# Vaccines and Down Syndrome: What the Research Shows

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on behalf of the DSMIG Immunology Working Group

# The Dream Team

Slide by Dr. Noemi Spinazzi

# Take home points

- People with Down syndrome (DS) are at higher risk of severe disease from (respiratory) infections

- Vaccines use natural biology to safely protect against severe disease

- Vaccines are safe and effective in people with Down syndrome
  - DSMIG review: A new open-access factual resource

# Respiratory infections are deadly in people with Down syndrome

Photo Credit: The Washington Post

- **Third highest cause of death** in people with DS.
- **10× mortality** versus individuals without DS.
- Leading cause of healthcare utilization, hospitalization, ICU admission
- High-risk pathogens include SARS-CoV-2, influenza, measles, pneumococcus, and RSV.

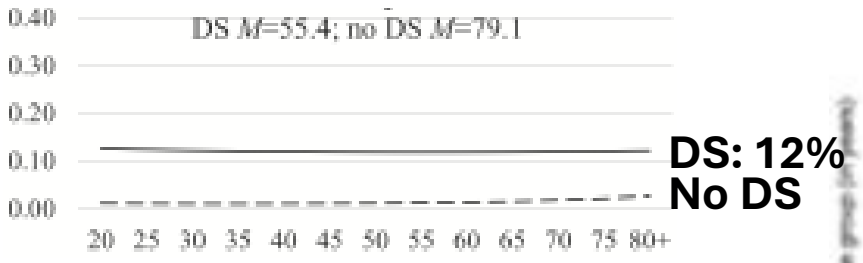
Slide by Dr. Noemi Spinazzi

# Respiratory infections are deadly in people with Down syndrome

## Influenza

10x mortality across lifespan

2nd leading cause of mortality

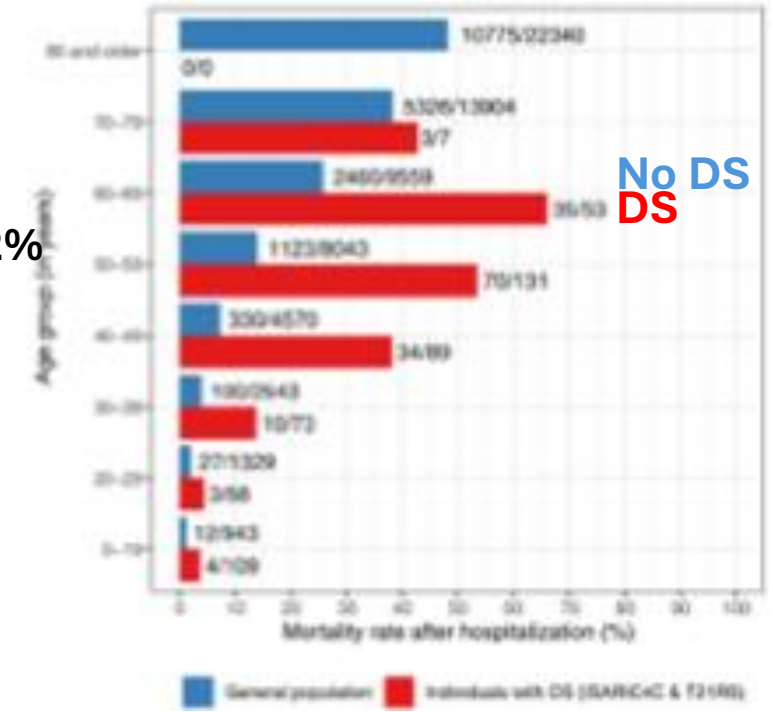



Landes et al, *Disabil Health J* 2021

## COVID-19

10x mortality

Begins 20 years earlier




Hüls et al, *EClinicalmed* 2021

## Measles

DS: 7% of all deaths '70-'83

Pneumonia most common cause

*Deaths from measles in (a) previously normal and (b) previously abnormal persons, and deaths from subacute sclerosing panencephalitis 1970-83*

| Year | Total measles deaths | Ratio/10 000 notifications | (a) Previously normal (No %) | (b) Previously abnormal | Subacute sclerosing panencephalitis |
|---|---|---|---|---|---|
| 1970 | 39 | 1·3 | 24 (62) | 15 | 5 |
| 1971 | 25 | 1·9 | 17 (68) | 8 | 9 |
| 1972 | 29 | 2·0 | 18 (62) | 11 | 15 |
| 1973 | 27 | 1·8 | 18 (67) | 9 | 15 |
| 1974 | 19 | 1·7 | 12 (63) | 7 | 12 |
| 1975 | 13 | 0·9 | 10 (77) | 3 | 14 |
| 1976 | 11 | 2·0 | 4 (36) | 7 | 15 |
| 1977 | 18 | 1·0 | 5 (28) | 13 | 18 |
| 1978 | 13 | 1·0 | 6 (46) | 7 | 15 |
| 1979 | 14 | 1·8 | 7 (50) | 7 | 15 |
| 1980 | 23 | 1·6 | 8 (35) | 15 | 12 |
| 1981 | 12 | 2·3 | 3 (25) | 9 | 15 |
| 1982 | 10 | 1·1 | 3 (30) | 7 | 13 |
| 1983 | 17 | 1·6 | 9 (50) | 8 | 2 |
| | 270 | 1·5 | 144 (53) | 126 | 175 |

Miller CL, *Br Med J* 1985

# “Milder Illness” impact people with Down syndrome

Even mild infections requiring outpatient care, emergency visits, or brief hospitalization can negatively impact individuals with DS

- Swabs, oxygen, IVs often required during these sick visits affect later participation in healthcare
- Missed therapies and school absences can **hinder skill development**.
- Missed workdays for caregivers, increasing **stress and financial burden**.

