Wilhelmina Children's Hospital

PRIDE

COVID vaccination response in adults and children with Down Syndrome

5.1.2e

Vision

Science
AAAS

COVID-19

People with Down syndrome face high risk from coronavirus

Advocates call for early vaccination of group made vulnerable by genetics and immune dysfunction

By Meredith Wadman

When the COVID-19 pandemic descended last winter, Catherine Ross was filled with dread. Her 36-year-old sister, Amanda Ross, has Down syndrome (DS), which makes her especially vulnerable to respiratory viruses. Amanda Ross had been hospitalized repeatedly with pneumonia. In 2017, she ended up on a ventilator and nearly died.

In April, she was back on a ventilator. She lives in a group home in Somers, New York and had been diagnosed with COVID-19 on 31 March. The doctor told her close-knit family that, given her history, they needed to prepare for the worst. "It shook us," Catherine Ross says. Her sister and others with DS, also known as trisomy 21, "are dealing with a cracked deck against them in terms of dealing with the virus," she says.

Among groups at higher risk of dying from COVID-19, such as people with diabetes, people with DS stand out. If inferred, they are five times more likely to be hospitalized and 10 times more likely to die than the general population, according to a large U.K. study published in October. Other recent studies back up the high risk.

Researchers suspect background immune abnormalities, combined with extra copies of key genes in people with DS—who have three copies of chromosome 21 rather than the usual two—make them more vulnerable to severe COVID-19. "This is a vulnerable population that may need protective policies put in place," says Julia Hippisley-Cox, a clinical epidemiologist at the University of Oxford's medical school and senior author on the U.K. study.

On 2 December, the United Kingdom's Joint Committee on Vaccination and Immunisation recommended prioritizing people with DS for speedy vaccination. But the more than 200,000 Americans with DS so far are not slated for early vaccination. Nor has the U.S. Centers for Disease Control and Prevention (CDC) included DS in its list of conditions it says boost the risk for severe COVID-19.

Hippisley-Cox and her colleagues analyzed a database of 8.26 million people in the United Kingdom for their paper, published in the *Annals of Internal Medicine*. The extraordinary risk they found emerged even after they corrected for many other factors including obesity, heart disease, diabetes, and living in a group home. Another recent preprint that includes findings from a large international survey found that people with DS hospitalized with COVID-19 who are 40 and older bear most of the increased risk, with a mortality of 23% versus 7% for those under 40. "At about the age of 40, things are getting really bad ... [with] a mortality rate comparable with those older than 80 in the general population," says first author Anke Huels, a biostatistician at the Rollins School of Public Health at Emory University.

Experts say the typical anatomy of people with trisomy 21, including large tongues, small jaws, and relatively large tonsils and adenoids, along with lax throat muscle tone, helps explain their higher rate of respiratory infections in general. But genetics may also make them particularly susceptible to SARS-CoV-2, the pandemic coronavirus. They have three copies of a gene on chromosome 21, *TMPRSS2*, which codes for an enzyme that the virus hijacks to help it enter human cells. The TMPRSS2 enzyme cleaves the spike protein that studs the virus' surface, launching a series of steps that allows the virus to invade the host cell.

Cells from people with DS typically express 1.5 times more *TMPRSS2* than those from people without the condition, according to an analysis posted as a preprint in June by Mara Dierssen, a systems biologist at the Center for Genomic Regulation in Barcelona, Spain, and her postdoc Haria De Toma. "Down syndrome individuals might be more susceptible to infection due to triplication of *TMPRSS2*," Dierssen says.

Immune system abnormalities likely add

PHOTO: GETTY/ISTOCK

Downloaded from http://science.sciencemag.org/ on January 12, 2021

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sciencemag.org SCIENCE

- **COVID-19** is **10 times deadlier** for **people** with **Down syndrome**
- **Susceptible by genetics and immune defect**
- **Early vaccination needed**

Wadman, *Science* 2020

PRIDE

UMCU /ReSViNET

- 5.1.2e *Principal Investigator*
- Dr. 5.1.2e *project manager*
- 5.1.2e

RIVM

- Dr. 5.1.2e, 5.1.2e

Vumc/Alrijne

- 5.1.2e

Tilburg University

- 5.1.2e specialist, 5.1.2e

Radboud / Elkerliek

- 5.1.2e

Stichting Down Syndroom (SDS)

