Persistenza di anticorpi anti-SARS-CoV-2 in bambini e adulti

Relatore: Costanza Di Chiara
Università di Padova

Per quanto concerne i moderatori, relatori, formatori, tutor, docenti è richiesta dall'Accordo Stato-Regioni vigente apposita dichiarazione esplicita dell'interessato, di trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali relativi agli ultimi due anni dalla data dell'evento.
La documentazione deve essere disponibile presso il Provider e conservata per almeno 5 anni.

Dichiarazione sul Conflitto di Interessi

Il sottoscritto Costanza Di Chiara in qualità di:

□ moderatore □ docente X relatore □ tutor

dell'evento "78° Congresso Italiano di Pediatria", Torino 25-28 ottobre 2023

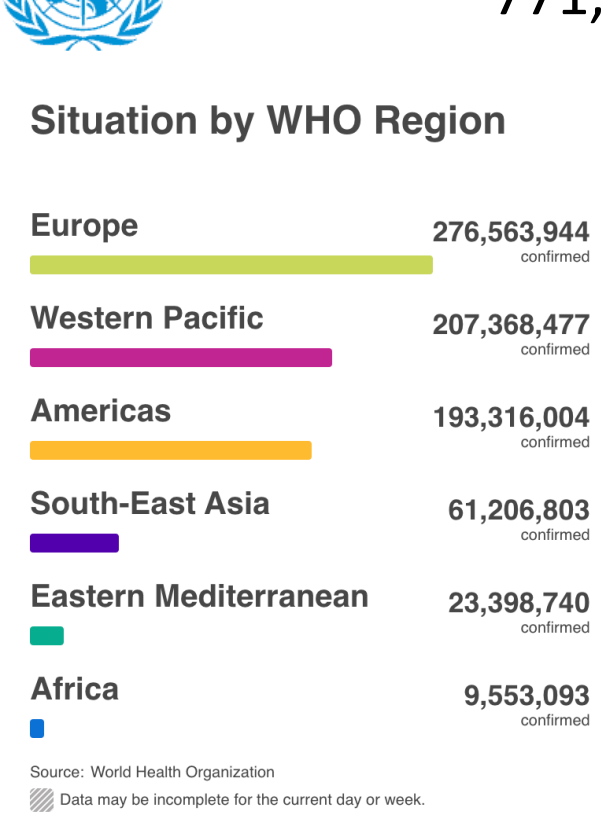
da tenersi per conto di **SIP n. 1172**
ai sensi dell'Accordo Stato-Regione in materia di formazione continua nel settore "Salute" (Formazione ECM) vigente,

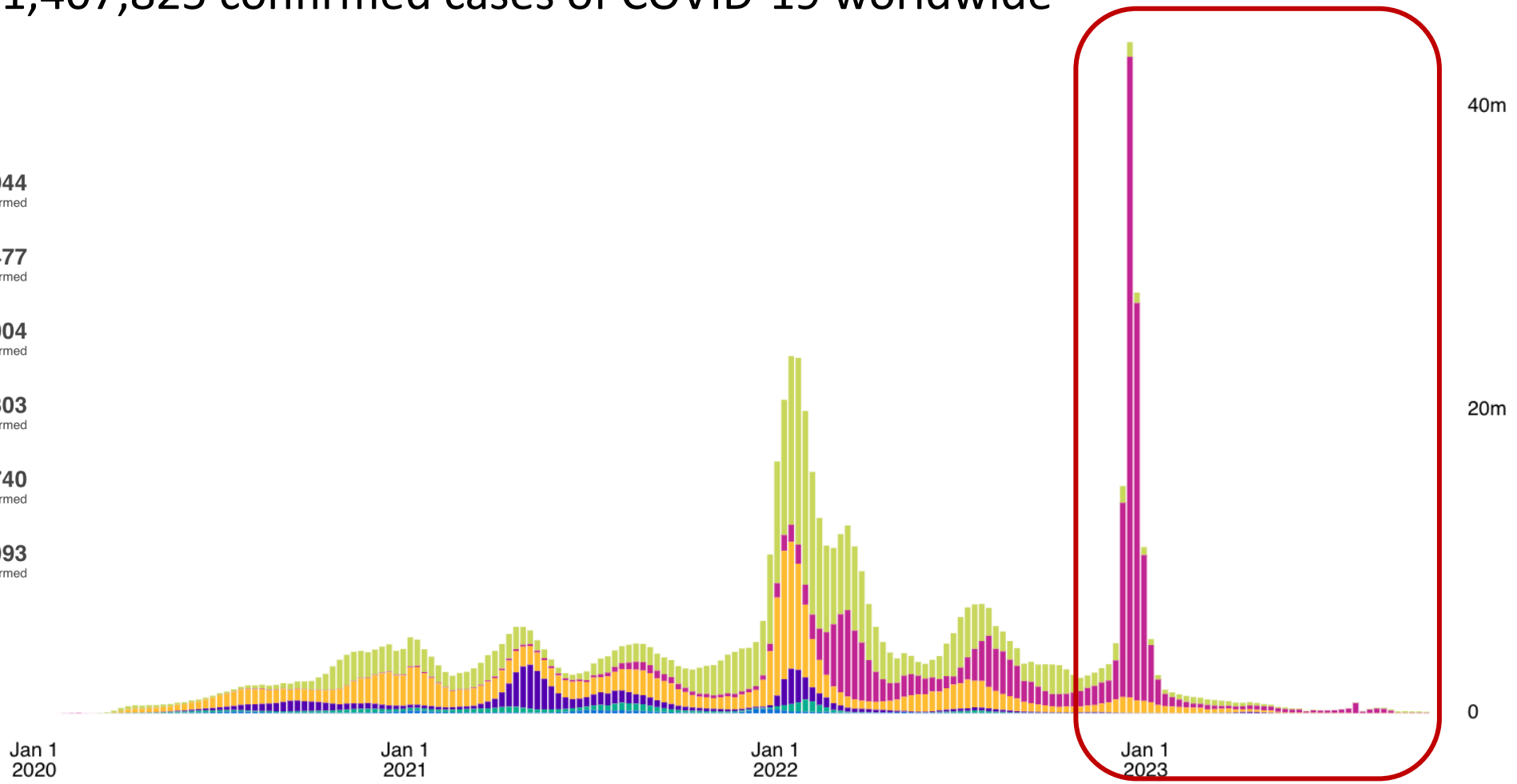
Dichiara

che negli ultimi due anni NON ha avuto rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

The global burden of COVID-19

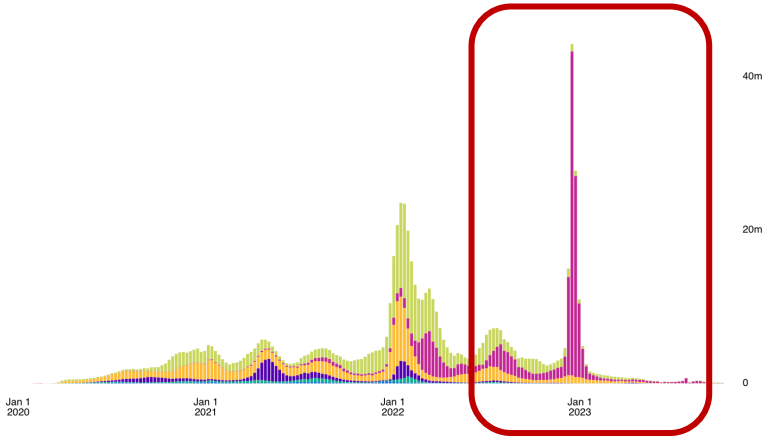
771,407,825 confirmed cases of COVID-19 worldwide



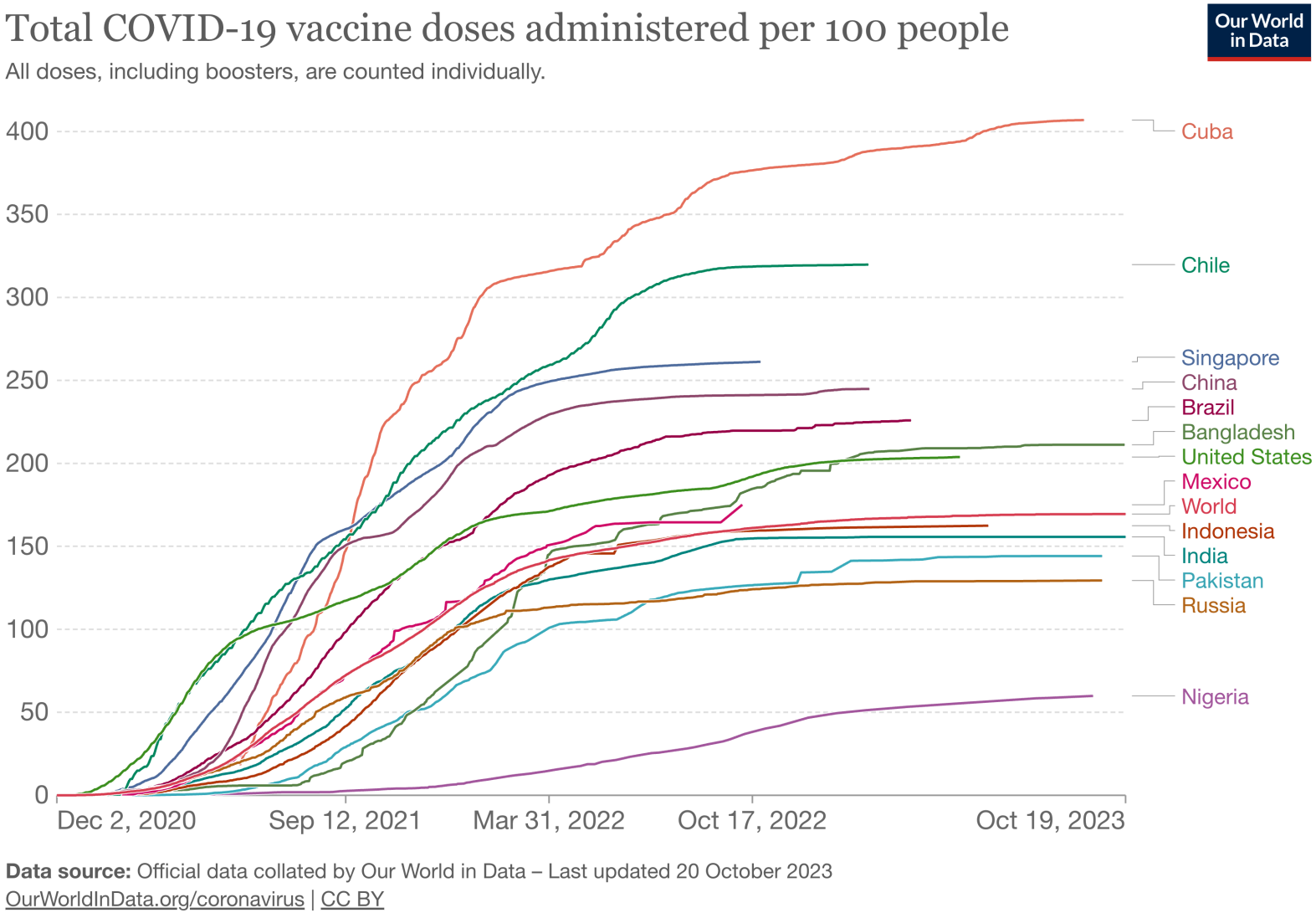


WHO Coronavirus (COVID-19) Dashboard Updated on October 18, 2023

The global burden of COVID-19



Achievement of a satisfactory **community immunity** to the SARS-CoV-2 virus from infection, vaccination, or both.



World Health Organization

On May 5, the WHO Director-General

Dr. Tedros Adhanom Ghebreyesus

declared an end to the global Public Health Emergency for COVID-19.

“This virus is here to stay.

It is still killing, and it’s still changing.

The risk remains of new variants emerging that cause new surges in cases and deaths”, warning countries to remain vigilant.

To a new phase of the global pandemic's response and recovery

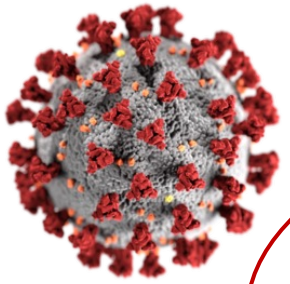
shifting towards a longer-term programmatic approach to COVID-19.

Document number: WHO/EURO:2023-7637-47404-69640

COVID-19 Preparedness

Prepare for New Variants

Prevent Economic and Educational Shutdowns



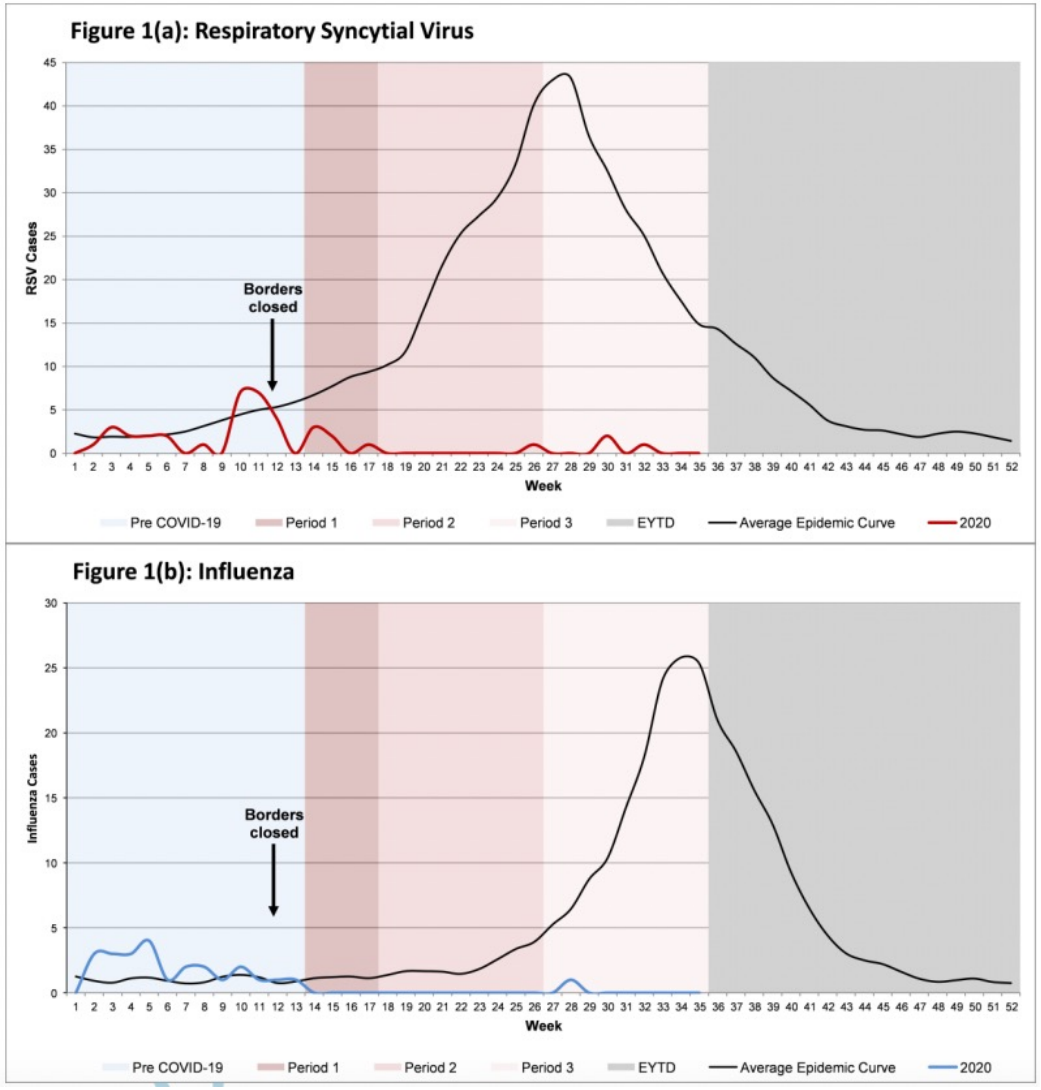
Protect Against and Treat Covid-19

Continue to Vaccinate the World

Community immunity

Document number: WHO/EURO:2023-7637-47404-69640

Immunity debt



Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 72(12), 2199–2202.

