COVID-19 Vaccination for pregnant women

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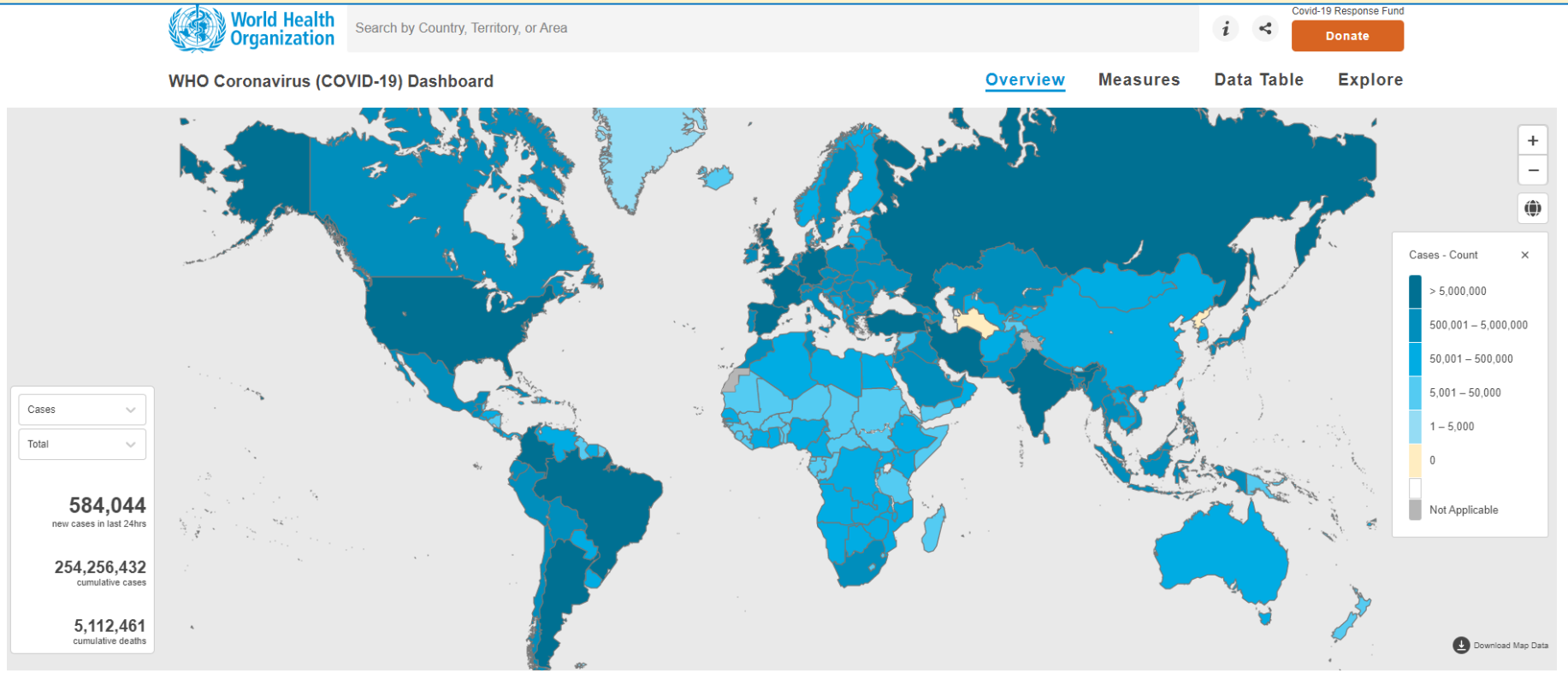
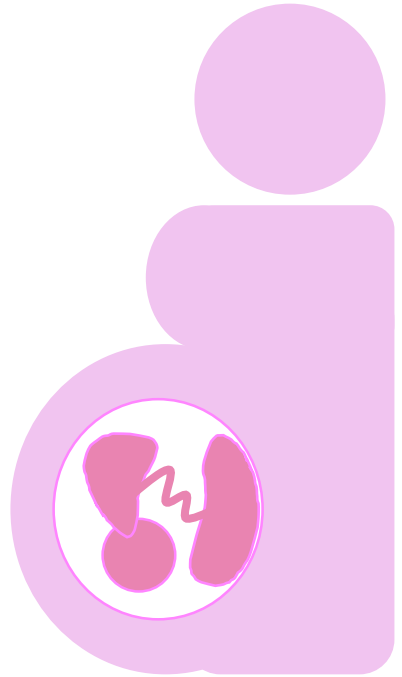
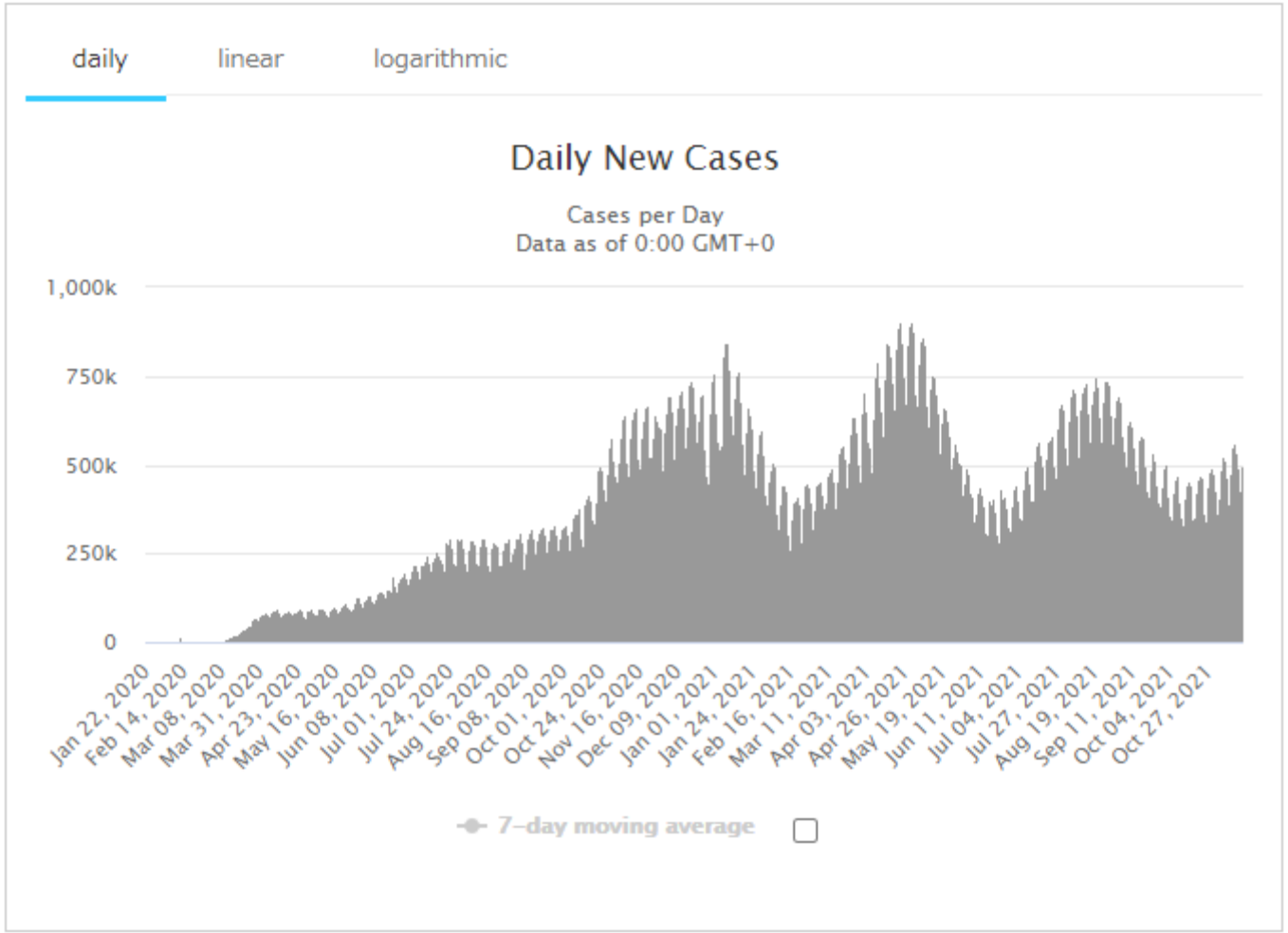
The outbreak of COVID-19 has emerged as the most critical global public health problem since 2020.





The vertical transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a serious concern for pregnant women with COVID-19.



COVID-19 CORONAVIRUS PANDEMIC

Last updated: November 17, 2021, 06:21 GMT

Weekly Trends - Graphs - Countries - News

Coronavirus Cases:

255,141,123

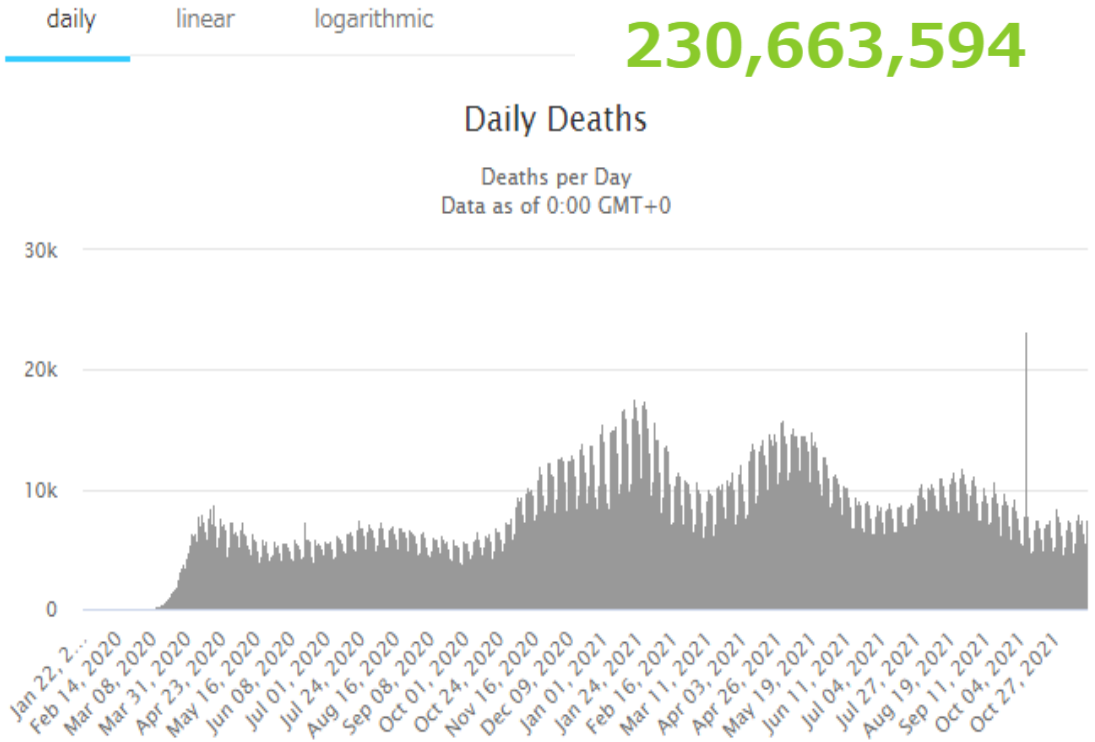
view by country

Deaths:

5,130,689

Recovered:

230,663,594

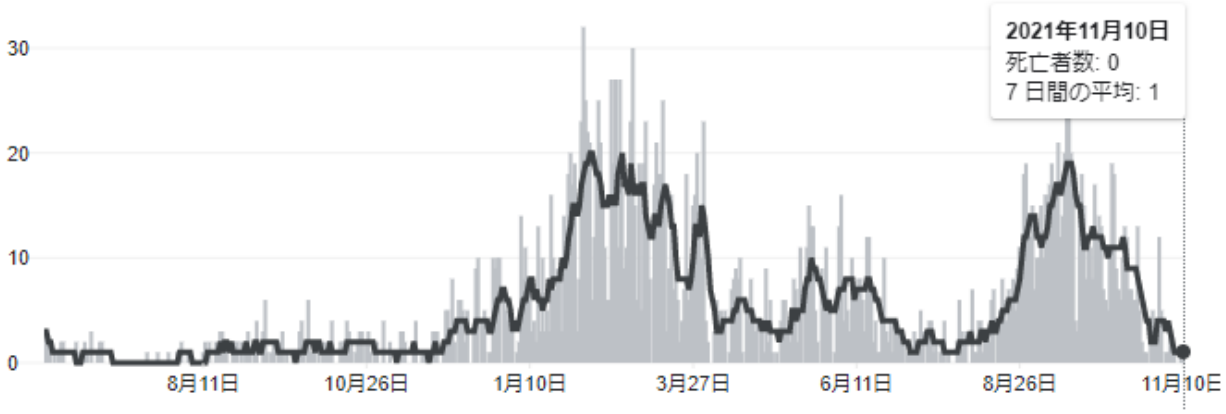


https://www.worldometers.info/coronavirus/?utm_campaign=homeAdvegas1?

