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2023 WEBINAR

RESPIRATORY SYNCYTIAL VIRUS UPDATE

23 AUGUST 2023



6:30 - 7:30PM AEDT

Presenter: Dr Gemma Saravanos

Moderator: Dr Andrew Minton, PhD

Respiratory Syncytial Virus (RSV): Preparing for prevention

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Respiratory Syncytial Virus (RSV): Preparing for prevention

Learning Outcomes:

Following this webinar, participants will be able to:

- Describe the burden and impact of RSV disease
- Identify existing & approaching RSV preventatives
- Consider activities needed to support the introduction of new RSV preventatives

Background to respiratory syncytial virus (RSV)

- Recovered from a coryzal chimpanzee in 1956 [1]
- Cytopathic effect in cell culture – caused formation of ‘syncytia’ (giant cells) [2]
- Temporal relationship with epidemics of seasonal childhood respiratory infections [2,3]
 - Bronchiolitis, pneumonia, croup etc.
- RSV re-infection throughout life [2]
- Transmission – droplet & contact, aerosol? [4]

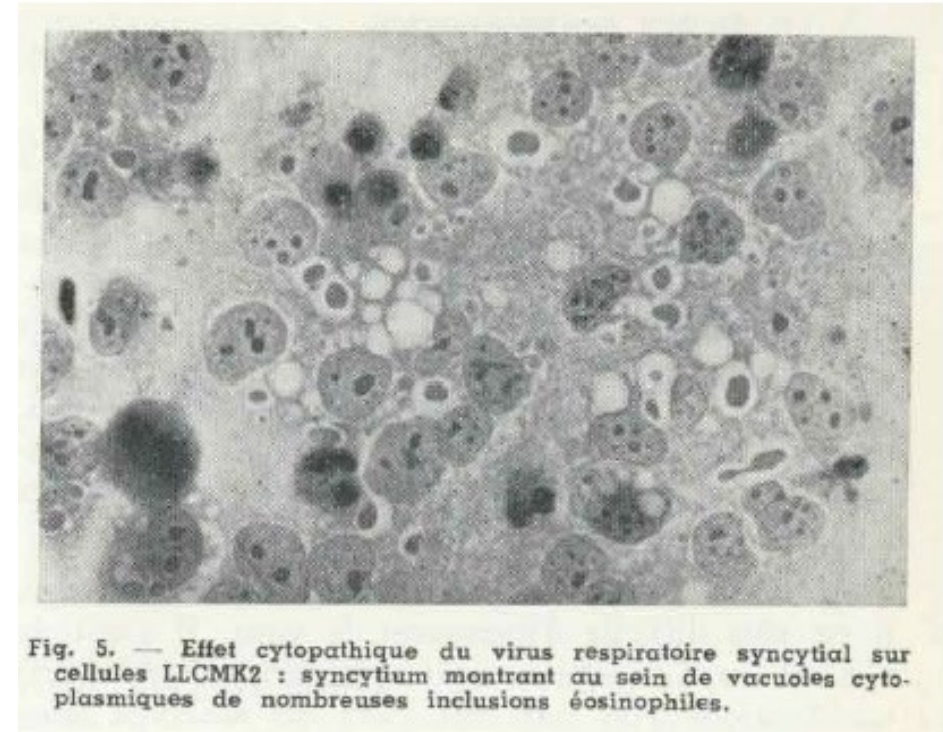
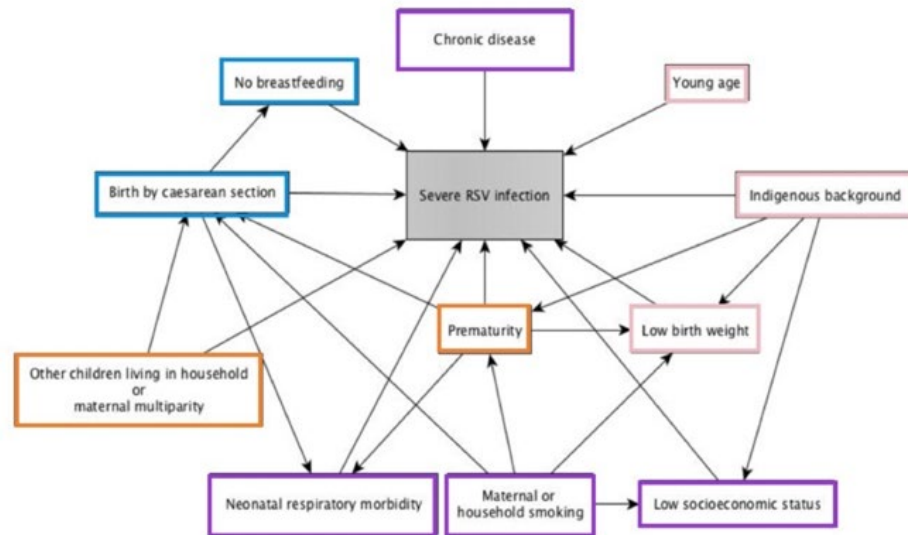