Photo Credit: Down Syndrome Alliance

Slide by Dr. Noemi Spinazzi

# The immune system:
# Key defender against infection

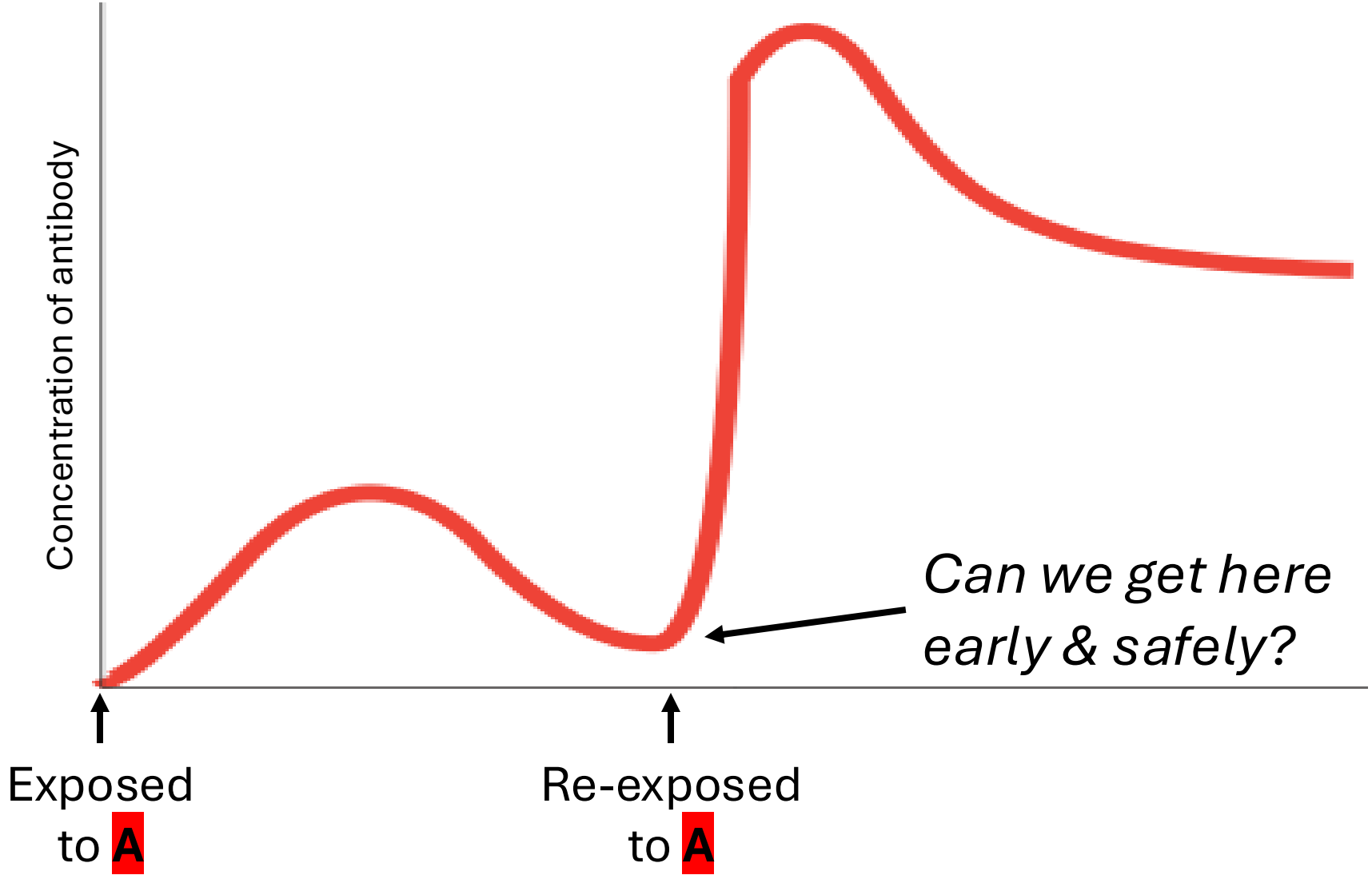
## Innate Immunity

- e.g. neutrophils, macrophages
- Quick response
- Responds to motifs

## Adaptive Immunity

- e.g. B cells, $CD4^+$/$CD8^+$ T cells
- Slower initial response
- Specificity
- Memory

# Adaptive Immunity: Memory and Specificity



# Adaptive Immunity: Memory and Specificity

**Immune Memory:**

- First documented in ancient Greece by Thucydides
- 430 BC, plague of Athens
- "the same man was never attacked twice”

- More recent examples include measles, chickenpox
  - Before 1995, 100-150 children died per year

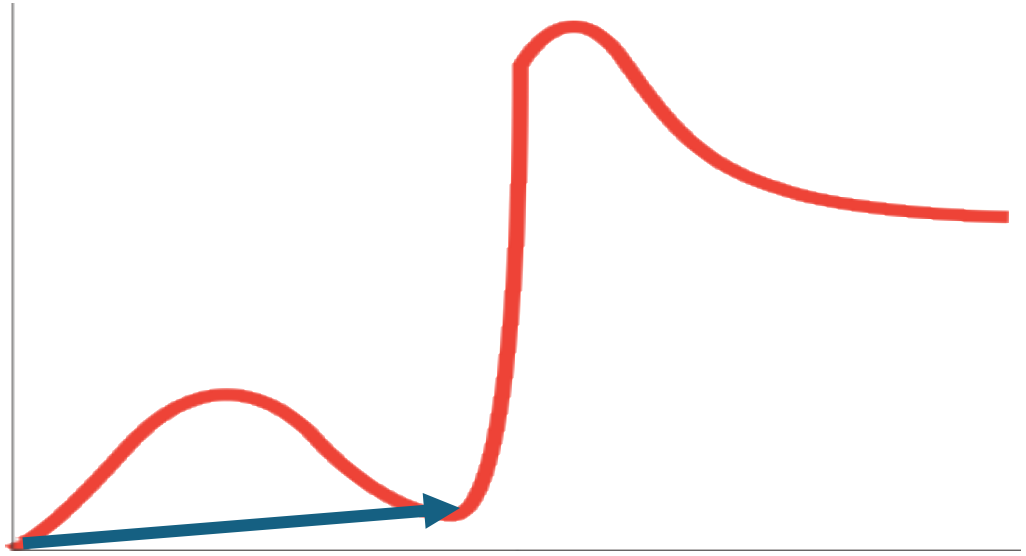
- Pox parties: Early attempts at immune memory
  - Dangerous: Risk of severe complications & death
  - **NOT** recommended