新たな感染者数 ▾ 日本 ▾ 東京都 ▾ 全期間 ▾

新たな感染者数 ▾ カンボジア ▾ 全期間 ▾

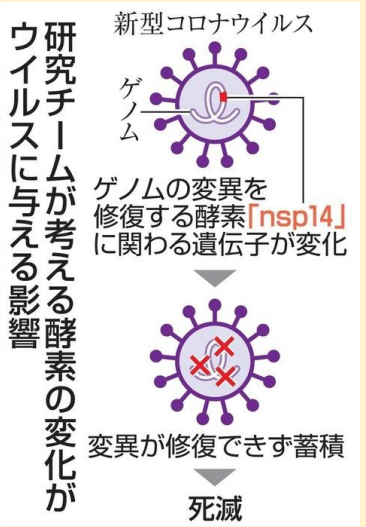
死亡者数 ▾ 日本 ▾ 東京都 ▾ 全期間 ▾



新たな感染者数 ▾ カンボジア ▾ 全期間 ▾

Why did the fifth wave end so quickly in Japan?

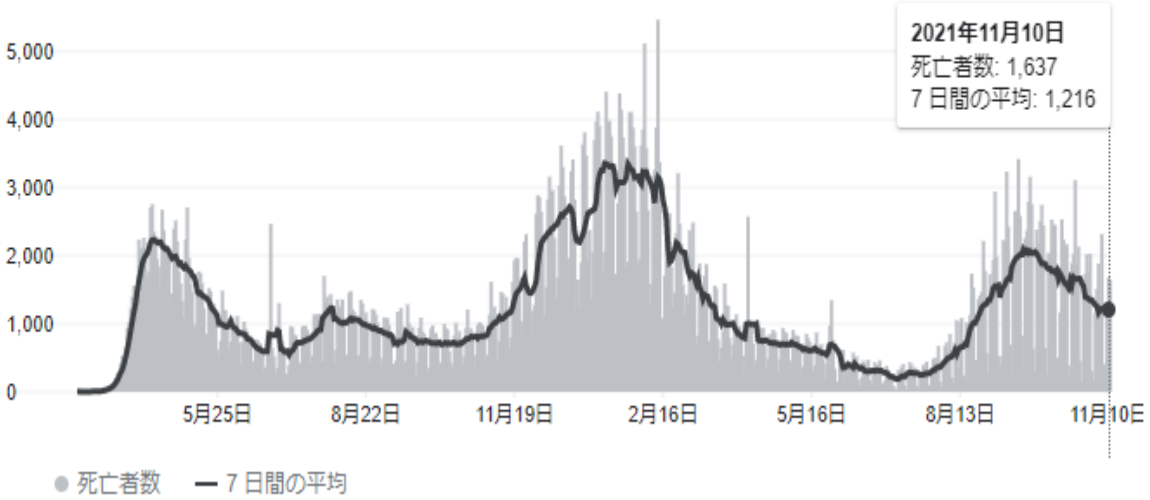
- Increased vaccination rates - 75% of the population as of November (58% in the US, 34% in Russia)
- National character? (wearing surgical masks, handwashing, avoidance of three-dense, ventilation, shoes off, no hugging)
- BCG? (this is denied in Russia), cross-immunity with existing corona　viruses?
- Natural disappearance of the virus due to suicide mutation?
- No invasion of new strains to replace the delta strains?