Image: Gerbeaux et al. Ann Pedatr, 1970

Risk factors for severe RSV disease

Risk factors in children

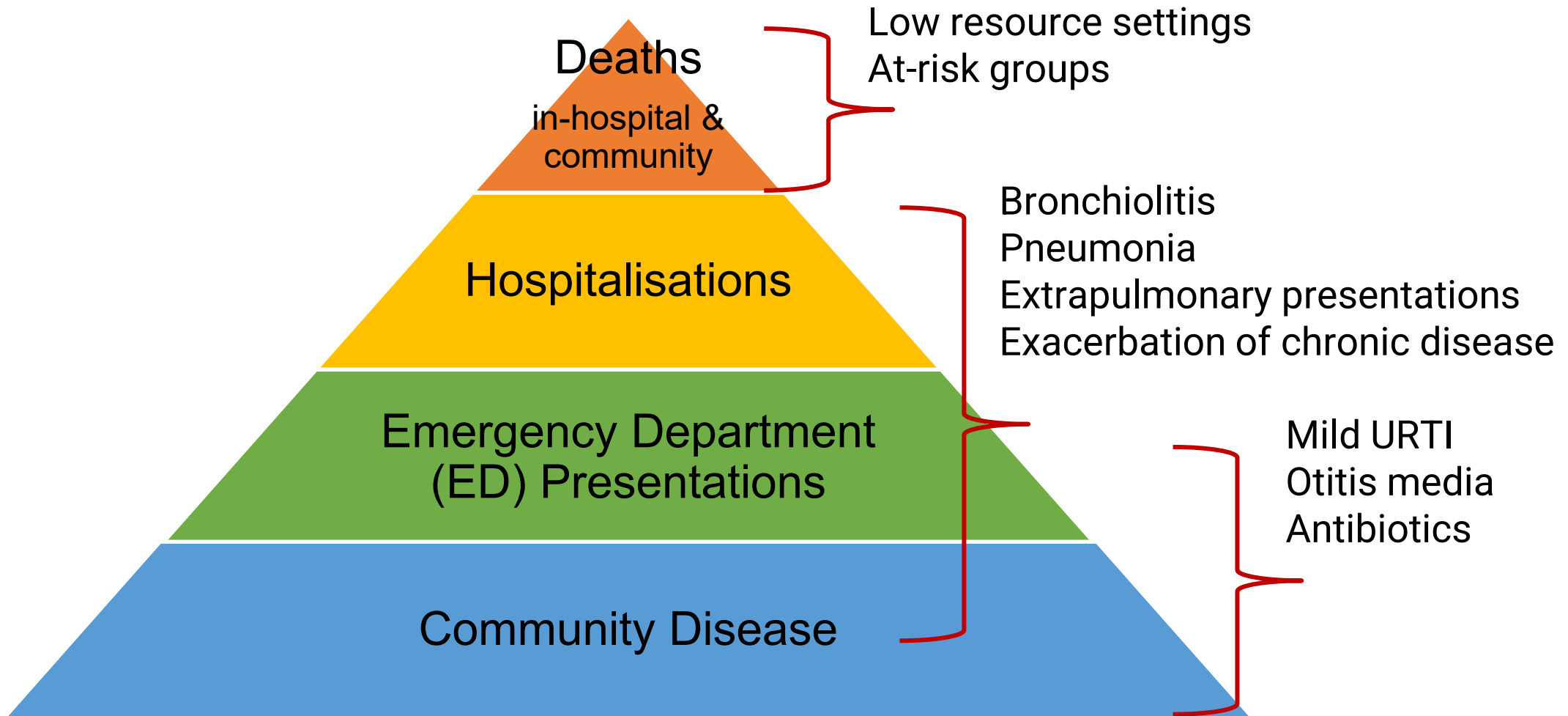


[Hall Pediatrics 2013] [Schuh J Ped 2018] [Shi J Global Health 2015] [Homaira BMJ Open 2016] [Hall NEJM 2009]
Figure by Dr Kimberley Chow



https://www.instagram.com/p/CwGGi8ksPs-/?utm_source=ig_web_copy_link&igshid=MzRIODBiNWFIZA==

The burden of RSV of disease



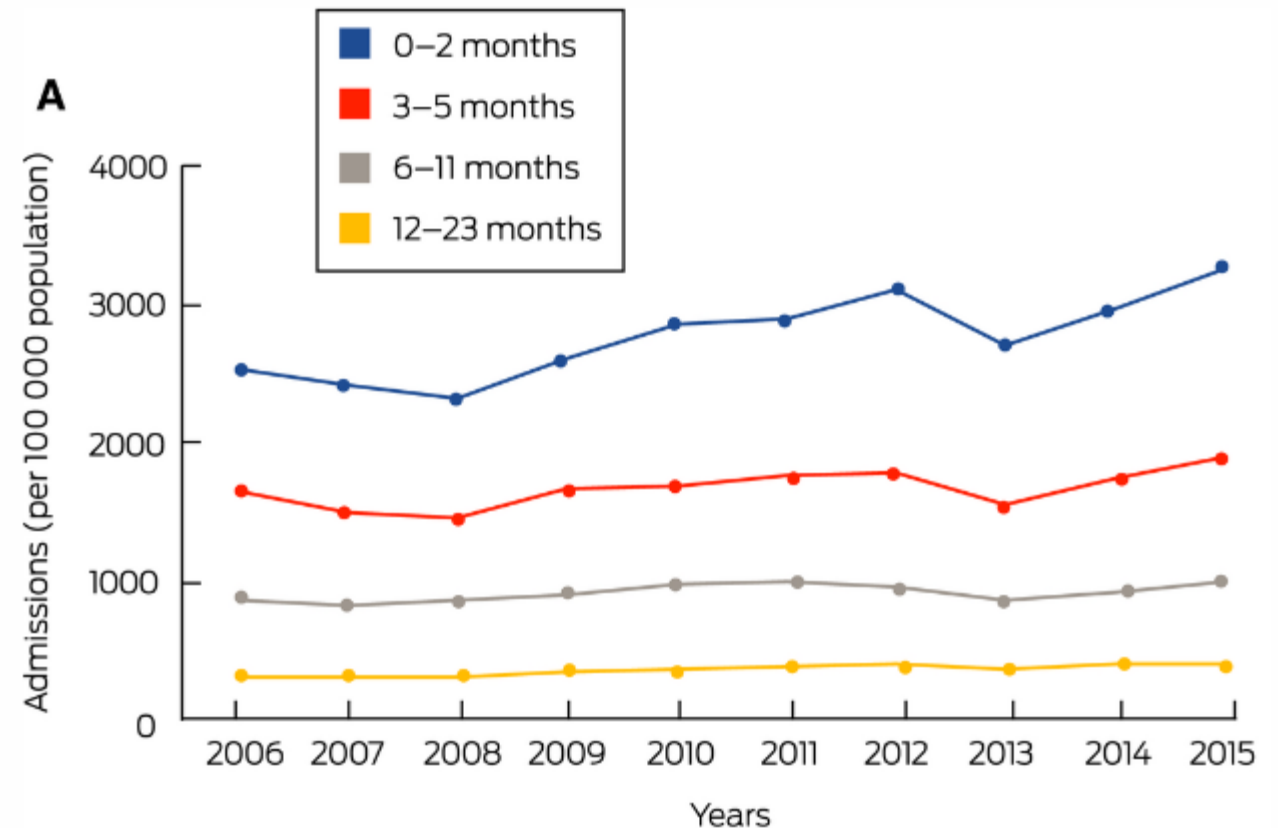
Burden of RSV disease in Australian children

Community disease [1]

- Most children infected by age 2-3y
- 34% community medical care
- 2% hospitalised

Hospitalisation [2]

- >7,000 children in 2015
- LOS 3 days (IQR 1-4)
- Indigenous children IR 1.8 (1.8-2.0)
- AU >\$6,350 per hospital episode [3]
- AU\$20,000 per ICU episode [4]