- 5.1.2e, psychologist, chair woman

National Institute of Health

- 5.1.2e

Sanquin

- 5.1.2e immunologist

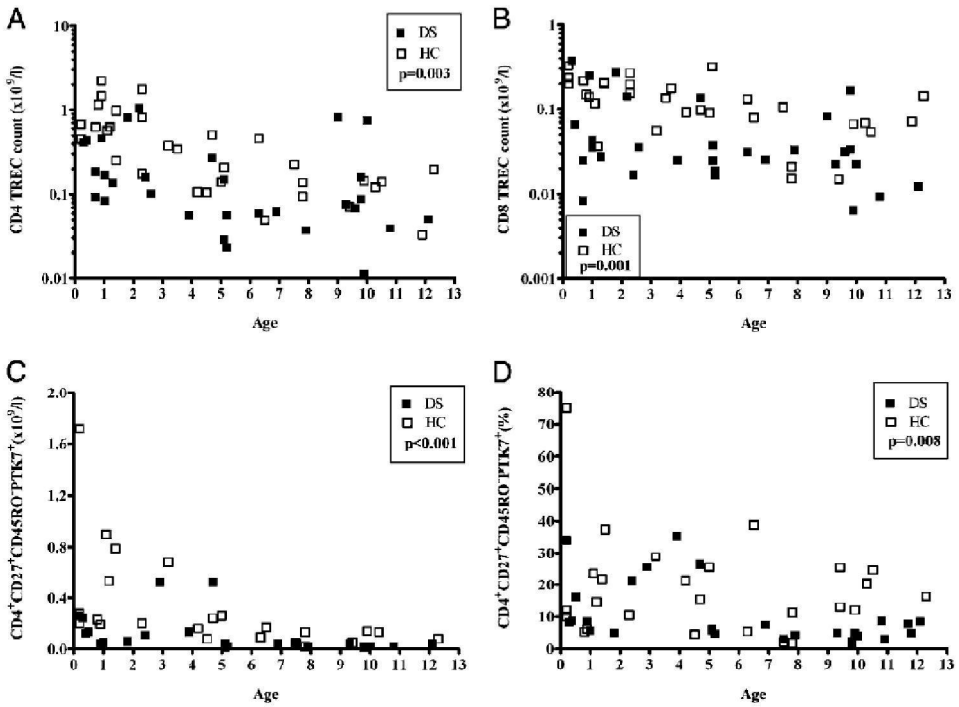
All in less than one month

Down Syndrome[1]

- Trisomy 21
- Incidence: 1 per 700 live births
- Comorbidities:
  - Organ disease (gut, heart)
  - Thymic Dysfunction (recurrent infections, auto-immunity)
  - Accelarated aging
- Prognosis: life expectancy 55 year

(1) Stichting Down Syndroom

T-cell defect in Down Syndrome



Bloemers, *Journal of Immunology* 2011

Vaccination response in Down Syndrome

- Reduced response to inactivated influenza vaccination
  (Joshi, *Vaccine* 2011; Kusters, *PIDJ* 2012). Remark: 8-fold increased risk of H1N1-related intubation (Pérez-Padilla, Emerg Infect Dis 2010)