*Wikipedia*

# Can we induce Immune Memory safely?

**Smallpox:**

- Prehistoric origin, ~10,000 years ago
- 20-60% fatality rate, survivors disfigured
  - 18th century Europe: 400,000 deaths per year




Mack, NEJM 2003; 348:460

# Vaccines generate Immune Memory ***safely***

**Smallpox:**

- Inoculation: lancet pustule -> subcutaneous implant
  - ~3% death

- Related virus: cowpox (*vaccinia* virus), very low death rate
- Rumor: Dairy maids who got cowpox were protected from smallpox

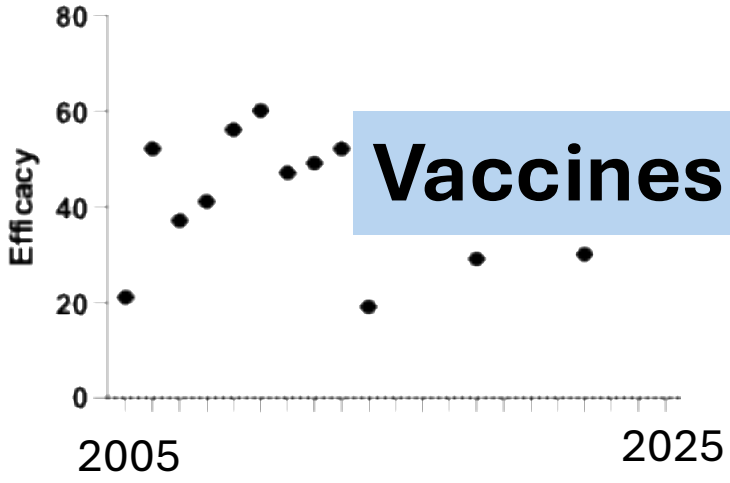
- 1796: Edward Jenner inoculates boy with cowpox
  - Boy is protected from smallpox
  - First published instance of vaccination

# Vaccines are safe and effective in the general population

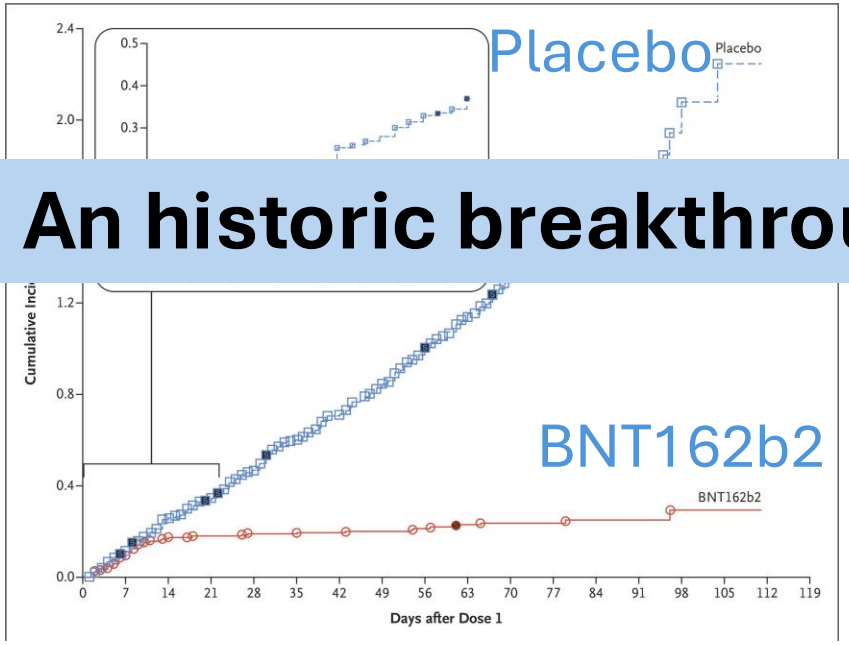
**Influenza**
Typically >40%

**COVID-19**
95% efficacy

**Measles**
~97% effective




CDC




Polack et al, *NEJM* 2020

**Vaccines: An historic breakthrough in medicine**

TABLE VII

PROTECTION OF MEASLES VACCINE AGAINST "REGULAR" CASES OF MEASLES

| Group | Time Post-vaccination | Attack Rate per 1,000 | | | Effectiveness of Vaccine (%) | |
|---|---|---|---|---|---|---|
| | | Placebo | KKK | KKL | KKK | KKL |
| I | 3 months | 76.6 | 5.0 | 0 | 94 | 100 |
| II | 4–10 months | 23.6 | 5.3 | 1.8 | 80 | 93 |
| III | 11–13 months | 48.0 | 12.7 | 1.8 | 75 | 97 |