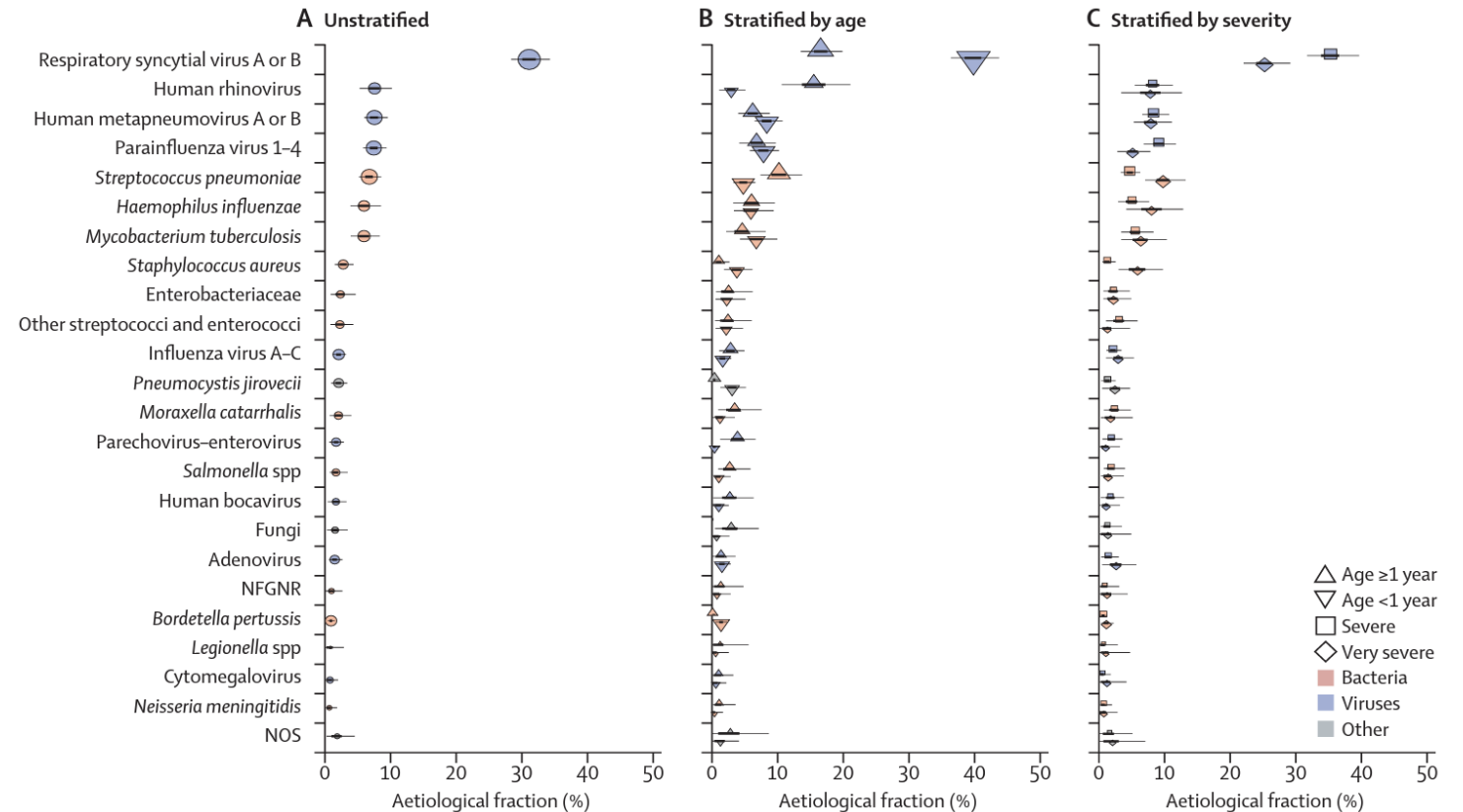
[1] Takashima et al. 2021 <https://doi.org/10.1007/s00431-021-03998-0> [2] Saravanos et al. 2019 <https://doi.org/10.5694/mja2.50159>; [3] Homaira et al. 2016 doi: 10.1017/S0950268815003015; [4] Pham et al. 2019 <https://doi.org/10.1111/jpc.14491>

RSV contribution to childhood pneumonia

The Pneumonia Etiology Research for Child Health (PERCH) study

- Case-control study in 7 LMIC
- Children aged 1-59 months hospitalised for pneumonia
- RSV had the greatest aetiological fraction (31%, 95% CI 28–34)
- More than three times greater than the next leading pathogen

PERCH Study Group 2019 [https://doi.org/10.1016/S0140-6736\(19\)30721-4](https://doi.org/10.1016/S0140-6736(19)30721-4)

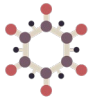


Childhood RSV disease burden compared to influenza

Table 1. Global burden of lower respiratory infections in children aged less than 5 years for key viral and bacterial pathogens.

Respiratory Pathogen	Annual number of LRI (95% uncertainty range [UR])	Annual number of LRI hospitalisations (UR)	Annual number of in-hospital LRI deaths (UR)	Annual number of all LRI deaths (UR)	Year of estimate (Source)
Respiratory Syncytial Virus*	33.0 million (25.4–44.6)	3.6 million (2.9–4.6)	26,300 (15,100–125,200)	109,600 (97,200–124,900)	2019 (Li et al. 2021) [3]
Influenza*	10.1 million (6.8–15.1)	870,000 (543,000–1.4 million)	15,300 (5800–43800)	34,800 (13,200–97,200)	2018 (Wang et al. 2020) [4]

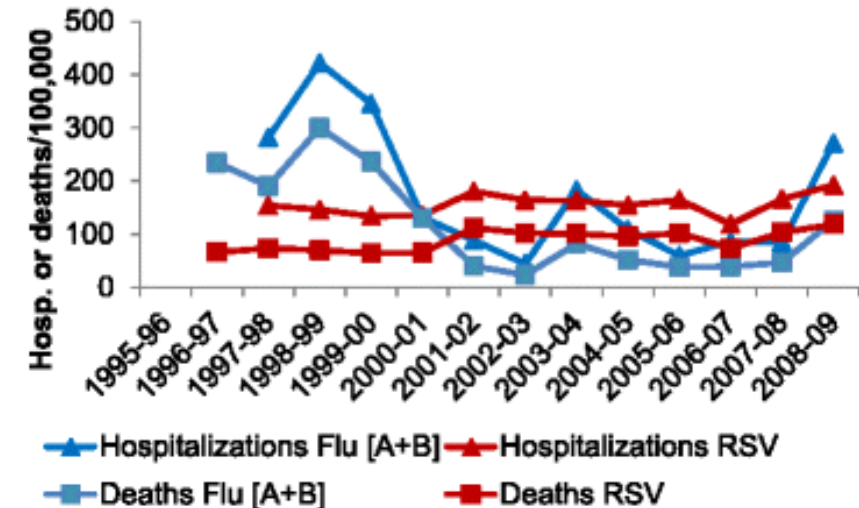
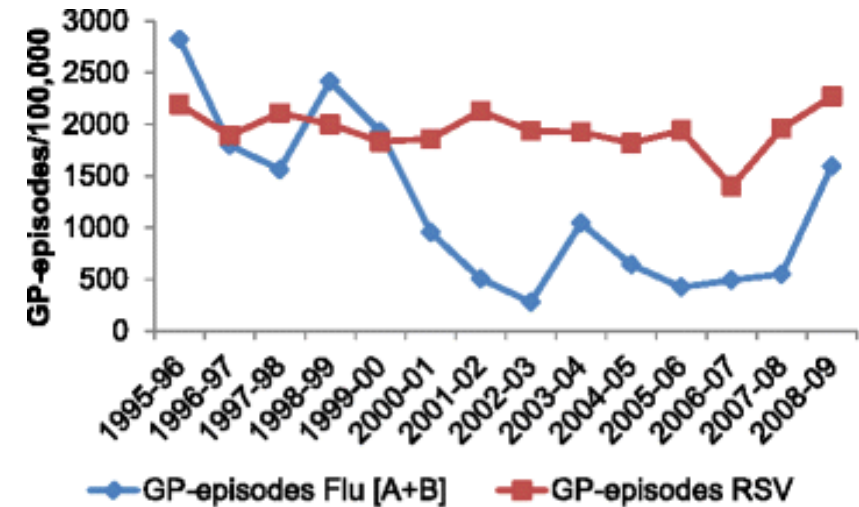
Adult RSV disease burden compared to influenza



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In most seasons, RSV contributes more primary care visits, hospitalisations & deaths in adults $\geq 65y$ compared to influenza

Incidence (per 100,000) of respiratory GP episodes, hospitalizations and deaths among 65+ year olds attributed to RSV or Influenza [A + B] in the seasons studied Fleming et al. 2015
<https://doi.org/10.1186/s12879-015-1218-z>