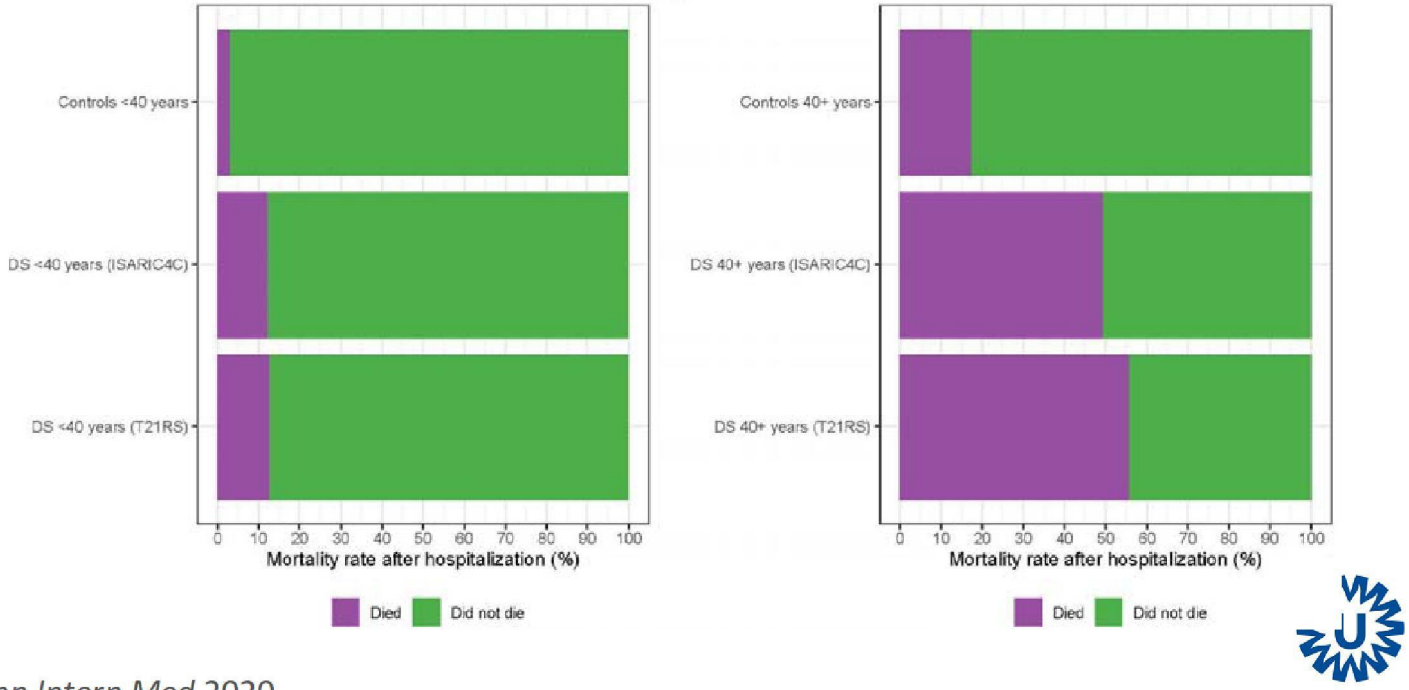
- Reduced Ab response to MenC (Kusters, *PIDJ* 2011)

- Impaired B-cell memory switch to pneumococcal vaccination (Valentini, *Vaccine* 2015)

- Normal response to HAV

COVID in Down Syndrome

QResearch, a population level primary care database
Adults with DS (n=4053) vs no DS (n=8,252,105)



Clift, *Ann Intern Med* 2020

COVID in Children with Down Syndrom

COVID-19 and children with Down syndrome: is there any real reason to worry? Two case reports with severe course

Ahmad Kantar[1*], Angelo Mazza[2], Ezio Bonanomi[3], Marta Odoni[1], Manuela Seminara[1], Ilaria Dalla Verde[1], Camillo Lovati[1], Stefania Bolognini[1] and Lorenzo D'Antiga[2]

Abstract

Background: Down syndrome (DS) is characterized by a series of immune dysregulations, of which interferon hyperreactivity is important, as it is responsible for surging antiviral responses and the possible initiation of an amplified cytokine storm. This biological condition is attributed to immune regulators encoded in chromosome 21. Moreover, DS is also characterized by the coexistence of obesity and cardiovascular and respiratory anomalies, which are risk factors for coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Case presentation: A total of 55 children were admitted to the pediatric ward in Bergamo, between February and May 2020 for COVID-19. Here, we describe the cases of two children with DS and a confirmed COVID-19 diagnosis who had a severe course. In addition, both cases involved one or more comorbidities, including cardiovascular anomalies, obesity, and/or obstructive sleep apnea.

Conclusions: Our observations indicate that children with DS are at risk for severe COVID-19 disease course.

