/11/2021.
- matched with unvaccinated controls, evaluated through January 7, 2022.
- Vaccine effectiveness at 7-21 after dose 2:
 - **51%** against documented SARS-CoV-2 infection.
 - **48%** against symptomatic infection.

A Documented SARS-CoV-2 Infection



B Symptomatic Covid-19



Cohen-Stavi C et al. N Engl J Med 2022, <https://doi.org/10.1056/nejmoa2205011>

Effectiveness of 2-Dose BNT162b2 in preventing SARS-CoV-2 infection among children 5–11 and adolescents 12–15 Years

- PROTECT cohort, US
- July 2021-February 2022
- Participants were tested x2 weekly regardless of symptoms

Results

- ~ 50% of Omicron infections were asymptomatic.
- Vaccine effectiveness of 2 doses of BNT162b2 against any infection:

31% in 5-11 year-old (at 14-82 days)

59% in 12-15 year-old (14-149 days)

Age group and COVID-19 vaccination status (no. of days since receipt of most recent dose)	VE, % (95% CI)	
	Unadjusted	Adjusted [†]
Children aged 5–11 yrs		
Omicron variant infections		
Unvaccinated (referent)	—	—
2 doses (14–82 days)	47 (32 to 59)	31 (9 to 48)
Adolescents aged 12–15 yrs		
Delta variant infections		
Unvaccinated (referent)	—	—
2 doses (≥14 days)	87 (70 to 95)	81 (51 to 93)
2 doses (14–149 days)	93 (76 to 98)	87 (49 to 97)
2 doses (≥150 days)	67 (0 to 89)	60 (–35 to 88)
Omicron variant infections		
Unvaccinated (referent)	—	—
2 doses (≥14 days)	64 (37 to 80)	59 (24 to 78)
2 doses (14–149 days)	62 (30 to 79)	59 (22 to 79)
2 doses (≥150 days)	74 (16 to 92)	62 (–28 to 89)

Fowlkes AL et al. MMWR 2022, https://www.cdc.gov/mmwr/volumes/71/wr/mm7111e1.htm?s_cid=mm7111e1_w

Effectiveness of BNT162b2 in children aged 5–11 years of age

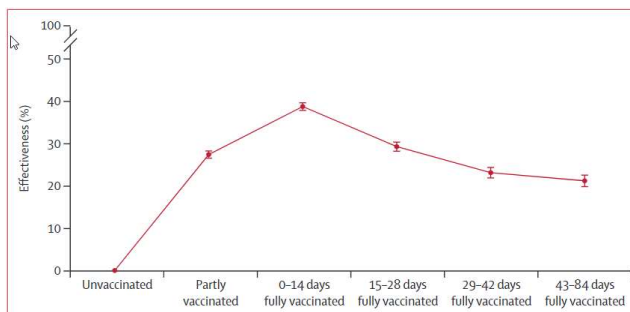
- Italy, January – April 2022.
- 2 doses vs. 1 dose vs. 0 doses.

Results

- protection against any infection **29%**.
- protection against severe COVID-19 **41%**.
- Effectiveness decreases over time after primary series.

Infection	Vaccine effectiveness (95% CI)	Adjusted vaccine effectiveness* (95% CI)
Unvaccinated group		
Unvaccinated group	NA	NA
Partly vaccinated group	24.4 (23.9-24.9)	27.4 (26.4-28.4)
Fully vaccinated group	45.1 (44.8-45.4)	29.4 (28.5-30.2)
Severe disease		
Unvaccinated group		
Unvaccinated group	NA	NA
Partly vaccinated group	40.7 (24.3-54.1)	38.1 (20.9-51.5)
Fully vaccinated group	55.2 (41.2-66.4)	41.1 (22.2-55.4)

IRR=incidence rate ratio. NA=not of the municipality of residence, se in children aged 5–11 years



Sacco C et al. Lancet 2022, [https://doi.org/10.1016/s0140-6736\(22\)01185-0](https://doi.org/10.1016/s0140-6736(22)01185-0)

Association of prior BNT162b2 with symptomatic SARS-CoV-2 infection in children and adolescents during Omicron predominance

US case-control study conducted December 2021 to February 2022.

Results

Effectiveness against symptomatic disease after 2 doses:

Children 5-11 years

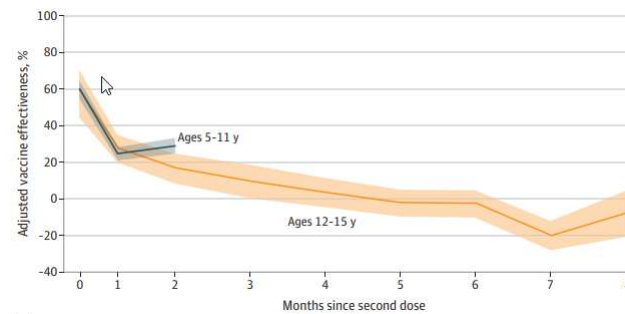
- 60.1% (2 to 4 weeks)
- **28.9%** (after 2 months)

Adolescents 12 to 15 years

- 59.5% (2 to 4 weeks)
- **16.6%** (after 2 months)

Booster dose in adolescents

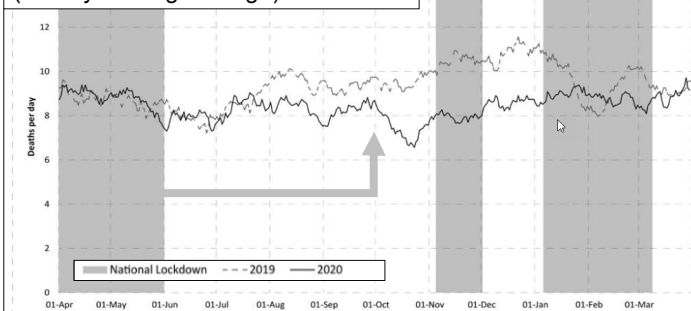
- **71.1%** (2-6 weeks)



Fleming-Dutra KE et al. N Engl J Med 2022. <https://doi.org/10.1001/jama.2022.7493>

Childhood mortality - UK 03/2019-03/2021

Mean number of deaths per day (21-day moving average)



Childhood death rates 0-18 years UK 2019+2020

Cause	2019	2020	abs diff	rel diff
All	3423	3067	-356	-10.4%
Infection	164	81	83	-50.6%
Underlying condition	1085	810	275	-25.3%

Table 3 Number of deaths by year (starting April) stratified by provisional category of death with estimates of relative risk (RR) between years and proportion of excess deaths

Measure	Comparison of deaths between 2019 and 2020 (April-March)		Excess deaths	RR	P value
	2019	2020			
All deaths	3423	3067	-356 (-514 to -198)	0.90 (0.85 to 0.94)	<0.001
Infection	164	81	-83 (-114 to -52)	0.49 (0.38 to 0.64)	<0.001
Underlying medical condition	1085	810	-275 (-360 to -190)	0.75 (0.68 to 0.82)	<0.001

Odd D et al. Arch Dis Child 2022. <https://pubmed.ncbi.nlm.nih.gov/34872905/>

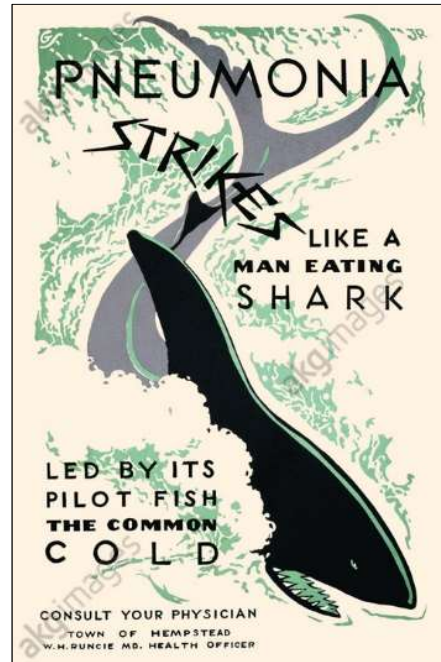
Topics

- (1) **COVID-19 in children ... mild disease; poor vaccine effectiveness.**
- (2) «entre parenthèses»
- (3) RSV - still greeting from the leader box
- (4) RSV seasons 2021/2022 and 2022/2023 – forecasting vs. reality
- (5) Influenza - more than meets our eyes
- (6) Other viruses
 - picornaviridae (rhinovirus/enterovirus) ... enterovirus D68
 - human metapneumovirus (hMPV)
 - parainfluenza, etc.
- (7) Virus-virus-interactions

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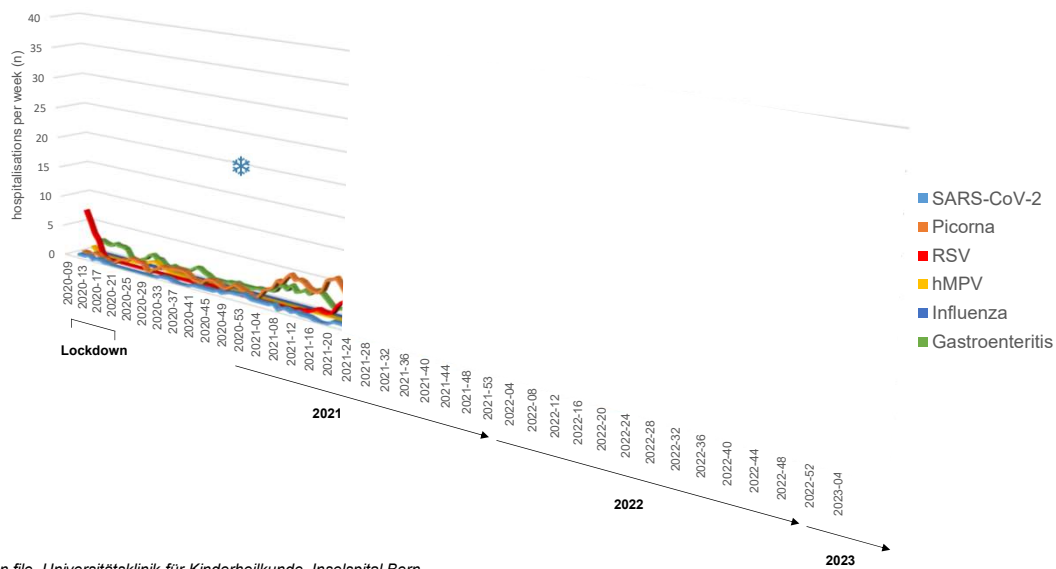
[... not only viruses !]



Work of Art Project, New York, Dec 1, 1937
 Library of Congress Prints and Photographs Division
 Washington, D.C. 20540 USA

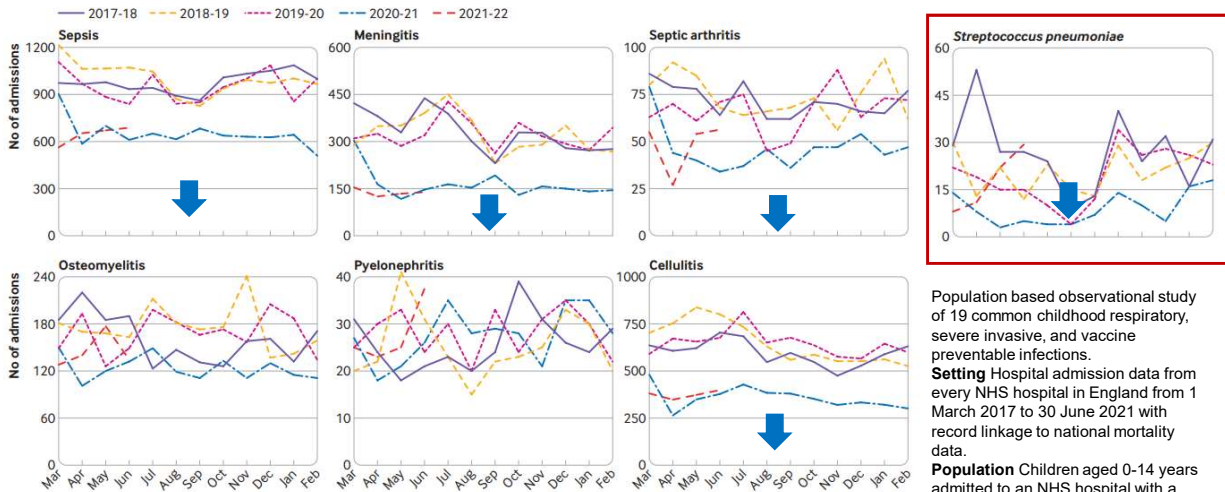
Hospitalizations with respiratory and enteric viruses

[Kinderklinik BE wk 09/2020 – 07/2023; 3-week moving averages]



Data on file, Universitätsklinik für Kinderheilkunde, Inselspital Bern

COVID-19 and bacterial childhood infections, England 2017-2022



Population based observational study of 19 common childhood respiratory, severe invasive, and vaccine preventable infections.
Setting Hospital admission data from every NHS hospital in England from 1 March 2017 to 30 June 2021 with record linkage to national mortality data.
Population Children aged 0-14 years admitted to an NHS hospital with a selected childhood infection from 1 March 2017 to 30 June 2021.