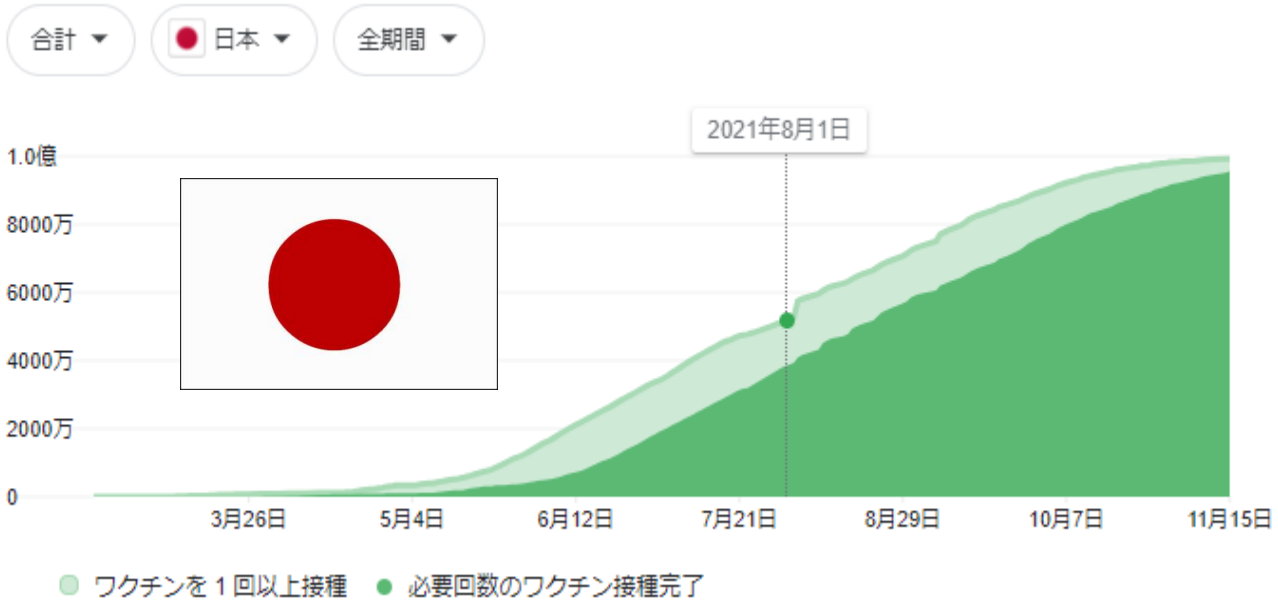
新たな感染者数 アメリカ合衆国 すべての地域 全期間

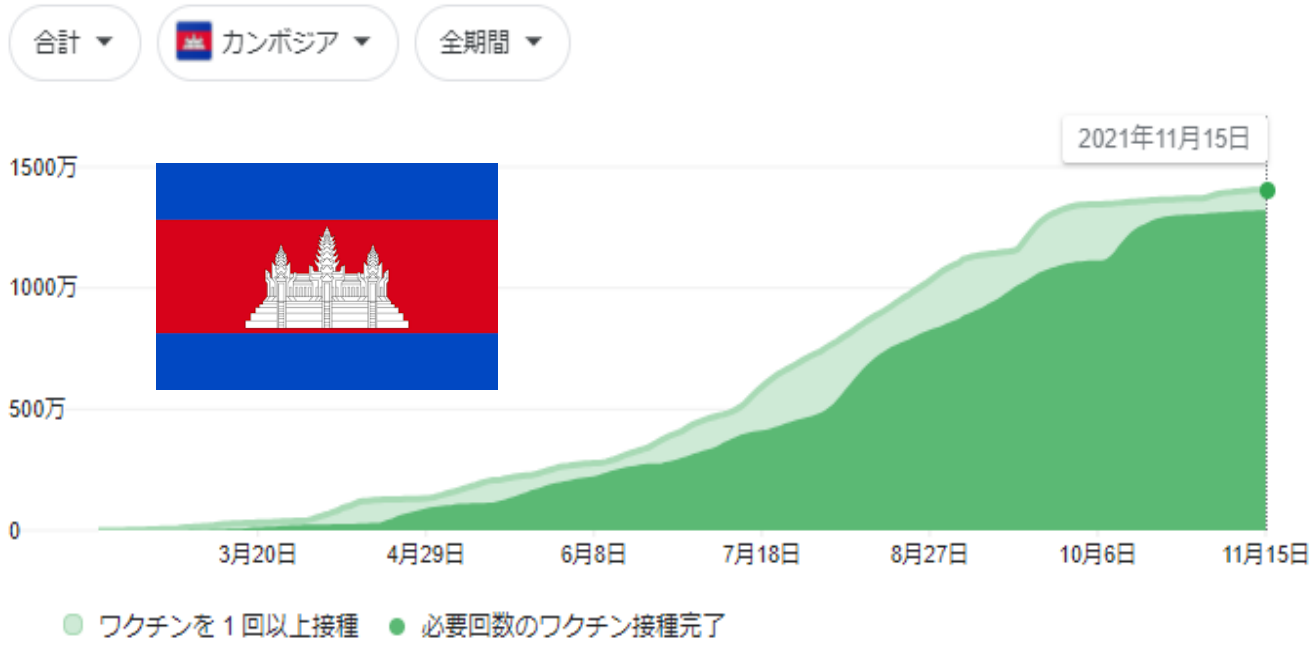
新たな感染者数 ロシア すべての地域 全期間

死亡者数 アメリカ合衆国 すべての地域 全期間

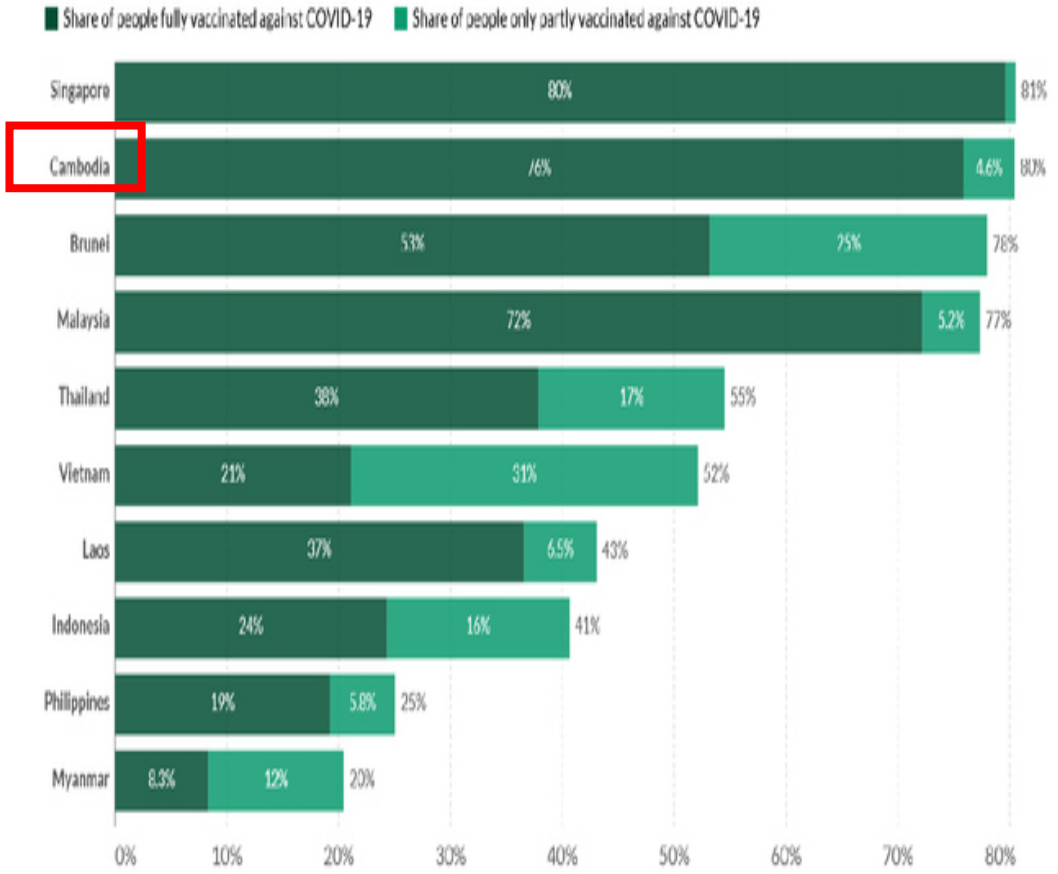


死亡者数 ロシア すべての地域 全期間



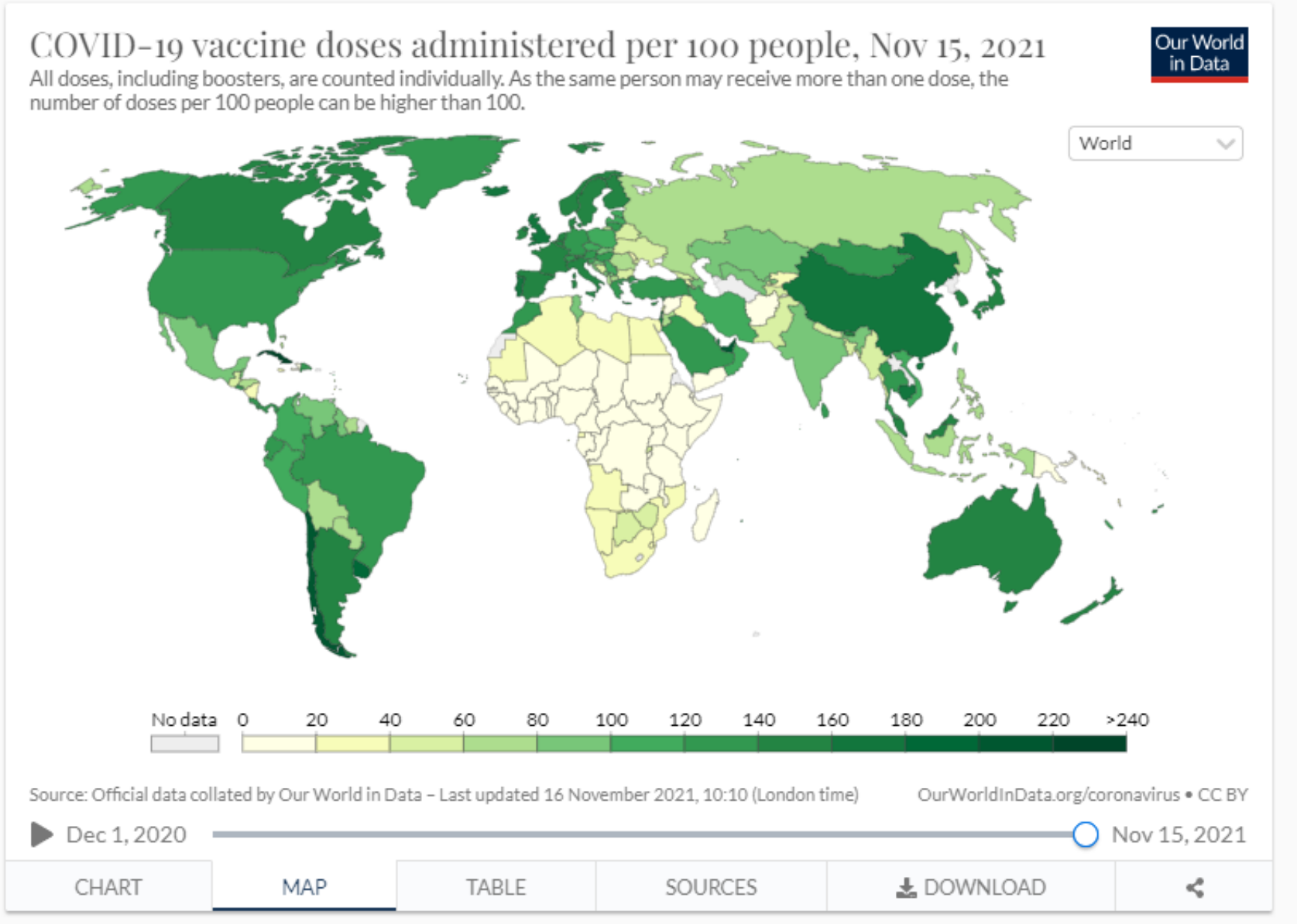


ASEAN諸国のワクチン接種率



注：2021 年 10 月 25 日時点

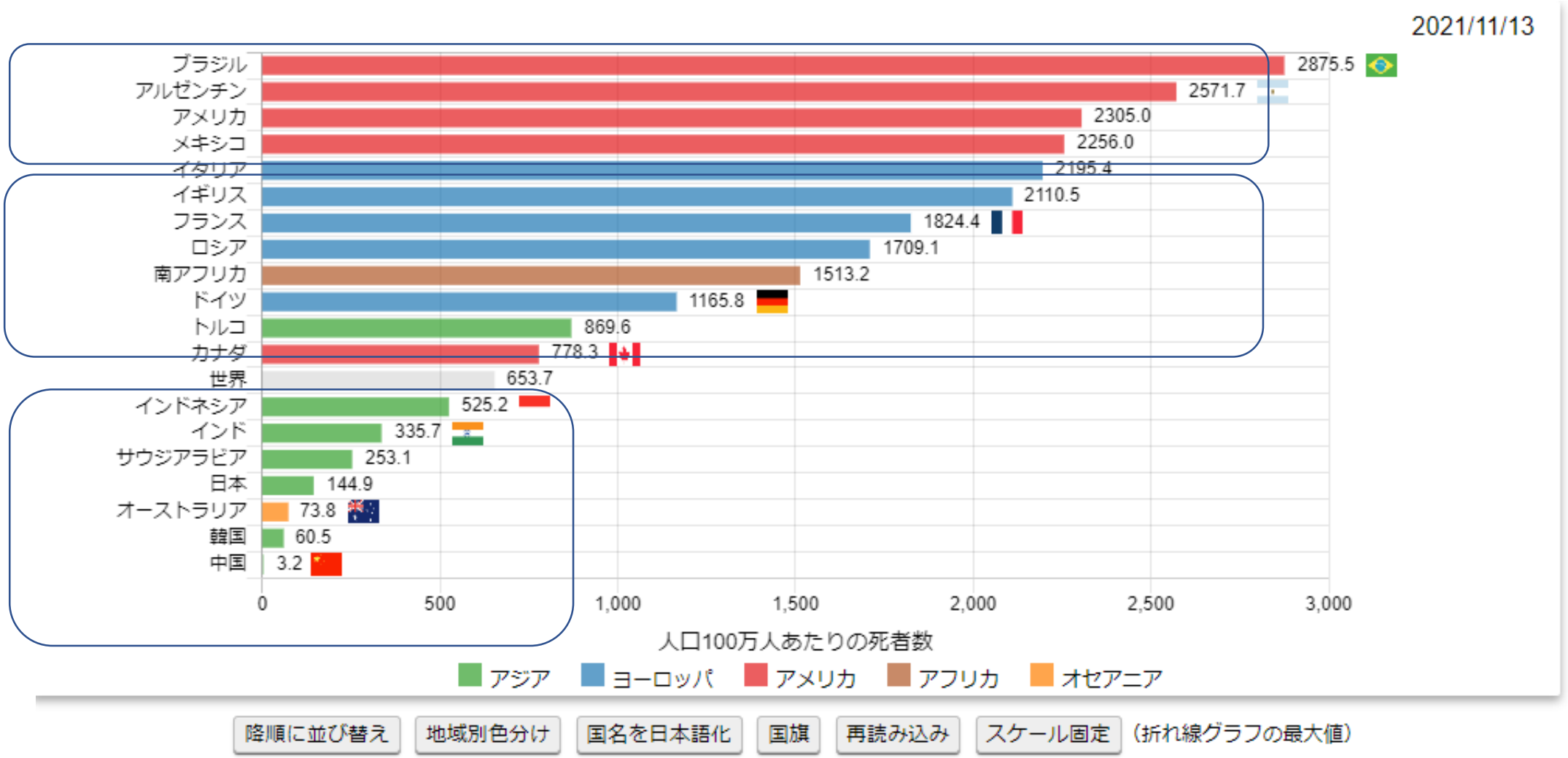
出所：オックスフォード大学「Our World in Data」。
https://ourworldindata.org/covid-vaccinations



https://ourworldindata.org/covid-vaccination-global-projections

Number of deaths per capita

- Frontier Research Institute, Sapporo Medical University



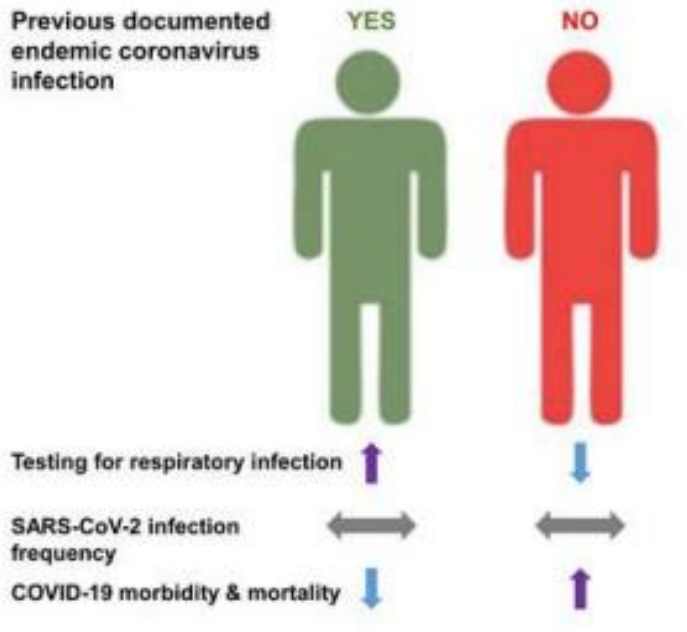
https://web.sapmed.ac.jp/canmol/coronavirus/death.html?s=y&f=y&n=j&c=1&p=1

JCI The Journal of Clinical Investigation

Recent endemic coronavirus infection is associated with less severe COVID-19

Manish Sagar, … , Laura White, Joseph P. Mizgerd

J Clin Invest. 2020. https://doi.org/10.1172/JCI143380.