Guinee et al, *Pediatrics* 1966

2025-26
191 pediatric deaths
85% unvaccinated

# Vaccines: Less used in people with Down syndrome

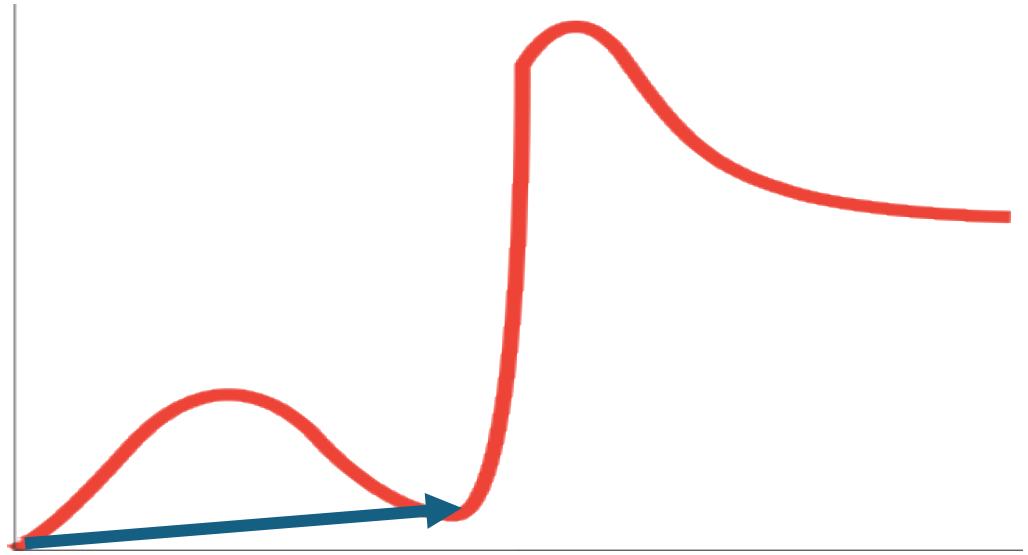
- **Combined 7-vaccine series, up to date @19 mths:**
  - **58% of children with DS** vs 71% of typical children
- Caregivers: **42% feared serious side effects**.
- **Barriers of perception**
  - Vaccines vs “natural” immunity
  - Safety and effectiveness specifically in people with DS
- **Barriers of biology**
  - Do vaccines work as well in people with DS?

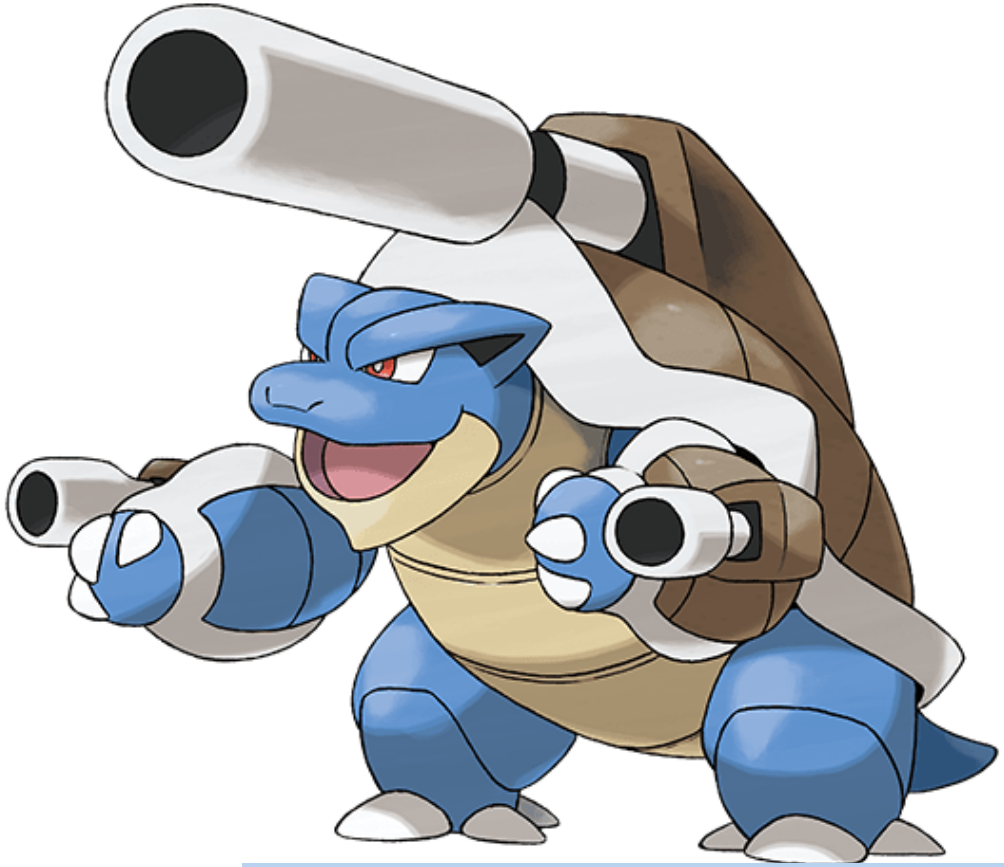
Slide by Dr. Noemi Spinazzi

# WHAT is a vaccine?


Any sufficiently advanced technology is indistinguishable from magic
- Arthur C. Clarke

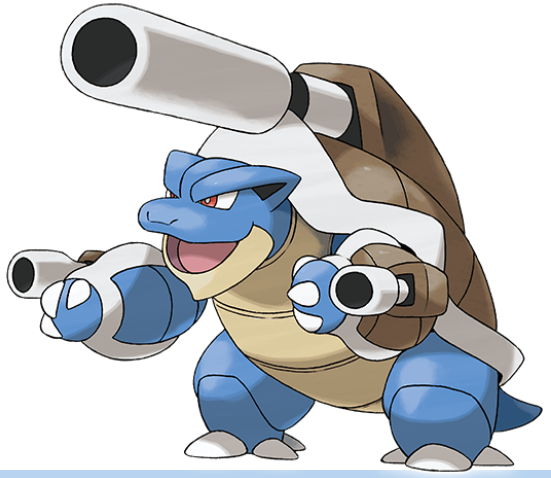
# WHAT is a vaccine?