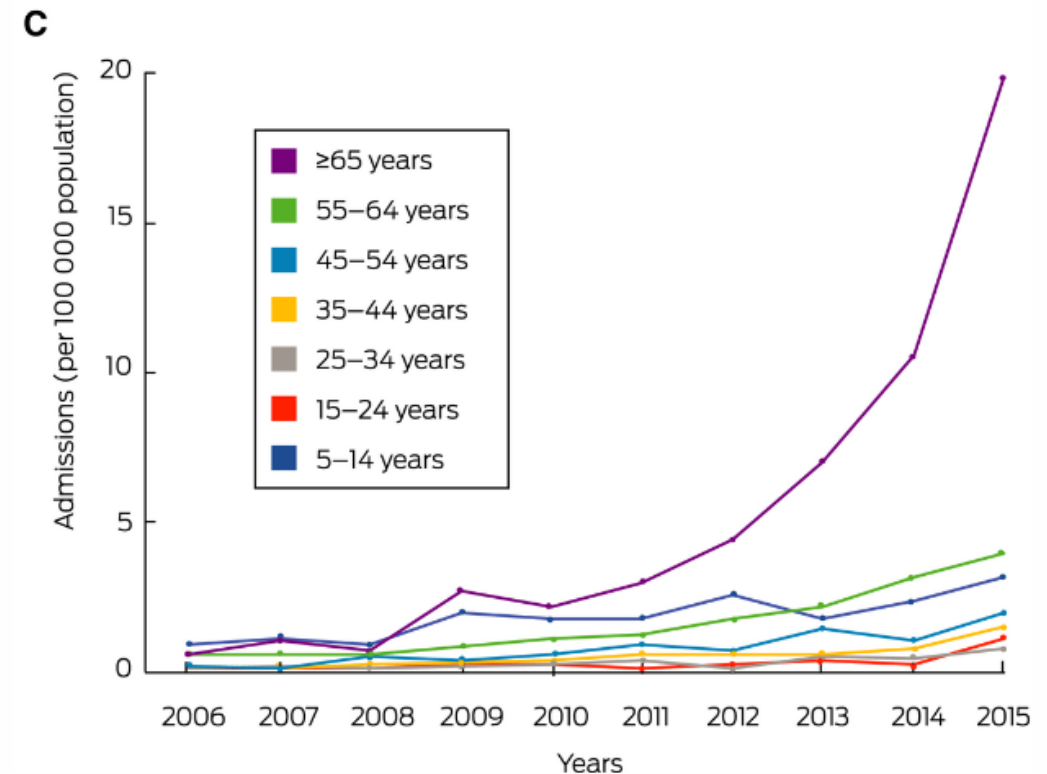
Burden of RSV disease in Australian adults

Hospitalisation [1]

- >700 adults aged ≥ 65 y in 2015
- Higher rates for Indigenous adults
- LOS 6 days (IQR 4-9)
- Substantial in-hospital deaths
- True number may be ~ 8 x higher in adults >75 years [2]

Laboratory Notifications [3]

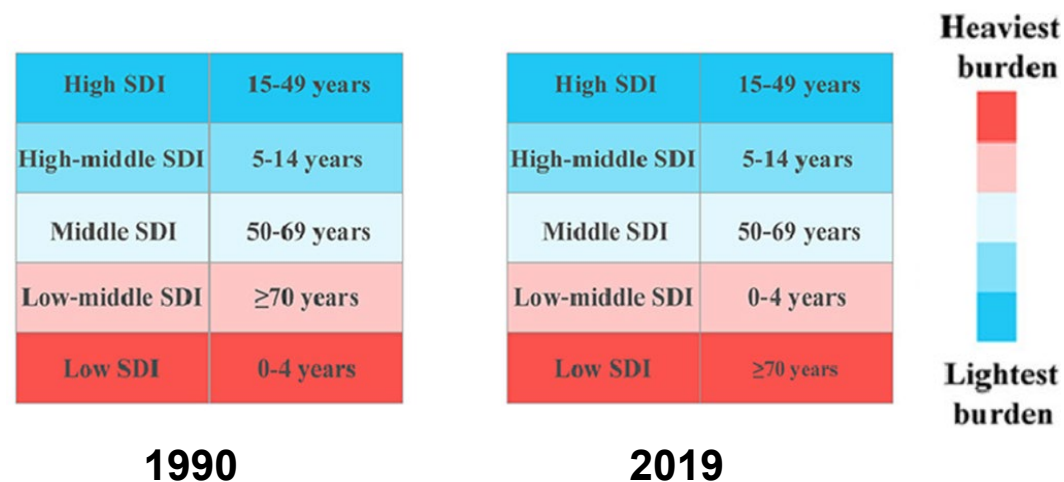
- 16,475 RSV notifications in adults aged ≥ 65 y in 2023 as at 20th August



Global burden of RSV disease

- Varies greatly by socio-demographic index (SDI)
- Death and disability adjusted life years (DALY)
 - Declined globally from 1990 to 2019
 - Decline not uniform across age and SDI groups
- Vaccine equity an important consideration

Global burden of RSV disease deaths by socio-demographic index



Other notable impacts of RSV disease...

- Asthma - infant RSV infection may cause ~15% later onset asthma [1]
- Increased risk of cardiovascular events in adults [2]
- Quality of Life e.g. RSV symptoms, parental concern, disrupted activities [3]
- Healthcare resource consumption – primary care, emergency, hospital & ICU [3]
 - ‘Winter Surge’
 - Overuse of non-recommended, low-value interventions in bronchiolitis [4]
- Overuse of antibiotics in children with RSV infection [5]
- Healthcare associated RSV infection [6]

RSV bronchiolitis: Oscar's story...



“The nurses and doctors from NETS and in ICU were so thoughtful, not only to Oscar but also to us as well. They were really supportive, friendly and calm which helped to keep us calm during a really difficult time,” Lisa said.

Source: <https://www.schn.health.nsw.gov.au/news/articles/2022/07/oscars-winter-battle-with-rsv>

Existing RSV prevention & approaching RSV preventatives

- RSV vaccines & monoclonal antibody (mAb) immunoprophylaxis

Existing RSV prevention

- Basic infection prevention and control measures
 - Isolation of infected individuals, hand/respiratory/environmental hygiene, face masks
- Passive immunisation - monoclonal antibody (mAb) palivizumab for high risk infants [1]
- Promotion of breastfeeding [2,3] and smoking cessation [3,4]
- Influenza vaccination? (possible non-specific protective effect) [5]

[1] Garegnani et al. Cochrane Review, 2021 <https://doi.org/10.1002/14651858.CD013757.pub2> ; [2] Mineva et al. BMJ Global Health, 2023 <http://dx.doi.org/10.1136/bmjgh-2022-009693> ; [3] Shi et al. Journal of Global Health, 2015 doi: 10.7189/jogh.05.020416; [4] Homaira et al. BMJ Open, 2016 <http://dx.doi.org/10.1136/bmjopen-2016-011398> ; [6] Le et al. Vaccine, 2023 <https://doi.org/10.1016/j.vaccine.2023.06.085>

Existing RSV prevention: Palivizumab (Synagis®)

- Short-acting, monoclonal RSV antibody which targets the F protein 'passive immunisation'
- Recommended for high-risk infants
 - Pre-term, chronic lung disease, congestive heart disease
- Monthly intramuscular, weight-based dose
 - Up to 5 doses during the RSV season
- Can reduce RSV hospitalisation by ~56% [2]
- High cost & variable guidelines [3]