Vaccinations disruption

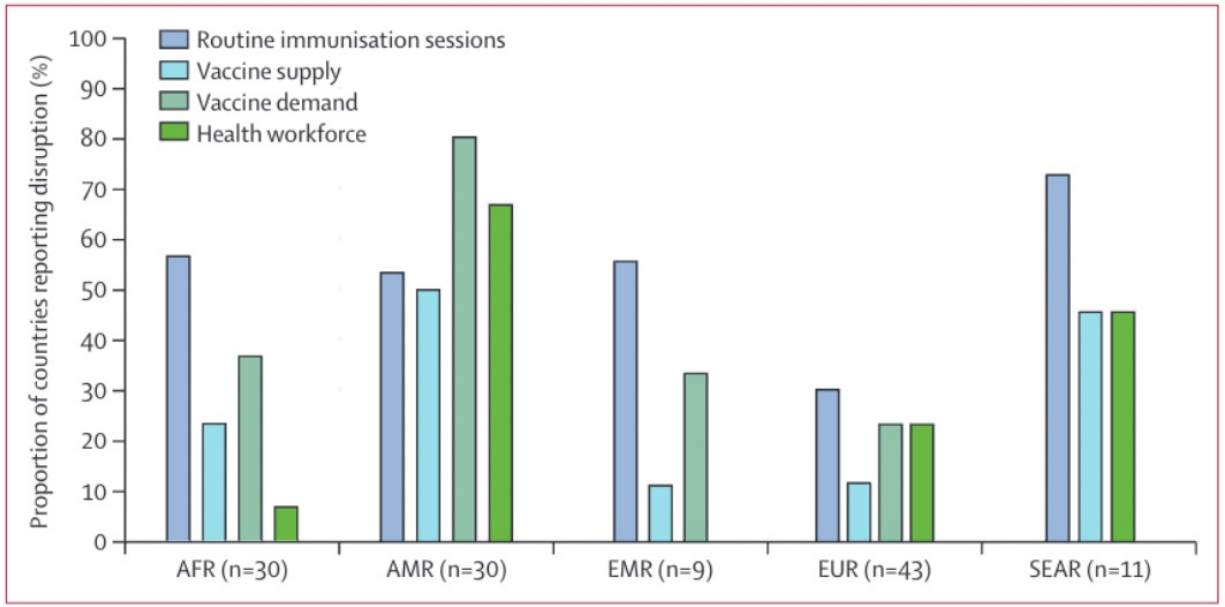


Figure 1: Proportion of countries reporting pandemic-related disruption to routine immunisation sessions,

region. WPR=Western Pacific region.

Growing proportion of "susceptible" people and declined herd immunity in the population.

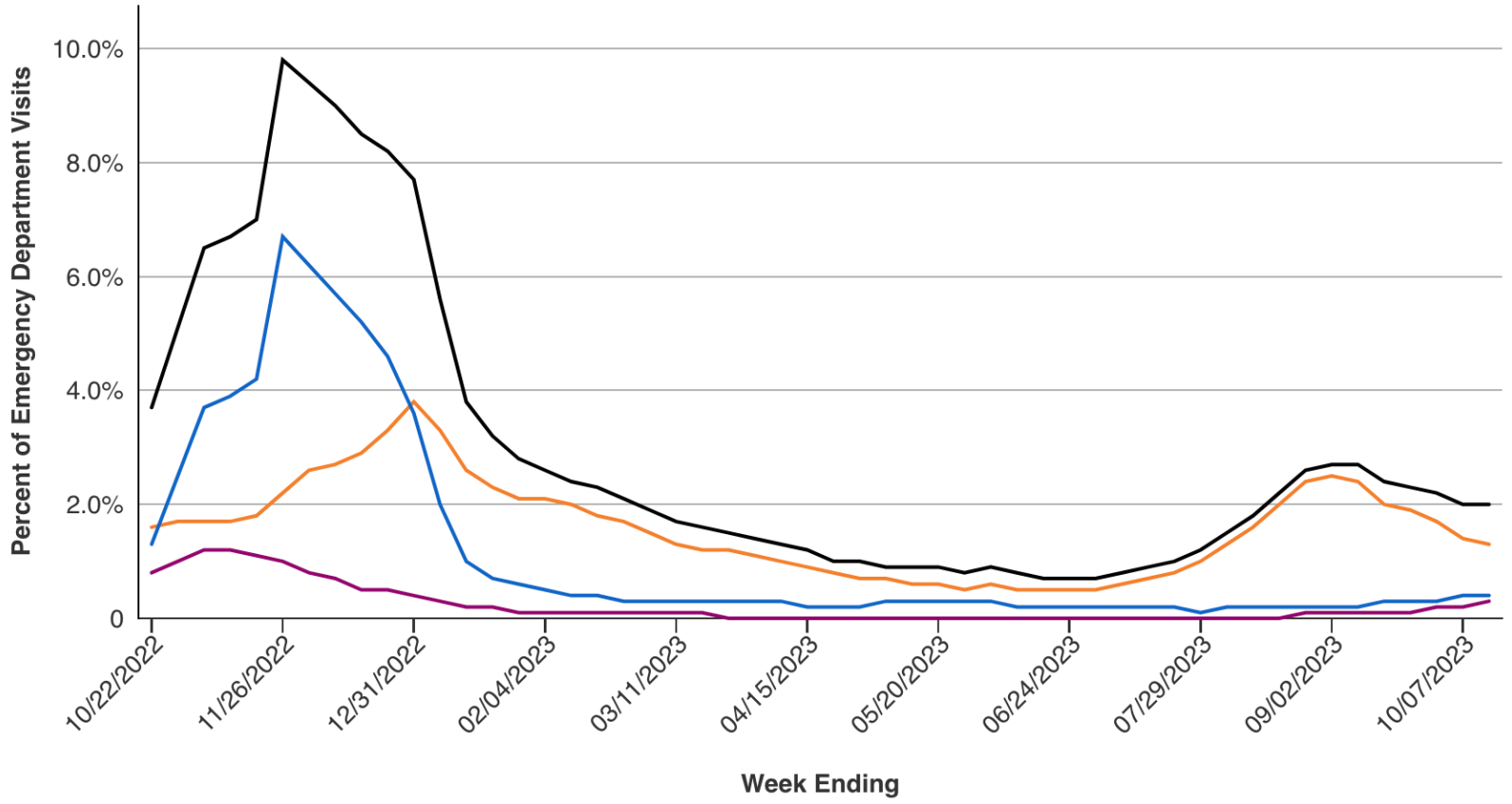
Lancet Glob Health 2022; 10: e186–94

The tripledemic of COVID-19, Flu, and RSV

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Emergency Department Visits for Viral Respiratory Illness

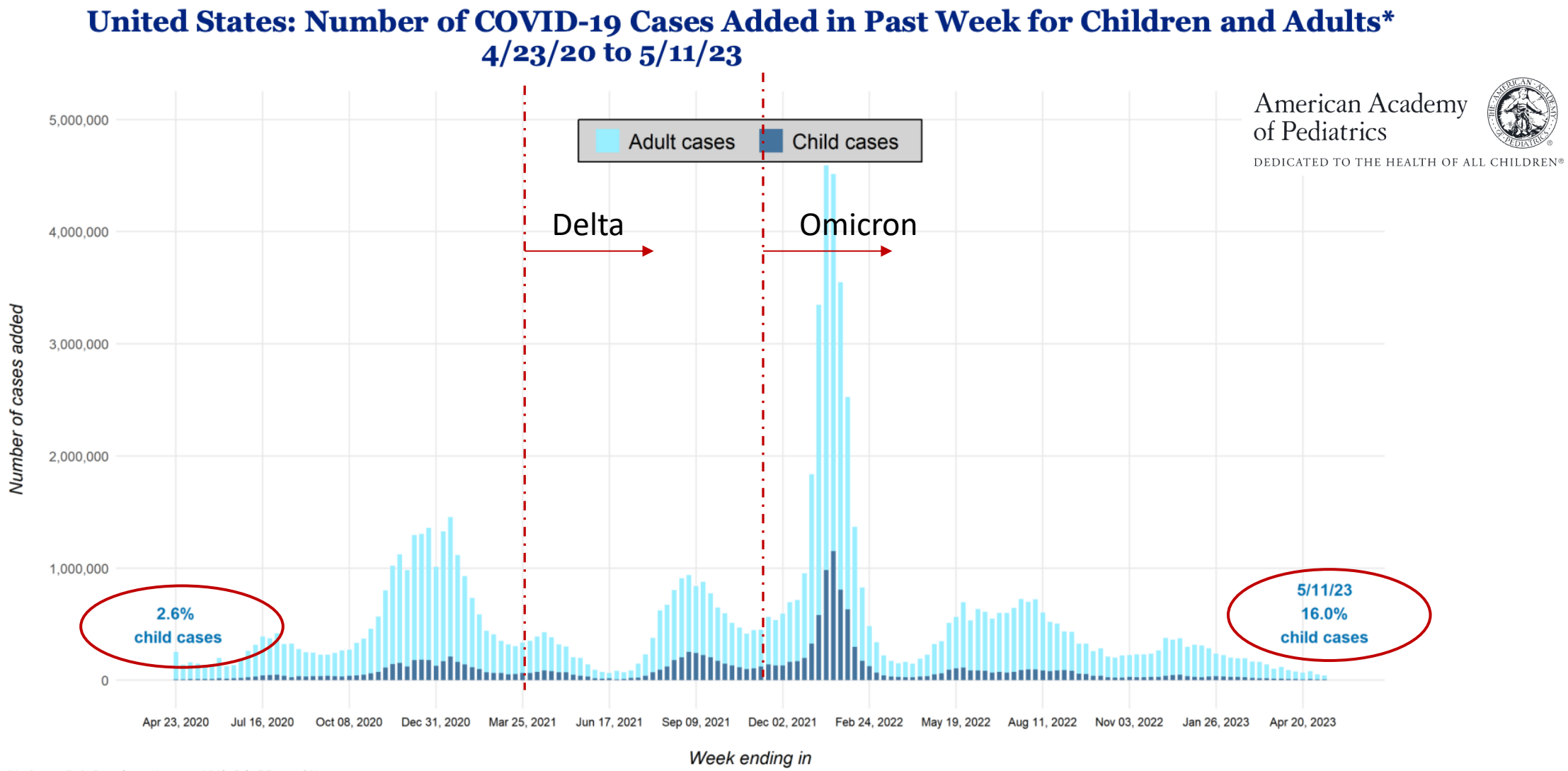
Weekly percent of total emergency department visits associated with COVID-19, influenza, and RSV



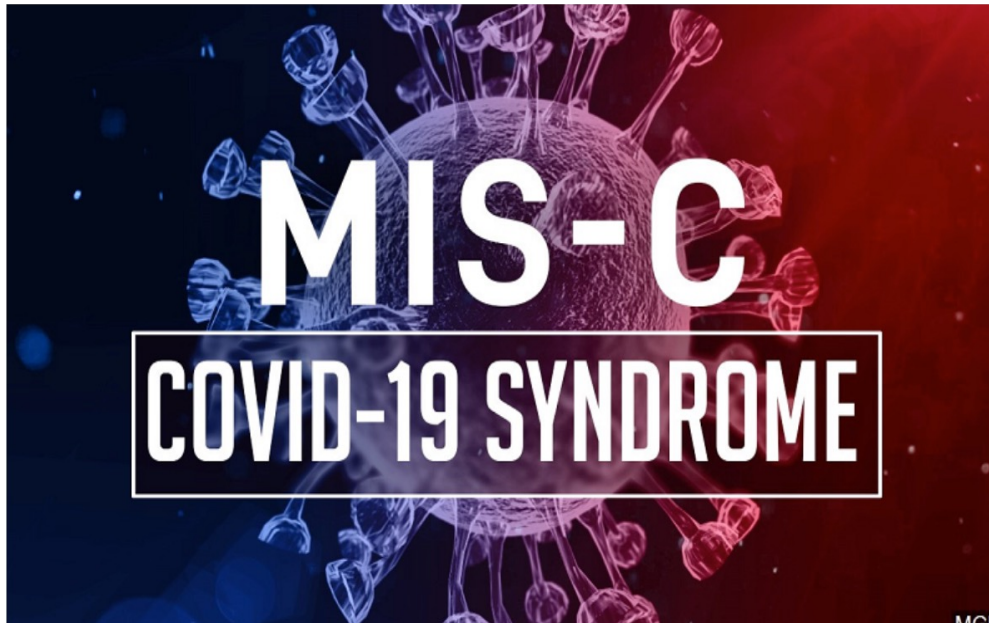
Updated on October 10, 2023

Wars may lead to local outbreaks of infectious diseases that threaten to spread into neighboring EU countries

The pediatric burden of COVID-19



Post-acute COVID syndrome (PASC)



CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-index.html


MEDICI
CON L'AFRICA
CUAMM
UN VACCINO
PER "NOI".