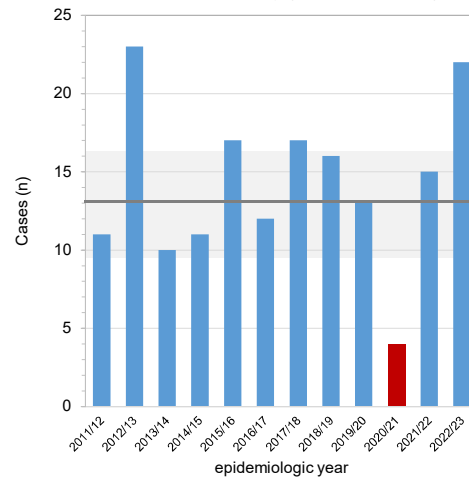
Kadambari S et al. *BMJ* 2022; <https://pubmed.ncbi.nlm.nih.gov/35022215/>

Bacterial pneumonia and pleural empyema

FOPH, reportable diseases, 25 May, 2021

	letzte 52 Wochen			Δ2021-19
	2021	2020	2019	
Respiratorische Übertragung				
Haemophilus influenzae: invasive Erkrankung	58	106	129	-55%
Influenzavirus-Infektion, saisonale Typen und Subtypen ^a	49	11821	13702	
	0.60	136.70	158.50	
Legionellose	497	516	586	-15%
	5.80	6.00	6.80	
Masern		61	220	
		0.70	2.50	
Meningokokken: invasive Erkrankung	9	39	50	-72%
	0.10	0.40	0.60	
Pneumokokken: invasive Erkrankung	346	717	894	-62%
	4.00	8.30	10.30	

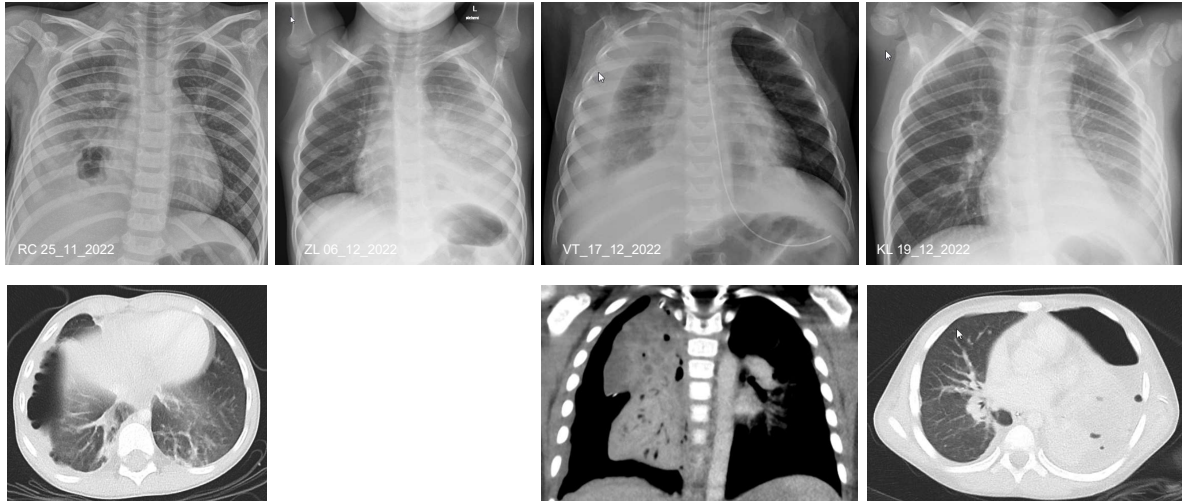
Pediatric pleural empyema, Bern (February 28, 2023)
 [mean 2010-2020, 13.2 cases py (95% CI, 9.9-16.5)]



[BU 22_21_DE \(2\).pdf](#)

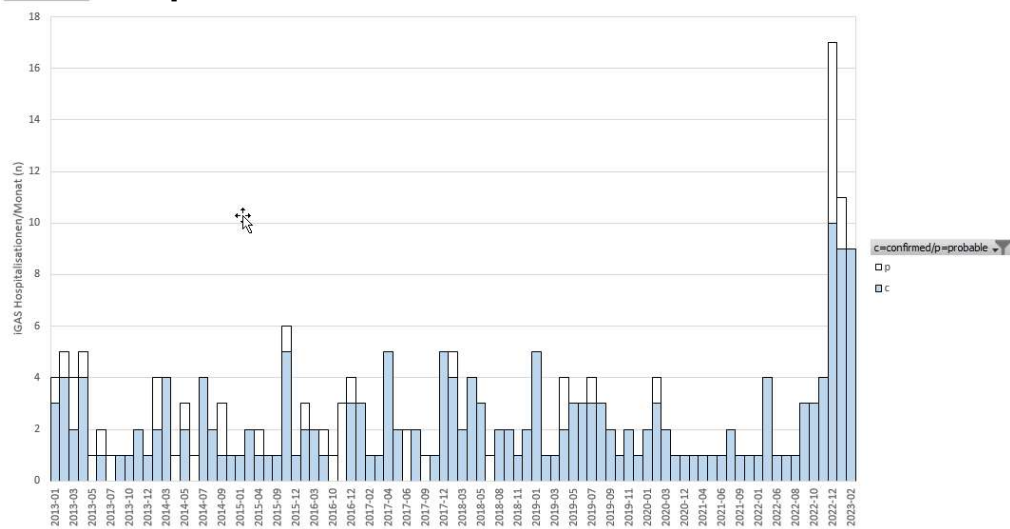
Data on file, Infektiologie - Universitätsklinik für Kinderheilkunde, Inselspital Bern

Patients with pleural empyema Kinderklinik Bern Q4 2022



Hospitalisations for invasive group A streptococcal disease

[BE 2013 – 1 March 2023]



Data on file, Universitätsklinik für Kinderheilkunde, Inselspital Bern

↑ Lockdown

Topics

- (1) COVID-19 in children
- (2) «entre parenthèses» ... no circulation of viruses ► no bacterial secondary infections.**
- (3) RSV - still greeting from the leader box
- (4) RSV seasons 2021/2022 and 2022/2023 – forecasting vs. reality
- (5) Influenza - more than meets our eyes
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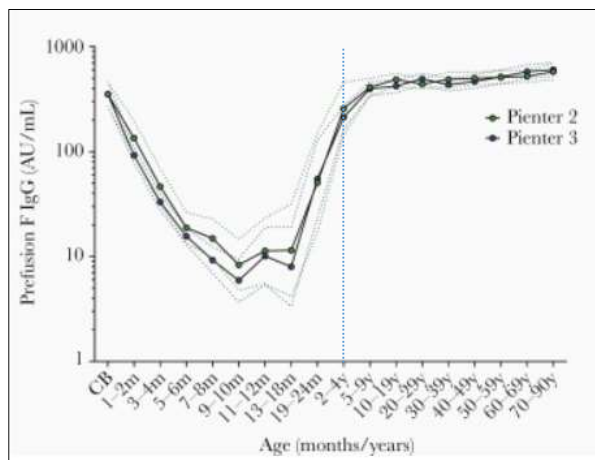
RSV – epidemiologic «Steckbrief»

- **60-90%** of all cases of bronchiolitis.
- **33 Mio** LRTI per year in the under 5s worldwide.
- **3.2 Mio** hospitalizations per year in the under 5s worldwide.
- **120'000** deaths per year in the under 5s worldwide.
- **1-2%** of the annual birth cohort are hospitalized because of RSV.

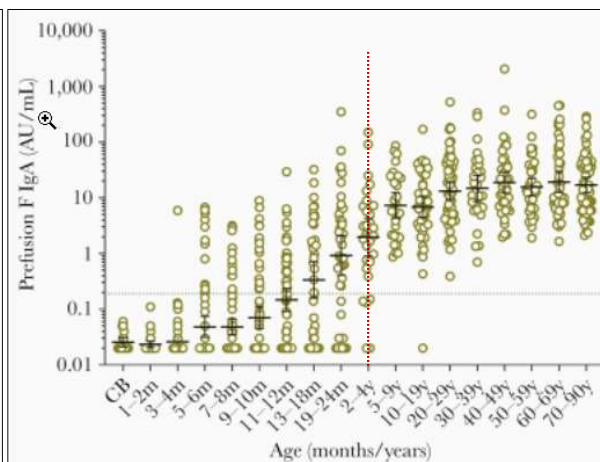
Taveras J. *Neoreviews* 2020; <https://pubmed.ncbi.nlm.nih.gov/32737172/>
 Collaborators GBDLRI. *Lancet Infect Dis* 2018; <https://pubmed.ncbi.nlm.nih.gov/30243584/>

Age-specific seroprevalence of (primary) RSV infection

prefusion F protein **IgG** (GMC, 95%CI)

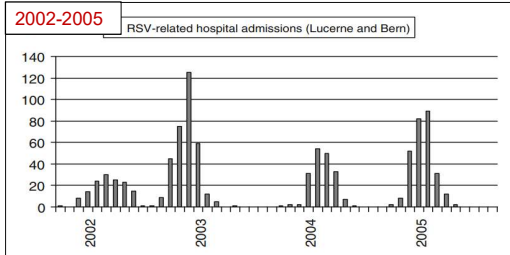
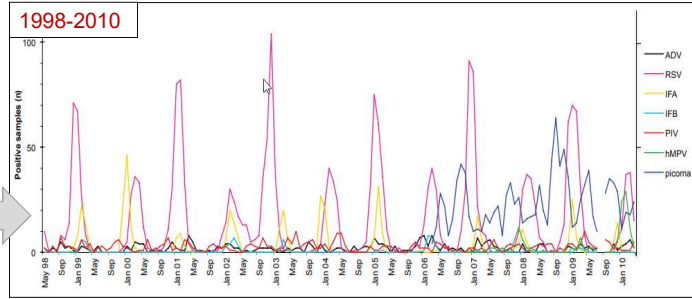
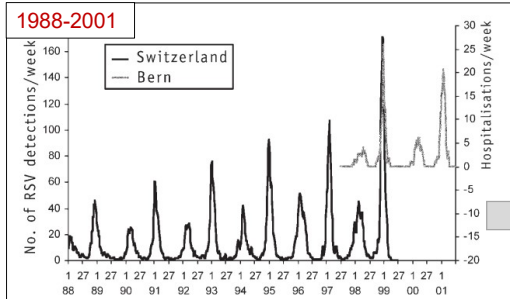


prefusion F protein **IgA**



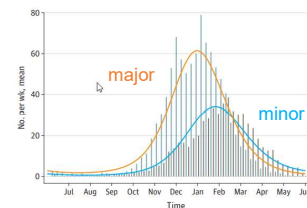
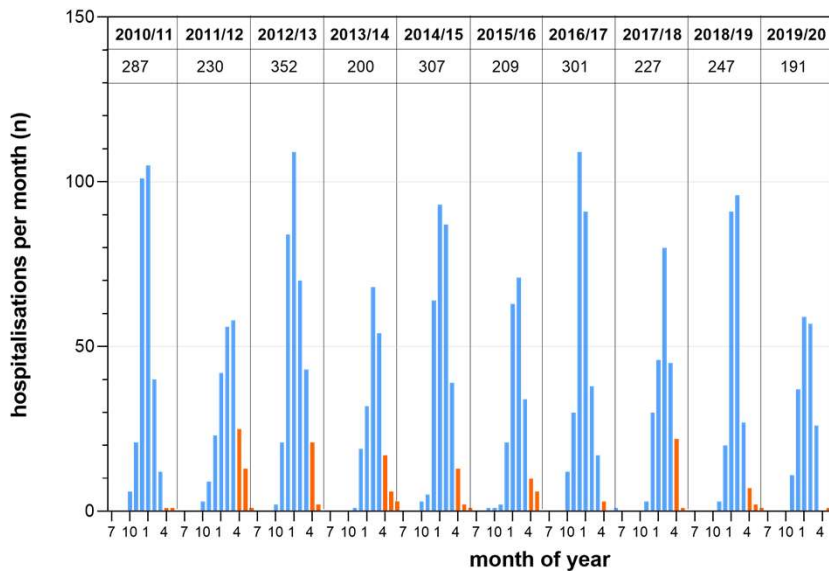
Berbers G et al. *J Infect Dis* 2021; <https://pubmed.ncbi.nlm.nih.gov/32964923/>