Keywords: Down syndrome, Trisomy 21, Coronavirus disease, Children, Case report

Kantar, *BMC Pediatr* 2021

COVID in Down Syndrome (international questionnaire)

Design

- Trisomy 21 Research Society (T21RS)
- India, US, Spain, UK, Brazil, France, Italy
- 1046 COVID+ patients with DS (591 reported by clinician, 455 by family member)
- All ages

Results

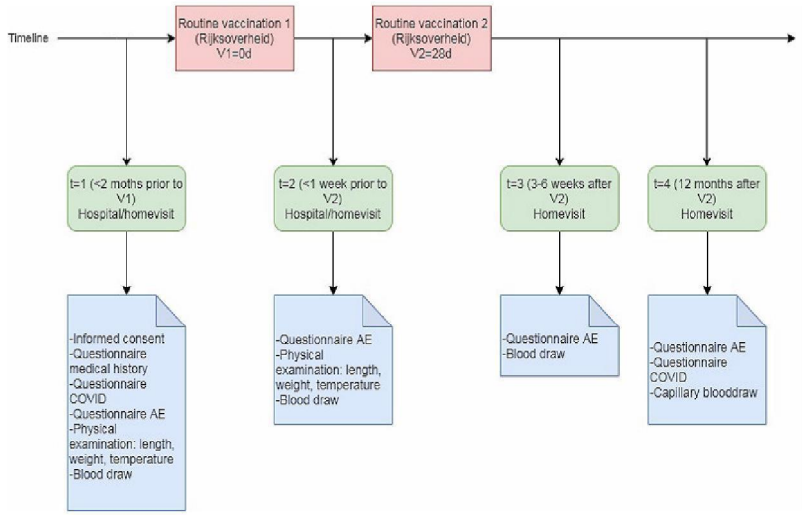
- 581 (56.0) hospitalization
- 207 (29%) required mechanical ventilation
- 131 (13%) mortality

Huls, *medRxiv* 2020

Aim: immunogenicity of COVID vaccination in adults and children with Down Syndrome

Methods

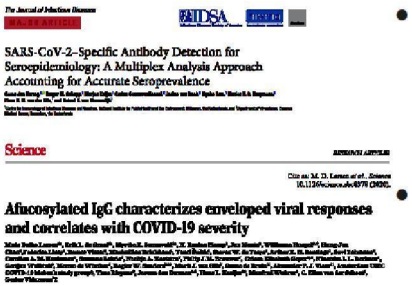
- Two studies: adults with DS and children with DS
- Each study: parallel cohort study comparing people with DS with people without DS (siblings)
- Safety and immunogenicity
- Alignment with other studies in this call
- Abs, T-cell, B-cell

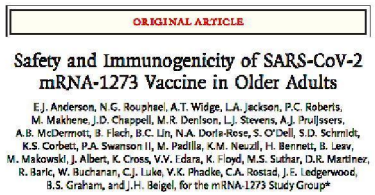


Add-on:

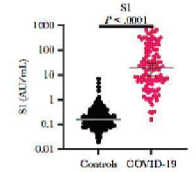
- etiology study on **Ab glycosylation** (Vidarsson, Science, 2021)
- **T-cell development over life**

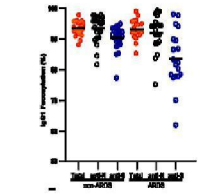
Methods

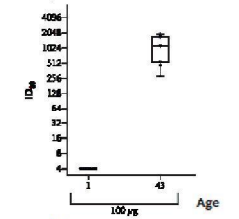


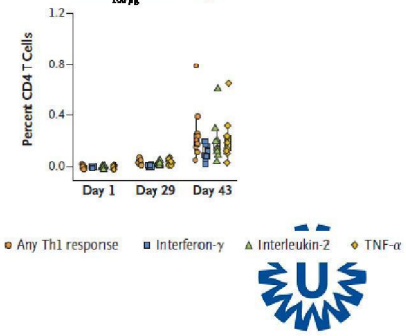


- IgG1 against S1 and N (multiplex immuno assay, MIA)
- Levels of fucosylation, sialylation and galactosylation
- Neutralization: a plaque-reduction neutralization testing (PRNT), using wild-type virus.
- Intracellular cytokine-staining assays were performed to quantify antigen-specific T-cell responses