**Pathogen (disease)**

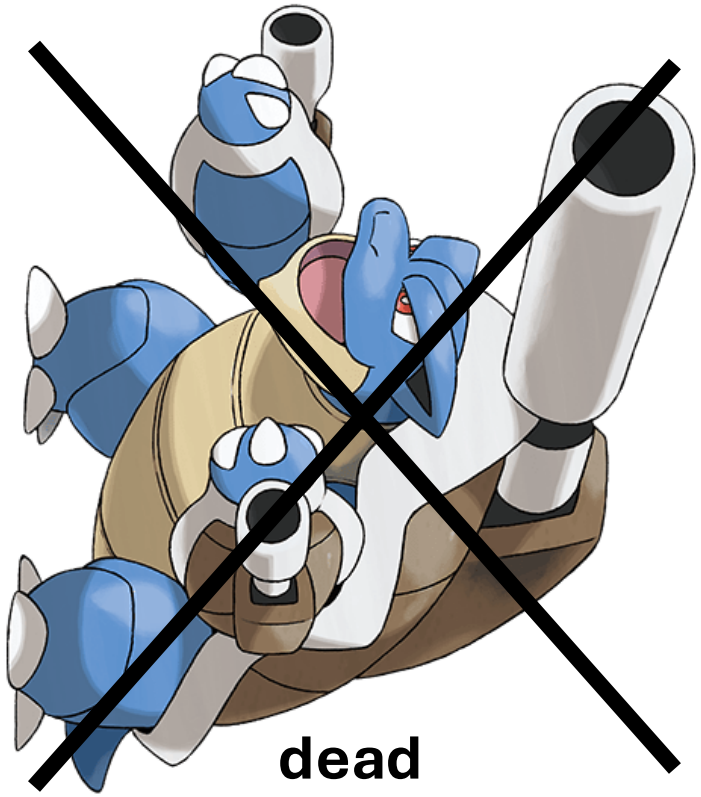
# Vaccines use natural biology: 3 types



**Live, attenuated**
e.g. MMR

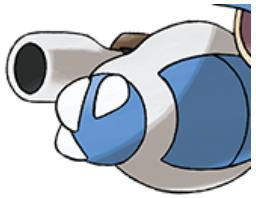
**weak**

**Inactivated**, e.g. flu



**dead**

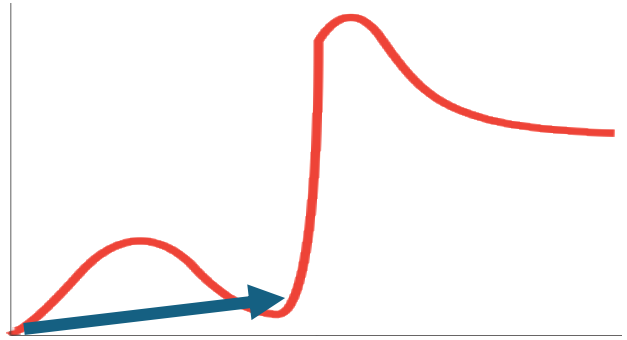
**Subunit, Toxoid**
e.g. tetanus



**piece**

# Vaccines use natural biology to safely protect

| | Composition | Immune response | Side effect risk |
|---|---|---|---|
| **Pathogen** | Naturally occurring | Yes | High (survivor immunity) |
| **Vaccines** | Weakened<br>Dead<br>Subunits/Protein | Yes | **Low** |



**71% ↓risk, <1yo**

# Why are there so many vaccines?

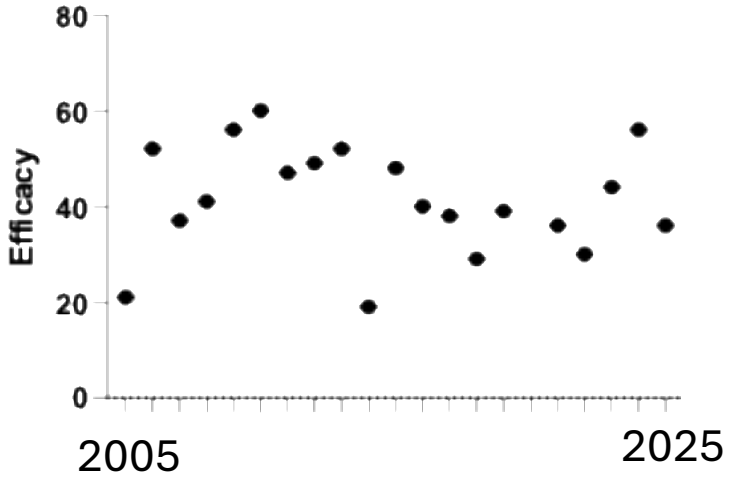
- Vaccines are used against diseases with high risk of serious complications and death in your area

- Is it OK to have several vaccines at the same time?
  - Clinical studies show this is safe and effective
  - Spaced vaccines mean longer unprotected windows

https://www.busybeeschildrencenter.com/mission-and-philosophy

# Vaccines are safe and effective in the general population

**Influenza**
Typically >40%




CDC

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85% unvaccinated

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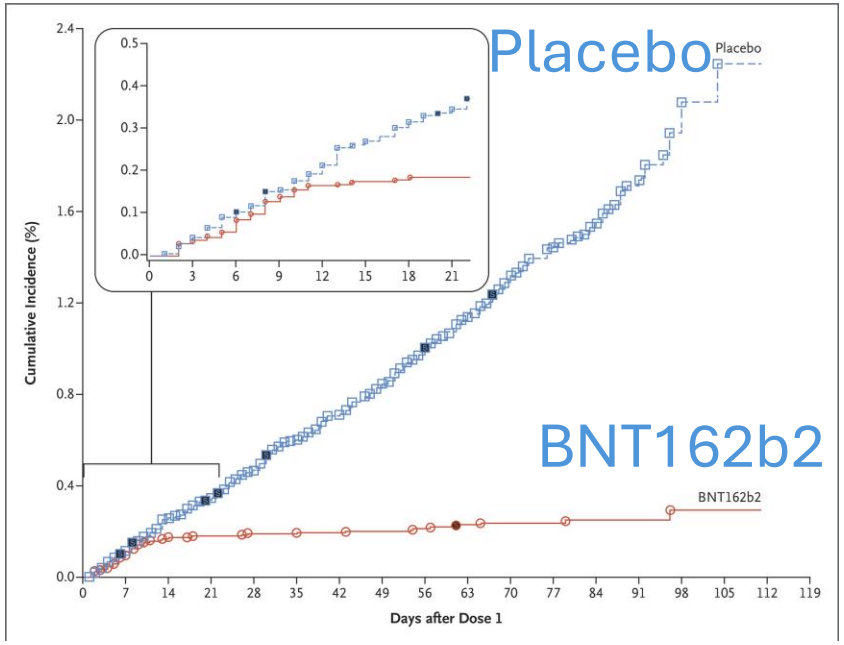
95% efficacy