Seasonality of RSV hospitalisations since 1988



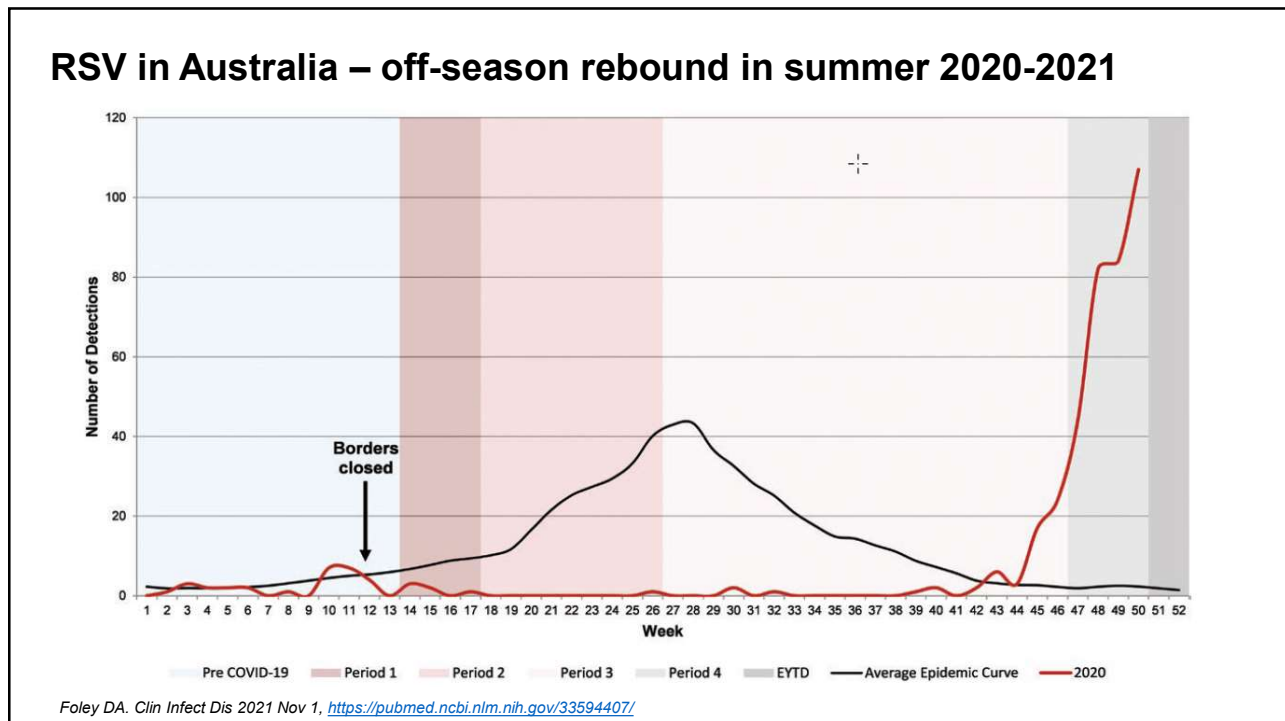
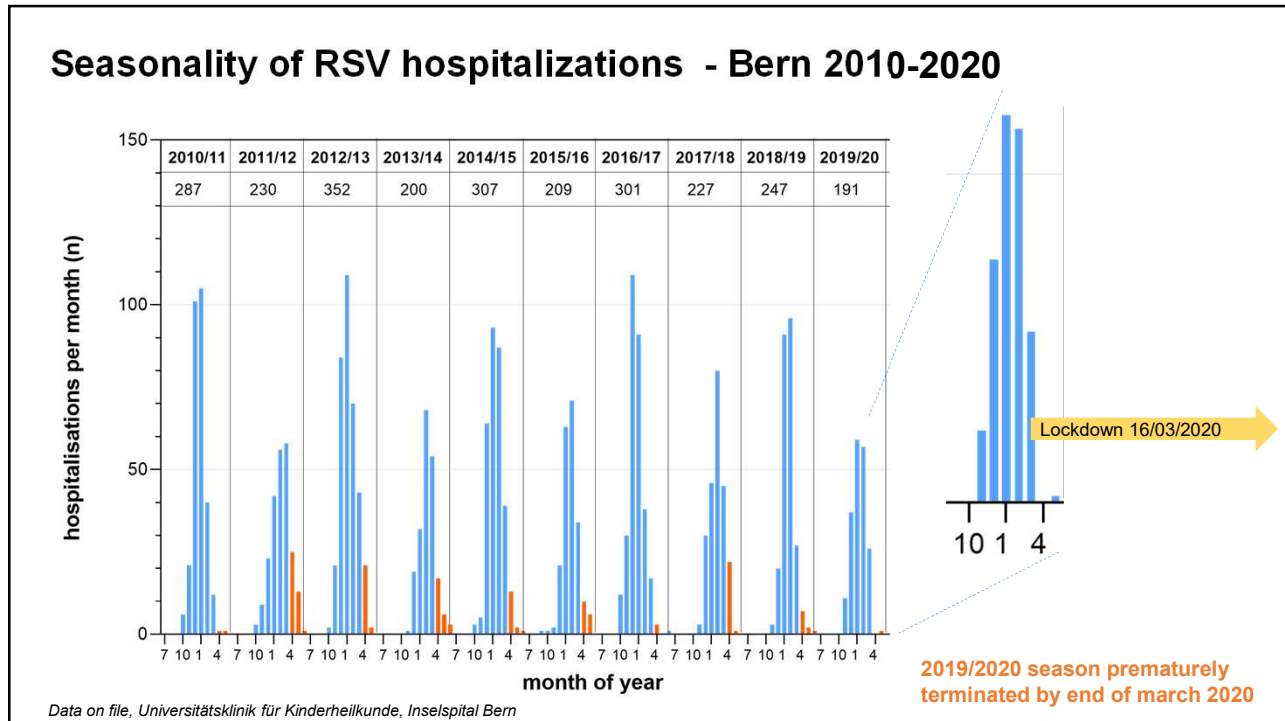
Duppenthaler A et al. *Infection* 2003, <https://pubmed.ncbi.nlm.nih.gov/12682811/>
 Sadeghi SD et al. *BMC Infect Dis* 2011, <https://pubmed.ncbi.nlm.nih.gov/21299840/>
 Berger TM et al. *Infection* 2009, <https://pubmed.ncbi.nlm.nih.gov/19412586/>

Seasonality of RSV hospitalizations - Bern 2010-2020



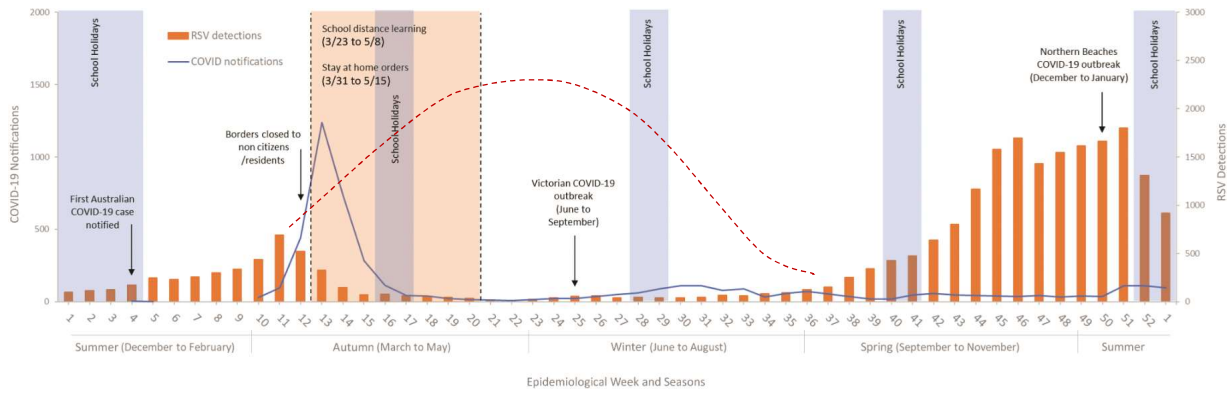
Hawkes MT et al. *JAMA Netw Open* 2021; <https://pubmed.ncbi.nlm.nih.gov/34529066/>

Data on file, Universitätsklinik für Kinderheilkunde, Inselspital Bern



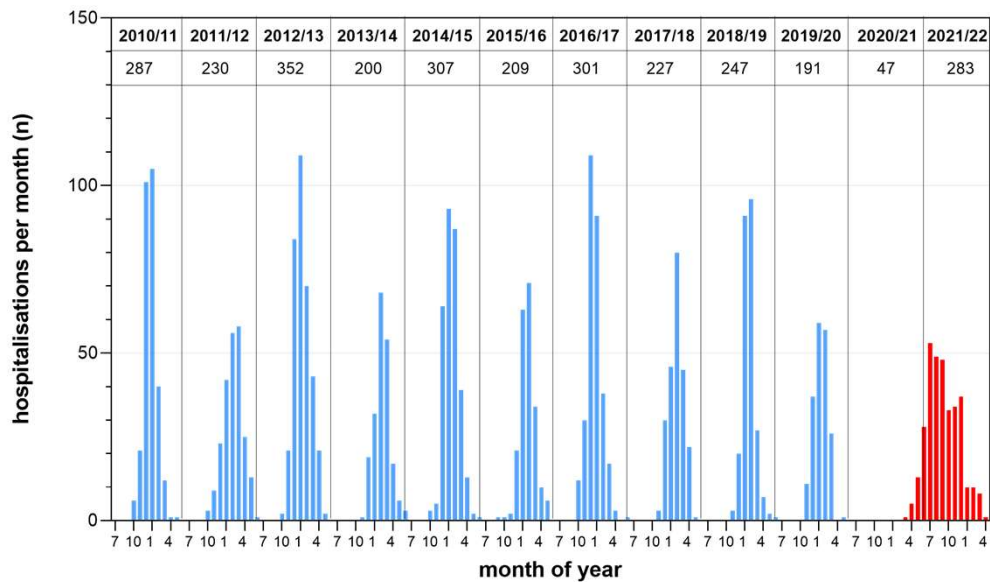
RSV in Australia – off-season rebound in summer 2020-2021

[Sydney Children’s Hospitals Network]



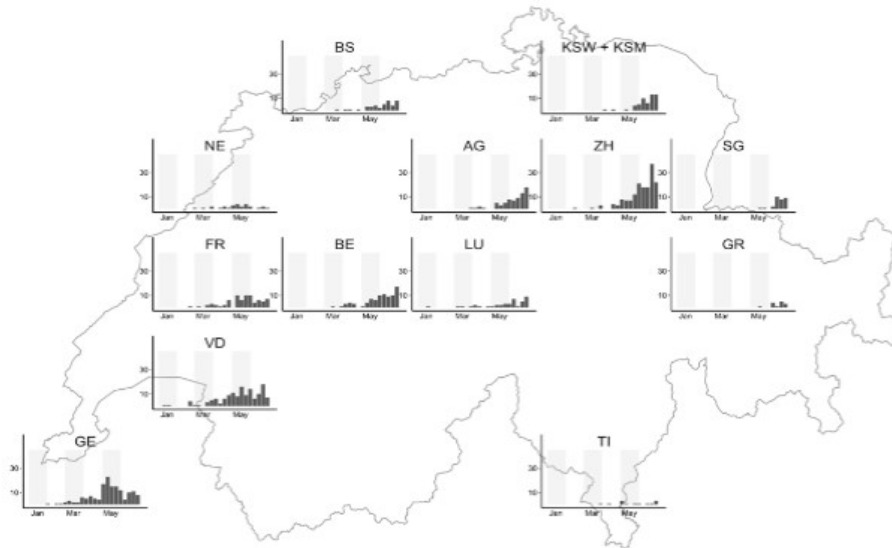
Saravanos GL et al. Pediatrics 2022; <https://pubmed.ncbi.nlm.nih.gov/35083489/>

Seasonality of RSV hospitalizations - BE 2010-2022



Data on file, Universitätsklinik für Kinderheilkunde, Inselspital Bern

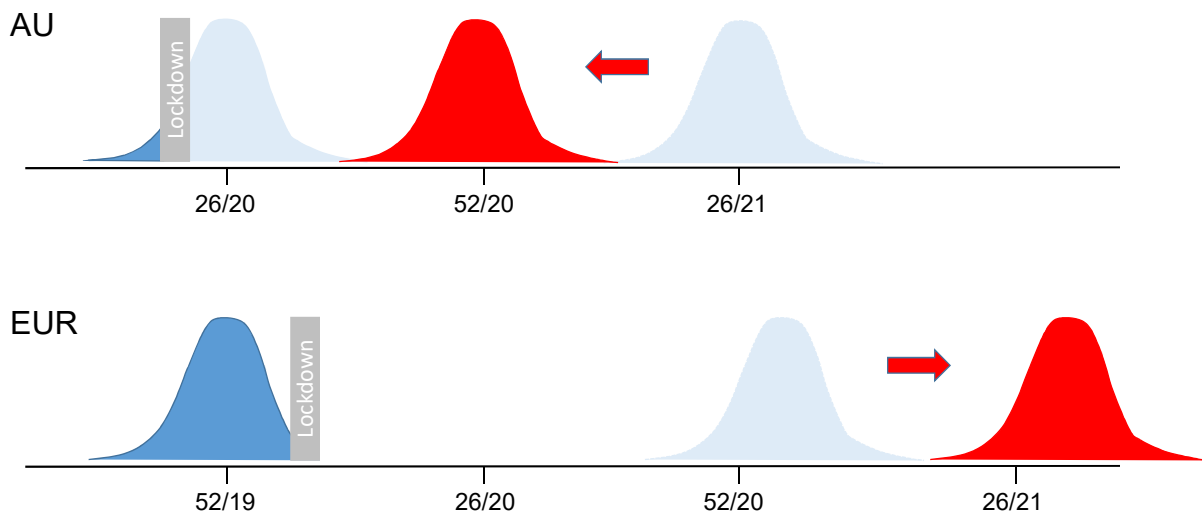
RSVepiCH project (PIGS)



RSV EpiCH (P. Agyeman, J. Trück)
m 30.11.2021 to 28.02.2022
1.03.2022

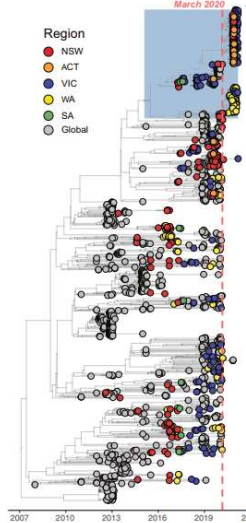
Von Hammerstein AL et al. Swiss Med Wkly 2021. <https://doi.org/10.4414/smw.2021.w30057>

Consequence of lockdown – Australia (NSW) vs. Europe

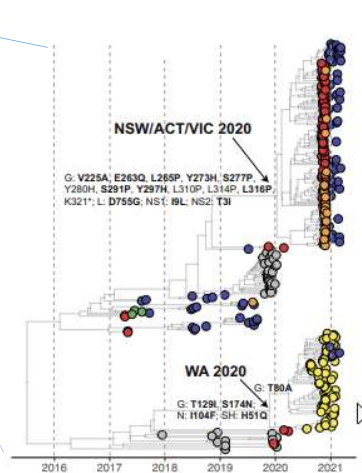


Pandemic-associated reduction of RSV genetic diversity

Global diversity



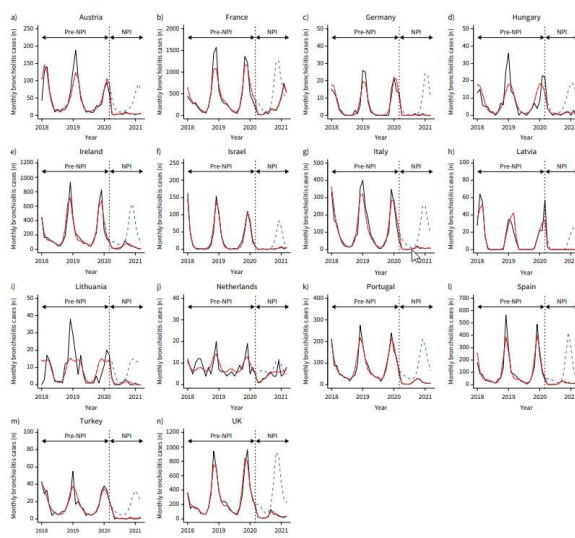
Diversity in Australia



“Through genomic sequencing we reveal a **major reduction in RSV genetic diversity following COVID-19 emergence** with two genetically distinct RSV-A clades circulating cryptically, likely localised for several months prior to an epidemic surge in cases upon relaxation of COVID-19 control measures. The NSW/ACT clade subsequently spread to the neighbouring state of Victoria and to cause extensive outbreaks and hospitalisations in early 2021.”