Understanding the magnitude and longevity of humoral immunity to SARS-CoV-2 is crucial to inform public health policies and optimize vaccination strategies in the pediatric population.

Evaluation of the **humoral response features** of children and parents beloging to a family clusters of COVID-19.

ALL FAMILY MEMBERS confirmed COVID-19 cases (Abs/NPSpos) at 1st F-UP

Families ENROLLMENT and BASELINE definition → 1° FOLLOW: 1-4 months from BASELINE → 2° FOLLOW: 5-9 months from BASELINE → 3° FOLLOW: ≥10 months from BASELINE

onset of symptoms

first positive NPS

family temporal outbreak

Evaluation included
Clinical data collection - WHO

Blood sample collection for:

Quantification of anti-SARS-CoV-2 **S-RBD IgG** Ab*

Serum **neutralizing antibodies**§

Follow-up included:
- collection of blood samples for evaluation on the Abs long-term kinetics

CASE cohort

* chemiluminescent assays (CLIA) MAGLUMI™ 2000 Plus (Snibe Diagnostics)

§ Plaque Reduction Neutralization Test (PRNT)

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

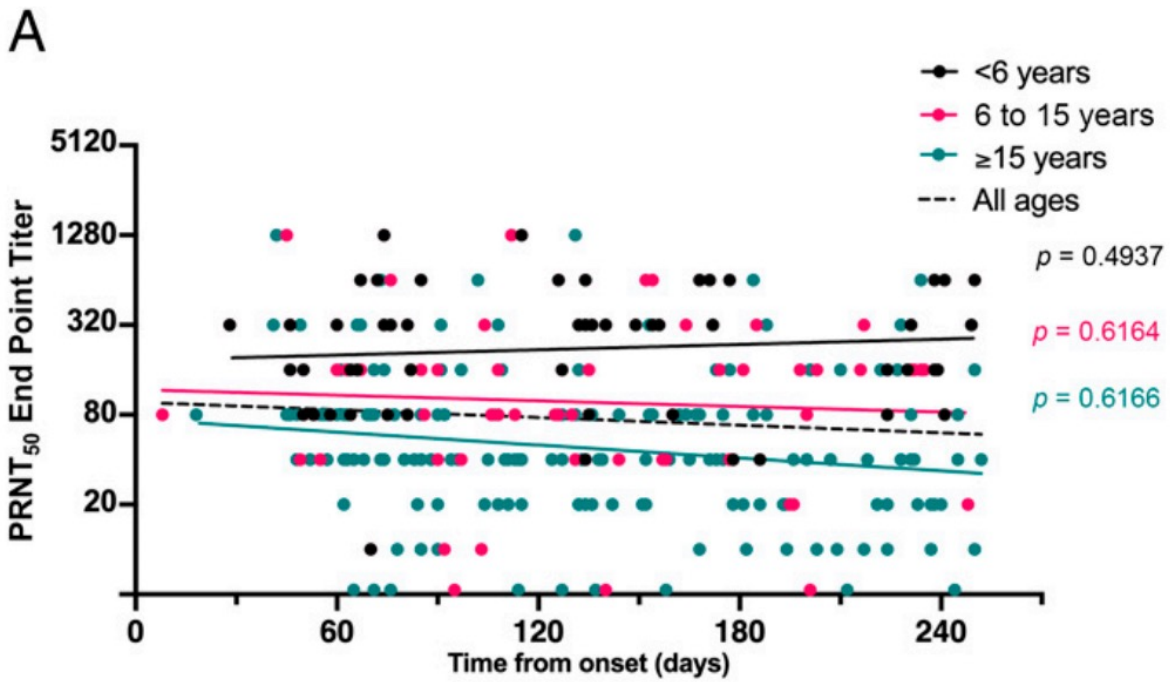
Mild SARS-CoV-2 Infections and Neutralizing Antibody Titers

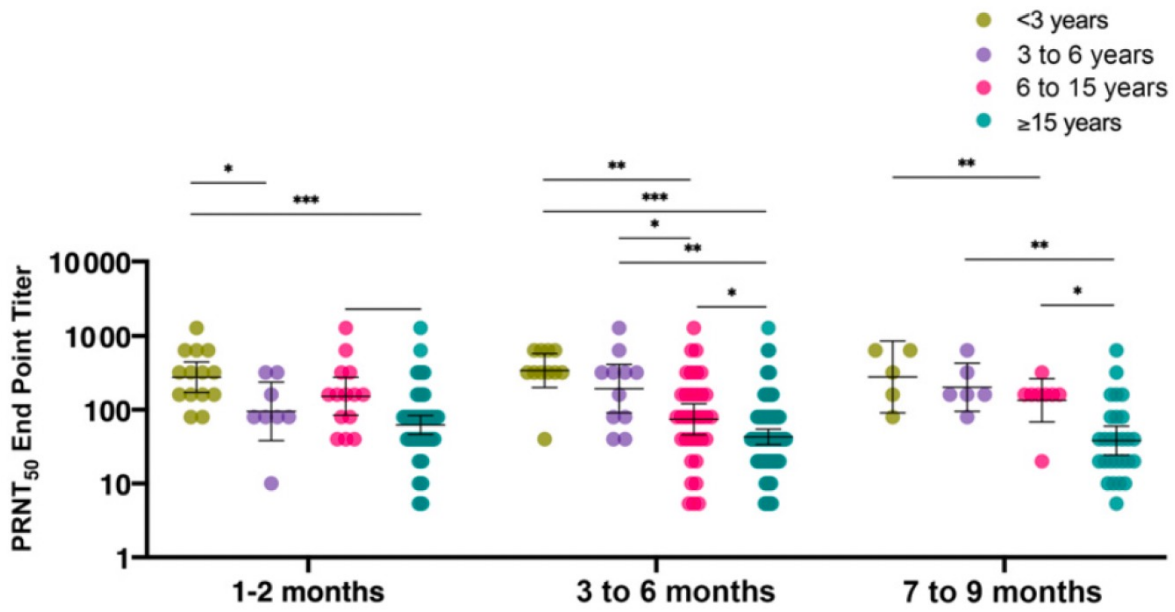
Francesco Bonfante, DVM,[a,*] Paola Costenaro, MD, DTM&H,[b,*] Anna Cantarutti, PhD,[c] Costanza Di Chiara, MD[b] Alessio Bortolami, DVM, PhD,[a] Maria Raffaella Petrara, PhD,[d] Francesco Carmona, BSc,[e] Matteo Pagliari, PhD,[a] Chiara Cosma, MD,[f] Sandra Cozzani, MD,[b] Eva Mazzetto, DVM,[a] Giovanni Di Salvo, MD,[g] Liviana Da Dalt, MD,[g] Paolo Palma, MD,[h,i] Luisa Barzon, MD,[j] Giovanni Corrao,[k,c] Calogero Terregino, MD,[a] Andrea Padoan, MD,[l] Mario Plebani, MD,[l,f] Anita De Rossi, PhD,[d,e] Daniele Donà, MD, PhD,[b] Carlo Giaquinto, MD[b]

High levels of SARS-CoV-2 NAbs are found up to 7-8 months after asymptomatic/mild COVID-19 in children

NAbs titers showed a negative correlation with age

Young kids showed significantly higher NAbs titers than adults



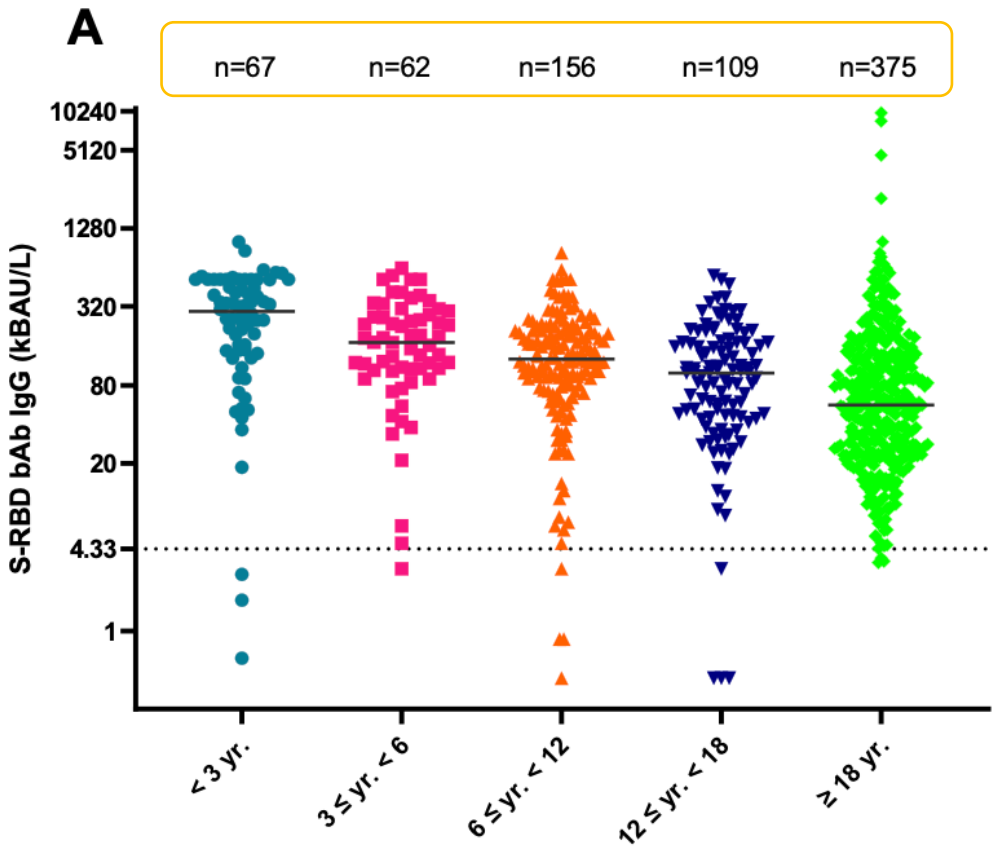


JAMA Network Open

Original Investigation | Pediatrics

Long-term Immune Response to SARS-CoV-2 Infection Among Children and Adults After Mild Infection

Costanza Di Chiara, MD; Anna Cantarutti, PhD; Paola Costenaro, MD, DTMH; Daniele Donà, MD, PhD; Francesco Bonfante, PhD; Chiara Cosma, PharmD, PhD; Martina Ferrarese, MD; Sandra Cozzani, MD; Maria Raffaella Petrara, PhD; Francesco Carmona, BSc; Cecilia Liberati, MD; Paolo Palma, MD; Giovanni Di Salvo, MD; Anita De Rossi, PhD; Mario Plebani, MD; Andrea Padoan, PhD; Carlo Giaquinto, MD



697 subjects

p<0.0001

Anti-S-RBD IgG titers differ among age classes

Young children showed significantly higher S-RBD IgG titers than older subjects

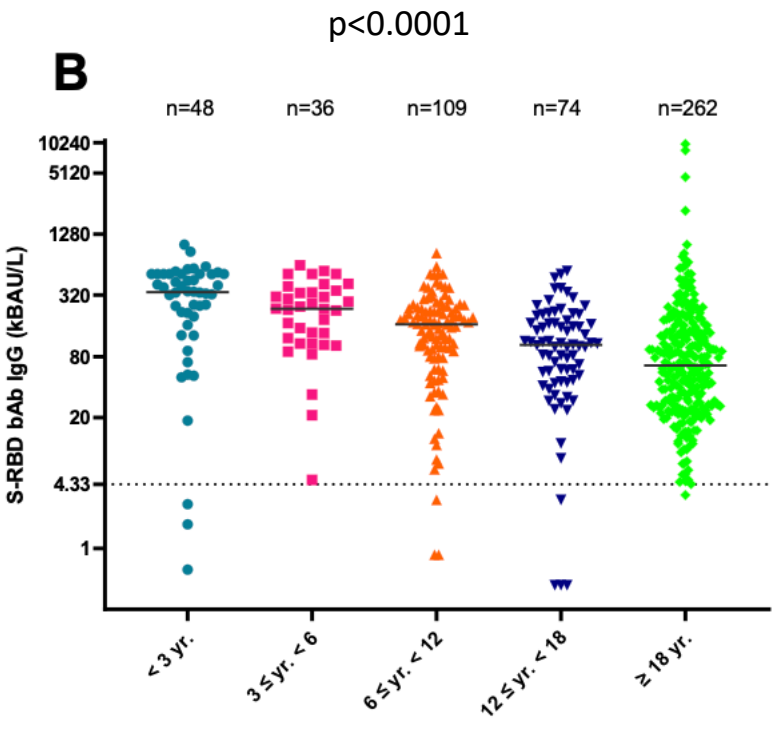
JAMA Network Open

Original Investigation | Pediatrics

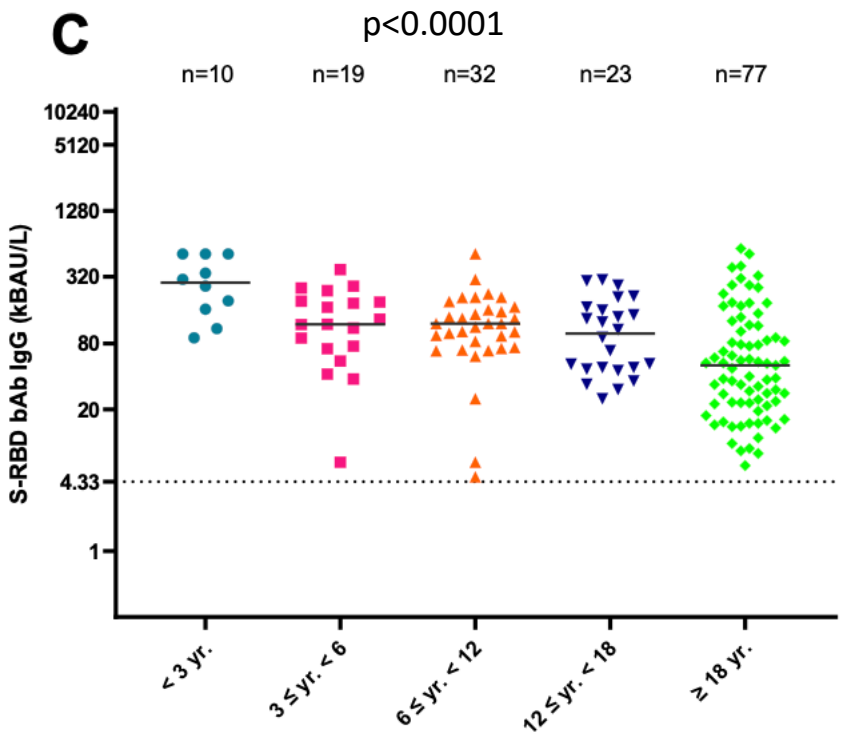
Long-term Immune Response to SARS-CoV-2 Infection Among Children and Adults After Mild Infection