Polack et al, *NEJM* 2020

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Guinee et al, *Pediatrics* 1966

But are vaccines safe for people with **Down syndrome**?

# The Dream Team

Slide by Dr. Noemi Spinazzi

npj | vaccines

Review

Published in partnership with the Sealy Institute for Vaccine Sciences

https://doi.org/10.1038/s41541-026-01489-7

# Vaccination in individuals with Down syndrome: immune vulnerability, safety, efficacy and opportunities

Check for updates

Bernard Khor[1] ✉, Noemi A. Spinazzi[2,14], Lina R. Patel[3,14], Erika Chelales[3,14], Nicole Baumer[4], Peter Bulova[5], Brian Chicoine[6], Arturo Borzutzky[7], Hana M. El Sahly[8], Joaquin M. Espinosa[3], Melissa D. Gans[9], Andrew A. McCormick[5], Rebecca Partridge[1], Eric Rubenstein[10], Jonathan D. Santoro[11,12], Cate Speake[1], Juanita Valdes Camacho[13] & Kishore Vellody[5]

Khor et al, npj Vaccines, 11:158

# Vaccines Are **Safe** for people with Down syndrome

- 45 studies
- 13 vaccine targets
- 2,411 people with DS
- Safety signals found: zero

**Supplemental Table 1**

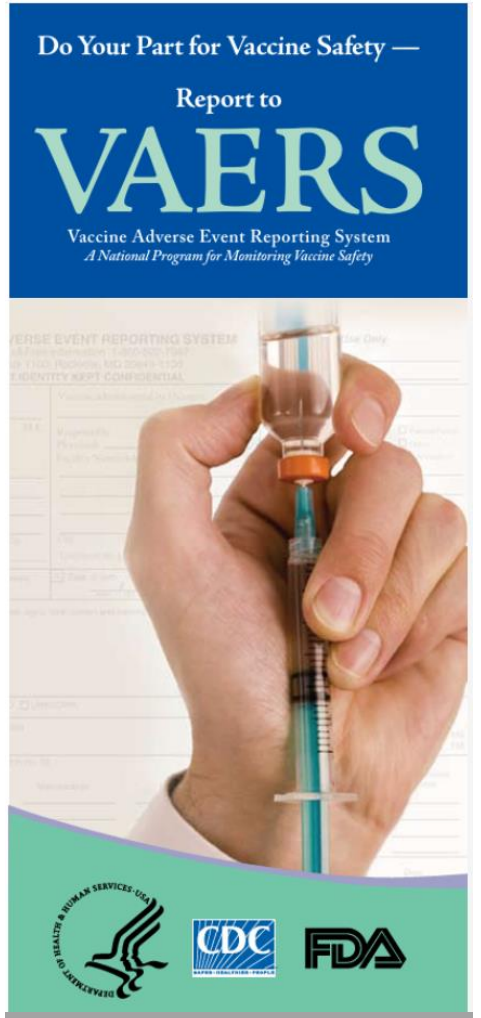
**Table of vaccine safety and immunogenicity studies**

| Paper | PMID | Vaccine | N (DS) | Age | Variable | Immuno-genic? | Defect? | Safety |
|---|---|---|---|---|---|---|---|---|
| 2022 James | 35891309 | flu | | | | | | |
| 2015 Valentini | 26518399 | flu | | | | | | |
| 2012 Kusters | 22986705 | flu | | | | | | |
| 2011 Joshi | 21596078 | flu | | | | | | |
| 1986 Philip | 2419411 | flu | | | | | | |
| 1978 Hawkes | 148342 | flu | | | | | | |
| 2023 Santoro | 37864360 | PCV | | | | | | |
| 2015 Valentini | 26518399 | PCV | | | | | | |
| 2013 Kusters | 24200977 | PCV PPS | | | | | | |
| 2024 Martins | 39053889 | PPS | | | | | | |
| 2011 Joshi | 21596078 | PPS | | | | | | |
| 2006 Costa-Carvalho | 17160268 | PPS | | | | | | |
| 1982 Nurmi | 6213331 | PPS | | | | | | |
| 2023 Valentini | 36813120 | CoV | | | | | | |
| 2023 Streng | 38616780 | CoV | | | | | | |
| 2023 Esparcia-Pinedo | 35869848 | CoV | | | | | | |
| 2022 Valentini | 35160144 | CoV | | | | | | severe |
| 2022 Streng | 35748853 | CoV2 | 253 (173) | adults | Ab up to 4 wks | Y | Y | |
| 2022 Sali | 35461998 | CoV2 | 84 (42) | adults | Ab up to 6 mths | Y | Y | |
| 1993 Oda | 8365667 | mumps | 72 (36) | both | Ab @convenience | Y | Y | |
| 1978 Hawkes | 148342 | mumps | 188 (110) | adults, inst | Ab @7 wks | Y | Y | |
| 2023 Familiar-Macedo | 38155740 | measles | 58 (34) | children | Ab @up tp 61 mths | Y | N | |
| | | | | | venience | Y | Y | |
| | | | | | 7 wks | Y | Y | |
| | | | | | up tp 61 | Y | Y | |
| | | | | | venience | Y | N | |
| | | | | | 7 wks | Y | N | |
| | | | | | 10 wks ooster, excretion | Y | Y | |
| | | | | | XSxn | Y | N | |
| | | | | | 4 wks post r, avidity ks post | Y | Y | |
| | | | | | eration, IL- | Y | Y | |
| | | | | | eration | N | Y | |
| | | | | | 2 wks | Y | N | |
| | | | | | XSxn | Y | N | |
| | | | | | 2 wks | Y | N | |
| | | | | | | UNK | Y* | |
| | | | | | rsistence 25 yrs | Y | Y | |
| | | | | | up to 6 | Y | Y | |
| | | | | | up to 132 | Y | Y | |
| | | | | | up to 3 yrs | Y | Y | |
| | | | | | up to 2 yrs | Y | Y | |
| Heijtink | | | | | up to 6 mths | Y | Y | |
| 1990 van Damme | 2139285 | HBV | 275 (18) | both, inst | Ab @up to 2 yrs | Y | Y | |
| 1985 Troisi | 2933533 | HBV | 62 (62) | both, inst | Ab @up to 1 yrs | Y | N | |
| 2004 Ferreira | 15448421 | HAV | 127 (63) | children | Ab @up to 7 mths | Y | N (trend Y) | no SAE |
| 2011 Kusters | 21849866 | Meningococcal ACWY | 19 (19) | children | Ab @up to 1 yrs | Y | Y | |