- Four different coronaviruses (eCoVs) are responsible for the common cold in humans
- 875 patients with a history of infection were compared with the four epidemic coronaviruses with 15053 patients without a history of infection by respiratory pathogen testing, which had been studied since 2015, to determine whether there was a difference in the clinical picture of COVID-19.
- The infection rate was similar in both groups, but the severity of COVID-19 (intensive care unit use and death) was significantly lower in patients with a history of epidemic coronavirus infection.
- The number of patients with common cold is higher in Asia Oceania than in Europe and the United States.
- Previous common cold infection was associated with less severe disease

nature

https://doi.org/10.1038/s41586-021-04186-8

Accelerated Article Preview

Pre-existing polymerase-specific T cells expand in abortive seronegative SARS-CoV-2

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Accelerated Article Preview Published online 10 November 2021

Cite this article as: Swadling, L. et al. Pre-existing polymerase-specific T cells expand in abortive seronegative SARS-CoV-2. *Nature* https://doi.org/10.1038/s41586-021-04186-8 (2021).

Leo Swadling, Mariana O. Diniz, Nathalie M. Schmidt, Oliver E. Amin, Aneesh Chandran, Emily Shaw, Corinna Pade, Joseph M. Gibbons, Nina Le Bert, Anthony T. Tan, Anna Jeffery-Smith, Cedric C. S. Tan, Christine Y. L. Tham, Stephanie Kucykowicz, Gloryanne Aidoo-Micah, Joshua Rosenheim, Jessica Davies, Marina Johnson, Melanie P. Jensen, George Joy, Laura E. McCoy, Ana M. Valdes, Benjamin M. Chain, David Goldblatt, Daniel M. Altmann, Rosemary J. Boyton, Charlotte Manisty, Thomas A. Treibel, James C. Moon, COVIDsortium investigators, Lucy van Dorp, Francois Balloux, Áine McKnight, Mahdad Noursadeghi, Antonio Bertoletti & Mala K. Maini

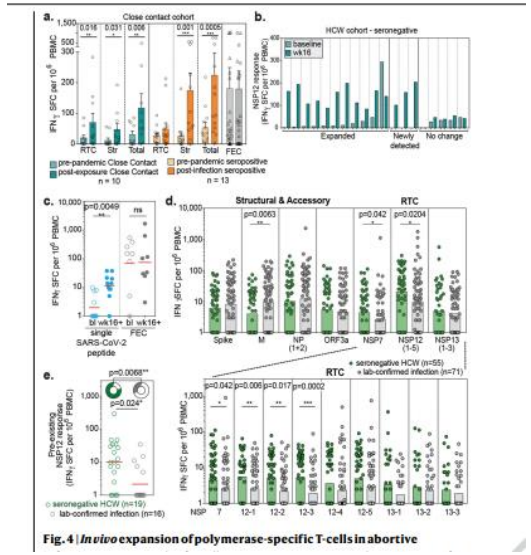
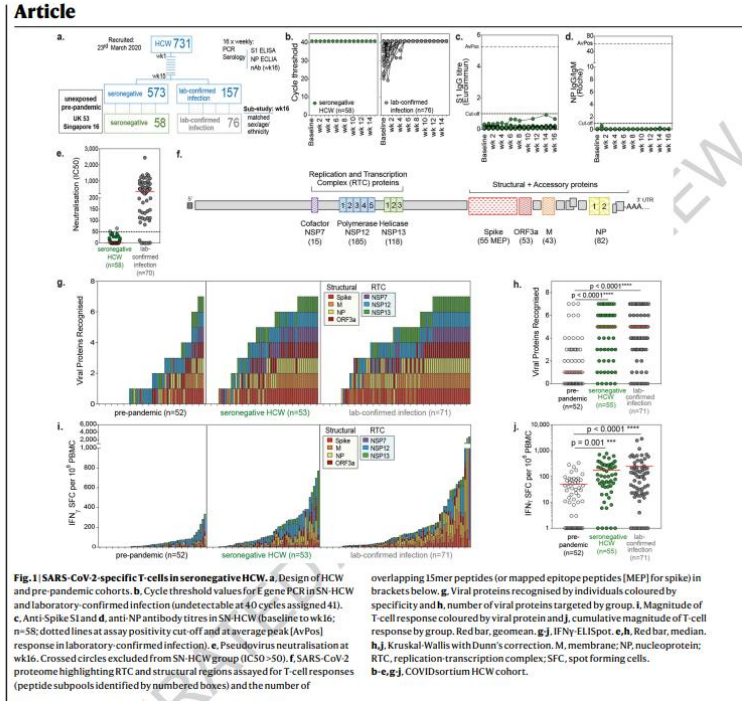


Fig. 4 | *In vivo* expansion of polymerase-specific T-cells in abortive

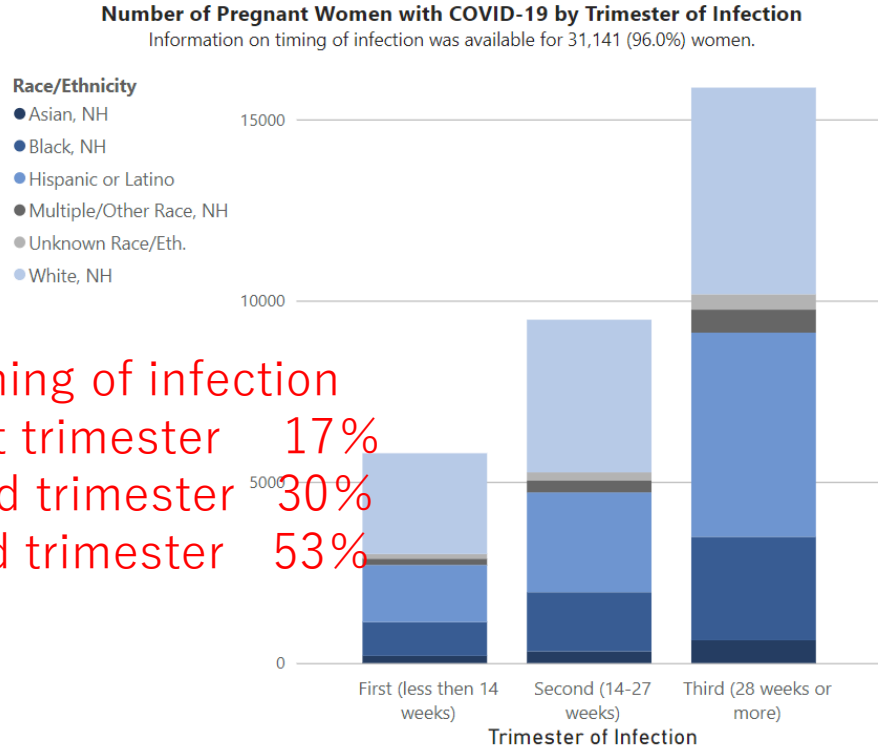


Article

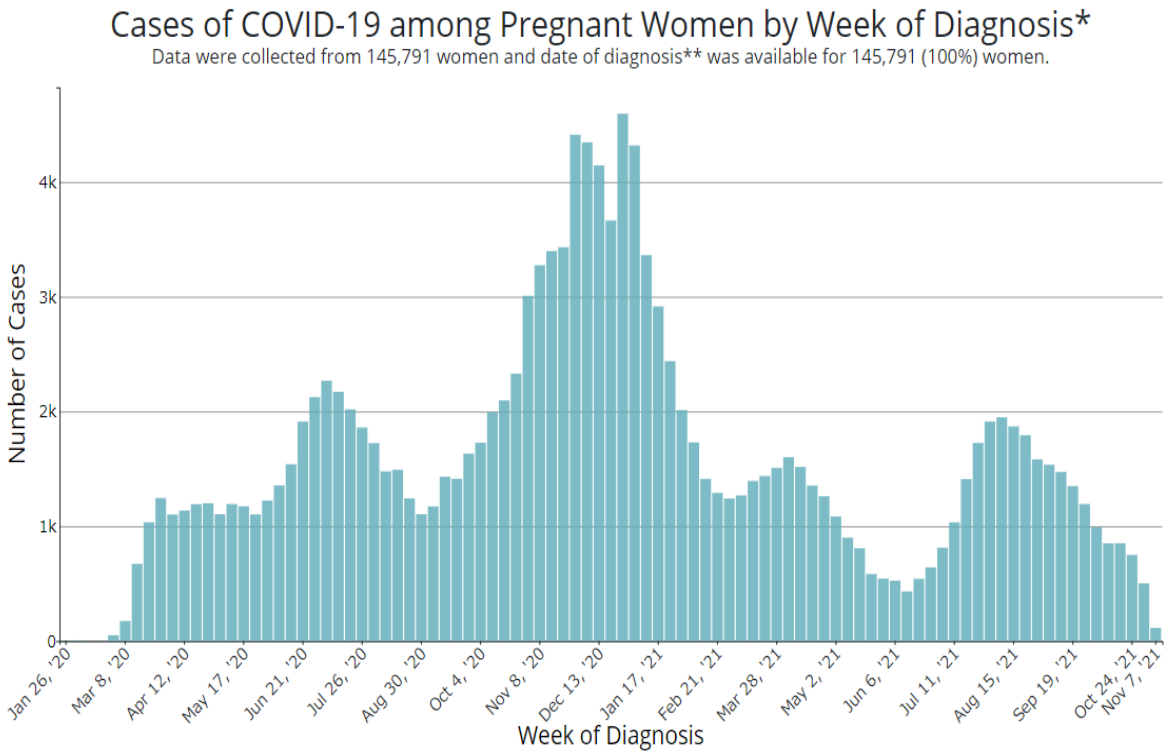
Fig. 1 | SARS-CoV-2-specific T-cells in seronegative HCW. a, Design of HCW and pre-pandemic cohorts. **b**, Cycle threshold values for E gene PCR in SN-HCW and laboratory-confirmed infection (undetectable at 40 cycles assigned 41). **c**, Anti-Spike S1and **d**, anti-NP antibody titres in SN-HCW (baseline to wk16; n=58; dotted lines at assay positivity cut-off and at average peak [AvPos] response in laboratory-confirmed infection). **e**, Pseudovirus neutralisation at wk16. Crossed circles excluded from SN-HCW group (IC50 >50). **f**, SARS-CoV-2 proteome highlighting RTC and structural regions assayed for T-cell responses (peptide subpools identified by numbered boxes) and the number of overlapping 15mer peptides (or mapped epitope peptides [MEP] for spike) in brackets below. **g**, Viral proteins recognised by individuals coloured by specificity and **h**, number of viral proteins targeted by group. **i**, Magnitude of T-cell response coloured by viral protein and **j**, cumulative magnitude of T-cell response by group. Red bar, geomean. **g-j**, IFNγ-ELISpot. **e**, **h**, Red bar, median. **h**, **j**, Kruskal-Wallis with Dunn's correction. M, membrane; NP, nucleoprotein; RTC, replication-transcription complex; SFC, spot forming cells. **b-e**, **g-j**, COVIDsortium HCW cohort.