Eden JS et al. Nat Commun 2022, <https://doi.org/10.1038/s41467-022-30485-3>

Role of non-pharmaceutical interventions (NPI) in suppressing RSV and other agents causing bronchiolitis in winter 2020/2021



- **full lockdown** (IRR 0.21, 95%CI [0.14;0.30], $p < 0.001$)
- **secondary-school closure** (IRR 0.33, 95%CI [0.20;0.52], $p < 0.0001$)
- **wearing a mask indoors** (IRR 0.49, 95%CI [0.25;0.94], $p = 0.034$)
- and **teleworking** (IRR 0.55, 95%CI [0.31;0.97], $p = 0.038$)

...were independently associated with reducing bronchiolitis.”

Lenglar L et al. Eur Respir J 2023, <https://doi.org/10.1183/13993003.01172-2022>

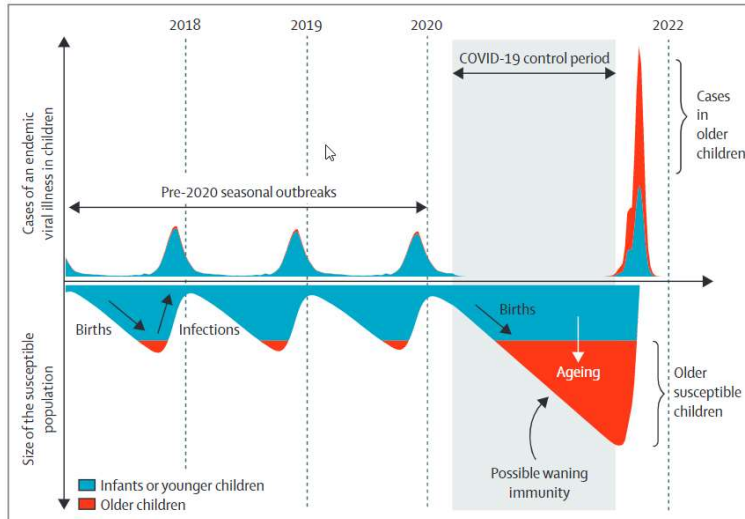
Topics

- (1) COVID-19 in children
- (2) «entre parenthèses»
- (3) RSV - still greeting from the leader box ... NPI completely suppressed RSV circulation.**
- (4) RSV seasons 2021/2022 and 2022/2023 – forecasting vs. reality
- (5) Influenza - more than meets our eyes
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 - picornaviridae (rhinovirus/enterovirus) ... enterovirus D68
 - human metapneumovirus (hMPV)
 - parainfluenza, etc.
- (7) Virus-virus-interactions

Topics

- (1) COVID-19 in children
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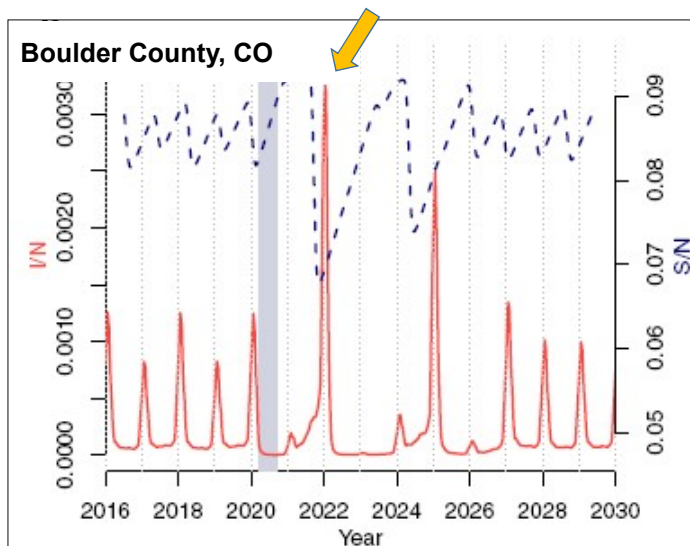
Modelling of endemic virus circulation in children following COVID-19 pandemic disruption



Messacar K et al. Lancet 2022, [https://doi.org/10.1016/s0140-6736\(22\)01277-6](https://doi.org/10.1016/s0140-6736(22)01277-6)
 Baker RE et al. PNAS 2020, <https://www.pnas.org/content/117/48/30547>

- increased pool of susceptible individuals.
- larger than usual season to be expected.
- shift in the age structure possible.
- difficult to predict how long it will take until normal epidemiology re-established

Mathematical simulations in 2020 for future RSV epidemics

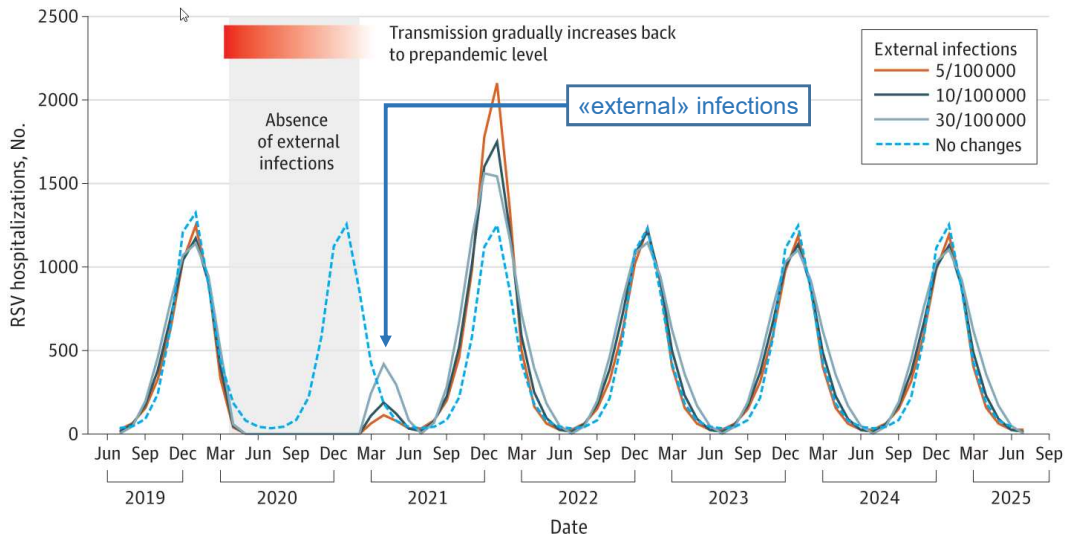


suggests

- low activity in summer 2021
- massive epidemic in winter 2021/22
- irregularities in subsequent years

Baker RE et al. PNAS 2020, <https://www.pnas.org/content/117/48/30547>

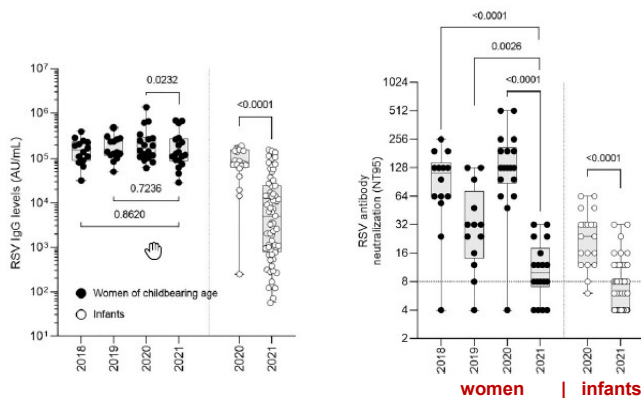
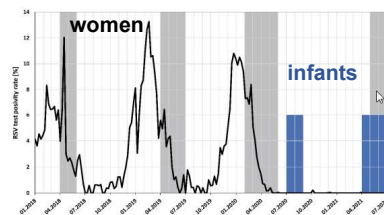
Model simulations in 2021 for future RSV epidemics



Eden JS et al. Nat Commun 2022; <https://pubmed.ncbi.nlm.nih.gov/35610217/>

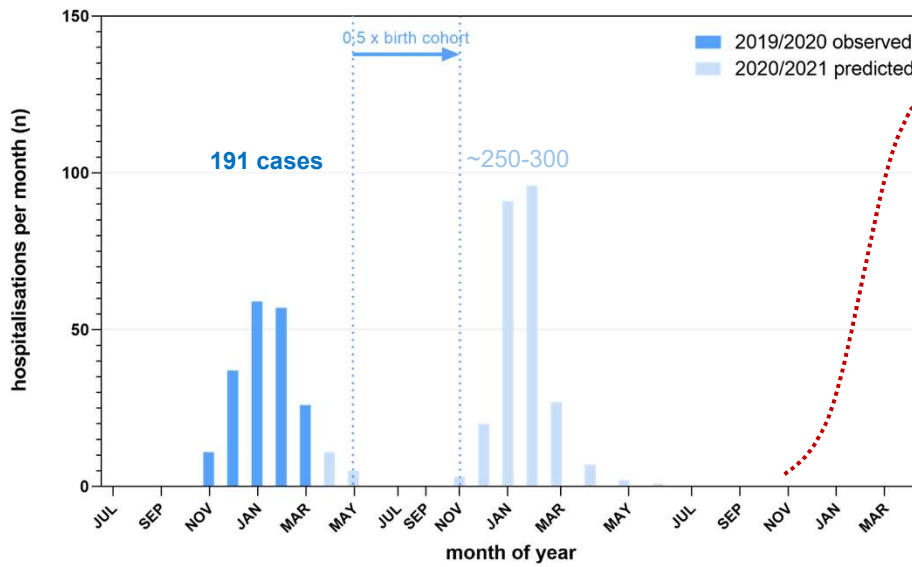
Waning humoral RSV immunity in pregnant women and their babies

- British Columbia, CND.
- sera obtained in spring 2018/2019/2020/2021 from women of childbearing age (gray) and infants and infants (blue).
- NOT paired mother-child samples.
- **significantly lower serum neutralizing activity in 2021 vs. 2020.**



Reicherz F et al. J Infect Dis 2022; <https://doi.org/10.1093/infdis/jiac192>

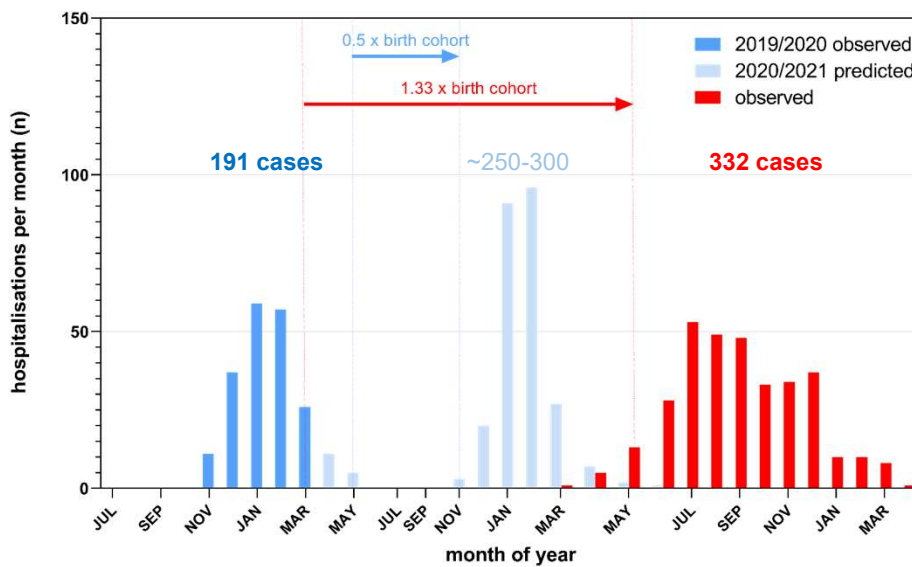
The pandemic and the RSV-susceptible infant and toddler population



what could have happened

- ▲ RSV hospitalisations
 - accumulation of susceptible infants/toddlers
 - waning population immunity
- ▲ average age at hospitalisation

The pandemic and the RSV-susceptible infant and toddler population

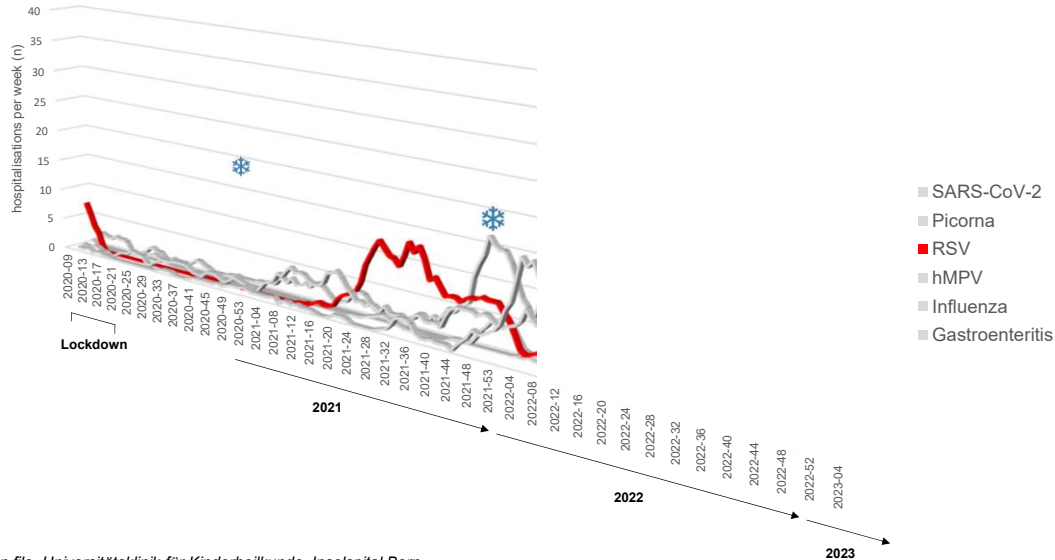


what did happen

- broad-based 2021/22 season
- usual case load
- ▲ population of susceptibles
- ▲ external infections (mobility)
- ▼ conditions for transmission?