Approaching RSV preventatives

RSV vaccine research & development has a long history [1,2]

- Vaccine-associated enhanced disease (VAED) in early clinical trials (1960s)
 - *Formalin-inactivated whole-virus RSV vaccine
 - Enhanced RSV disease in naïve children following wild-type infection

Currently, F protein subunit vaccine candidates reserved for adult population due concern about VAED



Review

Vaccine-associated enhanced disease: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data

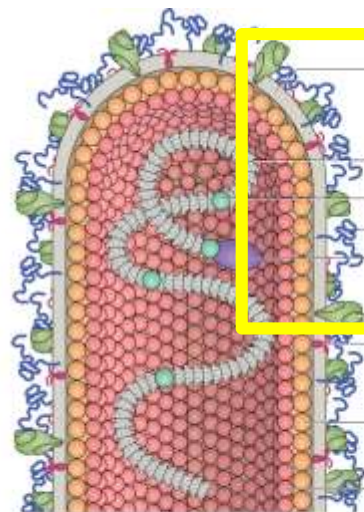


[1] Munoz et al. Vaccine, 2022 <https://doi.org/10.1016/j.vaccine.2021.01.055>; [2] Battles & McLellan, Nat Rev Microbiol, 2019 <https://doi.org/10.1038/s41579-019-0149-x>

*Corrected by G. Saravanos - 1st Sep 2023

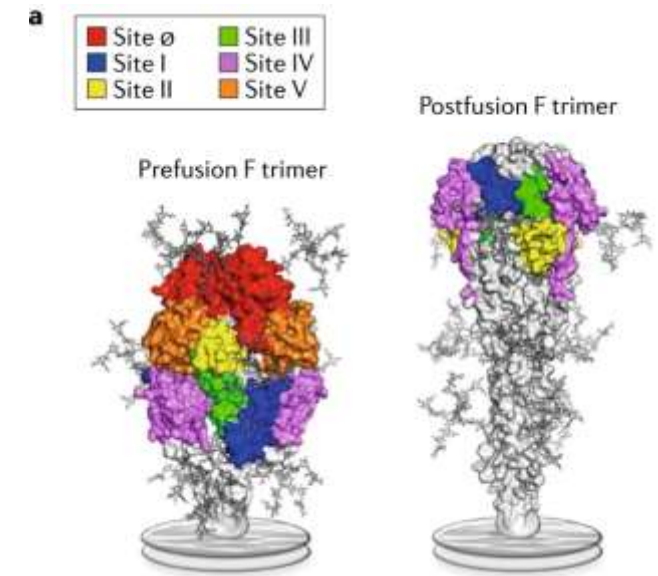
Approaching RSV preventatives

Paediatric	Maternal	Elderly
<p>Immunoprophylaxis (mAb)</p> <p>Vaccines:</p> <ul style="list-style-type: none"> • Live attenuated • Nucleic acid • Recombinant vectors 	<p>Vaccines:</p> <ul style="list-style-type: none"> • Protein-based (F) • Nucleic acid 	<p>Vaccines:</p> <ul style="list-style-type: none"> • Protein-based (F) • Nucleic acid • Recombinant vectors



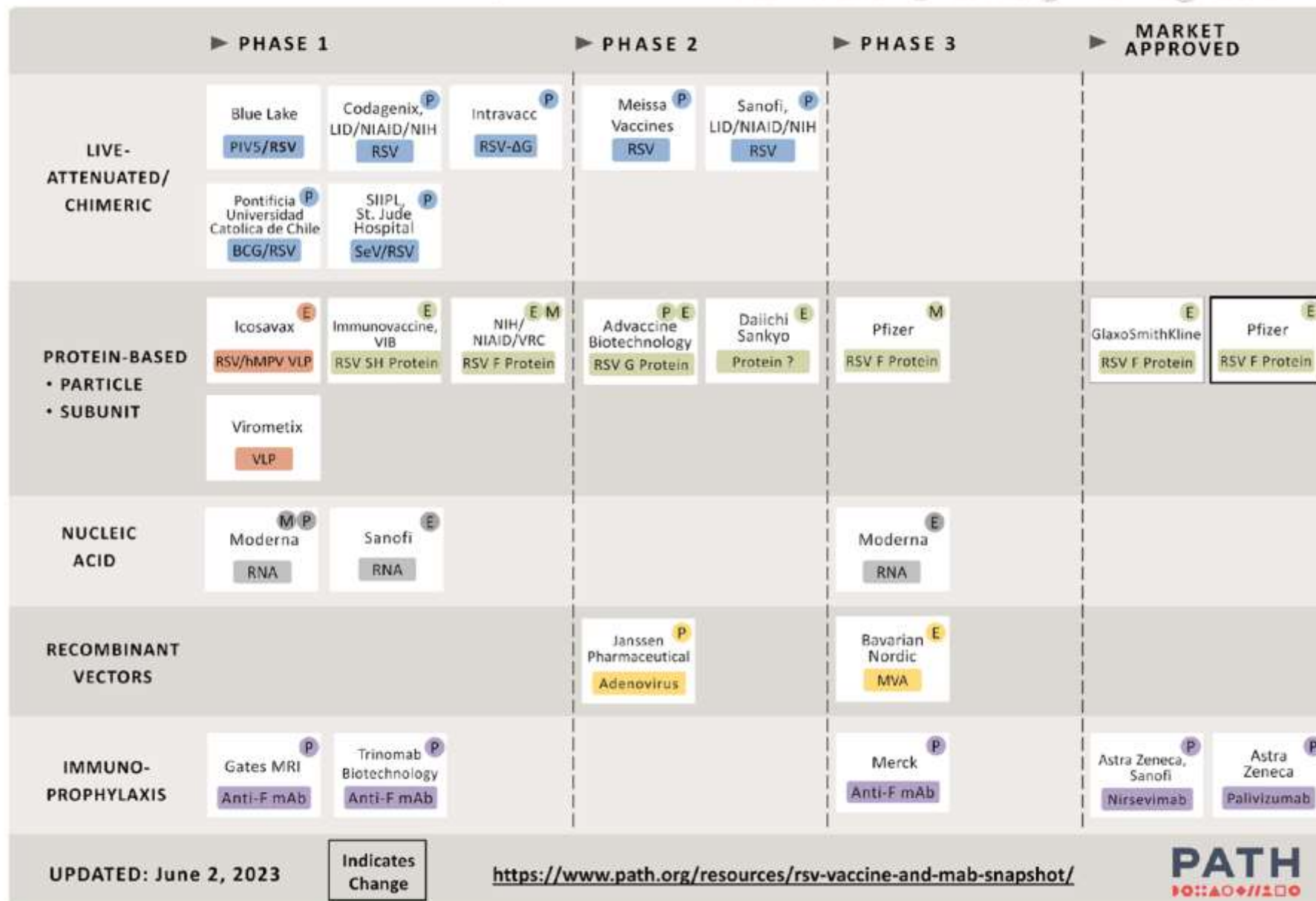
- **F (Fusion) protein**
 - Highly conserved
 - Most common vaccine & mAb target - pre-fusion conformation

- **G (attachment) glycoprotein**
 - Variable



RSV Vaccine and mAb Snapshot

TARGET INDICATION: **P** = PEDIATRIC **M** = MATERNAL **E** = ELDERLY



Approaching RSV preventatives

Product	Type	Target Group	Approvals
Arexvy® GSK	Pre-fusion F protein adjuvanted vaccine	Older adults (≥60y)	<ul style="list-style-type: none"> • FDA May 23 • EMA Jun 23 • TGA – under evaluation
Abrysvo® Pfizer	Pre-fusion F protein vaccine	Older adults (≥60y) <i>*Pregnant women (to protect infants)</i>	<ul style="list-style-type: none"> • FDA May 23 • EMA Jul 23 • TGA – under evaluation
Beyfortus® (nirsevimab) Sanofi-Aventis	<u>Long-acting</u> mAb – passive immunisation	Infants and young children (<24m)	<ul style="list-style-type: none"> • FDA Jul 23 • EMA Oct 22 • MHRA Nov 22 • TGA – under evaluation

**Approval granted by the EMA only*

Footnotes: FDA – Federal Drug Agency (FDA); EMA (European Medicines Agency (EMA), Medicines; Medicines and Healthcare products Regulatory Agency (MHRA); Therapeutic Goods Agency (TGA).