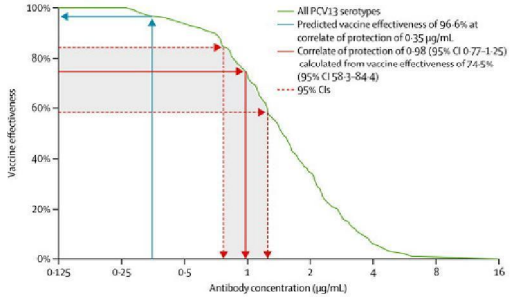


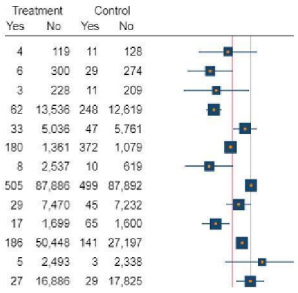




What are the implications of lower antibody responses for efficacy?

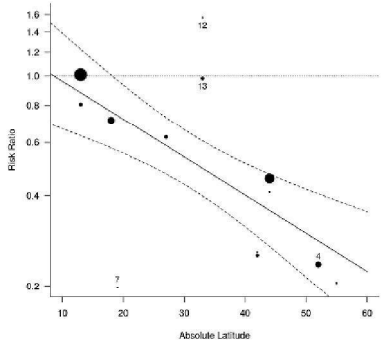
Observed relationship between antibody concentration and Vaccine Efficacy (**example** from PCV13)





Treatment Yes	Treatment No	Control Yes	Control No
4	119	11	128
6	300	29	274
3	228	11	209
62	13,536	248	12,619
33	5,036	47	5,761
180	1,361	372	1,079
8	2,537	10	619
505	87,886	499	87,892
29	7,470	45	7,232
17	1,689	65	1,600
186	50,448	141	27,197
5	2,493	3	2,338
27	16,886	29	17,825

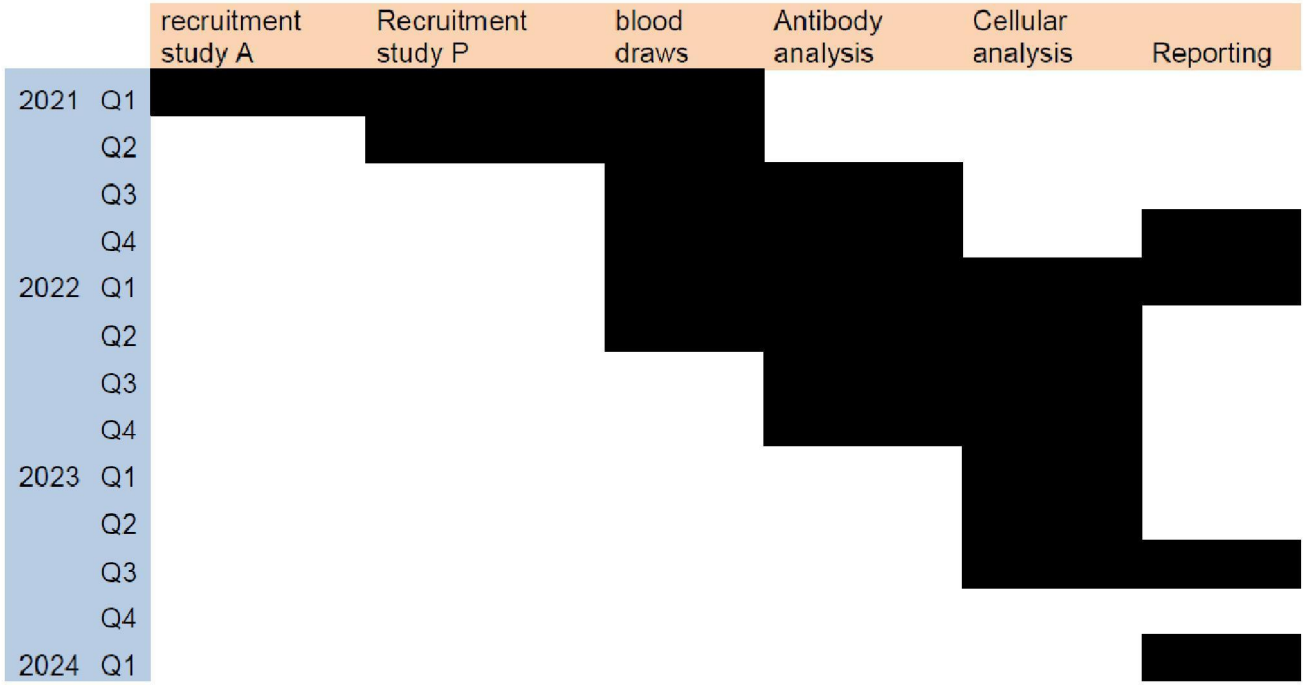
Plug in antibody data from **PRIDE** to determine expected effectiveness for different groups