Hospitalizations with RSV

[Kinderklinik BE wk 09/2020 – 07/2023]



Data on file, Universitätsklinik für Kinderheilkunde, Inselspital Bern

Blick

SCHWEIZ

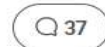
🏠 | Schweiz | RS-Virus: Spitäler und Kinderpraxen am Anschlag

Fallzahlen explodieren

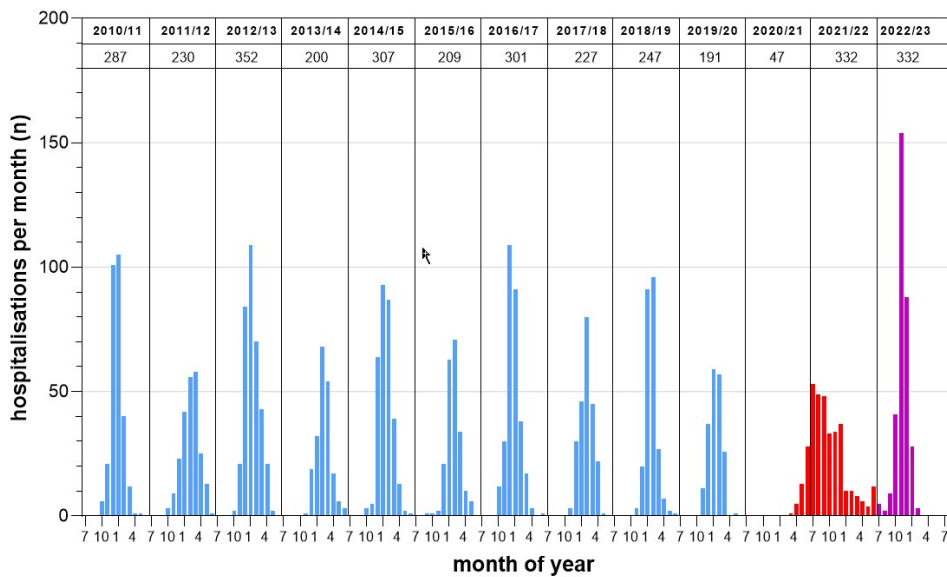
Babys mit Blaulicht ins Spital

Seit Oktober gehen Ansteckungen mit dem RS-Virus durch die Decke. Die Atemwegserkrankung ist für Säuglinge besonders gefährlich. Spitäler und Kinderarztpraxen sind am Anschlag.

Publiziert: 20.11.2022 um 09:11 Uhr | Aktualisiert: 27.11.2022 um 12:59 Uhr



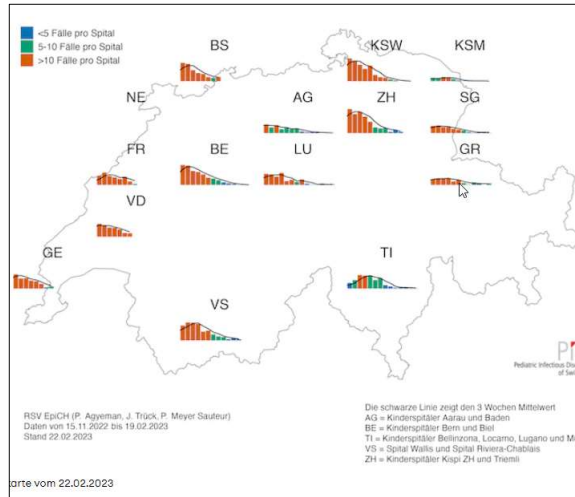
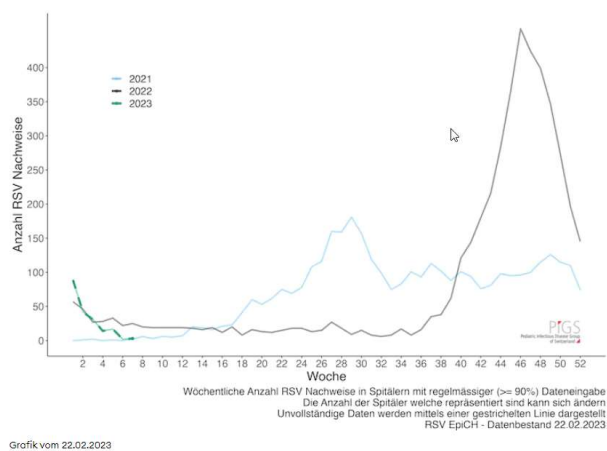
Seasonality of RSV hospitalizations - BE 2010-2023



Data on file, Universitätsklinik für Kinderheilkunde, Inselspital Bern

RSV season 2022/2023

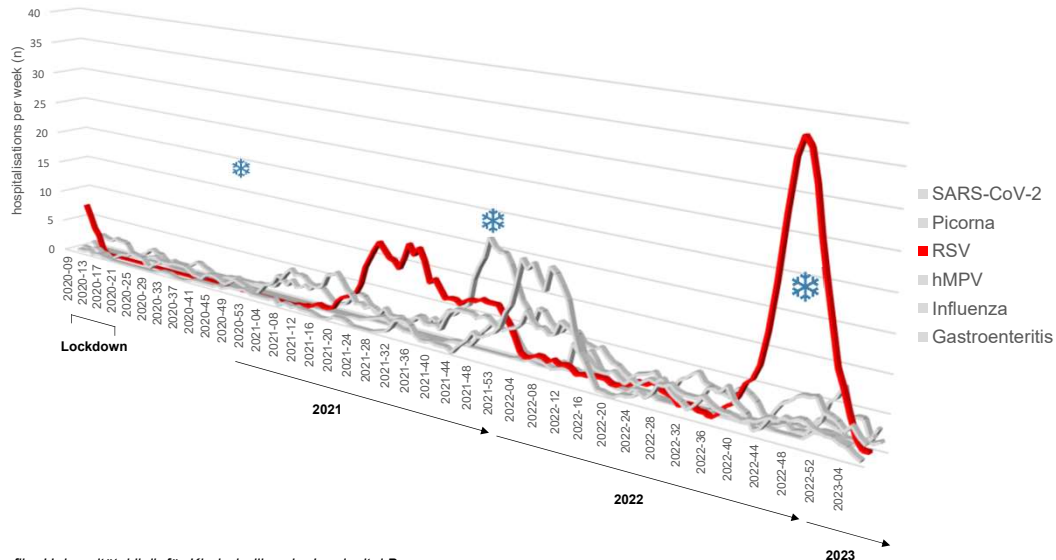
Epidemiologische Zahlen vom 22. Februar 2023



<https://www.paediatricschweiz.ch/news/rsv-infektionen-epidemiologie-zahlen/>

Hospitalizations with RSV

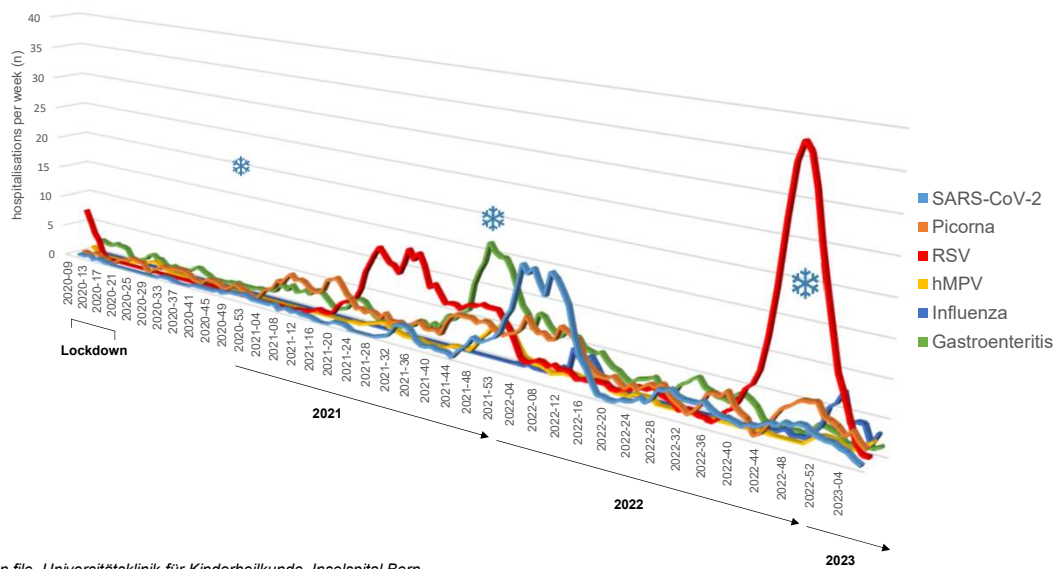
[Kinderklinik BE wk 09/2020 – 07/2023]



Data on file, Universitätsklinik für Kinderheilkunde, Inselspital Bern

Hospitalizations with respiratory and enteric viruses

[Kinderklinik BE wk 09/2020 – 07/2023; 3-week moving averages]



Data on file, Universitätsklinik für Kinderheilkunde, Inselspital Bern

RSV – state of vaccine development

- **Passive immunization** of high-risk infants with a monoclonal antibody:

Palivizumab (Synagis®) in use since ~20 years.

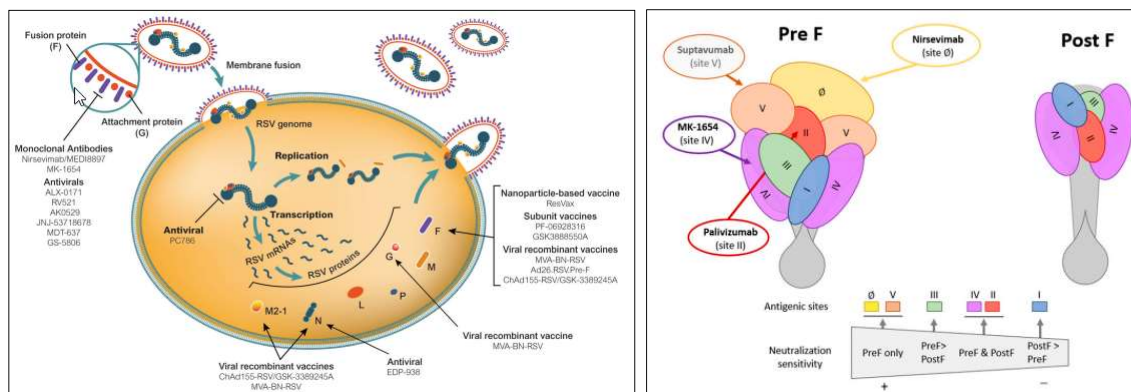
- directed against the antigenically conserved F protein of RSV.
- expensive (5'000-7'500 CHF per patient).
- moderately effective (prevents ~50% of hospitalizations).
- inconvenient (monthly i.m. administration during RSV season).

new: *Nirsevimab*

- **Active immunization** ideally for all infants:

- several products in various stages of clinical development.

Nirsevimab – an improved alternative for palivizumab (Synagis®)



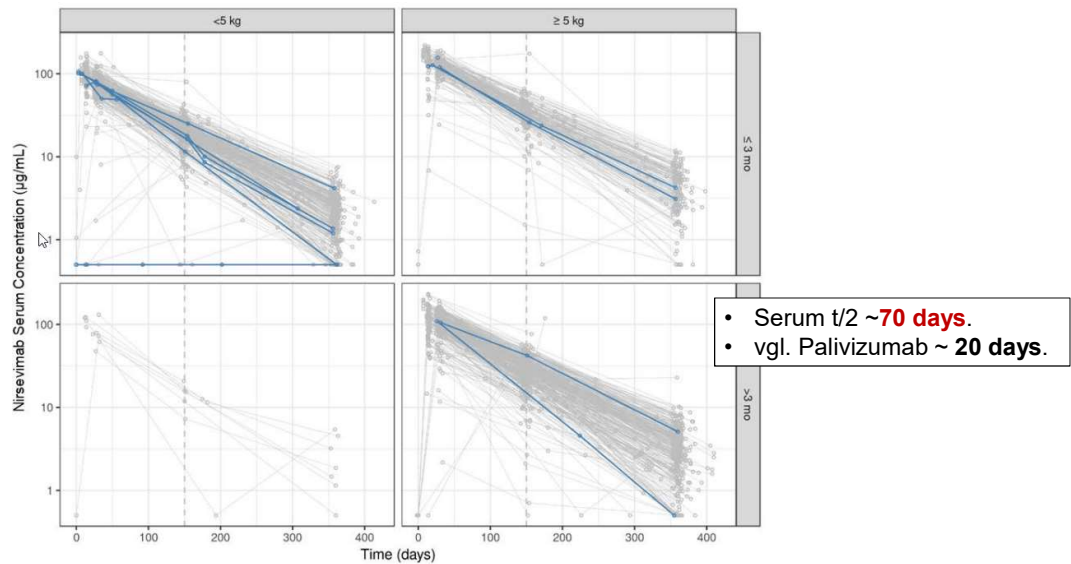
Neutralizing capacity

- Nirsevimab **50x**
- Palivizumab ref.