Costanza Di Chiara, MD; Anna Cantarutti, PhD; Paola Costenaro, MD, DTMH; Daniele Donà, MD, PhD; Francesco Bonfante, PhD; Chiara Cosma, PharmD, PhD; Martina Ferrarese, MD; Sandra Cozzani, MD; Maria Raffaella Petrara, PhD; Francesco Carmona, BSc; Cecilia Liberati, MD; Paolo Palma, MD; Giovanni Di Salvo, MD; Anita De Rossi, PhD; Mario Plebani, MD; Andrea Padoan, PhD; Carlo Giaquinto, MD

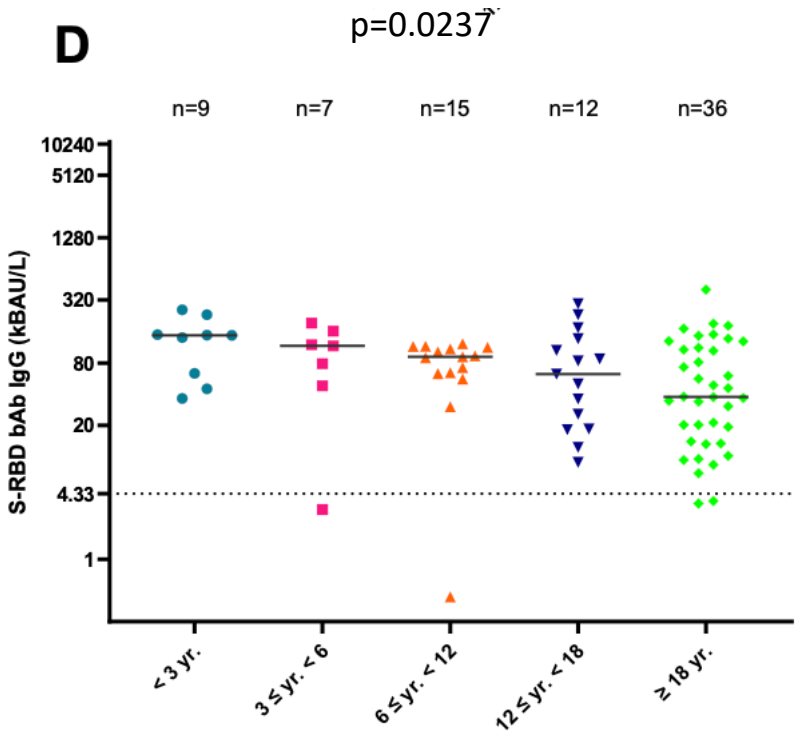
Differences in S-RBD IgG titers among all age classes were also observed when samples were stratified by time of collection



1-4 months, from infection (529 samples)



5-9 months, from infection (161 samples)



≥10 months, from infection (79 samples)

JAMA Network Open

Original Investigation | Pediatrics

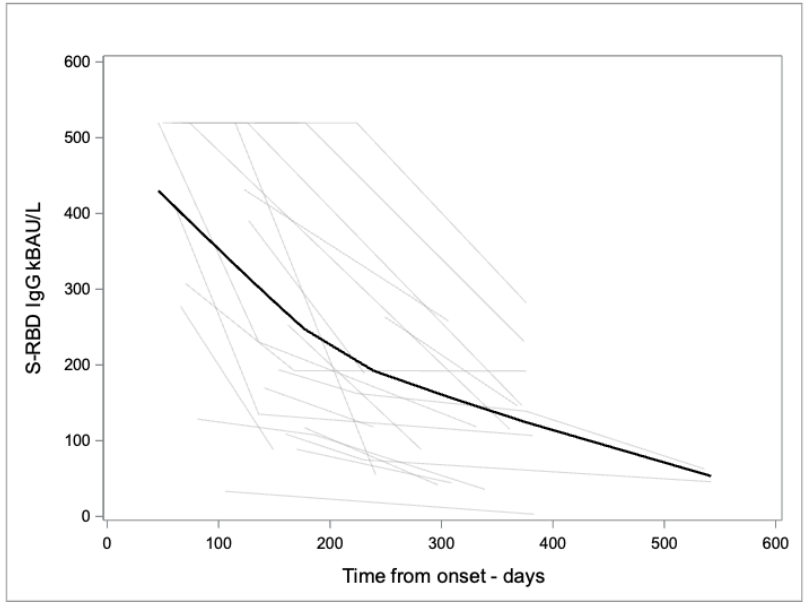
Long-term Immune Response to SARS-CoV-2 Infection Among Children and Adults After Mild Infection

Costanza Di Chiara, MD; Anna Cantarutti, PhD; Paola Costenaro, MD, DTMH; Daniele Donà, MD, PhD; Francesco Bonfante, PhD; Chiara Cosma, PharmD, PhD; Martina Ferrarese, MD; Sandra Cozzani, MD; Maria Raffaella Petrara, PhD; Francesco Carmona, BSc; Cecilia Liberati, MD; Paolo Palma, MD; Giovanni Di Salvo, MD; Anita De Rossi, PhD; Mario Plebani, MD; Andrea Padoan, PhD; Carlo Giaquinto, MD

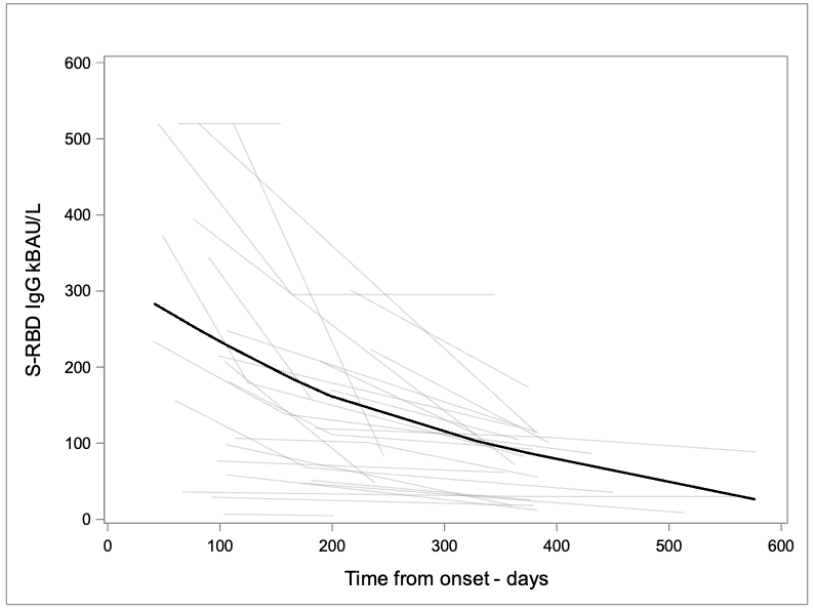
Anti-S-RBD IgG persist over time, with a progressive decline ranged between 2.0-2.3 fold and 2.5-3.6 fold reductions for the medium and long intervals, respectively.

The rate of Abs waning was more rapid during the first 200 days and progressively slower thereafter.

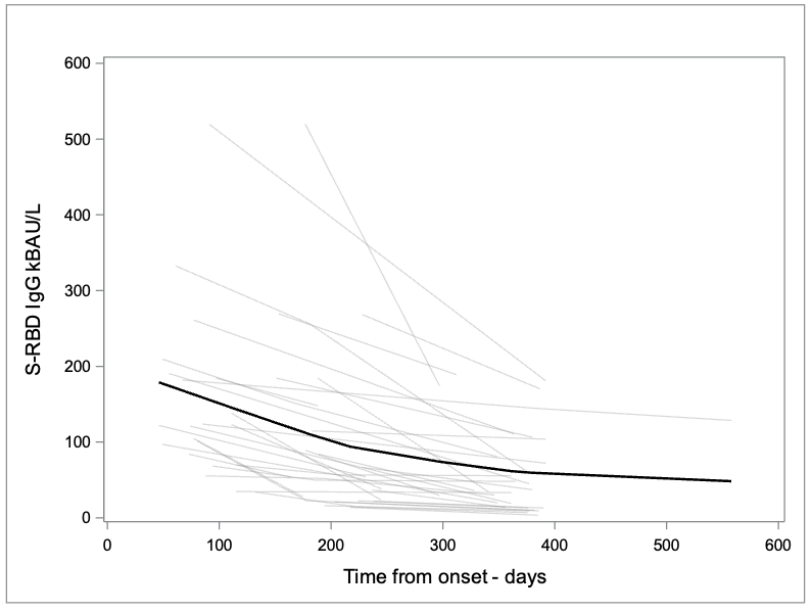
Children younger than 6 years showed an apparently faster early waning of Abs titers.



Age < 6 years



Age 6-18 years



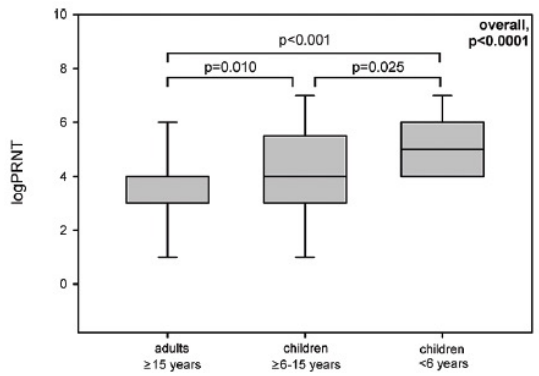
Age ≥ 18 years

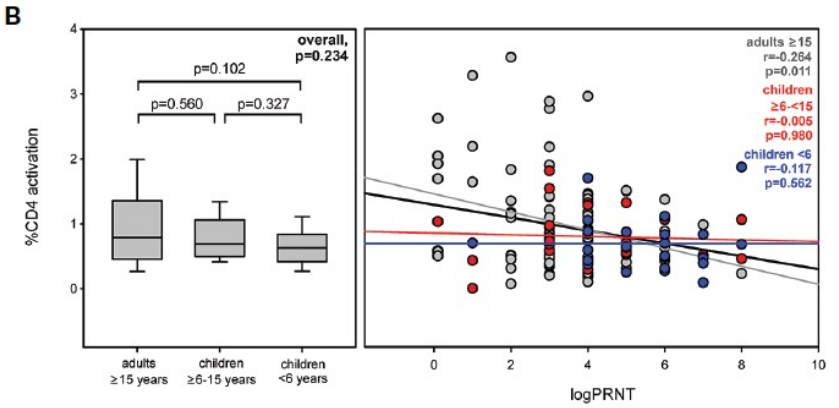
Asymptomatic and Mild SARS-CoV-2 Infections Elicit Lower Immune Activation and Higher Specific Neutralizing Antibodies in Children Than in Adults

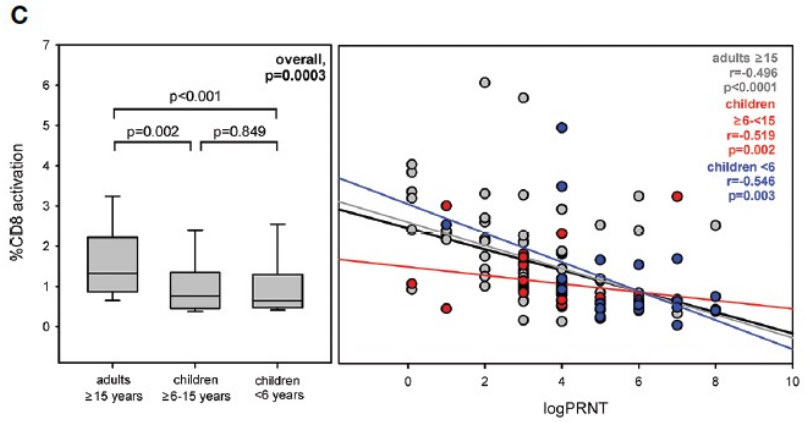
*Maria Raffaella Petrara[1], Francesco Bonfante[2], Paola Costenaro[3], Anna Cantarutti[4], Francesco Carmona[5], Elena Ruffoni[5], Costanza Di Chiara[3], Marisa Zanchetta[5], Luisa Barzon[6], Daniele Donà[3], Liviana Da Dalt[3], Alessio Bortolami[6], Matteo Pagliari[2], Mario Plebani[7,8], Paolo Rossi[9,10], Nicola Cotugno[9,10], Paolo Palma[9,10], Carlo Giaquinto[3] and Anita De Rossi[1,5]**