Meta-analysis and **Bayesian regression** to synthesize findings from multiple studies

https://www.metafor-project.org/
Andrews, Lancet ID , 2021
https://www.stata.com/stata-news/news34-5/forest-plots/

Timeline


recruitment study A
Recruitment study P
blood draws
Antibody analysis
Cellular analysis
Reporting
2021 Q1
Q2
Q3
Q4
2022 Q1
Q2
Q3
Q4
2023 Q1
Q2
Q3
Q4
2024 Q1

Evaluation

	Kwaliteit	Relevantie	Begroting
Beoordelaar 1	-Onderzoek naar fucosylering draagt niet bij. -Beschrijving plan van aanpak onvolledig (antistof testen, T-cel onderzoek).	-Weinig internationale samenwerking.	budget mogelijk te laag ingeschat.
Eindbesluit	Goed	Zeer relevant	Te laag
Beoordelaar 2	-kleinere groep deelnemers (exploratieve studie)	-Fucosylering is interessant.	Honorering exploratieve studie.
Eindbesluit	Matig	Relevant	Te hoog
Beoordelaar 3	-Goede samenwerking met patiënt vertegenwoordiger -Goed: gebruik maken van siblings, maar wel outcome bias beschrijven.	-Niet mijn expertise. -Advies: waarom geen DSMB?	Honorering van een exploratieve studie.
Eindbesluit	Goed	-	Reëel
Beoordelaar 4	-Groepsgrootte berekening overtuigend. mensen met DS worden eerder gevaccineerd dan siblings. Heeft dit invloed op vergelijkingen?	-Fucosylering is interessant.	-
Eindbesluit	Zeer goed	Relevant	Reëel
Beoordelaar 5	-Uitleggen waarom T- en B-cellen belangrijk zijn voor effectiviteit van vaccinatie. - details over welke assays gebruikt worden.	-	-
Eindbesluit	Goed	-	-
Beoordelaar 6	-Goede samenwerking met patiënt vertegenwoordiger -Advies: geef deze kwetsbare groep extra tijd om PIF door te nemen.	-	-
Eindbesluit	Zeer goed	Zeer relevant	Reëel
Beoordelaar 7	-Fucosylering is interessant. -Niet duidelijk wat de flow-cytometrische analyse om T-cel respons te bekijken. -Powerbereking lastig te volgen. -Waarom statistische analyses in Yale? -Nog melden dat publiceren zal gaan via Open Acces. Marin: dit staat wel in datamanagementplan.	-In poweranalyse wordt nu uitgegaan van 75%, dit suggereert dat het probleem minder urgent is. -Er zijn op www.clinicaltrials.gov twee hits met DS en COVID. Handig om mee samen te werken?	
Eindbesluit	Zeer goed	Relevant	Te hoog
Beoordelaar 8	-Aantal patiënten lijkt realistisch. -Advies: de grootte van de studiegroep geeft de mogelijkheid om meer inzicht te krijgen in grenswaarden van bescherming, deze exploratie toevoegen.	-Gemis internationale samenwerking.	-Personele lastente hoog, met name UMCU budget.
Eindbesluit	Goed	Zeer relevant	Te hoog

- Details immuno assays
  - *Nu beter?*
- Onderzoek fucosylering
  - *Anders bij DS*
  - *vaccinatierespons*
- Budget
  - *klinische studie, spoed*

Conclusie

1. Consortium: expertise

2. Down Syndrome: complex disease, severe course of disease, T-cell defect, fucosylation defect

3. Two clinical followup studie before/after vaccination for Ab responses as well as cellular responses