Taveras J. Neoreviews 2020; <https://pubmed.ncbi.nlm.nih.gov/32737172/>

Domachowse JB. Infect Dis Ther 2021; <https://link.springer.com/content/pdf/10.1007/s40121-020-00383-6.pdf>

Nirsevimab – pharmacokinetics



Griffin MP. N Engl J Med 2022, <https://pubmed.ncbi.nlm.nih.gov/35235726/>

Single dose Nirsevimab – clinical efficacy in preterm infants

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 30, 2020 VOL. 383 NO. 5

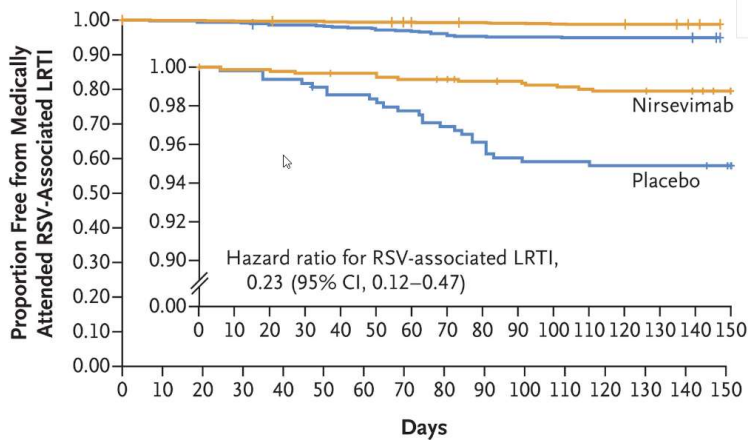
Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants

M. Pamela Griffin, M.D., Yuan Yuan, Ph.D., Therese Takas, B.S., Joseph B. Domachowski, M.D., Shabir A. Madhi, M.B., B.Ch., Ph.D., Paolo Manzoni, M.D., Ph.D., Eric A.F. Simões, M.D., Mark T. Esser, Ph.D., Anis A. Khan, Ph.D., Filip Dubovsky, M.D., Tonya Villafana, Ph.D., and John P. DeVincenzo, M.D., for the Nirsevimab Study Group*

- 1447 **healthy** preterm infants 29 – 35 wks.
- design: 2:1 placebo controlled.
- f/u **150 d** post intervention.
- intervention: **1** i.m. injection of nirsevimab vs. placebo.
- **Nirsevimab**: monoclonal antibody with prolonged t/2.
- outcome I: **70.1%** reduction of RSV associated consultations.
- outcome II: **78.4%** reduction of RSV-associated hospitalizations.
- Swissmedic registration anticipated for 2023.

Griffin MP. N Engl J Med 2020, <https://pubmed.ncbi.nlm.nih.gov/35235726/>

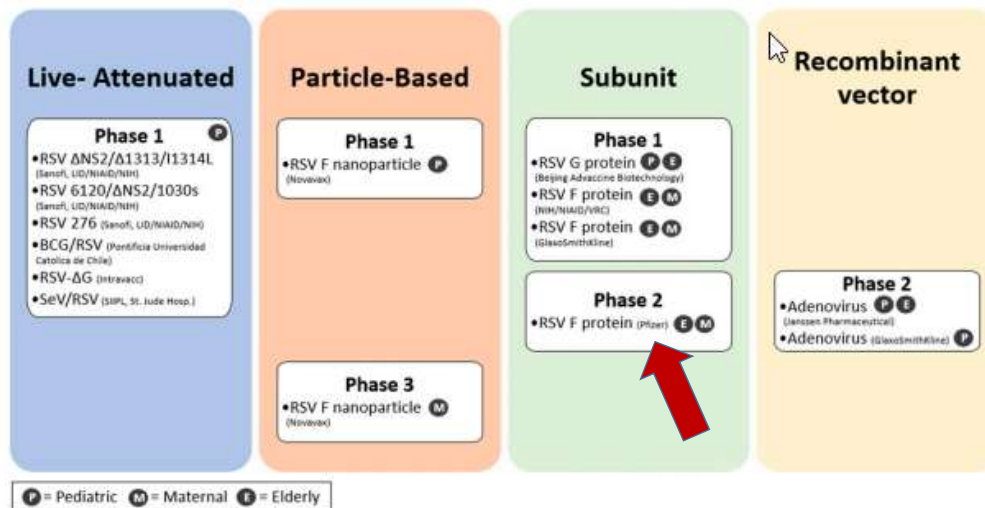
Single dose Nirsevimab – clinical efficacy in term infants



outcome I: reduction of RSV associated consultations **74.5%** (95% CI 49.6-87.1)
 outcome II: reduction of RSV-associated hospitalizations **62.1%** (95% CI -8.6 to 86.8)

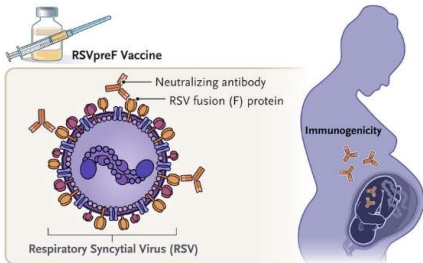
Griffin MP. N Engl J Med 2022, <https://pubmed.ncbi.nlm.nih.gov/35235726/>

Development of active RSV vaccines



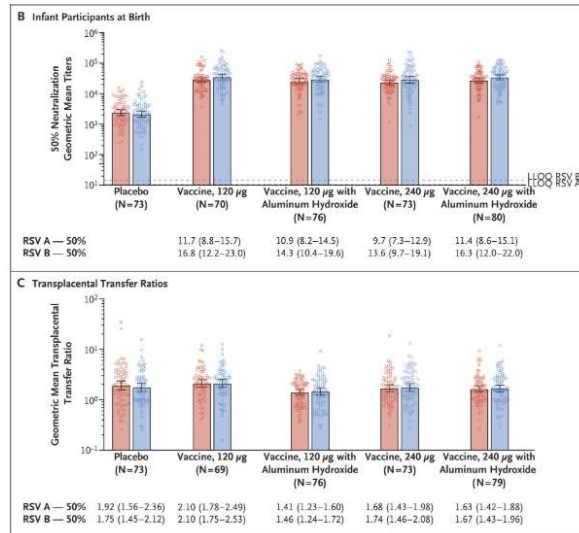
Taveras J. Neoreviews 2020; <https://pubmed.ncbi.nlm.nih.gov/32737172/>
 Collaborators GBDLRI. Lancet Infect Dis 2018; <https://pubmed.ncbi.nlm.nih.gov/30243584/>

Prefusion F protein-based RSV immunization in pregnancy



Phase 2b; 406 mother&child pairs

- demonstrates effective transplacental transfer of maternal IgG directed against RSV and RSV B
- well tolerated
- local adverse events in mothers more common with alum-adjuvanted preparation



Simoes EAF et al. *N Engl J Med* 2022; <https://doi.org/10.1056/nejmoa2106062>

Interim efficacy data of Pfizer recomb prefusion F protein vaccine

MATISSE Trial (1:1 placebo-controlled phase 3 study; 7400 women at 24-36 wks' gestation, < 49 years)

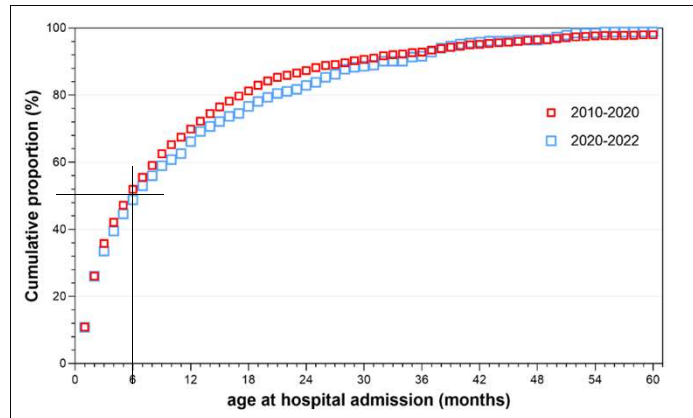
Intervention: maternal immunization with a single dose RSV vaccine (120 µg RSVpreF vs. placebo)

Outcome	Efficacy (95% CI)	f/u until infant age
«Severe medically attended RSV associated lower respiratory tract illness»	81.8% (40.6-96.3)	90 days
	69.4% (44.3-84.1)	6 months
«Clinically meaningful medically attended RSV associated lower respiratory tract illness»»	57.1% (14.7-79.8)	90 days
	51.3% (29.4-66.8)	6 months

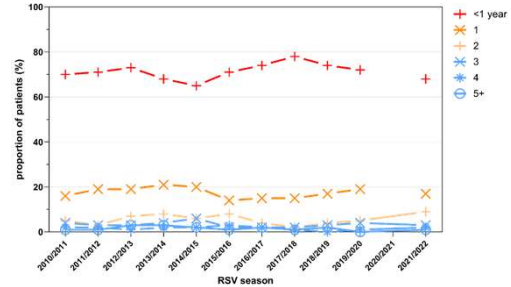
<https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-positive-top-line-data-phase-3-global>

Nirsevimab – proportion of preventable hospitalizations?

Cumulative age distribution at RSV admission



Age at RSV admission: stable over time



Data on file, Infektiologie - Universitätsklinik für Kinderheilkunde, Inselspital Bern

Topics

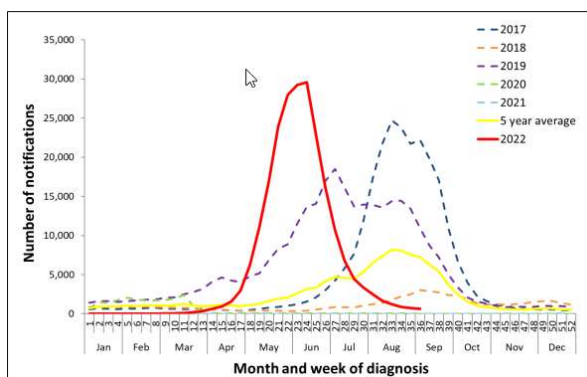
- (1) COVID-19 in children
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- (3) RSV - still greeting from the leader box
- (4) RSV seasons 2021/2022 and 2022/2023 – overwhelms health services; vaccine needed.**
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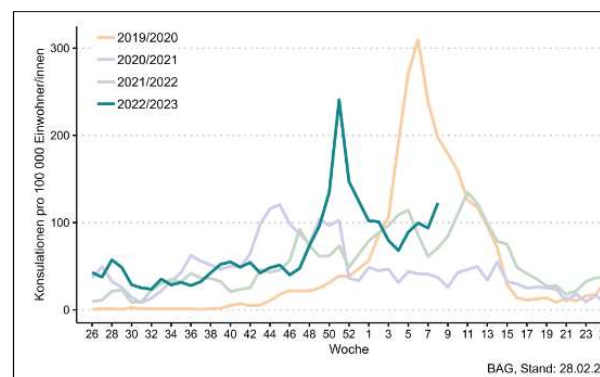
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2022 Influenza season in Australia; 2022/2023 season in CH

AU



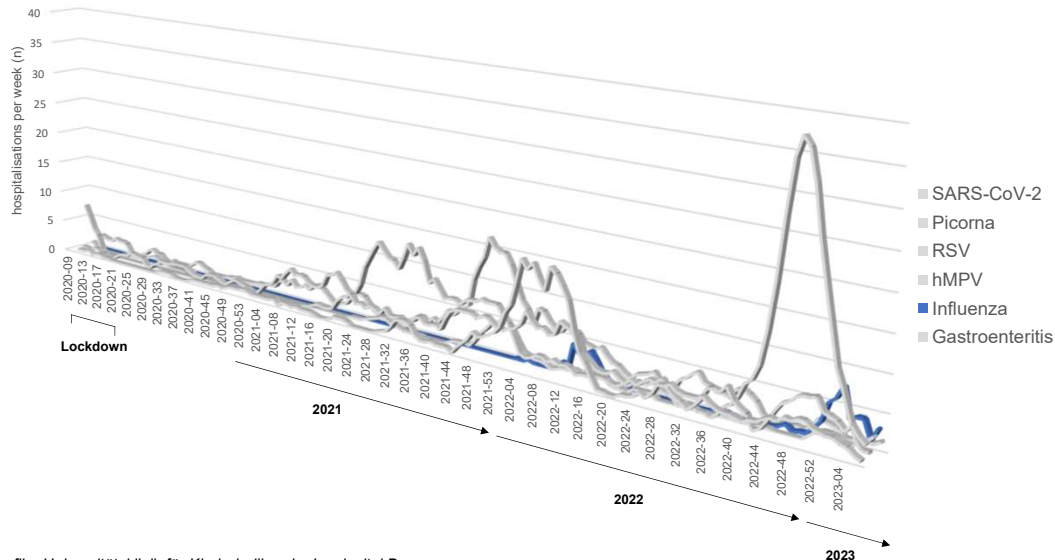
CH



[Australian Influenza Surveillance Report No. 11 – 15 August to 28 August 2022 \(health.gov.au\)](https://www.health.gov.au/australian-influenza-surveillance-report-no-11-15-august-to-28-august-2022)
[Saisonale Grippe – Lagebericht Schweiz \(admin.ch\)](https://www.admin.ch/saisonale-grippe)