- **<u>T cell responses to previously infected coronaviruses control infection</u>**
- In particular, SARS-CoV-2 reactive T cells, including **<u>responses to replication transcription complexes (RTCs)12,13</u>**, are important and are **not accompanied by elevated neutralizing antibody titers.**

COVID-19 during Pregnancy: Birth and Infant Outcomes (CDC)



Timing of infection
1st trimester 17%
2nd trimester 30%
3rd trimester 53%



Pregnant women[1] with COVID-19, United States, January 22, 2020 - November 15, 2021

TOTAL CASES[1]
145,791

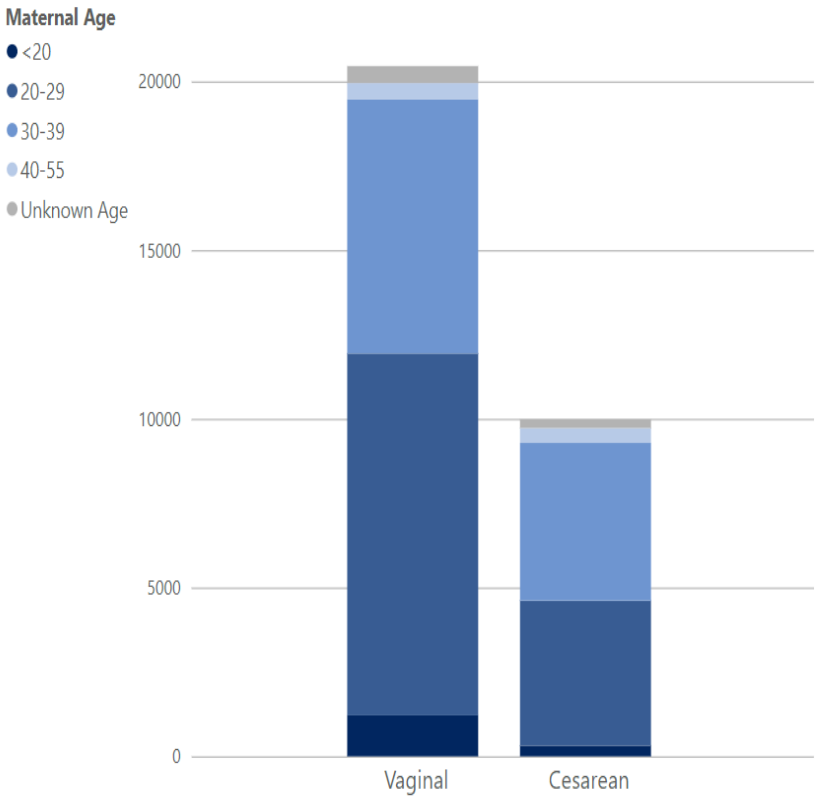
TOTAL DEATHS
229

Maternal mortality 0.16 %

https://covid.cdc.gov/covid-data-tracker/#pregnant-population

Number of Infants Born Via Vaginal or Cesarean Delivery to Women with COVID-19

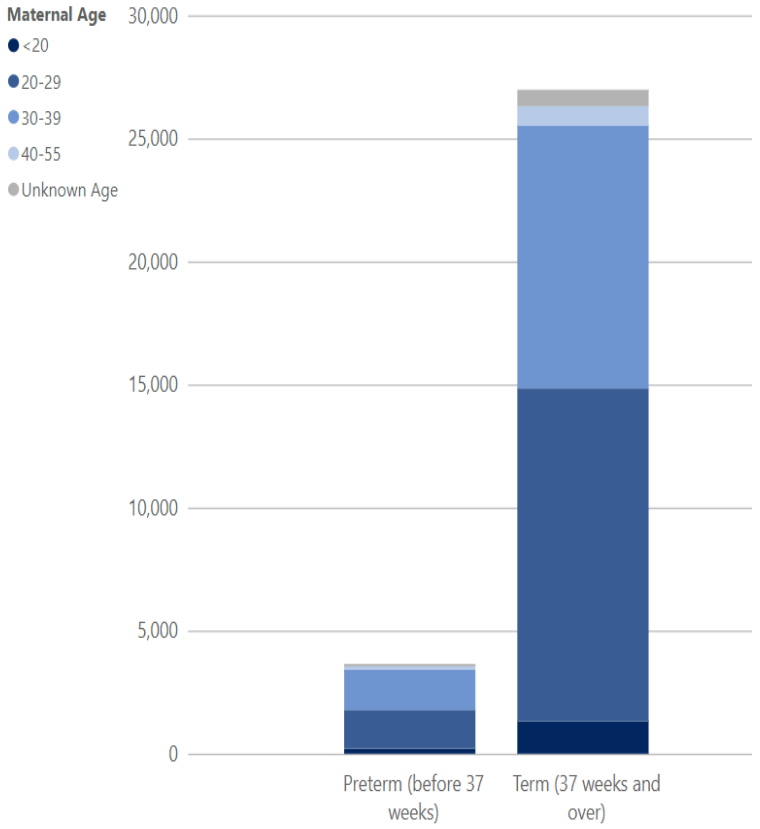
Information on delivery type was available for 30,440 (92.3%) of birth outcomes.



68% Vaginal delivery
32% Caesarean section

Number of Infants Born Term and Preterm to Women with COVID-19

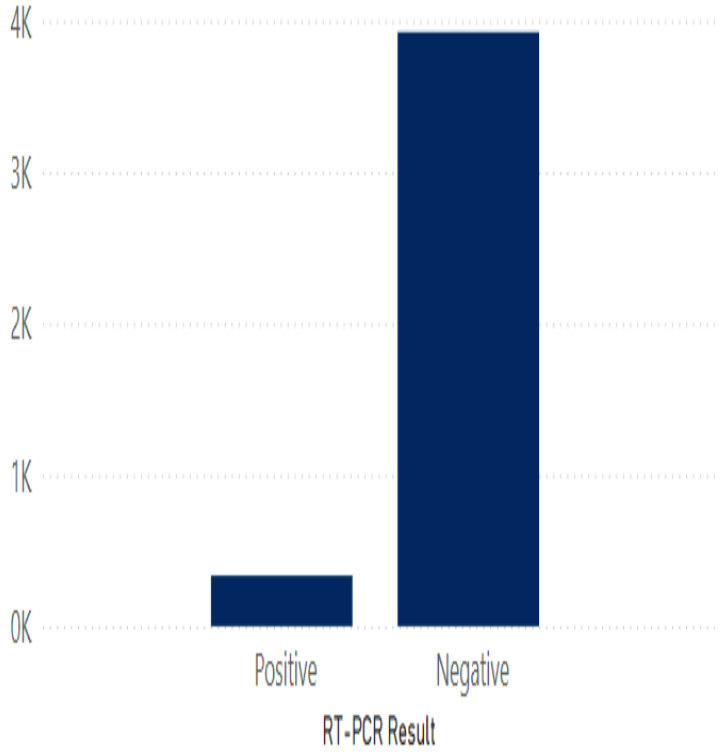
Gestational age (in weeks) was available for 30,629 (93.8%) live born infants.



88% term delivery
12% premature delivery

Laboratory Testing Results for SARS-CoV-2 among Infants Born to Women with COVID-19

Laboratory testing information was available for 4285 (13.1%)* infants.

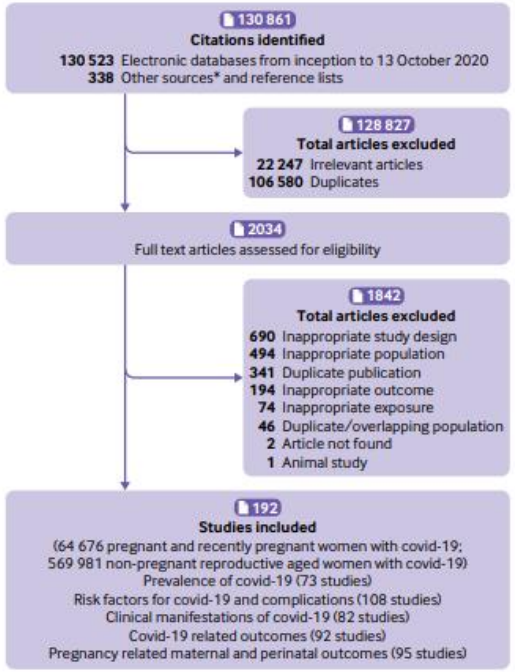


Vertical transmission rate 6%

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

Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis

John Allotey,[1,2] Elena Stallings,[3,4] Mercedes Bonet,[5] Magnus Yap,[6] Shaunak Chatterjee,[6] Tania Kew,[6] Luke Debenham,[6] Anna Clavé Llavall,[6] Anushka Dixit,[6] Dengyi Zhou,[6] Rishab Balaji,[6] Siang Ing Lee,[1] Xiu Qiu,[7,8,9] Mingyang Yuan,[1,7] Dyuti Coomar,[1] Jameela Sheikh,[6] Heidi Lawson,[6] Kehkashan Ansari,[2] Madelon van Wely,[10] Elizabeth van Leeuwen,[11] Elena Kostova,[10] Heinke Kunst,[12,13] Asma Khalil,[14] Simon Tiberi,[12,13] Vanessa Brizuela,[5] Nathalie Broutet,[5] Edna Kara,[3] Caron Rahn Kim,[5] Anna Thorson,[5] Ramón Escuriet,[15] Olufemi T Oladapo,[5] Lynne Mofenson,[16] Javier Zamora,[2,3,4] Shakila Thangaratinam,[2,18] on behalf of the PregCOV-19 Living Systematic Review Consortium



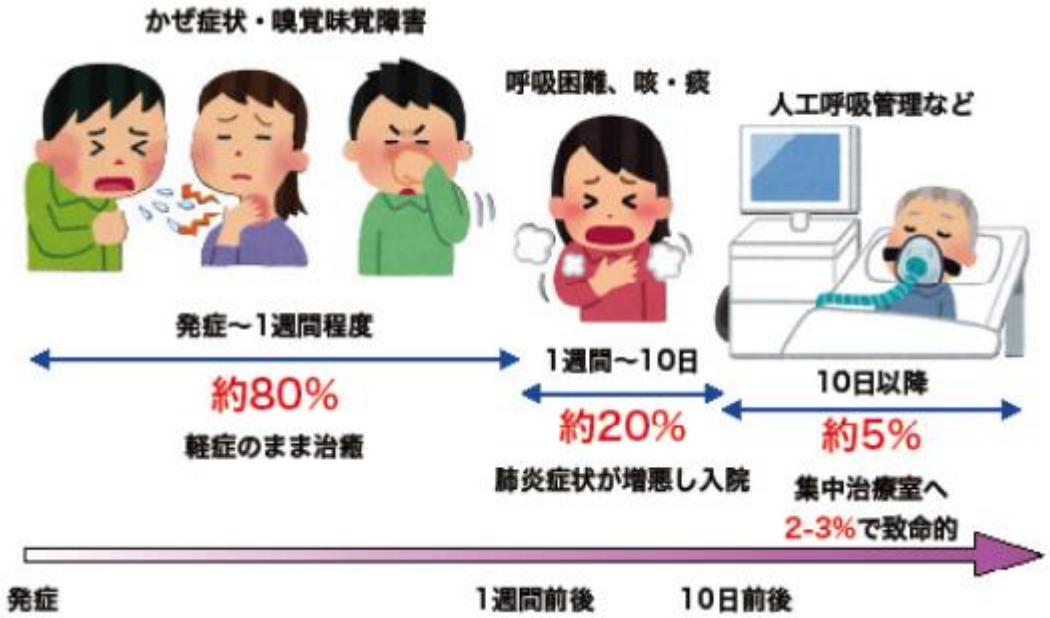
the bmj | BMJ 2020;370:m3320 | doi: 10.1136/bmj.m3320

- A systematic review based on 192 independent studies.
- Prognosis of 67271 pregnant women and postpartum mothers infected with COVID-19 was analyzed.
- Compared to non-pregnant women, higher rates of ICU admission and need for ventilator and ECMO management in the 3rd trimester.
- Among 41664 pregnant women, 339 (0.02%) died.
- Obese, non-Caucasian, hypertensive, and diabetic patients were more common among the critically ill and those who died.