Approaching RSV preventatives

Product	Type	Target Group	Approvals
Arexvy® GSK	Pre-fusion F protein adjuvanted vaccine	Older adults ($\geq 60y$)	<ul style="list-style-type: none">• FDA May 23• EMA Jun 23• TGA – under evaluation

Phase 3 RCT (17 countries, 24,973 immunocompetent participants $\geq 60y$ enrolled)

- **Vaccine efficacy:** 82% (95% CI 58-94%) for RSV-associated LRTD in 1st season
75% (95% CI 60-85%) for RSV-associated LRTD over 2 seasons
- **Vaccine safety:** Serious adverse events (SAE) similar in the intervention & control group
Higher reactogenicity (solicited local/systemic reactions) 3.8 to 0.9%

Approaching RSV preventatives

Product	Type	Target Group	Approvals
Abrysvo® <i>Pfizer</i>	Pre-fusion F protein vaccine	Older adults (≥60y)	<ul style="list-style-type: none">• FDA May 23• EMA Jul 23• TGA – under evaluation

Phase 3 RCT (7 countries, 36,862 immunocompetent participants ≥60y enrolled)

- ***Vaccine efficacy:*** 90% (95% CI 54-99%) for RSV-associated LRTD in 1st season
84% (95% CI 60-95%) for RSV-associated LRTD over 2 seasons
- ***Vaccine safety:*** Serious adverse events (SAE) similar in the intervention & control group
Slightly higher reactogenicity (solicited local/systemic reactions) 1.0% to 0.7%

Approaching RSV preventatives

Product	Type	Target Group	Approvals
Abrysvo® <i>Pfizer</i>	Pre-fusion F protein vaccine	<i>*Pregnant women (to protect infants)</i>	• EMA Jul 23

**EMA only*

Phase 3 RCT (18 countries, 7,392 pregnant women enrolled)

- ***Vaccine efficacy:*** 82% (99.5% CI 41-96%) medically attended severe RSV-associated LRTI within 90 days after birth
69% (97.6% CI, 44 to 84) within 180 days after birth.
- ***Vaccine safety:*** Serious adverse events (SAE) similar in the intervention & control group
Reactogenicity – injection site pain, muscle pain & headache more common in the intervention group

RSV immunisation programme for older adults

ACIP (US) recommend that adults aged ≥ 60 years may receive a single dose of an RSV vaccine, using shared clinical decision-making [1]

**Six cases of inflammatory neurologic events (including GBS, ADEM) were reported after RSV vaccination (0.01-0.02%) and post-marketing surveillance will be important to determine if this is due to chance or causal.*

JCVI (UK) advises a programme adults ≥ 75 years as a one-off campaign then a routine programme for those turning 75 years. Currently, there is no product preference with all demonstrating comparable efficacy. [2]

[1] Melbar et al. MMWR 2023 <https://www.cdc.gov/mmwr/volumes/72/wr/pdfs/mm7229a4-H.pdf>; [2] <https://www.gov.uk/government/publications/rsv-immunisation-programme-jcvi-advice-7-june-2023/respiratory-syncytial-virus-rsv-immunisation-programme-jcvi-advice-7-june-2023#programme-to-protect-neonates-and-infants>

Approaching RSV preventatives

Product	Type	Target Group	Approvals
Beyfortus® (nirsevimab) Sanofi-Aventis	<u>Long-acting</u> mAb – passive immunisation	Infants and young children (<24m)	<ul style="list-style-type: none">• FDA Jul 23• EMA Oct 22• MHRA Nov 22• TGA – under evaluation

Phase 3b HARMONIE RCT (France, UK, Germany - 8,058 infants enrolled) *single dose pre RSV season*

- ***Vaccine efficacy:*** 83% (95% CI 68-92%) for RSV hospitalisation
58% (95% CI 40-71%) for all-cause LRTI hospitalisation
- ***Vaccine safety:*** Serious adverse events higher than placebo (29 to 25%) but not significant
Common & expected adverse events similar e.g. injection site reaction, rash

<https://www.cdc.gov/vaccines/acip/meetings/slides-2023-08-3.html>; <https://www.clinicaltrials.gov/study/NCT05437510/>

Nirsevimab (Beyfortus®) recommendations

ACIP (US) determined that nirsevimab is eligible for inclusion in childhood immunisation schedule & vaccines for children program [1]

- Recommended for
 - All infants aged <8 months born during or entering their first RSV season
 - Children aged 8-19 months who are at increased risk of severe RSV disease & entering their second season
- Optimal site for administration for US infants – new born nursery (vs first outpatient visit)? [2]

JCVI (UK) reported preference for a year-round program to support high uptake & reduce operational complexity [3]

[1] <https://www.cdc.gov/vaccines/acip/meetings/slides-2023-08-3.html> ; [2] Nelson et al. Vaccine 2023 <https://doi.org/10.1016/j.vaccine.2023.06.089> ; [3] <https://www.gov.uk/government/publications/rsv-immunisation-programme-jcvi-advice-7-june-2023/respiratory-syncytial-virus-rsv-immunisation-programme-jcvi-advice-7-june-2023#programme-to-protect-neonates-and-infants>

Byefortus (nirsevimab) product information

- Intramuscular injection using single dose*
 - Varies by weight/age
- Can be administered simultaneously with other vaccines
 - clinical trials demonstrated no safety or reactogenicity concerns
- Cold chain - 2-8°C refrigerator storage, room temperature for up to 8 hours

<https://www.cdc.gov/vaccines/acip/meetings/slides-2023-08-3.html>;



Image:
<https://static.foxnews.com/foxnews.com/content/uploads/2023/07/Beyfortus.jpg>

Approaching RSV preventatives



Product	Type	Target Group	Approvals
mRNA-1345 <i>Moderna</i>	m-RNA for RSV pre-fusion F protein	Older adults ($\geq 60y$)	<ul style="list-style-type: none">FDA – under review (fast track designation)EMA – under reviewTGA – under review (priority pathway)

Phase 3 RCT ConquerRSV study ongoing (22 countries ~37,000 participants $\geq 60y$ enrolled)

- ***Vaccine efficacy:*** 83.7% (95.9% CI 66.1-92.2%) for RSV-associated LRTD
- ***Vaccine safety:***
 - Reported to be well tolerated with a favourable safety profile
 - Solicited adverse reactions were mild or moderate and included injection site pain, fatigue, headache, myalgia, and arthralgia