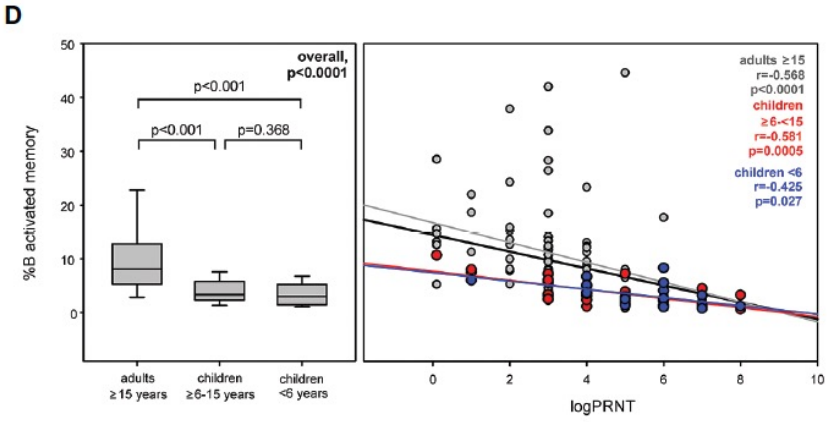
frontiers in Immunology

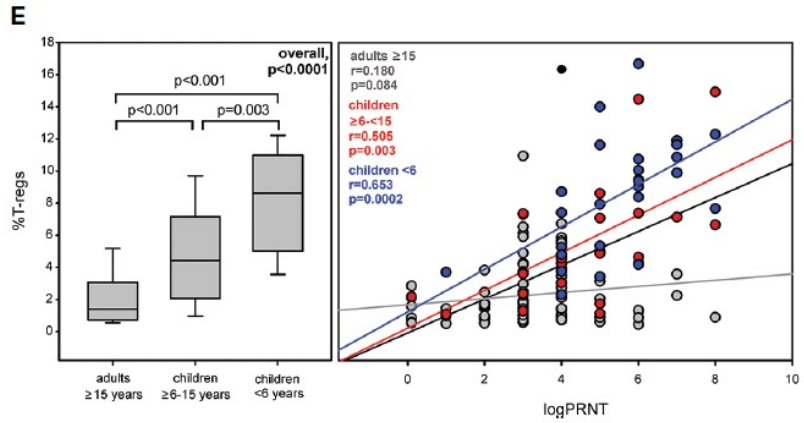
ORIGINAL RESEARCH
published: 30 September 2021
doi: 10.3389/fimmu.2021.741796

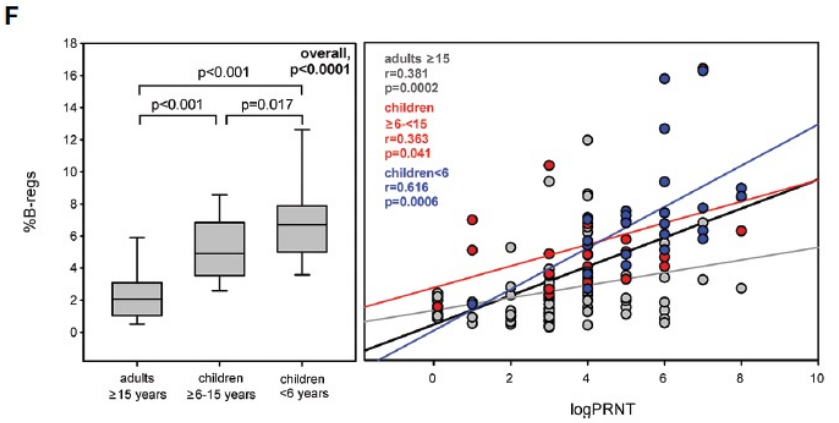












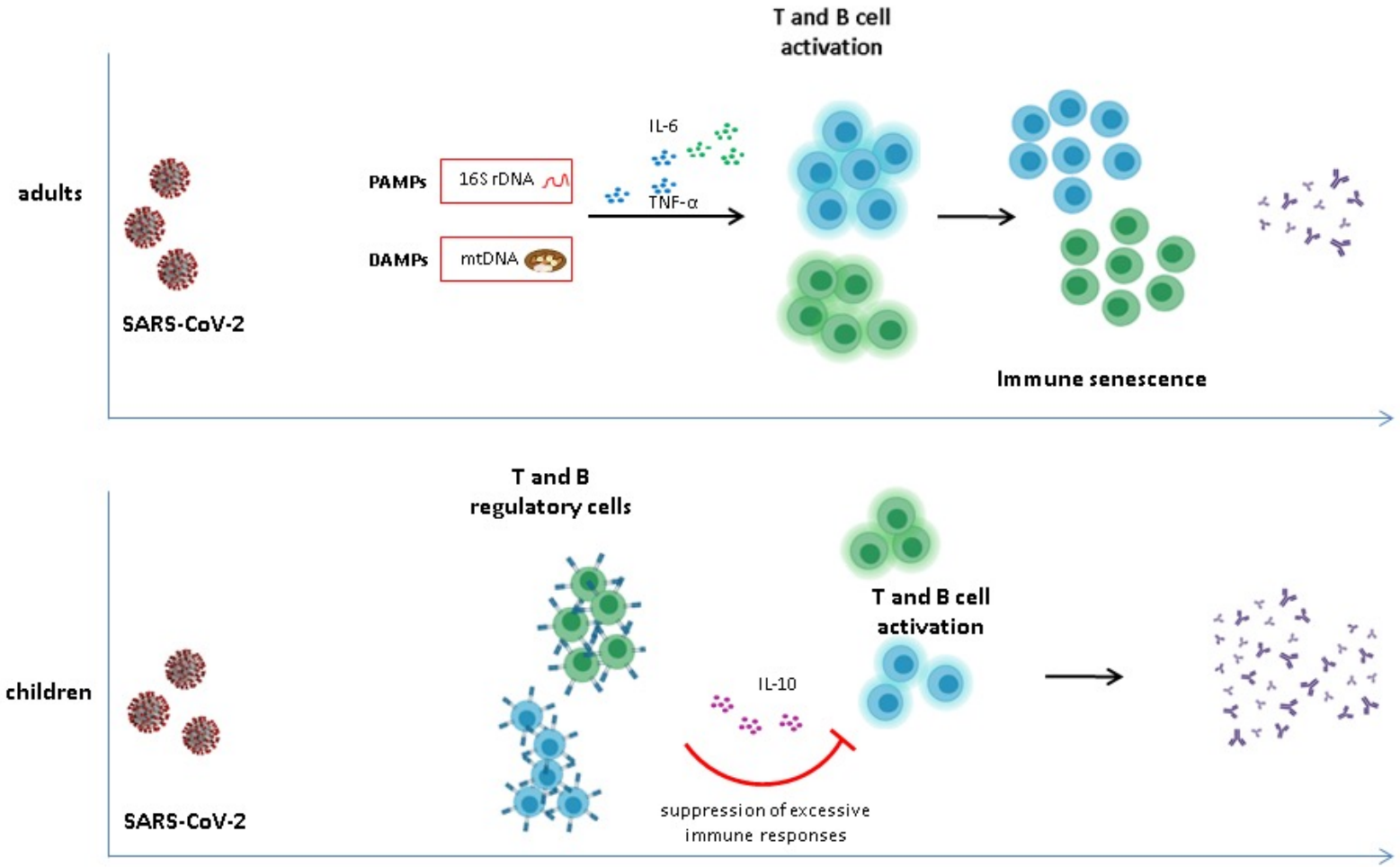
CASE cohort

Activated cells were higher in adults than in children and inversely correlated with the NAbs levels.

Tregs and Bregs regulatory cells were higher in children compared to adults and positively correlated with NAbs.

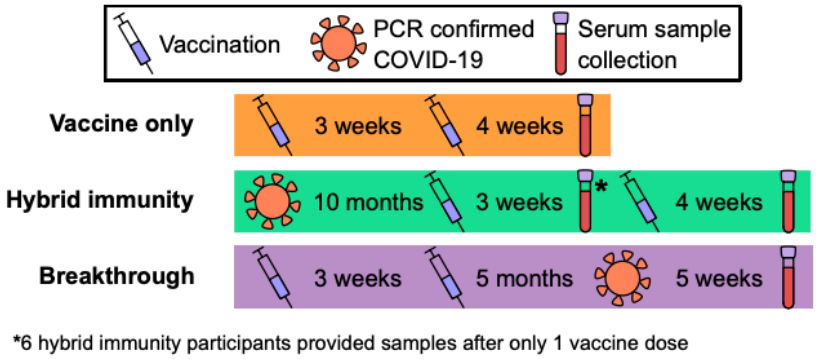
frontiers in Immunology
ORIGINAL RESEARCH
published: 30 September 2021
doi: 10.3389/fimmu.2021.741796

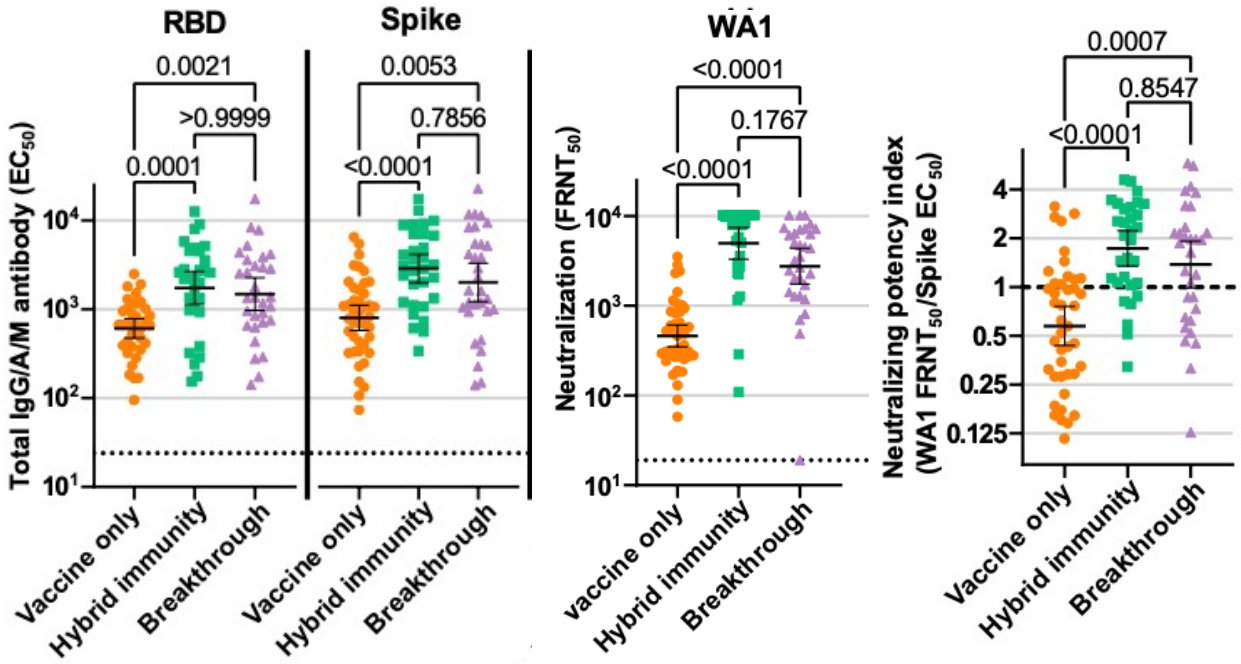
The higher expression of regulatory cells in children may contribute to reduce the immune activation, thus leading to a greater specific response against the virus.



Immune response to mRNA vaccines

In adolescents and adults, mRNA vaccines trigger an higher and durable humoral response to SARS-CoV-2 after previous SARS-CoV-2 infection compared to naïve-vaccinated.





Bates, T. A., et al. *Science immunology*, *7*(68), eabn8014. https://doi.org/10.1126/sciimmunol.abn8014
Bobrovitz, N., et al. *The Lancet. Infectious diseases*. https://doi.org/10.1016/S1473-3099(22)00801-5

The evaluation of the early and long-term immune response to the BNT162b2 vaccine in children aged 5-11 years with or without a previous SARS-CoV-2 infection.

CASE cohort

Patient ENROLLMENT
&
Immune status definition

3 weeks

6-12 months

pre-Omicron

re-exposed children were excluded from the analysis

1 month → 6 months

COVID-19 case (Group A)

PCR-confirmed

non COVID-19 case (Group B)

absence of specific antibodies

Serum and **PBMC** samples collection for:

Quantification of anti-SARS-CoV-2 **S-RBD IgG** Ab*

Serum **neutralizing antibodies**§

B and T **cells phenotype**#

§ chemiluminescent assays (CLIA) MAGLUMI™ 2000 Plus (Snibe Diagnostics)

§ Plaque Reduction Neutralization Test (PRNT)

Flow cytometry

Di Chiara et al. Stronger and Durable SARS-CoV-2 Immune Response to mRNA Vaccines in 5-11 Years Old Children with Prior COVID-19. Under review JVAC, Elsevier

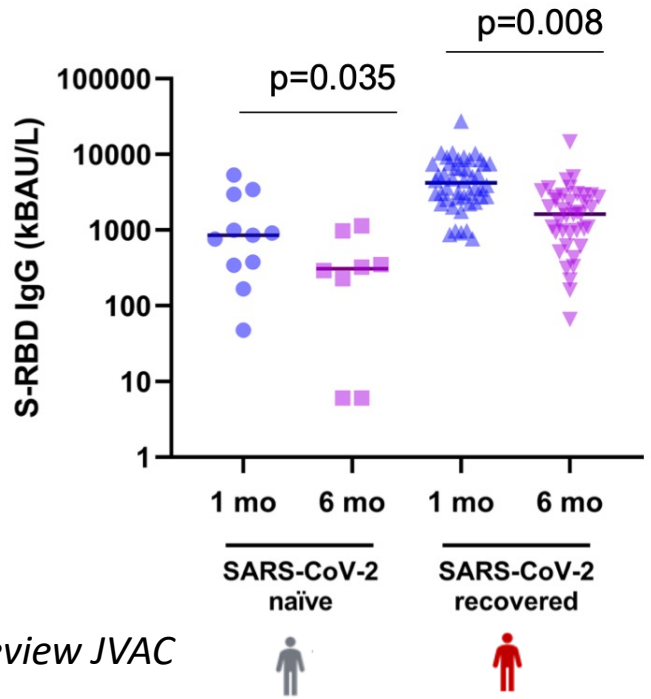
135 longitudinal samples were collected from 60 children