COVID-19 registry of pregnant women in Japan

- 367 cases have been reported until 15 Apr 2021
- 61 cases were matched analysis category
- 53 cases with asymptomatic or mild
- 6 cases with moderate symptoms
- 2 severe cases but no one died
- Severe cases were complicated with obesity, DM and/or preeclampsia
- No cases of in utero vertical infection
- 1 case of SARS-CoV-2 positive baby (unknown route)

新型コロナウイルス感染症
COVID-19
診療の手引き 第５版



Risk factors of severe COVID-19

2 重症化のリスク因子

COVID-19 の入院患者レジストリ COVIREGI-JP では，併存疾患がない症例と比較し，慢性腎臓病，肝疾患，肥満，脂質異常症，高血圧，糖尿病を有する症例は入院後に重症化する割合が高い傾向にある．また併存疾患がない症例と比較し，心疾患，慢性肺疾患，脳血管障害，慢性腎臓病を有する症例は死亡する割合が高い傾向にあり，重症化因子と死亡因子は異なる可能性があることが示唆されている．

表 2-1　重症化のリスク因子

重症化のリスク因子	評価中の要注意な基礎疾患など
・65 歳以上の高齢者[1)] ・悪性腫瘍[2)] ・慢性閉塞性肺疾患（COPD）[3)] ・慢性腎臓病[4)] ・２型糖尿病[5)] ・高血圧[6), 7)] ・脂質異常症[1)] ・肥満（BMI 30 以上）[8)] ・喫煙[6)] ・固形臓器移植後の免疫不全[9)] ・妊娠後期[13,14)]	・ステロイド[10)]や生物学的製剤[11)]の使用 ・HIV 感染症（特に CD4 <200 /μL）[12)]

3rd Trimester

Frequently asked questions

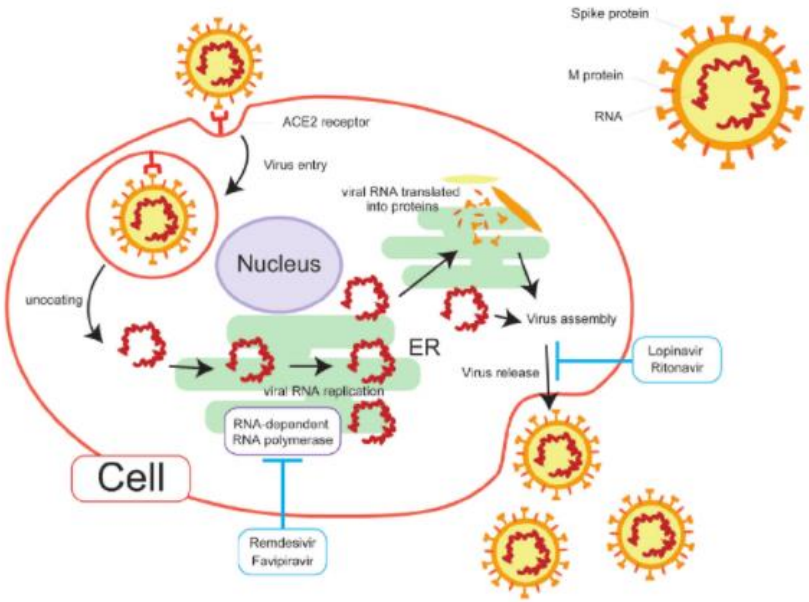
- Are we pregnant women more susceptible and severe?
- Can virus be transmitted vertically?
- Is there any effect on the fetus?
- Are there any medications that can be used during pregnancy?
- What is the method of delivery? (Cesarean section or vaginal delivery?)
- Can I breastfeed my baby?

THE JOURNAL OF
Obstetrics and Gynaecology Research
doi:10.1111/jog.14384
J. Obstet. Gynaecol. Res. Vol. 46, No. 10: 1958–1966, October 2020

Covid-19 pandemic and pregnancy

Satoshi Hayakawa[1], Shihoko Komine-Aizawa[1] and Gil G. Mor[2]

[1]Division of Microbiology, Department of Pathology and Microbiology, Nihon University School of Medicine, Tokyo, Japan
[2]Department of Obstetrics and Gynecology, C.S. Mott Center for Human Growth and Development, Wayne State University, Detroit, Michigan, USA



Ostacoli et al. BMC Pregnancy and Childbirth (2020) 20:703
https://doi.org/10.1186/s12884-020-03399-5

BMC Pregnancy and Childbirth

RESEARCH ARTICLE Open Access

Psychosocial factors associated with postpartum psychological distress during the Covid-19 pandemic: a cross-sectional study

Luca Ostacoli[1,2], Stefano Cosma[3], Federica Bevilacqua[3], Paola Berchialla[1], Marialuisa Bovetti[3], Andrea Roberto Carosso[3], Francesca Malandrone[1], Sara Carletto[2,4*] and Chiara Benedetto[3]

Table 2 Clinical data of the cohort, overall and by presence of symptoms

	Overall	IES-R < 24	IES-R ≥ 24	*p-value*	EPDS < 11	EPDS ≥ 11	*p-value*
	N = 163	*n* = 93	*n* = 70		*n* = 91	*n* = 72	
First pregnancy (%)	74 (45.4)	37 (39.8)	37 (52.9)	0.134	36 (39.6)	38 (52.8)	0.127
Type of birth (%)				0.577			0.353
Vaginal	78 (47.9)	45 (48.4)	33 (47.1)		43 (47.3)	35 (48.6)	
Planned caesarean section	43 (26.4)	27 (29.0)	16 (22.9)		26 (28.6)	17 (23.6)	
Urgent caesarean section	32 (19.6)	17 (18.3)	15 (21.4)		19 (20.9)	13 (18.1)	
Forceps/vacuum	10 (6.1)	4 (4.3)	6 (8.6)		3 (3.3)	7 (9.7)	
Perceived support by healthcare staff during childbirth (median [IQR])	9 [7, 10]	10 [8, 10]	8 [6, 10]	0.002	10 [8, 10]	8 [6, 10]	0.002
Pain level during childbirth (median [IQR])	8 [2, 9]	7 [1, 9]	8 [5, 10]	0.156	7 [0.5, 9]	8 [5, 10]	0.036
Breastfeeding (%)	144 (88.3)	82 (88.2)	62 (88.6)	1.000	81 (89.0)	63 (87.5)	0.958
Confirmed diagnosis of Covid-19 (%)	5 (3.1)	3 (3.2)	2 (2.9)	1.000	1 (1.1)	4 (5.6)	0.237
Contact with Covid positive people (%)	8 (4.9)	7 (7.5)	1 (1.4)	0.156	5 (5.5)	3 (4.2)	0.980
Relatives/loved ones with a confirmed Covid-19 diagnosis (%)	21 (12.9)	13 (14.0)	8 (11.4)	0.807	11 (12.1)	10 (13.9)	0.916
Perceived safety during hospitalization (median [IQR])	8 [6;9]	8 [7, 9]	7.5 [6, 9]	0.385	8 [7, 9]	8 [6, 9]	0.340
Discomfort due to absence of partner	10 [8, 10]	10 [8, 10]	10 [9, 10]	0.009	10 [8, 10]	10 [8,75, 10]	0.315
Quiet on the ward related to the absence of visitors	7 [5, 8.5]	7 [6, 9]	6 [4, 8]	0.005	7 [5,9]	7 [5,8]	0.42
Time between childbirth and questionnaire completion ≤15 days (%)	25 (15.3)	15 (16.1)	10 (14.3)	0.917	15 (16.5)	10 (13.9)	0.812
Attachment style (%)				0.083			0.044
RQ1	65 (41.1)	42 (45.7)	23 (34.8)		44 (50.6)	21 (29.6)	
RQ2	60 (38.0)	37 (40.2)	23 (34.8)		30 (34.5)	30 (42.3)	
RQ3	8 (5.1)	4 (4.3)	4 (6.1)		3 (3.4)	5 (7.0)	
RQ4	25 (15.8)	9 (9.8)	16 (24.2)		10 (11.5)	15 (21.1)	

IES-R denotes Impact of Event Scale-Revised, *EPDS* Edinburgh Postnatal Depression Scale, *RQ* Relationship Questionnaire, *IQR* Interquartile range

- Psychological survey of women who gave birth during the COVID-19 pandemic (March 8-June 15) in Torino
- Edinburgh Postnatal Depression Scale (EPDS), Impact of Event Scale-Revised (IES-R), and Relationship Questionnaire (RQ)were performed
- Of the 163 women ,prevalence of depressive symptoms was **44.2% (EPDS cut-off score ≥ 11)**
- The prevalence **of PTSS was 42.9% (IES-R cut-off score ≥24).**
- Pain during childbirth was a risk factor for postpartum depression; support from medical staff and quietness in the ward were protective factors.
- Early detection of anxiety during pregnancy and preventive and therapeutic psychological interventions are important.

Backstories

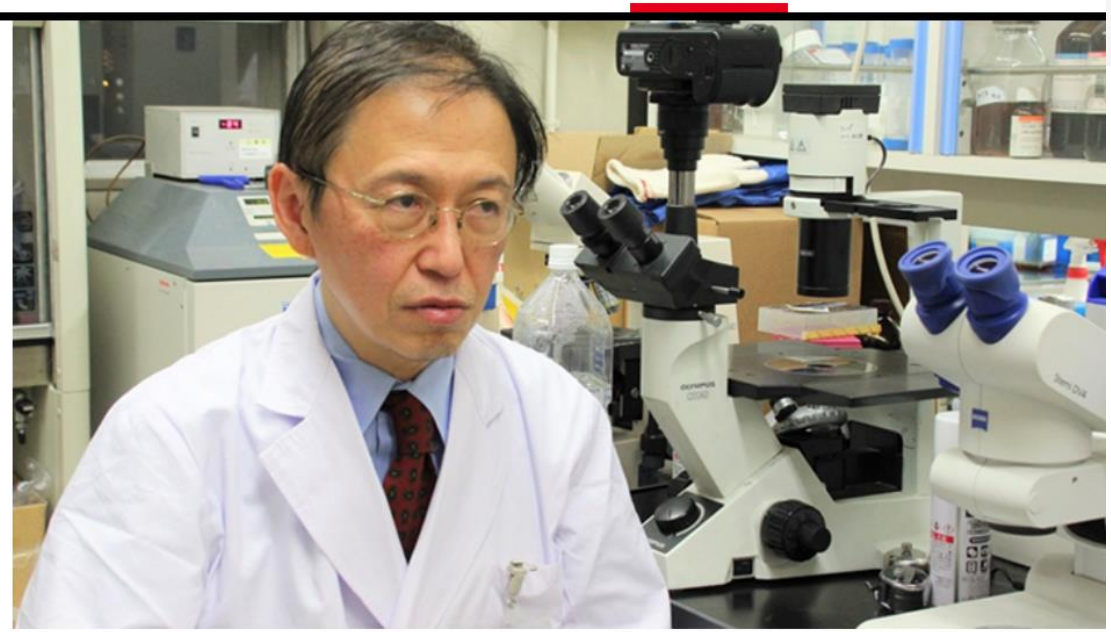
Pregnant during a pandemic: "Don't panic but protect yourself."

#Health & Welfare #Japan #Coronavirus

Thursday April 23, 2020

Yamamoto Saori
NHK World Correspondent

News Top Stories Backstories At a Glance Jap



Dr. Hayakawa Satoshi, the vice president of the Japan Society for Infectious Diseases in Obstetrics and Gynecology.