<https://www.tga.gov.au/resources/prescription-medicines-under-evaluation/tbc-moderna-australia-pty-ltd>

<https://investors.modernatx.com/news/news-details/2023/Moderna-Announces-Global-Regulatory-Submissions-For-Its-Respiratory-Syncytial-Virus-RSV-Vaccine-MRNA-1345/default.aspx>

Supporting the introduction of new RSV preventatives

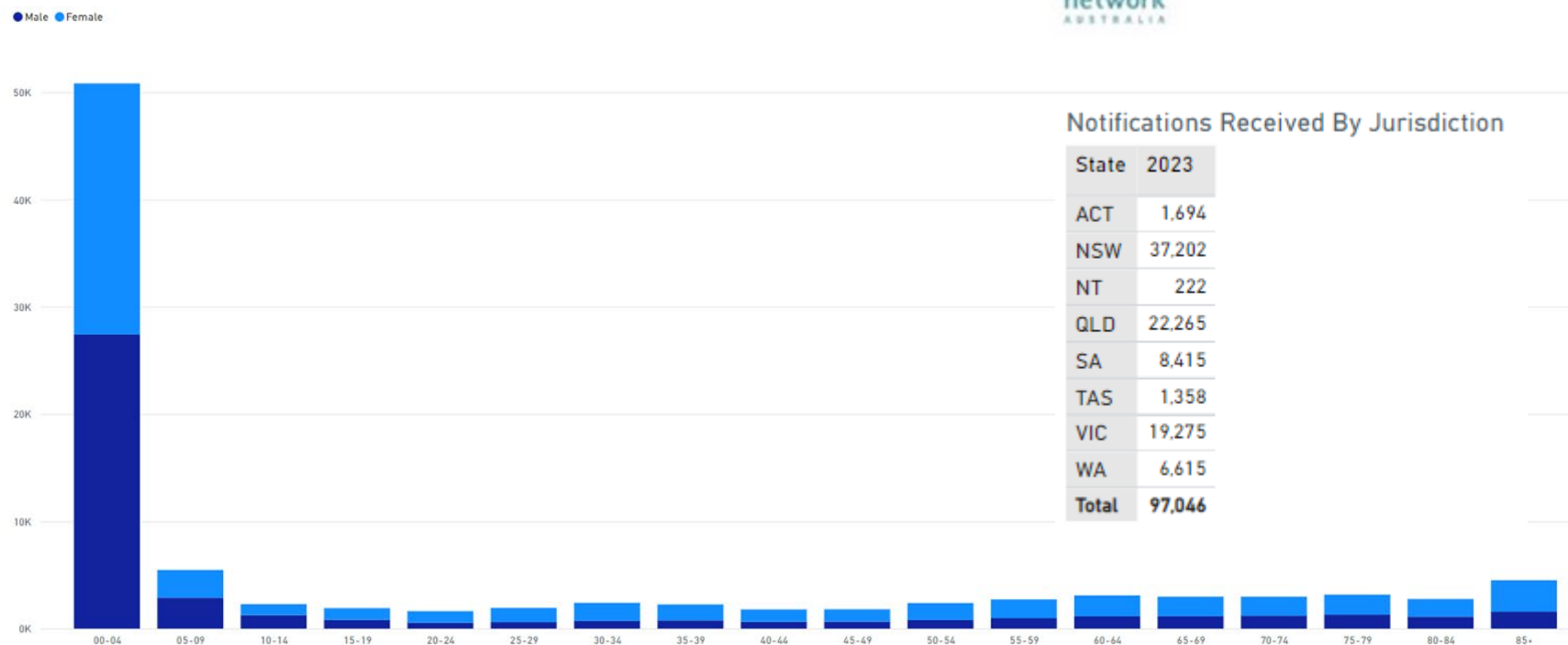
RSV testing and surveillance

RSV surveillance in Australia

- Nationally notifiable since 2021 (laboratory confirmed)
- 97,046 notifications in 2023 as at 19th August



Respiratory Syncytial Virus
Australian national notifiable
diseases case definition



RSV notifications by age groups and sex in 2023 as at 19th August 2023 source: <https://nindss.health.gov.au/pbi-dashboard/>

RSV testing and surveillance

Figure 1. Daily seven-day rolling average rate of RSV notifications per 100,000 population, by age group, NSW, 1 January 2023 to 12 August 2023.

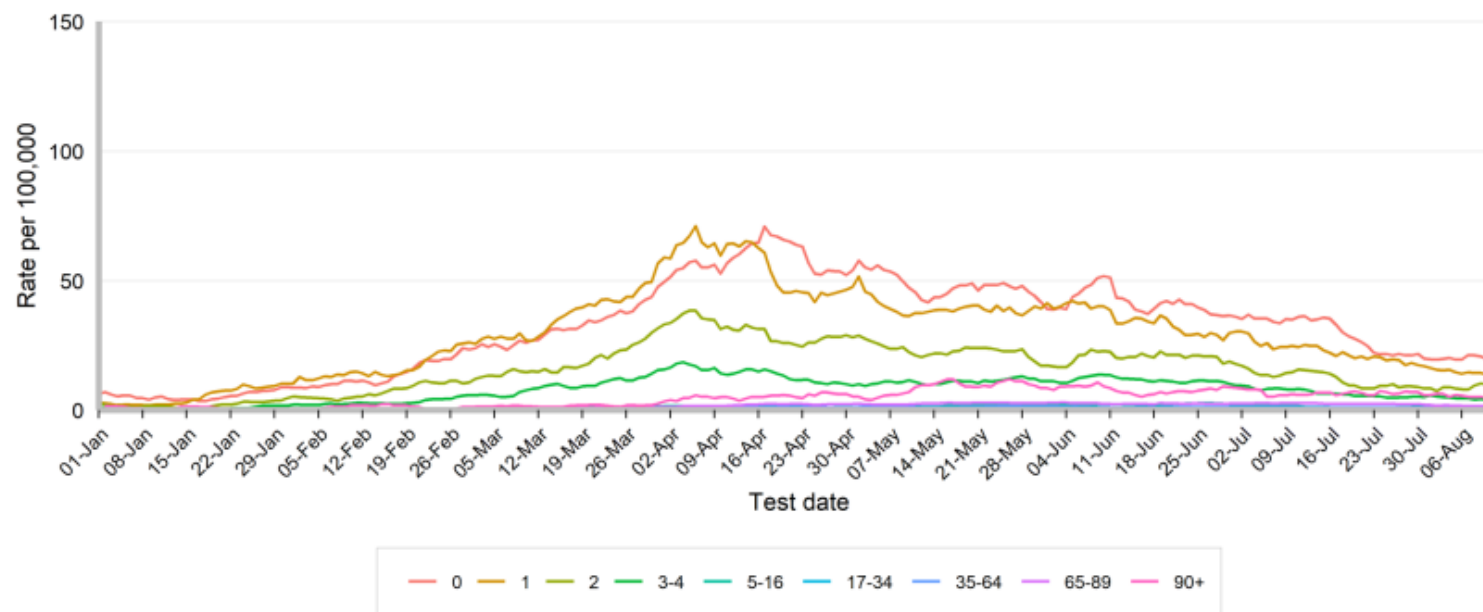
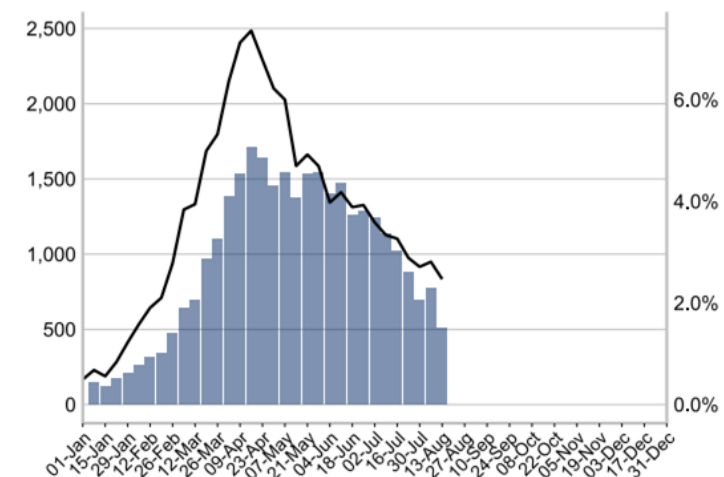