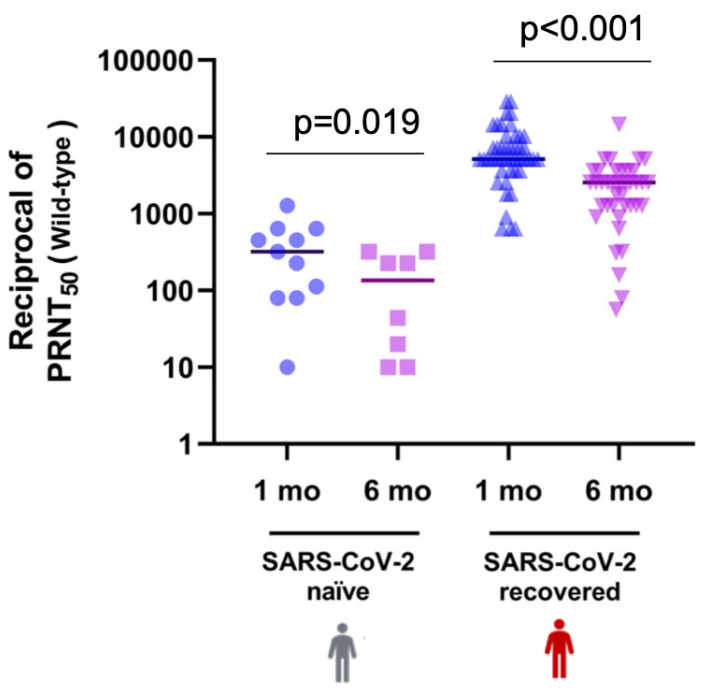
- 46/60 (77%) were SARS-CoV-2-recovered
- 14/60 (23%) SARS-CoV-2-naïve

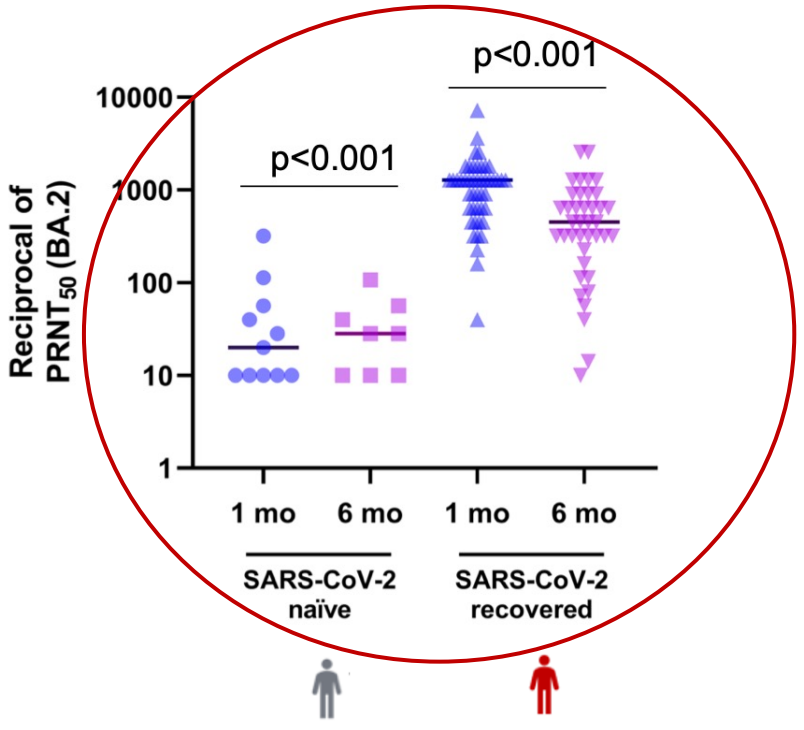
Anti-S-RBD IgG titers & NAbs differ between Group A and Group B

mRNA vaccines elicited a significantly higher anti-S-RBD and NAbs response in children with a previous COVID-19 than naïve-vaccinated peers at both **1- and 6-mo follow-up** after vaccination.

Omicron VOC

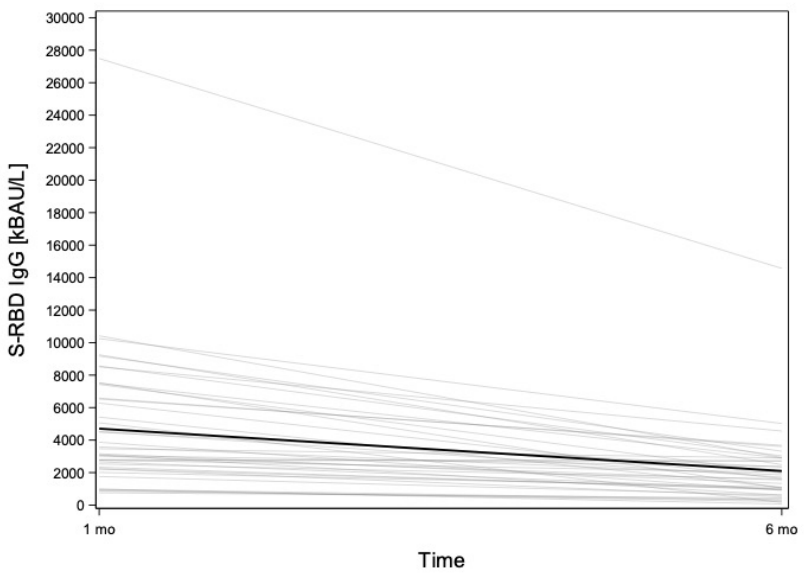


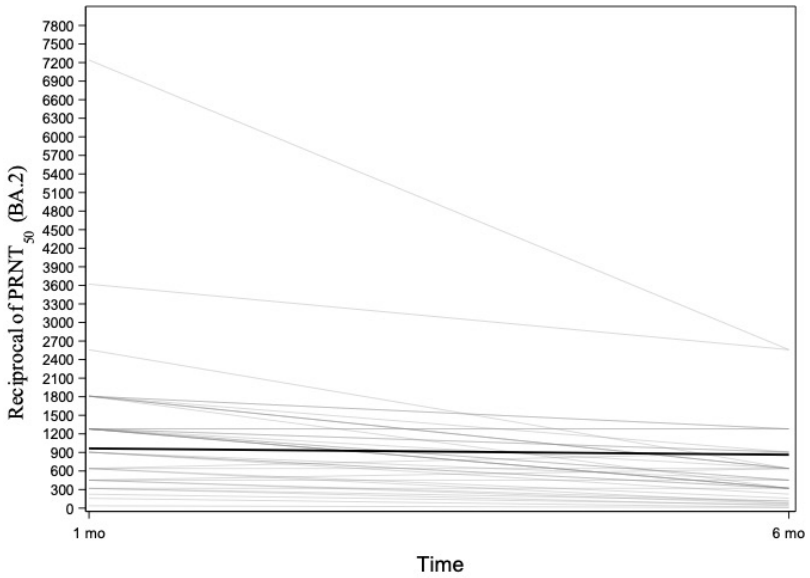


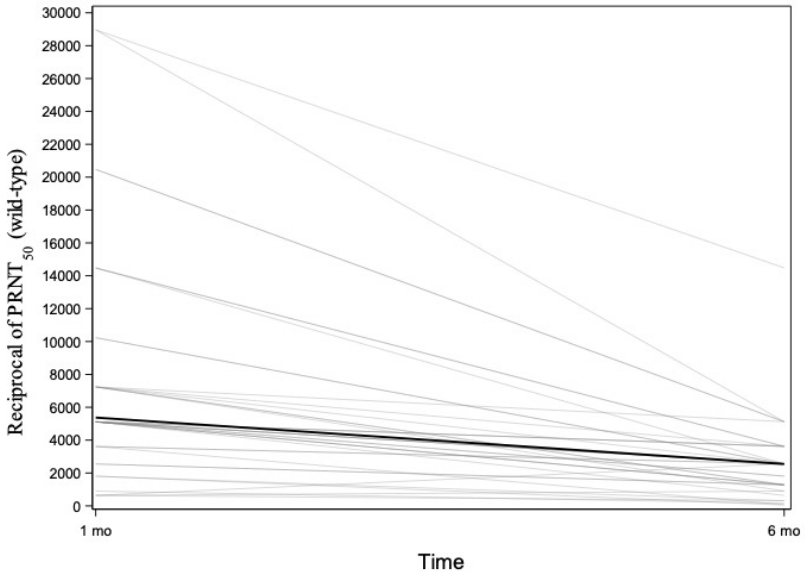


Under review JVAC

All individuals showed decreased anti-S-RBD IgG and WT and BA.2 NAbs titers, regardless of previous COVID-19

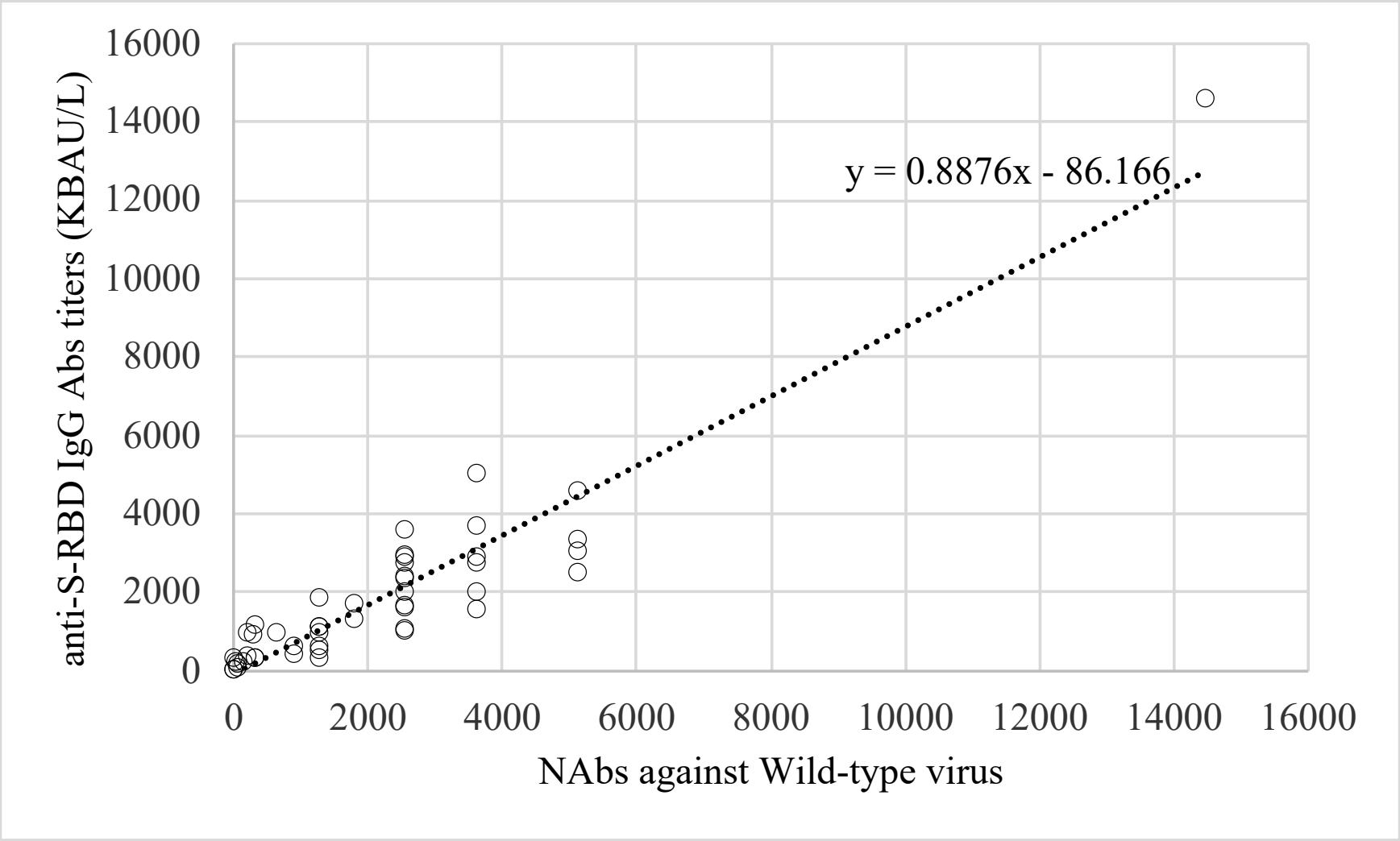






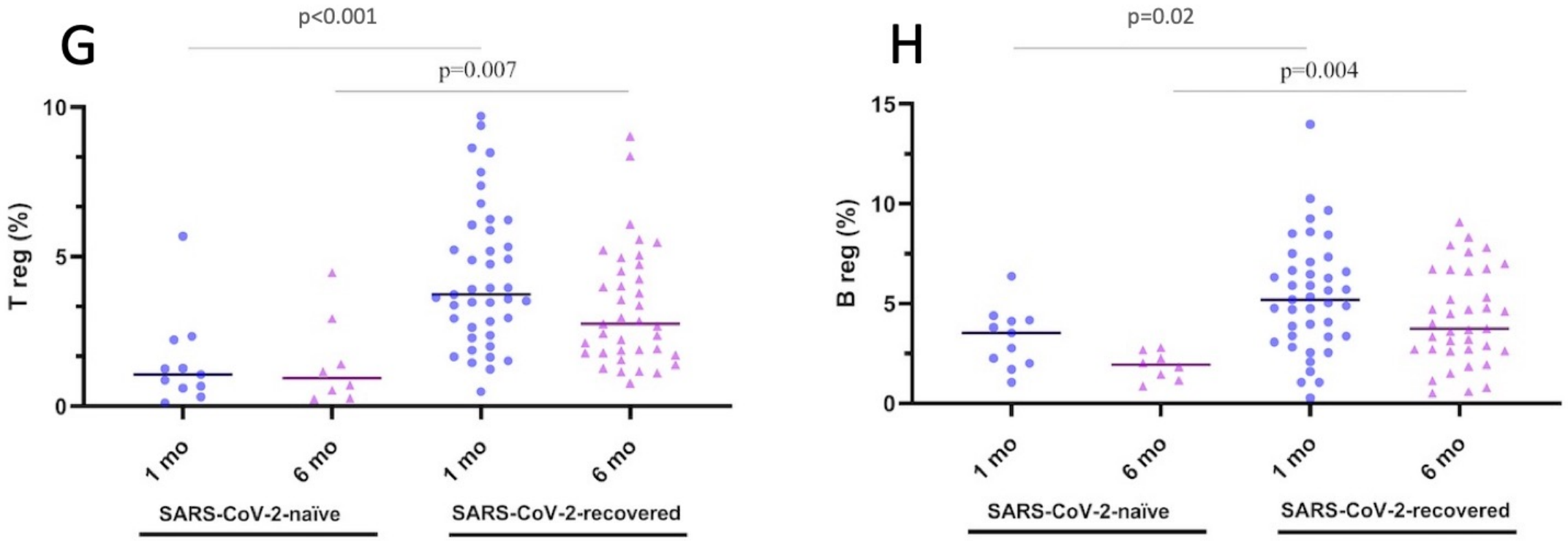
Under review JVAC

At 6-month post-vaccination, anti-S-RBD IgG remained highly correlated with NAbs, indicating that anti-S-RBD IgG antibodies retain their functional characteristics and neutralization capacity over time.