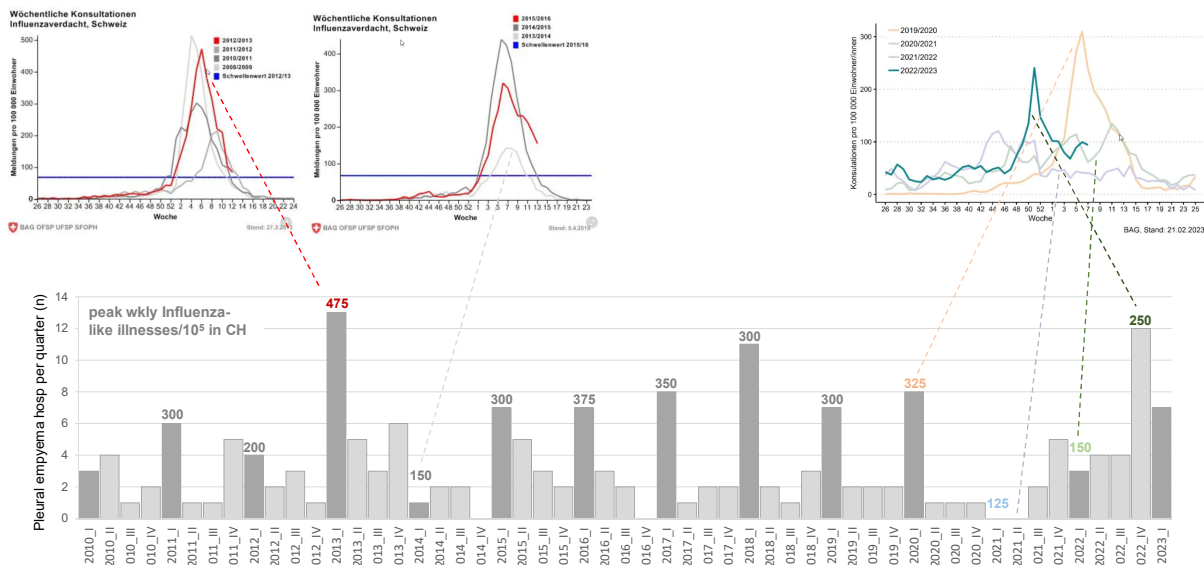
Hospitalizations with Influenza A,B

[Kinderklinik BE wk 09/2020 – 07/2023; 3-week moving averages]



Data on file, Universitätsklinik für Kinderheilkunde, Inselspital Bern

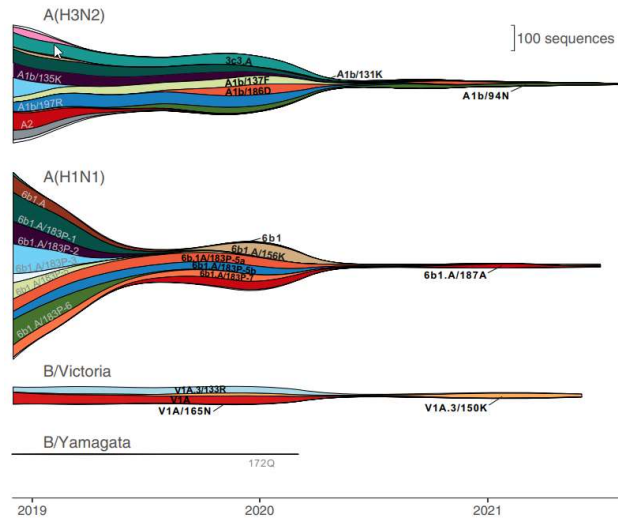
Pleural empyema in Bern and severity of influenza season



Saisonale Grippe – Lagebericht Schweiz (admin.ch); Data on file, Infektiologie - Universitätsklinik für Kinderheilkunde, Inselspital Bern

Global reduction of genetic diversity of circulating influenza strains

Temporal changes in influenza lineage circulation



- “*seasonal influenza transmission lineages continue to perish globally*”
- challenges to selection of vaccine strains.
- waning immunity could lead to increased severity of next influenza epidemic.
- lack of «immunological imprinting» could affect further influenza epidemics.

Dhanasekran V et al. Nat Commun 2022, <https://doi.org/10.1038/s41467-022-29402-5>

Pediatric influenza vaccines

Standard inactivated tetravalent influenza vaccines

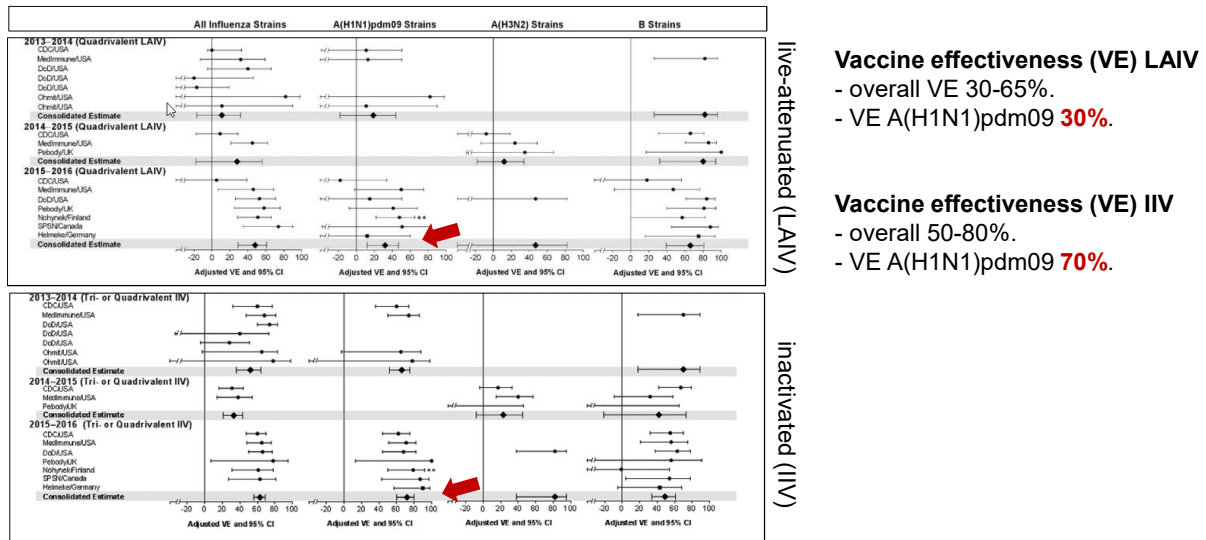
- effectiveness **50-70%**.
- require 2 doses in 0.5-8 year-old in first year.
- Intramuscular administration.

Live-attenuated influenza vaccine (LAIV)

- cold-adapted, attenuated tetravalent vaccine
- intranasal administration.
- approved for 2-18 years only.
- contraindicated in patients with immunodeficiency.
- effectiveness **~50%**.
- poor effectiveness against A(H1N1)pdm09?



Effectiveness of LAIV vs. IIV influenza vaccines [metaanalysis 2013-2016]



Caspard H et al. *Open Forum Infect Dis* 2017; <https://doi.org/10.1093/ofid/ofx111>

Topics

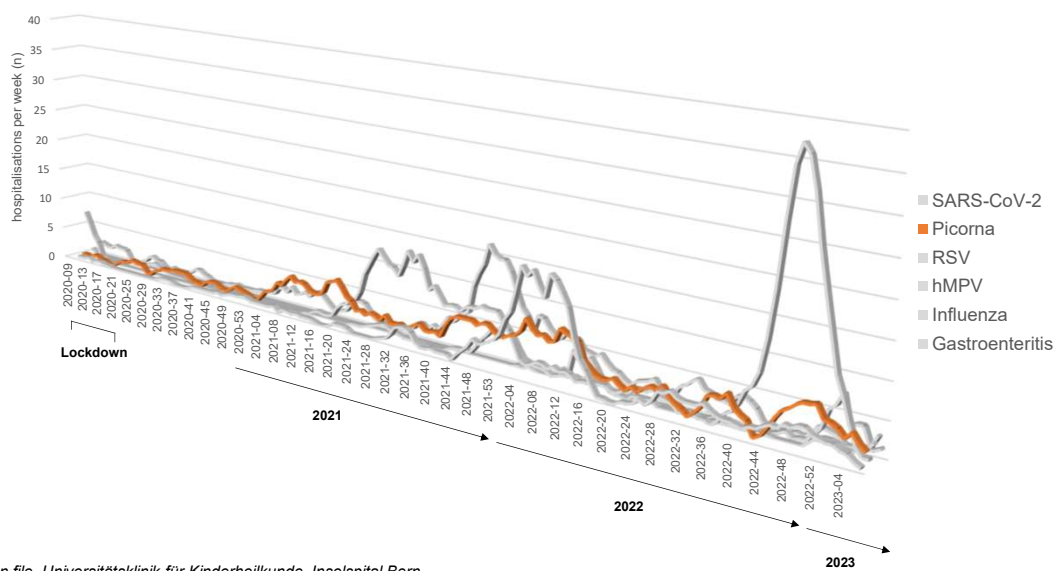
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- (4) RSV seasons 2021/2022 and 2022/2023 – forecasting vs. reality
- (5) Influenza - more than meets our eyes ... underestimated burden, underused vaccines.**
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Hospitalizations with picornaviruses

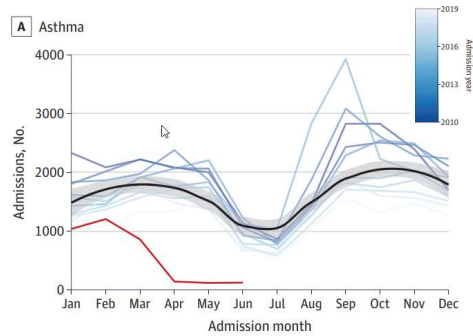
[Kinderklinik BE wk 09/2020 – 07/2023; 3-week moving averages]



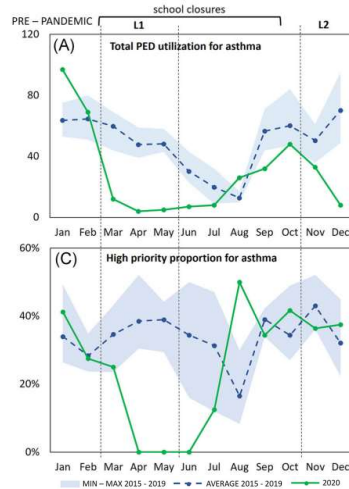
Data on file, Universitätsklinik für Kinderheilkunde, Inselspital Bern

Wheezy bronchitis and asthma attacks during the early pandemic

USA (nationwide)



Italy (Bologna)



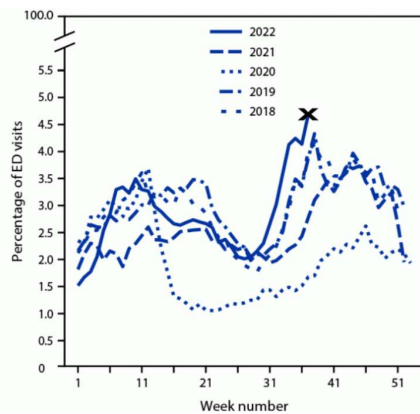
Reasons for drop in asthma consultations/admission

- ▼ viral circulation.
- ▼ exposure to allergens and pollutants.
- ▲ health care avoidance.
- ▲ virtual consultations.