Khor et al, *npj Vaccines* 2026

# Vaccines Are **Safe** for people with Down syndrome

- No signal of increased adverse events in people w/ DS
  - Including regression, autism, autoimmunity, etc
- Prospective trials **of hepatitis A and SARS-CoV-2 vaccines** in children and adults with DS found no increase in severe adverse events.
- Studies on **pneumococcal vaccine** confirm safety in people with DS
- Multiple studies also confirm that vaccines are safe in individuals with immune compromise.
- **Continued monitoring remains critical** to detect rare or unexpected adverse events
  - Dr. Spinazzi looked as part of the review!



Source: HHS

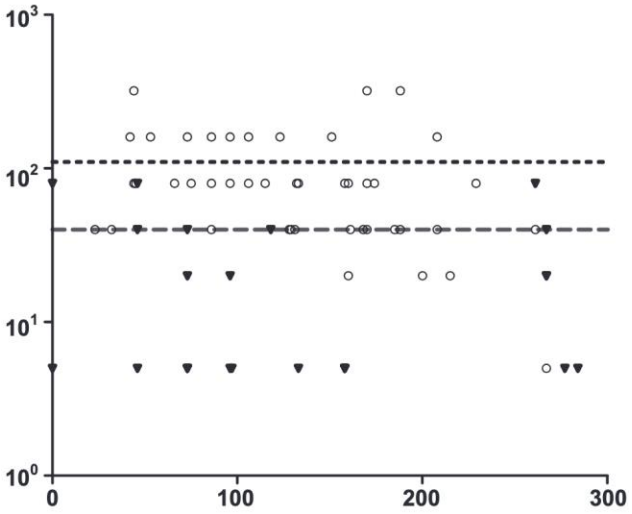
Slide by Dr. Noemi Spinazzi

# Vaccines work in people with Down syndrome

>95% of all studies show vaccines are immunogenic in people with DS

**Influenza**

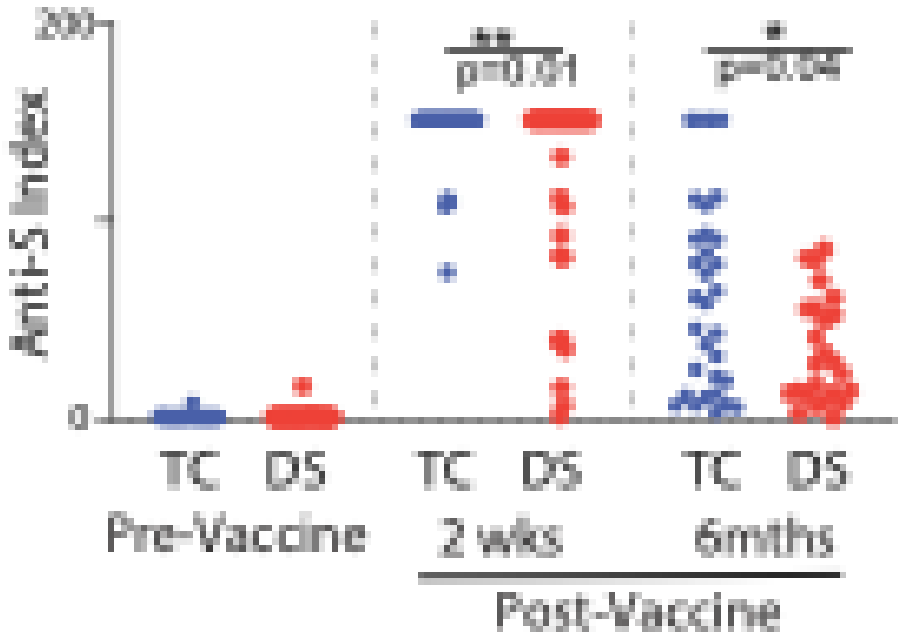
92% children >1:40
($EC_{50}$ in adults)