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Obstetrics and Gynaecology Research
doi:10.1111/jog.14748 J. Obstet. Gynaecol. Res. 2021

Anti-SARS-CoV-2 vaccination strategy for pregnant women in Japan

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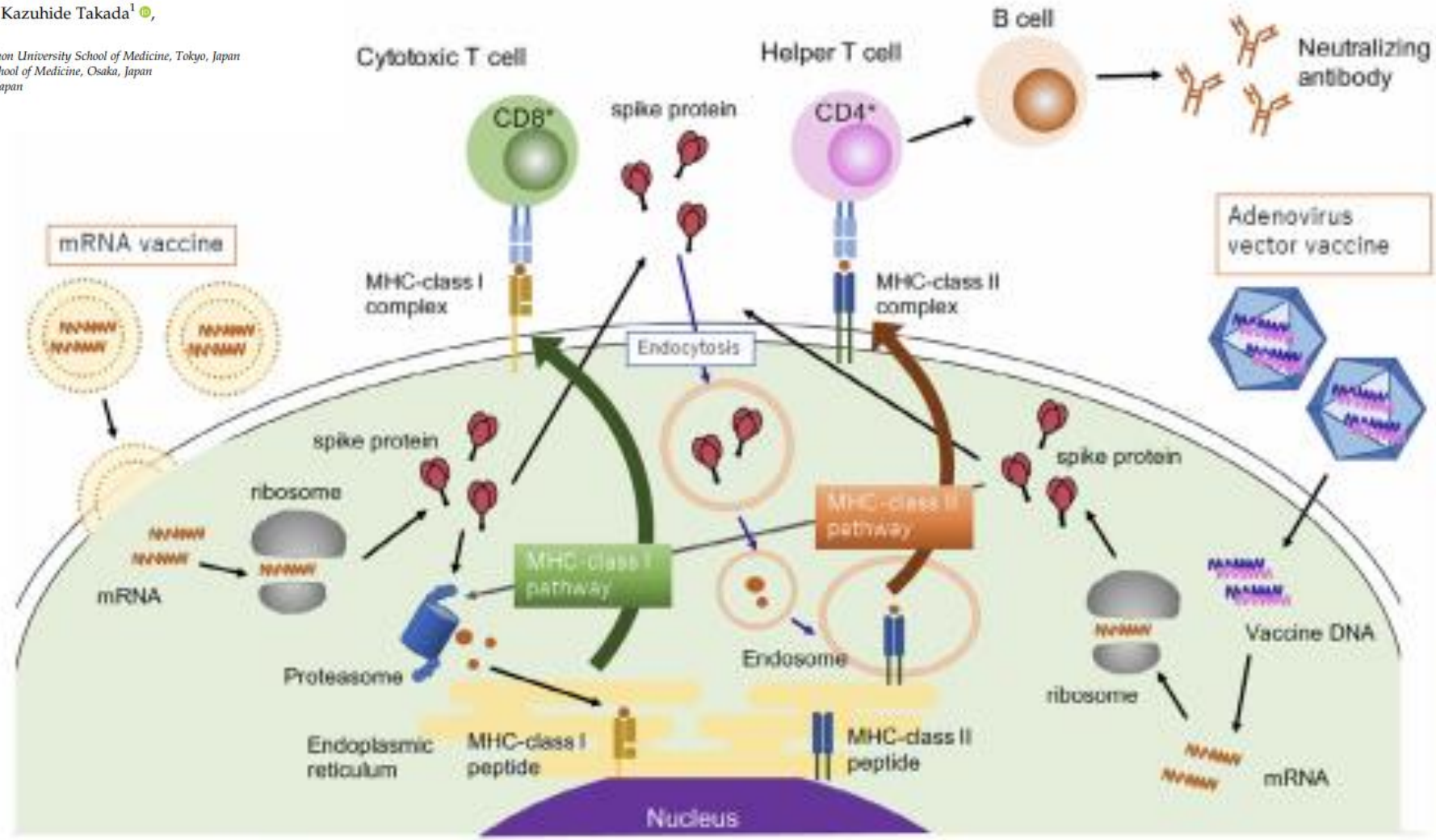

Figure 1 How SARS-CoV-2 vaccines are processed in antigen-presenting cells and recognized by immune cells

Research

JAMA | Original Investigation

Association Between mRNA Vaccination and COVID-19 Hospitalization and Disease Severity

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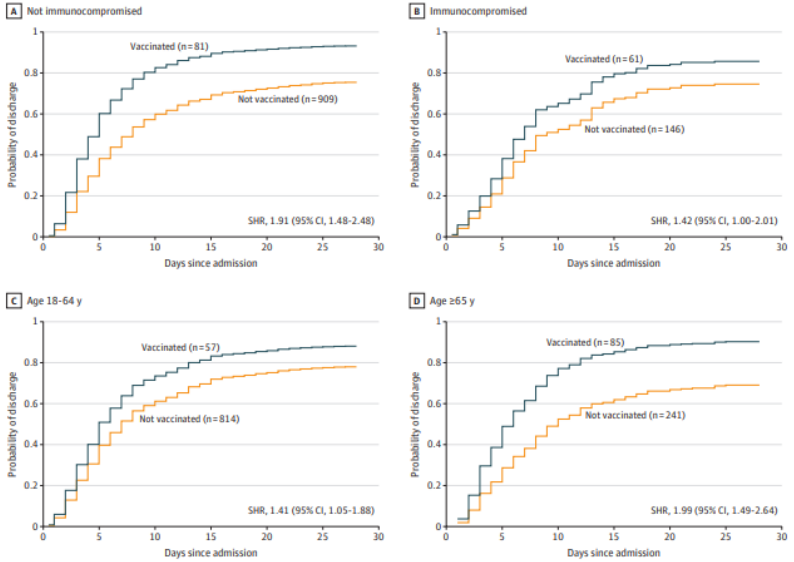
CONCLUSIONS AND RELEVANCE Vaccination with an mRNA COVID-19 vaccine was significantly less likely among patients with COVID-19 hospitalization and disease progression to death or mechanical ventilation. These findings are consistent with risk reduction among vaccine breakthrough infections compared with absence of vaccination.

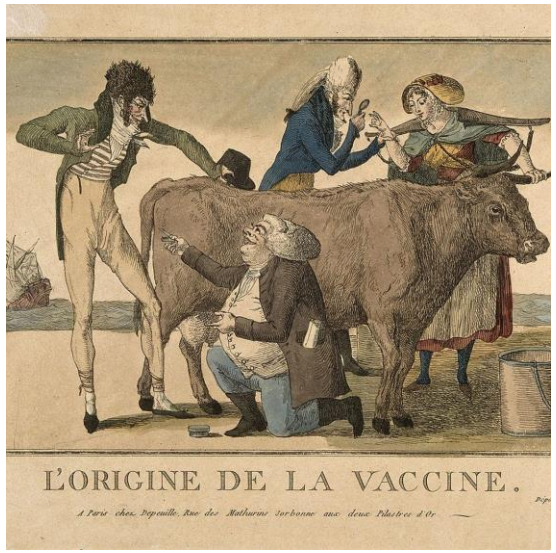
JAMA. doi:10.1001/jama.2021.19499
Published online November 4, 2021.

Figure 4. Competing Risks Regression of Hospital Discharge for Adults Hospitalized With COVID-19

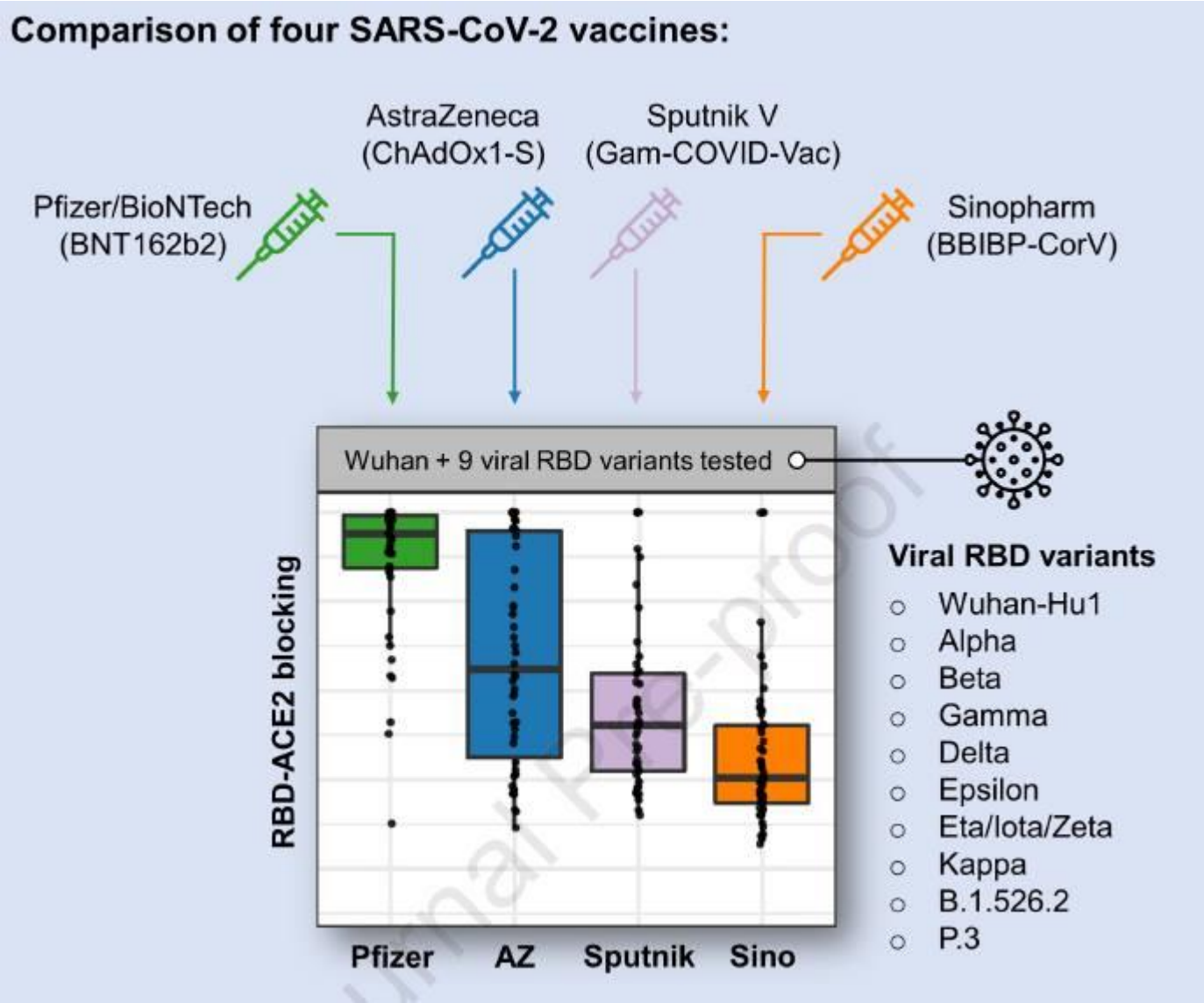


- CDC reported that full vaccination reduced the rate of hospitalization down to 1/20th compared to un-vaccinated.
- Vaccination reduces the chance of household infections by 40-60%, for every strain including delta strain.
- At four months after two doses of vaccine, the efficacy rate of Pfizer vaccine is reduced by about 30%, while that of the Moderna vaccine remains unchanged (doi:10.1001/jama.2021.19499).
- The amount of RNA contained in the Moderna vaccine is about three times higher than that in the Pfizer vaccine, and this might be responsible for the longer duration of immunity.


The Cow-Pock — or — the Wonderful Effects of the New Inoculation! — Vide the Publications of y Ana Vaccine Society.


L'ORIGINE DE LA VACCINE.