Figure 2. Number of RSV positive PCR test results & proportion of tests positive at sentinel NSW laboratories, 1 January 2023 to 13 August 2023



Source: <https://www.health.nsw.gov.au/Infectious/covid-19/Documents/weekly-covid-overview-20230812.pdf>

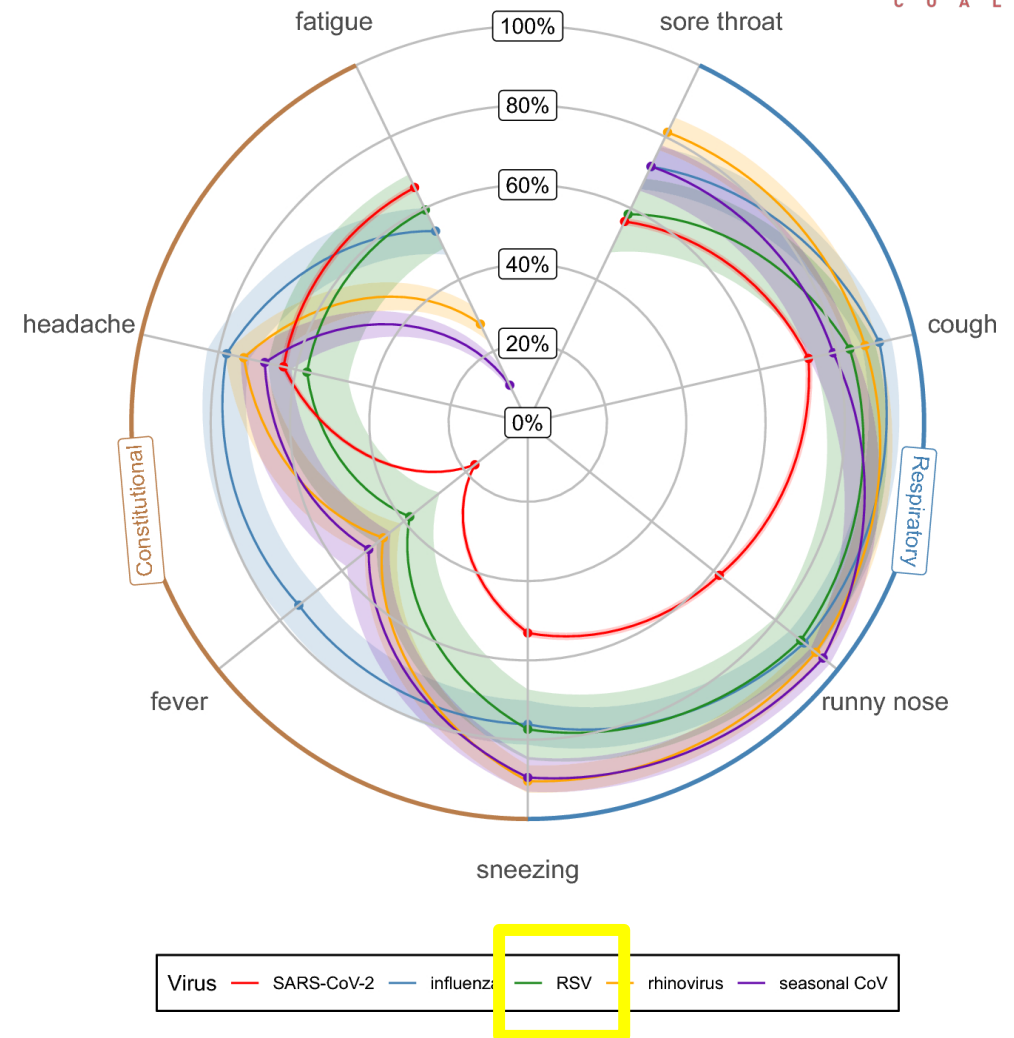
RSV testing and surveillance



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Respiratory pathogen testing

- Overlapping symptomatology of infections [1]
- Testing can support [2,3]
 - Accurate surveillance & disease burden estimates
 - Vaccine effectiveness studies
 - Clinical management e.g. antivirals for influenza
 - Other benefits e.g. reduce antibiotics?
- Need for evidence-based clinical guidelines [3]



Education and advocacy

Identify & address gaps for health professionals, parents, carers & consumers



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RSV is everywhere right now. What parents need to know about respiratory syncytial virus

Published: July 26, 2023 10.32am AEST

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This winter, we're having to get our heads around another respiratory virus – RSV. It's less well known than COVID or flu, but it's also responsible for unplanned visits to the GP or emergency department, and days off school, childcare and work. It's the most common cause of hospitalisation in infants. Most children have at least one RSV infection by the age of three years and yet, many Australians have not heard of RSV or know little about this potentially serious winter virus.

Read more: Monday's medical myth: you can catch a cold by getting cold

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What is RSV?

RSV stands for respiratory syncytial (pronounced sin-CITY-al) virus. This common respiratory virus usually causes a mild cold with symptoms such as a

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Preparing for improved RSV prevention

Actions for health professionals

- Promote basic primary prevention for respiratory infections
 - Hygiene measures, isolation when symptomatic
 - Promote breastfeeding, smoking cessation, routine vaccinations
- Consider your role in RSV testing & surveillance
 - Patient & population benefits
- Education & advocacy within your community
- Recommendation & delivery of approved preventatives
 - Approaching 2024 RSV season?



Acknowledgements

- The University of Sydney, Sydney Infectious Diseases Institute
- A/Professor Philip Britton & Becci Burrell from Centre for Perinatal & Paediatric Infections Research, Children's Hospital at Westmead
- Dr Nusrat Homaira, A/Professor Margie Danchin & Danielle Wurzel



Questions

Thank you to our speaker tonight and the audience for engagement and questions.

Next events – see IC website (www.immunisationcoalition.org.au)

- **7 October**, Inaugural Primary Care Infectious Disease Meeting
1 day hybrid; short and long presentations, workshops and panel discussions
 - **13 September**, 'Pertussis update webinar' presented by Dr Baird
-
- The EF form you should already have it, and we look forward to hearing your feedback.
 - Thank you again for your participation, good night and see you next time.