Kusters et al, *Pediatr Inf Dis J* 2012

**COVID-19**

100% responders




Khor et al, *unpublished*

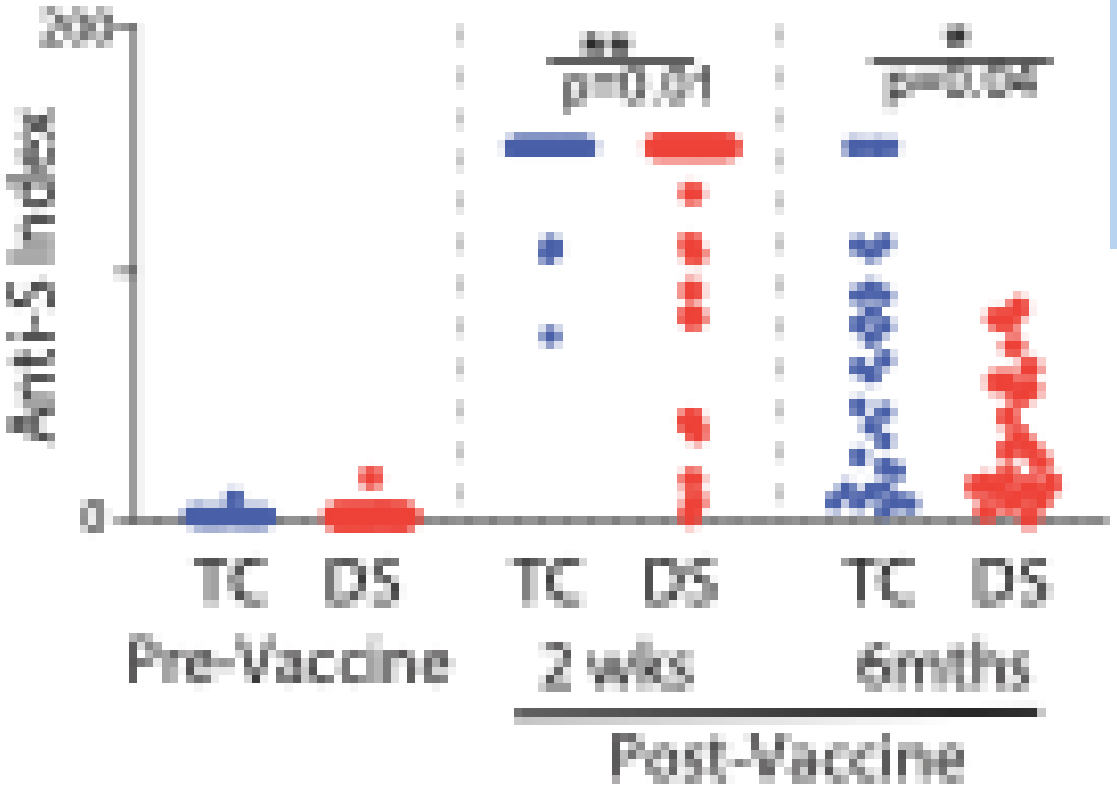
# Vaccination and Down Syndrome

- Vaccines are safe and immunogenic in people with DS.
- **The American Academy of Pediatrics recommends all children with DS receive routine immunizations, including influenza vaccines,** unless specifically contraindicated

Slide by Dr. Noemi Spinazzi

# Making vaccines work better for people with Down syndrome:

**COVID-19**

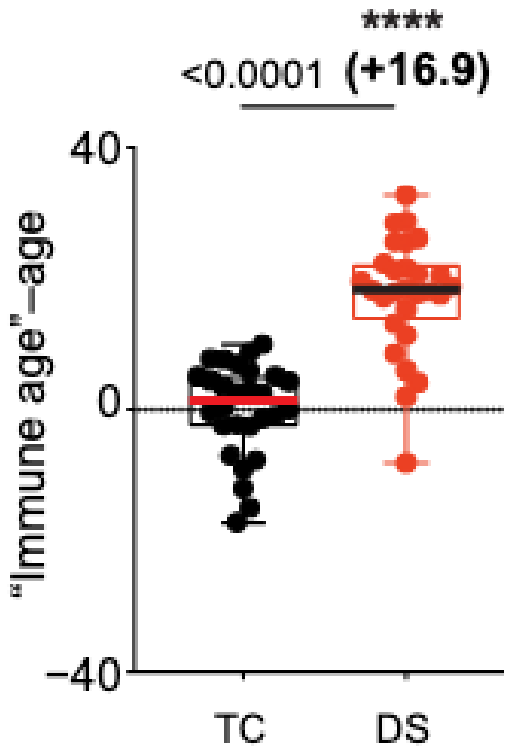



- Similar findings in influenza, etc.
- Clinical significance is a research gap

Khor et al, *unpublished*

# Making vaccines work better for people with Down syndrome: Immune contributors

## Immune aging




Lambert et al, *Sci Transl Med* 2022

## Innate immune

- ↑ Inflammatory cytokines
- ↓ phagocytosis
- ↓ pathogen clearance
- ↓ mannan-binding lectin
- ↑ Interferon signaling

## Adaptive immune

- ↓ IgG/IgM/IgE
- ↓ switched B memory
- Thymic hypoplasia
- ↓ T naive
- ↑ T exhaustion
- ↑ Interferon signaling

Khor et al, *npj Vaccines* 2026

# Making vaccines work better for people with Down syndrome: Available and emerging solutions

**Available now:**

Utilization of existing vaccines

Prioritization for boosters, especially influenza and SARS-CoV2

**Near term, to be evaluated:**

High-dose influenza vaccine

Adjuvanted influenza vaccine

**Potential longer-term candidates:**

JAK inhibitors

Metformin

Rapalogs

Senolytics

Khor et al, *npj Vaccines* 2026

# Summary

- People with DS are susceptible to respiratory infections (**high-risk group**)
- Vaccines are a key component of care for people with DS
  - They use natural biology to ***safely*** protect against severe disease
- Lower vaccine utilization in DS: A major opportunity
- DSMIG team review: A key resource for conversations
- Vaccines are **safe** and **immunogenic** in people with DS
  - Continue to monitor safety in studies and postmarketing surveillance
- **Recommend**
  - All standard vaccinations for typical individuals of same age
  - Prioritization for boosters and additional specific vaccines
  - Continued research to improve vaccine response in people with DS


npj Vaccines
https://doi.org/10.1038/s41541-026-01489-7
Article in Press

**Vaccination in individuals with Down syndrome: immune vulnerability, safety, efficacy and opportunities**

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