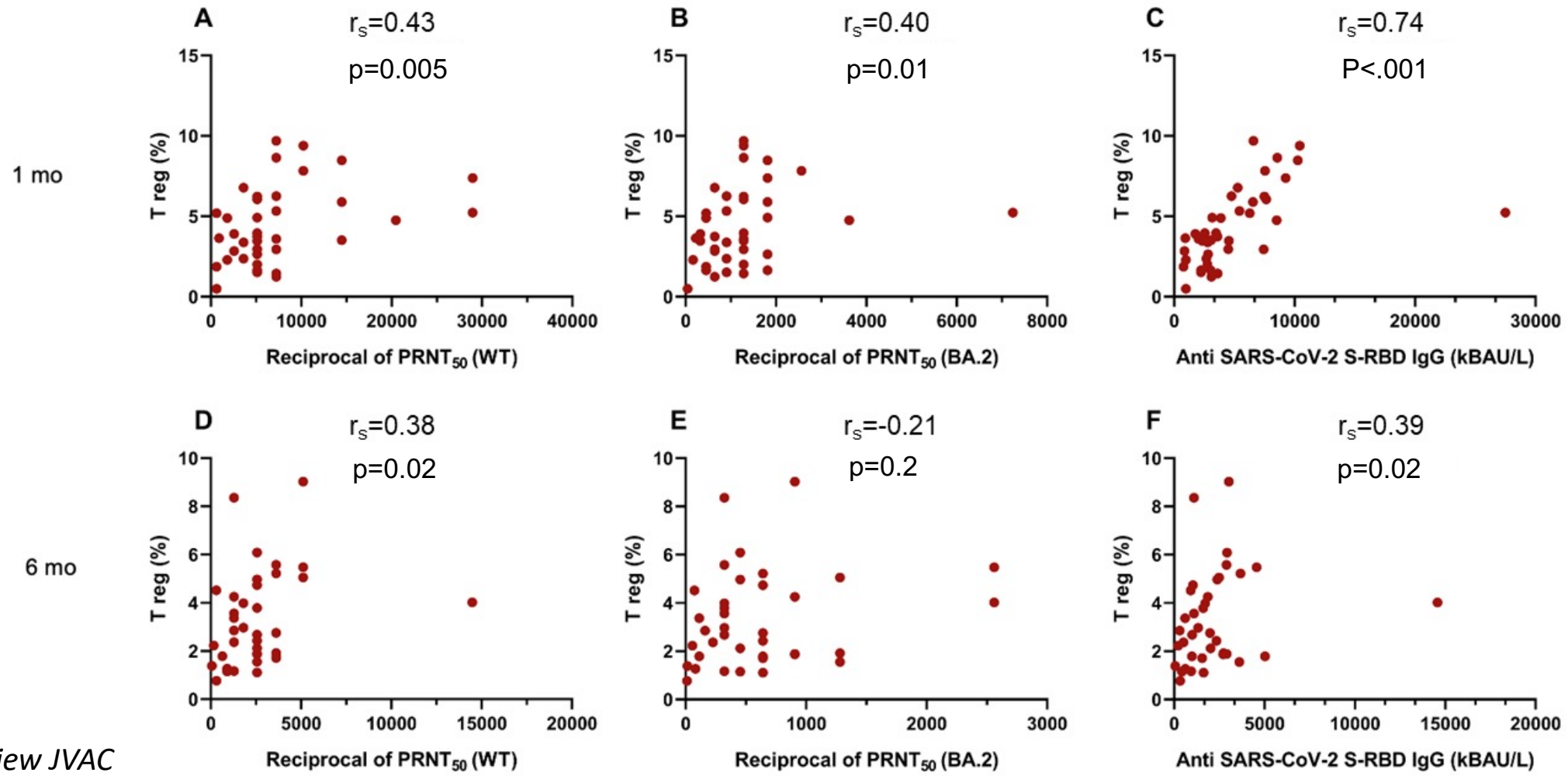
Under review JVAC

The frequencies of Tregs and Bregs were higher in SARS-CoV-2-recovered than in SARS-CoV-2-naïve children both at 1- and 6-months after vaccination.



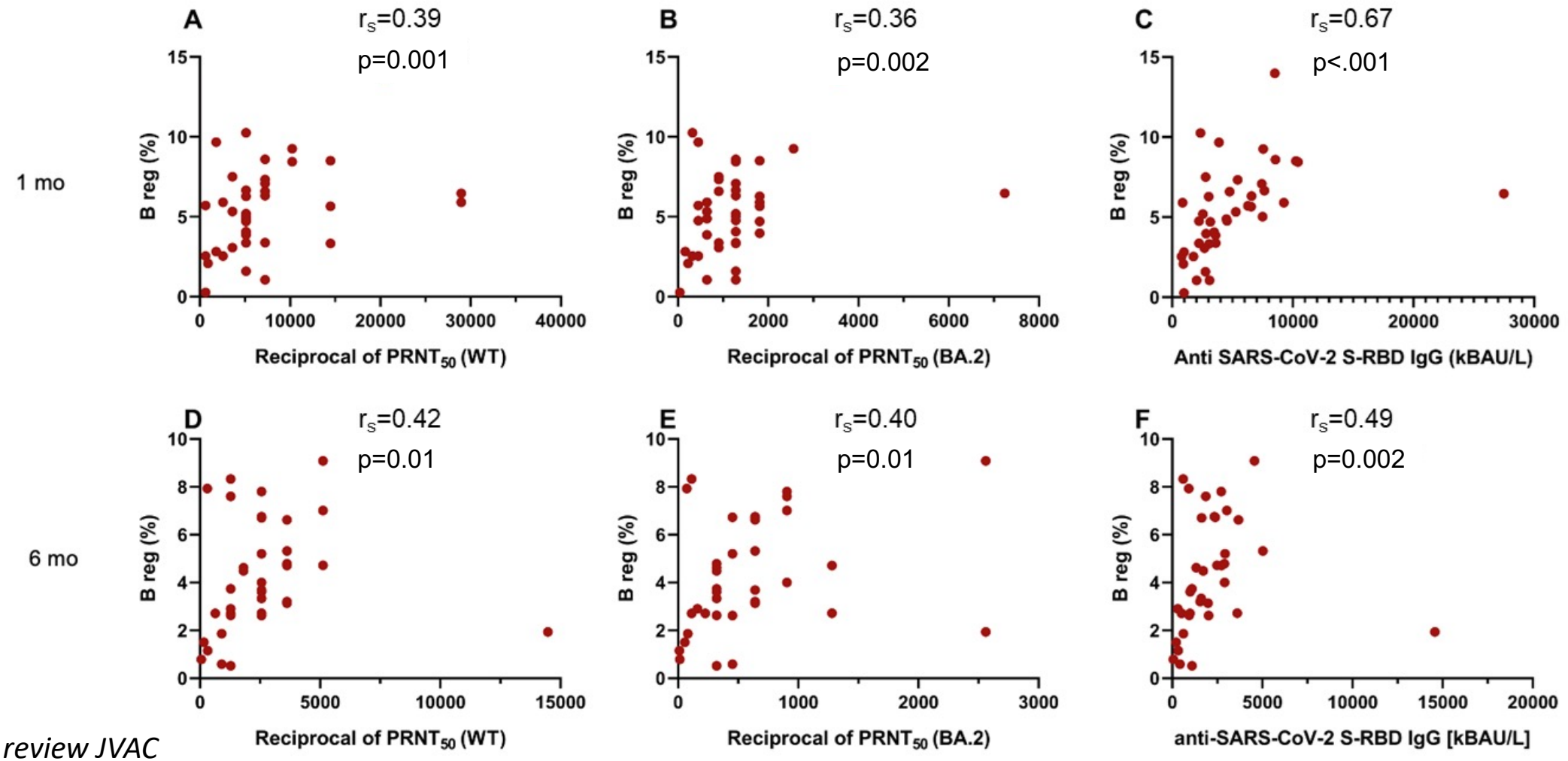
Under review JVAC

Tregs frequencies were positively correlated with levels of anti-S-RBD IgG antibody, WT NAbs, and BA.2 NAbs titers at both 1- and 6-months after vaccination.



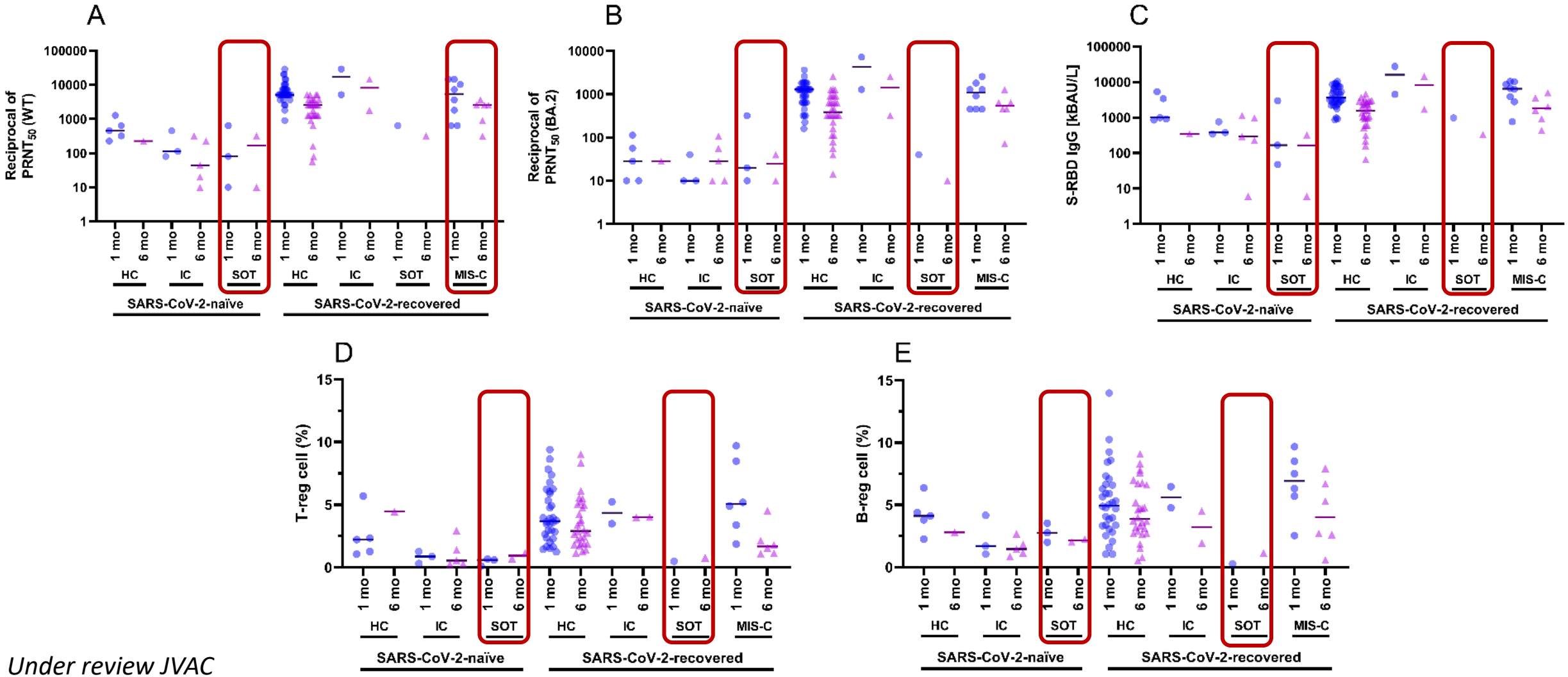
Under review JVAC

Bregs frequencies were positively correlated with levels of anti-S-RBD IgG antibody, WT NAbs, and BA.2 NAbs titers at both 1- and 6-months after vaccination.



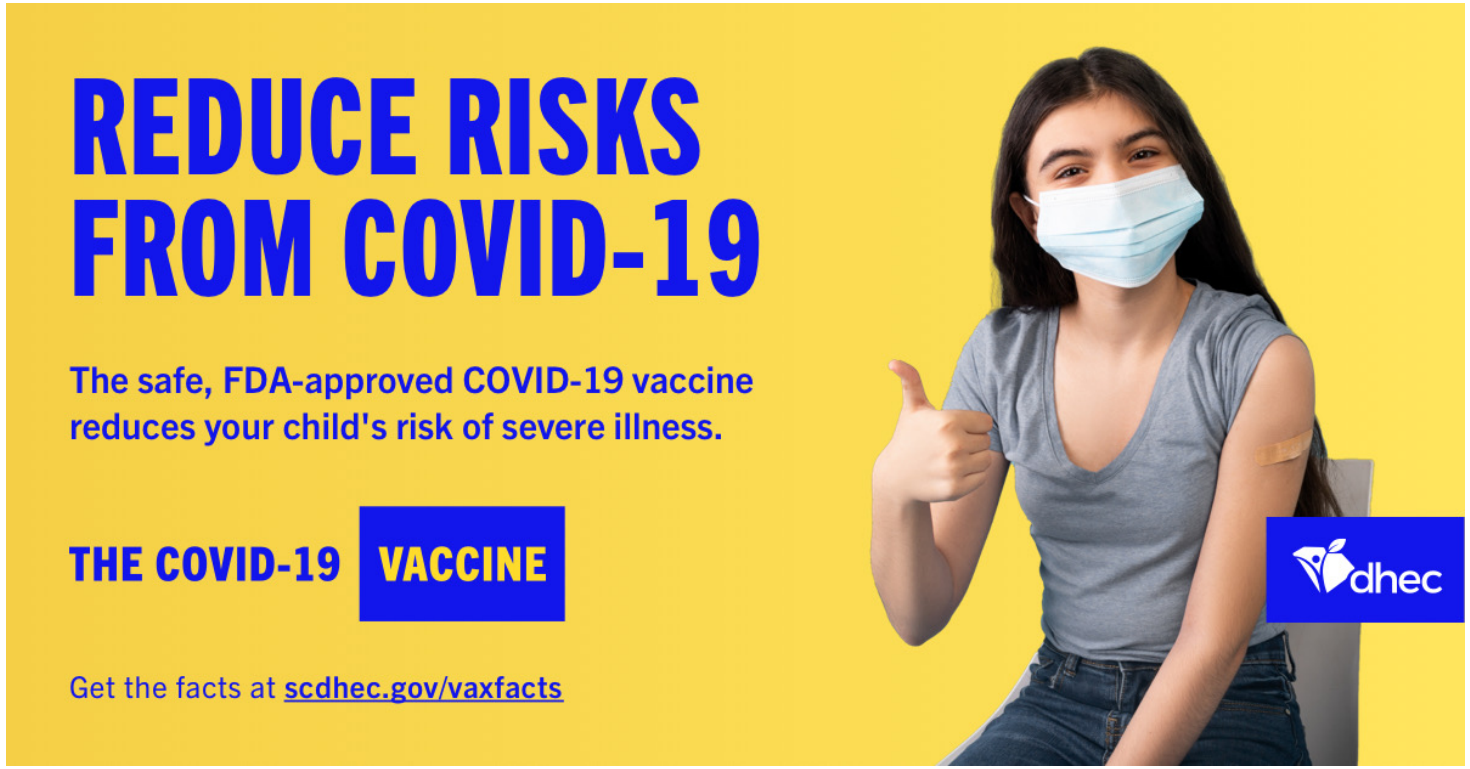
Under review JVAC

Solid Organ Transplant recipients recorded lower anti-S-RBD and NAbs titers compared to HC, IM, and MIS-C



Under review JVAC

What about protection against reinfection?