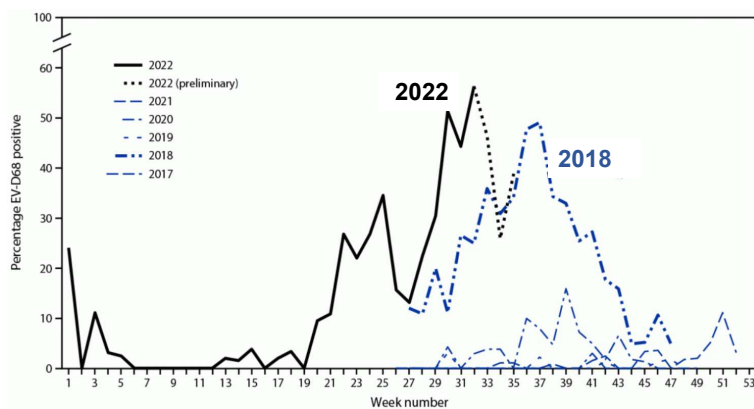
Pelletier JH et al. JAMA Netw Open 2021; <https://pubmed.ncbi.nlm.nih.gov/33576819/>
 Dondi A et al. Pediatr Pulmonol 2021; <https://pubmed.ncbi.nlm.nih.gov/34606693/>

Increase in ARI among children associated with rhino- and enteroviruses including **enterovirus D68** — USA 07-00/2022

Asthma/reactive airway disease in children aged 0–4 years
 (National Syndromic Surveillance Program (NSSP))

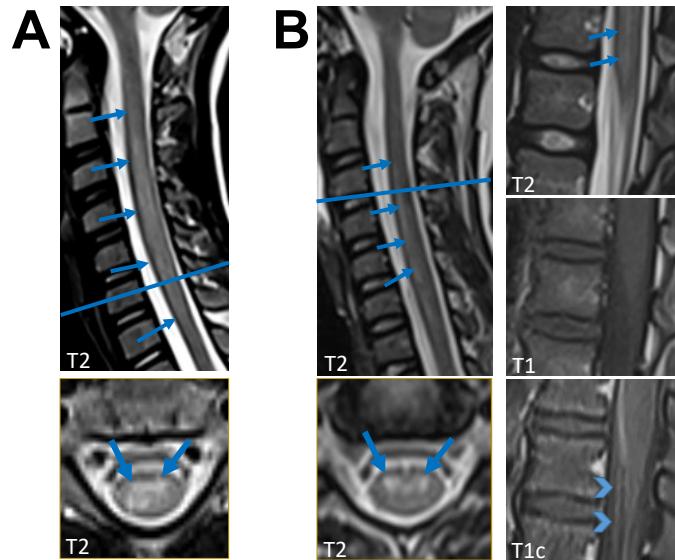


Weekly trends in reported percentage of positive EV-D68 test results among patients aged <18 years with ARI and positive rhinovirus/enterovirus test results who received care in ER or inpatient units (New Vaccine Surveillance Network)



Ma KC et al. MMWR 2022, <http://dx.doi.org/10.15585/mmwr.mm7140e1>

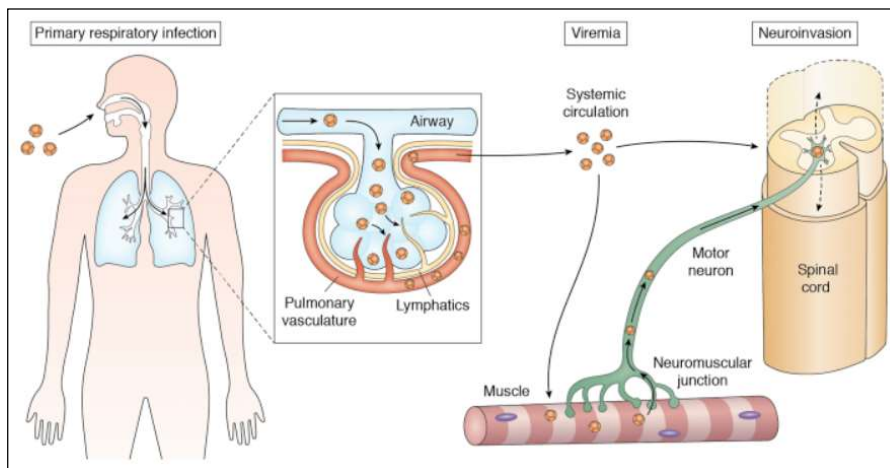
Acute flaccid myelitis (AFM) associated with EV-D68



Bigi S et al. *Swiss Med Wkly* 2023, <https://doi.org/10.57187/smw.2023.40045>

Acute flaccid myelitis (AFM) associated with EV-D68

Pathogenesis



Elrick M.J. *J Biol Chem* 2021, DOI: [10.1016/j.jbc.2021.100317](https://doi.org/10.1016/j.jbc.2021.100317)

Topics

- (1) COVID-19 in children
- (2) «entre parenthèses»
- (3) RSV - still greeting from the leader box
- (4) RSV seasons 2021/2022 and 2022/2023 – forecasting vs. reality
- (5) Influenza - more than meets our eyes
- (6) **Other viruses ... molecular epidemiologic surveillance needed.**
 - picornaviridae (rhinovirus/enterovirus) ... enterovirus D68
 - human metapneumovirus (hMPV)
 - parainfluenza, adenovirus, etc.
- (7) Virus-virus-interactions

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- (7) **Virus-virus-interactions**

NEWS

health Life, But Better Fitness Food Sleep Mindfulness Relationships

NEWS

Check for updates

New York
 Cite this as: [BMJ 2022;379:e2681](https://doi.org/10.1136/bmj.n2681)
<http://dx.doi.org/10.1136/bmj.n2681>
 Published: 07 November 2022

US faces triple epidemic of flu, RSV, and covid

Janice Hopkins Tanne

The US is now in a flu epidemic, according to the Centers for Disease Control and Prevention (CDC), and faces a triple epidemic of flu, respiratory syncytial virus (RSV) in young children, and covid-19.

Until recently t but two new vi increasing fro about 11% now


By Alex Rees, CNN
 Published 7:33 AM EST, Fri December 9, 2022

What to know about the triple threat of influenza, Covid and RSV

NEWS

US faces triple epidemic of flu, RSV, and covid

Published 3 months ago on 2022/11/20




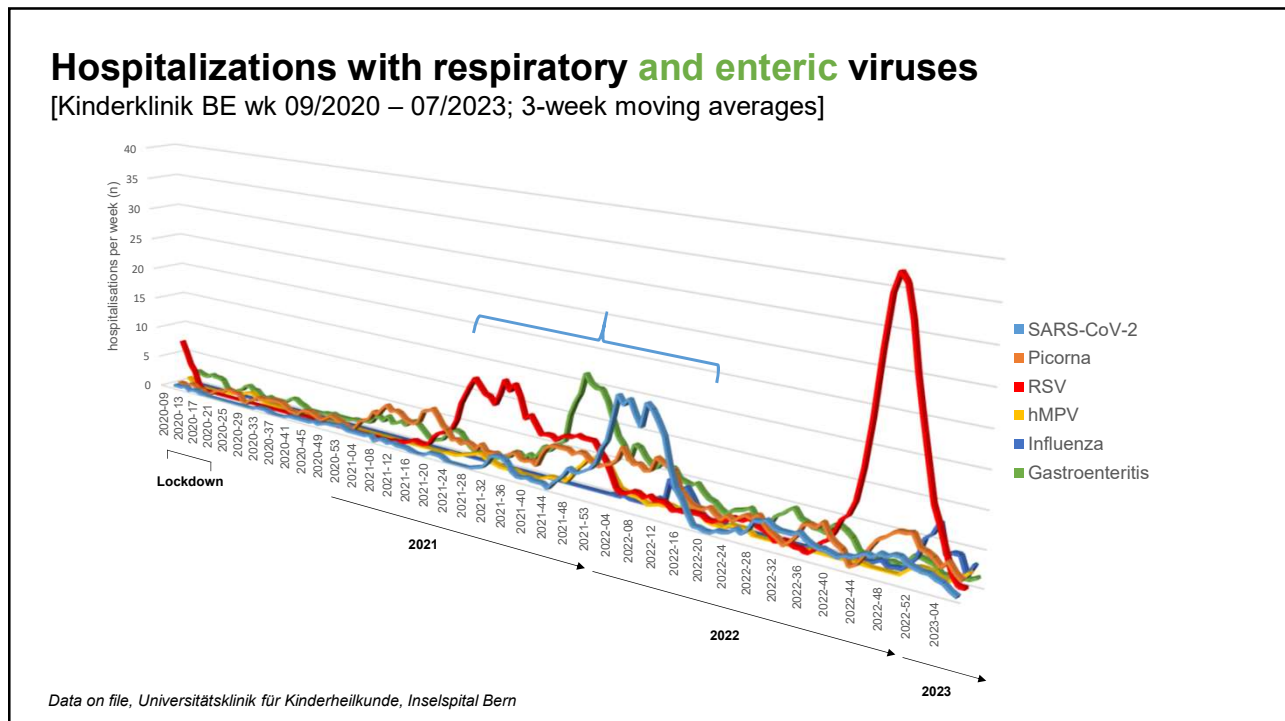
Im Bann der Dreifach-Epidemie

Grippevirus, RSV und Corona bringen das Gesundheitssystem an den Anschlag. Ausgerechnet jetzt fallen auch noch die repetitiven Corona-Tests weg.

Andrea Kučaja, Mirko Plüss, Theres Lüthi • 24.12.2022, 21.45 Uhr

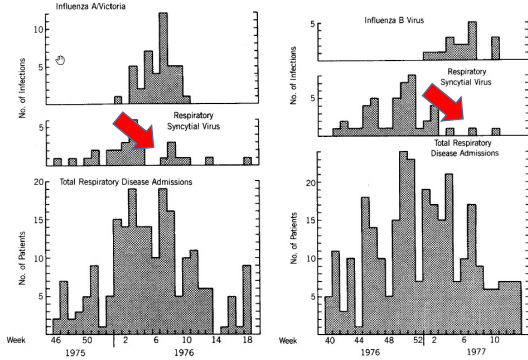
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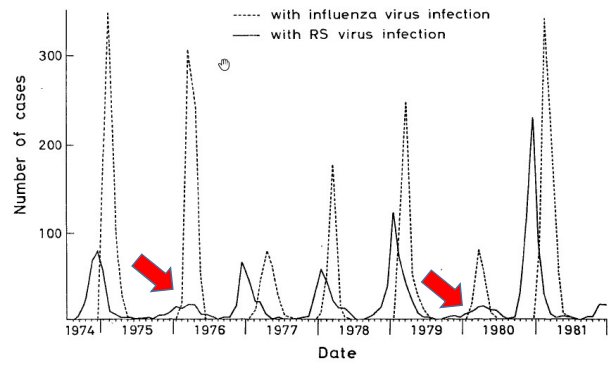


Virus-virus interactions at the host-level – long suspected

Houston, TX 1975-1977
«Influenza suppresses RSV»



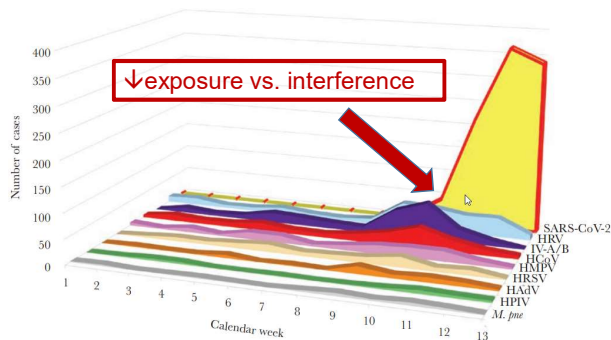
Norway, 1974-1981
«Influenza suppresses RSV»



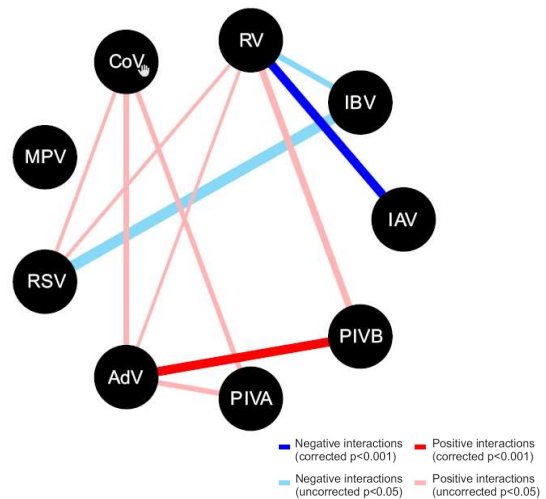
Glezen WP et al. JAMA 1980; <https://pubmed.ncbi.nlm.nih.gov/6244421/>
Anestad G. Lancet 1982; <https://pubmed.ncbi.nlm.nih.gov/6121154/>

Virus-virus interactions in pediatric/adult epidemiology

Basel, 2020
«SARS-CoV-2 suppresses other respiratory viruses»

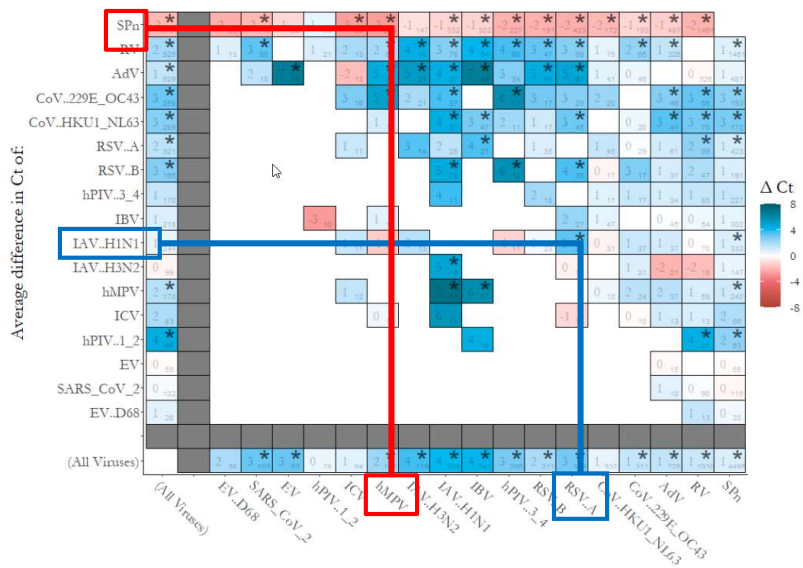


Glasgow, 2005-2013
«Influenza suppresses RSV»



Leuzinger K et al. J Infect Dis 2020; <https://pubmed.ncbi.nlm.nih.gov/32726441/>
Nickbakhsh S et al. PNAS 2019; <https://pubmed.ncbi.nlm.nih.gov/31843887/>

Quantitative pathogen-pathogen interaction NPA samples



Burstein R et al. medRxiv 2022. <https://doi.org/10.1101/2022.02.04.22270474>

- **115'087** nasal samples of symptomatic patients of all ages.
- **29%** positive for at least 1 out of 17 respiratory pathogens.
- **Outcome:** difference in Ct value between mono-infection and co-infection.
- Positive interactions (facilitation) rare, **except *S. pneumoniae* with all viruses.**
- Virus-virus interactions mostly negative (**interference**).

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 - human metapneumovirus (hMPV)
 - parainfluenza, etc.
- (7) **Virus-virus-interactions ... more research needed ► integration into prediction algorithms.**

THANK YOU