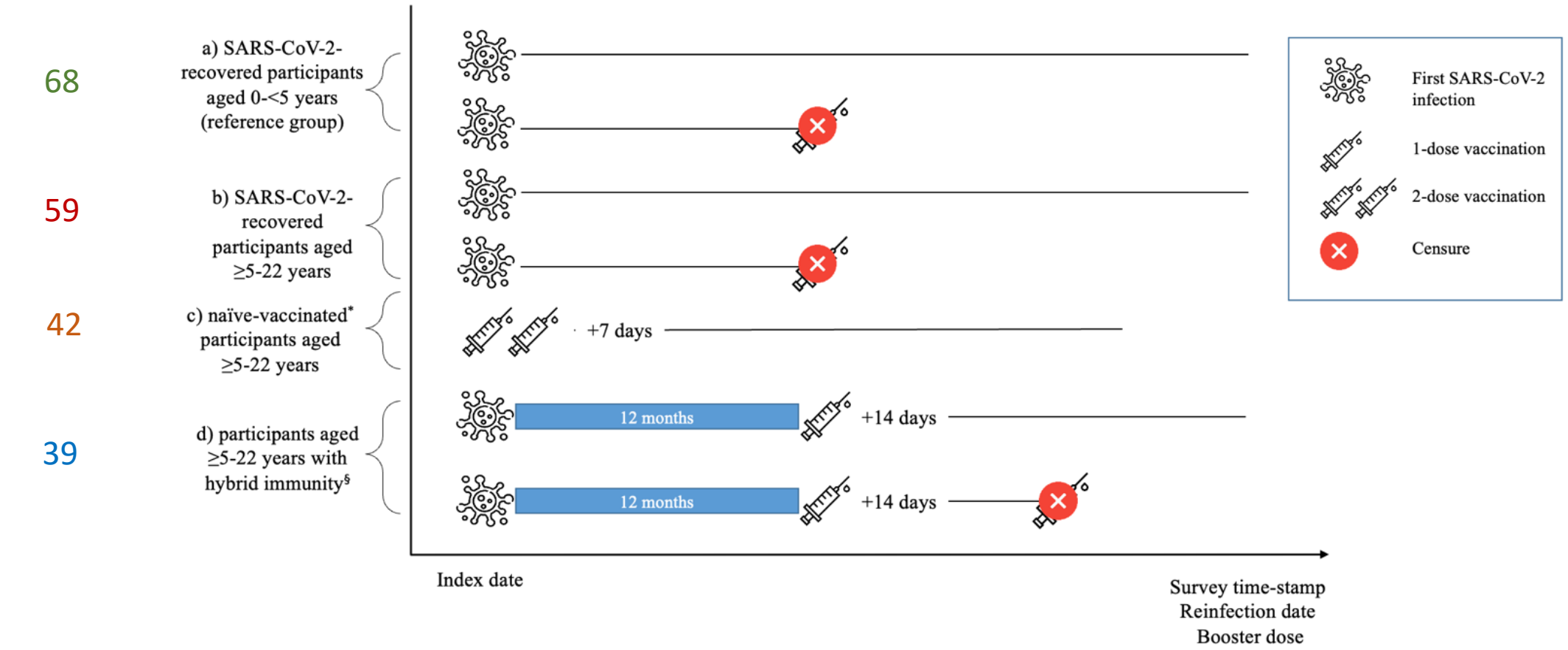
Antibody titers elicited by SARS-CoV-2 infection or COVID-19 vaccination are associated with protection against SARS-CoV-2 reinfection in adults.

Understanding the **correlation between immune response and protection** from COVID-19 will play a pivotal role in predicting the effectiveness of vaccines in children and targeting pediatric COVID-19 vaccination campaigns.

To investigate the **risk of SARS-CoV-2 reinfection** in children of different age in the 12 months post-immunization.

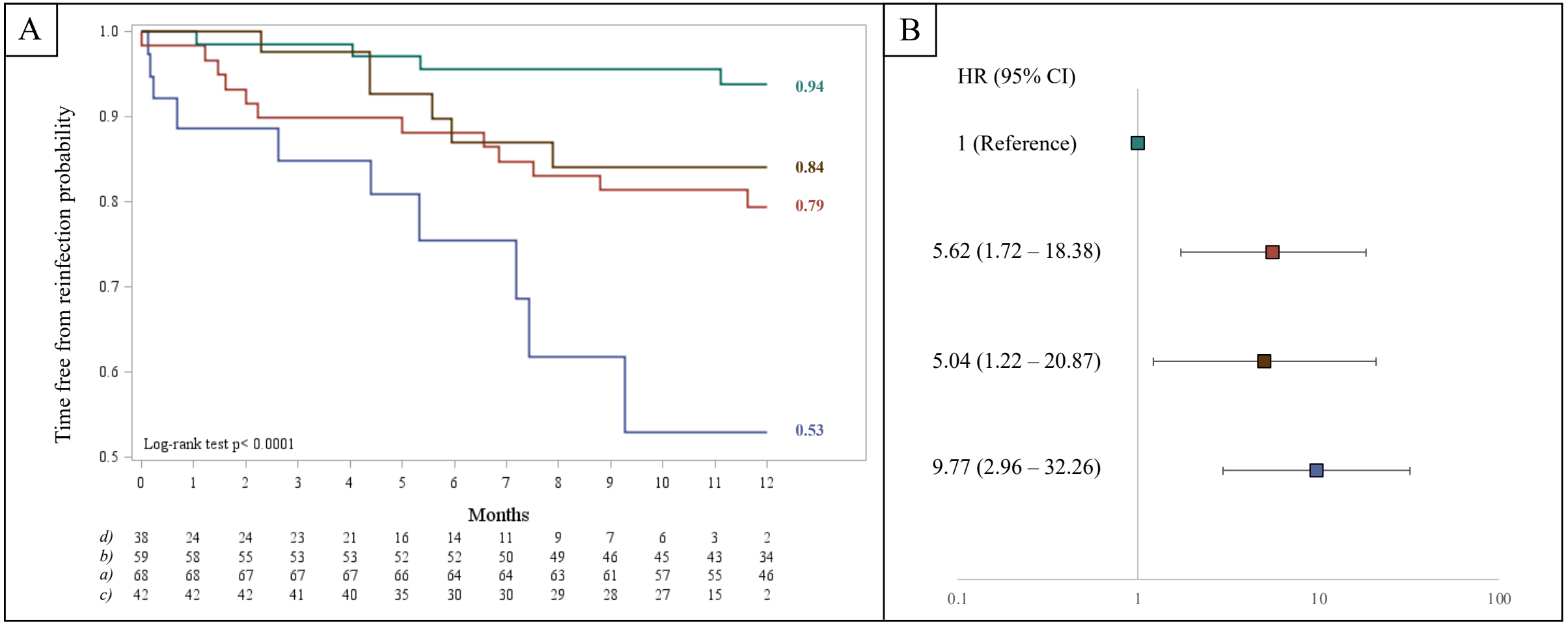
CASE cohort

208 subjects



Di Chiara et al. Risk of SARS-CoV-2 Reinfection in Children within the 12 Months Following Mild COVID-19: Insights from a Survey Study , Under review, The Pediatric Infectious Disease Journal

The probability of remaining free from SARS-CoV-2 reinfection was significantly higher in children aged <5 years (94%) compared to older



Under review The Pediatric Infectious Disease Journal

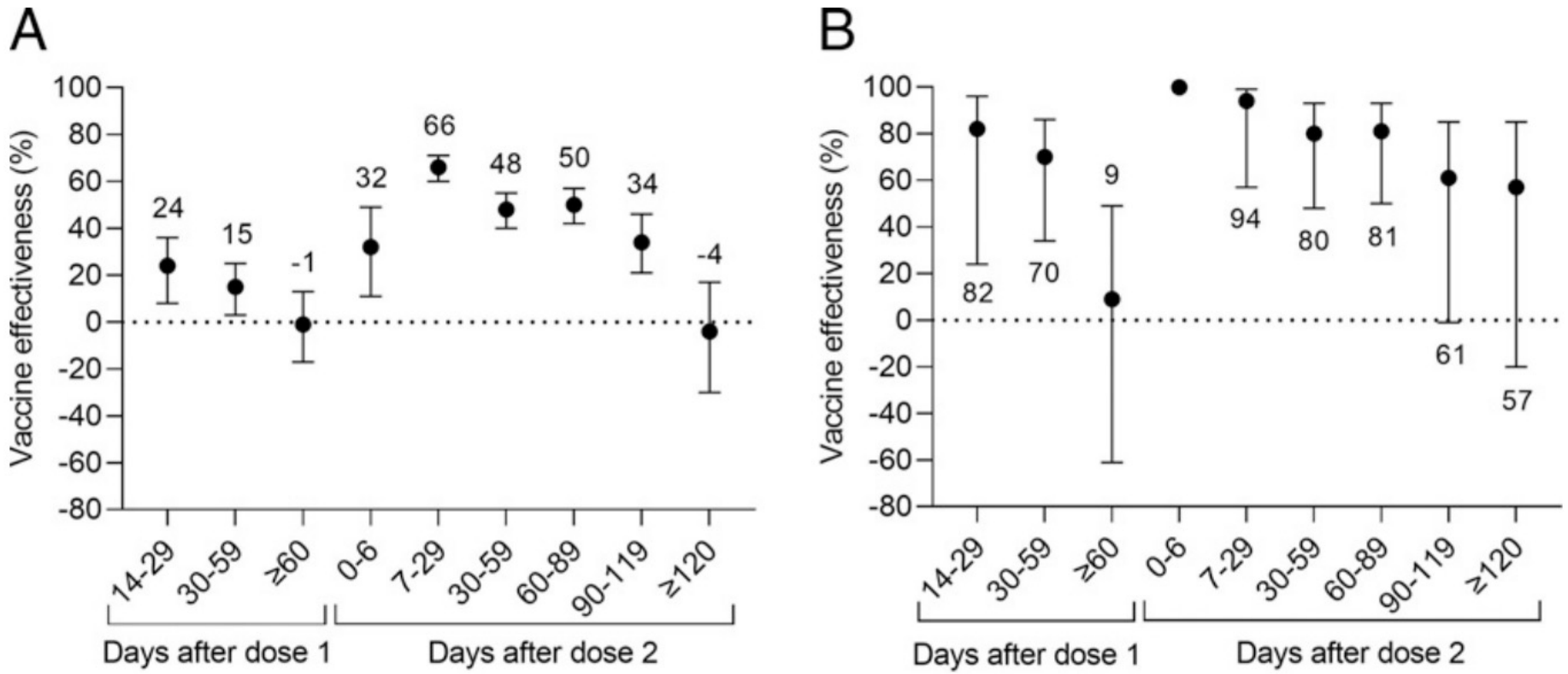
PEDIATRICS®

ARTICLES | MARCH 03 2023

COVID-19 Vaccine Effectiveness Against Omicron Infection and Hospitalization

Pierre-Philippe Piché-Renaud, MD; Sarah Swayze, MSc; Sarah A. Buchan, PhD, MSc; Sarah E. Wilson, MD, MSc; Peter C. Austin, PhD; Shaun K. Morris, MD, MPH; Sharifa Nasreen, PhD; Kevin L. Schwartz, MD, MSc; Mina Tadrous, PharmD, PhD; Nisha Thampi, MD, MSc; Kumanan Wilson, MD, MSc; Jeffrey C. Kwong, MD, MSc ✉; CANADIAN IMMUNIZATION RESEARCH NETOWRK (CIRN) PROVINICAL COLLABORATIVE INVESTIGATORS

Vaccine effectiveness against Omicron VOC appeared to wane 4-6 months post-vaccination



Pediatrics. 2023;151(4):e2022059513.

Conclusions

Understanding the immune response to SARS-CoV-2 is crucial to optimize pediatric vaccination strategies

- Children develop higher SARS-CoV-2 antibody titers compared to adults, possibly due to enhanced T and B regulatory responses.
- mRNA vaccines induce stronger and longer-lasting humoral and cellular responses in SARS-CoV-2-recovered children.
- SARS-CoV-2 antibody titers gradually decrease, with a more rapid decline during the first 6 months, leading to reduced protection against reinfection.
- Humoral responses to SARS-CoV-2 in infants and young children may offer robust protection against reinfection in the pediatric population.
- Two-dose hybrid immunity demonstrates superior efficacy.

Booster doses should be considered as part of immunization strategies for children.

Acknowledgments to:

This work is partially supported by ORCHESTRA and VERDI.

ORCHESTRA is a four-year international research project aimed at tackling the coronavirus pandemic, funded by the European Union's Horizon 2020 research and innovation program (H2020-RIA GA No.101016167).

VERDI is a four-year international research project aimed at prioritizing pregnant women, children and high-risk populations in research on new SARS-CoV-2 variants of concern, funded by the European Union (101045989).

Thank you!

costanza.dichiara@phd.unipd.it