佐賀城本丸歴史館



- **Two doses of Pfizer(mRNA), AstraZeneca(DNA), Sputnik (Russian), or Sinopharm (Chinese inactivated vaccine) were administered to 196 people in Mongolia.**
- **The serum levels of neutralizing antibodies were then compared.**
- **The ability to induce neutralizing antibodies, Pfizer was by far the best, followed by AstraZeneca, and then Sputnik and Sinopharm.**

Naranjargal J. Dashdorj et al. Cell Host Microbe (in press)

https://reader.elsevier.com/reader/sd/pii/S1931312821005102?token=3BFDE7793FD5D49686755C85D76E443E5A7C31D854B62F0CB45B86DBC18C6500FED3B8A519DF39E7F9BEEB68C696520F&originRegion=us-east-1&originCreation=20211115012623

THE JOURNAL OF
Obstetrics and Gynaecology Research
doi:10.1111/jog.14748 J. Obstet. Gynaecol. Res. 2021

Anti-SARS-CoV-2 vaccination strategy for pregnant women in Japan

Satoshi Hayakawa[1], Shihoko Komine-Aizawa[1], Kazuhide Takada[1], Tadashi Kimura[2] and Hideto Yamada[3]

[1]Division of Microbiology, Department of Pathology and Microbiology, Nihon University School of Medicine, Tokyo, Japan
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1. pregnant women should not be excluded from vaccination;
2. informed consent should be obtained before vaccination;
3. healthcare workers and pregnant women with complications such as diabetes, hypertension, and obesity should be vaccinated preferentially;
4. vaccination should be avoided until 12 weeks of gestation during organogenesis;
5. spouse and family members should be vaccinated actively;
6. nursing mothers are not particularly affected.
7. This policy has been adopted in government guidelines. Additional efforts should be made to protect pregnant women from infection and severe illness with COVID-19 by eliminating vaccine hesitancy.

Revised recommendations from (June 17)

1. Every pregnant woman is encouraged to be vaccinated.
2. Abolish the 12-week limit. (Originally, there was no clear evidence for this, but the purpose was to avoid the period of organogenesis in order to prevent problems caused by accidental birth defects.)
3. Omission of confirmation of fetal heartbeat before and after inoculation (This is possible for individual inoculation at obstetric facilities, but impossible at mass inoculation:
4. Routine medical checkup of pregnant women before and after innoculation by local Obstetricians.

Reproductive Toxicology 103 (2021) 28–35

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

Lack of effects on female fertility and prenatal and postnatal offspring development in rats with BNT162b2, a mRNA-based COVID-19 vaccine

Christopher J. Bowman [a,*], Marie Bouressam [b], Sarah N. Campion [a], Gregg D. Cappon [a], Natasha R. Catlin [a], Mark W. Cutler [c], Jan Diekmann [d], Cynthia M. Rohde [e], Rani S. Sellers [e], Claudia Lindemann [d]

[a] Drug Safety Research and Development, Pfizer Worldwide Research, Development & Medical, Groton, CT, USA
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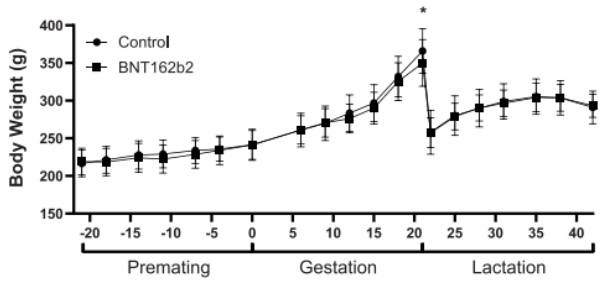
[c] Vaccine Research and Development, Pfizer Worldwide Research, Development & Medical, Pearl River, NY, USA
[d] Non-Clinical Safety, BioNTech SE, Mainz, Germany
[e] Drug Safety Research and Development, Pfizer Worldwide Rese



- A study in rats on the reproductive toxicity and fetal-placental damage of Pfizer-Biontech vaccine.
- No toxicity was observed at all.

Table 1
Summary of fertility data from female rats administered control (saline) or BNT162b2.

	Control (saline)	BNT162b2
Fertility (n)[a]	**44**	**44**
Mean Estrous Cycle Length (days)[b,c]	4.02 ± 0.19	4.00 ± 0.11
Females with Acyclic Period[d]	8/44 (18.2 %)	8/44 (18.2 %)
Days in Cohabitation[b]	3.0 ± 2.2	2.8 ± 1.7
Mating (Copulation) Index[e]	44/44 (100 %)	44/44 (100 %)
Fertility Index[f]	43/44 (98 %)	42/44 (95 %)
Pregnancy Rate[g]	43/44 (98 %)	42/44 (95 %)

Table 2
Cesarean section observations and fetal weights from the female rats in the cesarean section cohort administered control (saline) or BNT162b2.

	Control (saline)	BNT162b2	CRL-Lyon HC Mean (min–max)[a]
C-Section Cohort (n)[b]	**21**	**21**	–
Gravid uterine weight (g)	86.32 ± 7.69[c]	87.65 ± 13.48	75.6 (64.6–86.8)
Corpora lutea	14.7 ± 1.6	15.5 ± 2.1	13.2 (11.6–14.3)
Implantation sites	14.1 ± 1.6	14.0 ± 2.2	12.1 (10.4–13.8)
Pre-implantation loss (%)	4.09 ± 6.56	9.77 ± 8.09*	8.4 (1.4–16.2)
Post-implantation loss (%)	6.10 ± 7.64	5.85 ± 7.28	8.8 (2.4–17.3)
Number live fetuses	13.2 ± 1.6	13.1 ± 2.1	11.0 (9.3–12.7)
Mean fetal body weight (g)	4.89 ± 0.23	4.90 ± 0.30	5.09 (4.87–5.24)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons

Tom T. Shimabukuro, M.D., Shin Y. Kim, M.P.H., Tanya R. Myers, Ph.D., Pedro L. Moro, M.D., Titilope Oduyebo, M.D., Lakshmi Panagiotakopoulos, M.D., Paige L. Marquez, M.S.P.H., Christine K. Olson, M.D., Ruiling Liu, Ph.D., Karen T. Chang, Ph.D., Sascha R. Ellington, Ph.D., Veronica K. Burkel, M.P.H., Ashley N. Smoots, M.P.H., Caitlin J. Green, M.P.H., Charles Licata, Ph.D., Bicheng C. Zhang, M.S., Meghna Alimchandani, M.D., Adamma Mba-Jonas, M.D., Stacey W. Martin, M.S., Julianne M. Gee, M.P.H., and Dana M. Meaney-Delman, M.D., for the CDC v-safe COVID-19 Pregnancy Registry Team*

- ✓ An initial safety study of mRNA Covid-19 vaccine in pregnant women in the United States from December 14, 2020 to February 28, 2021.
- ✓ Injection site pain was reported more frequently in pregnancy, but headache, myalgia, chills, and fever were reported less frequent.
- ✓ The frequency of adverse events, including spontaneous abortion, did not differ from that of non-vaccinated subjects.

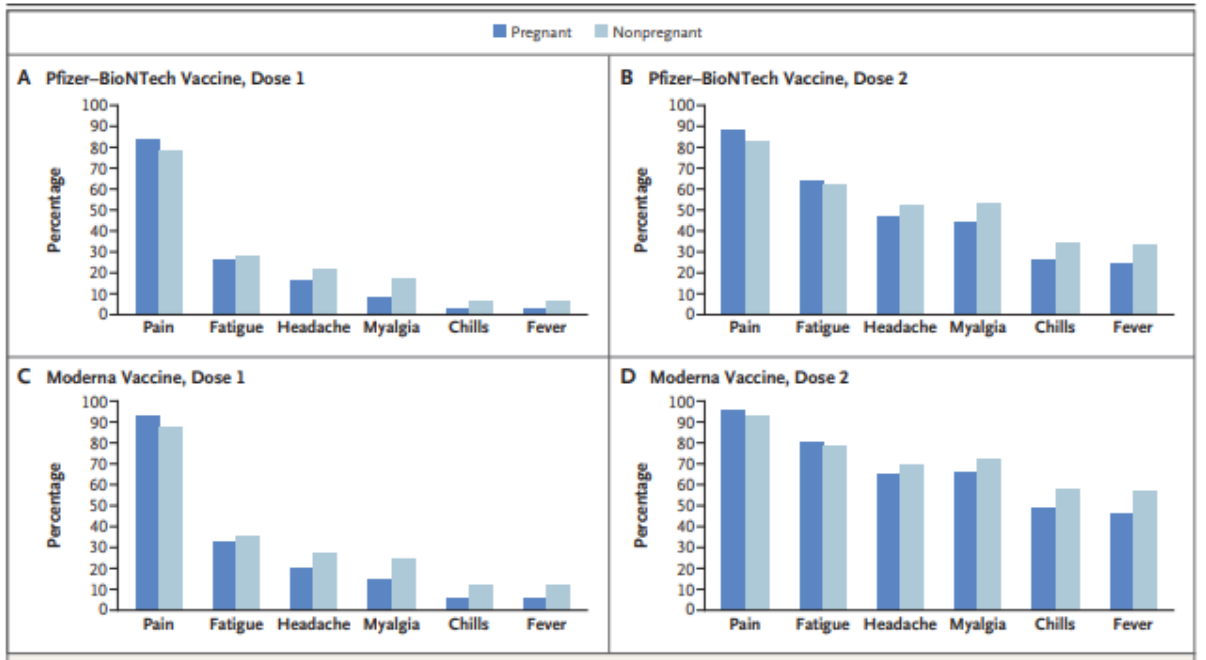


Figure 1. Most Frequent Local and Systemic Reactions Reported in the V-safe Surveillance System on the Day after mRNA Covid-19 Vaccination.
Shown are solicited reactions in pregnant persons and nonpregnant women 16 to 54 years of age who received a messenger RNA (mRNA) coronavirus disease 2019 (Covid-19) vaccine — BNT162b2 (Pfizer–BioNTech) or mRNA-1273 (Moderna) — from December 14, 2020, to February 28, 2021. The percentage of respondents was calculated among those who completed a day 1 survey, with the top events shown of injection-site pain (pain), fatigue or tiredness (fatigue), headache, muscle or body aches (myalgia), chills, and fever or felt feverish (fever).

Table 4. Pregnancy Loss and Neonatal Outcomes in Published Studies and V-safe Pregnancy Registry Participants.

Participant-Reported Outcome	Published Incidence*	V-safe Pregnancy Registry†
	%	*no./total no. (%)*
Pregnancy loss among participants with a completed pregnancy		
Spontaneous abortion: <20 wk[15-17]	10–26	104/827 (12.6)‡
Stillbirth: ≥ 20 wk[18-20]	<1	1/725 (0.1)§
Neonatal outcome among live-born infants		
Preterm birth: <37 wk[21,22]	8–15	60/636 (9.4)¶
Small size for gestational age[23,24]‖	3.5	23/724 (3.2)
Congenital anomalies[25]**	3	16/724 (2.2)
Neonatal death[26]††	<1	0/724

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Covid-19 Vaccination during Pregnancy and First-Trimester Miscarriage

Table 1. Odds Ratios for Covid-19 Vaccination in a 5-Week or 3-Week Window before Miscarriage or Confirmation of an Ongoing Pregnancy.

Vaccination Status	5-Week Exposure Window				3-Week Exposure Window			
	Ongoing Pregnancies	Miscarriages	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*	Ongoing Pregnancies	Miscarriages	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
	number				*number*			
Among all women								
Unvaccinated	13,184	4,290	Reference	Reference	13,507	4,375	Reference	Reference
Vaccinated	772	231	0.92 (0.79–1.07)	0.81 (0.69–0.95)	449	146	1.00 (0.83–1.21)	0.91 (0.75–1.10)
Among health care personnel								
Unvaccinated	2,419	756	Reference	Reference	2,533	788	Reference	Reference
Vaccinated	261	75	0.92 (0.70–1.20)	0.93 (0.70–1.22)	147	43	0.94 (0.66–1.33)	0.92 (0.64–1.32)

* The odds ratios among all women were adjusted for age, country of birth, marital status, educational level, household income, number of children, employment in a health care profession, underlying risk conditions for coronavirus disease 2019 (Covid-19), and previous test positive for severe acute respiratory syndrome coronavirus 2. The odds ratios among health care personnel were adjusted for the same variables as among all women except for employment in a health care profession.

Letters

RESEARCH LETTER

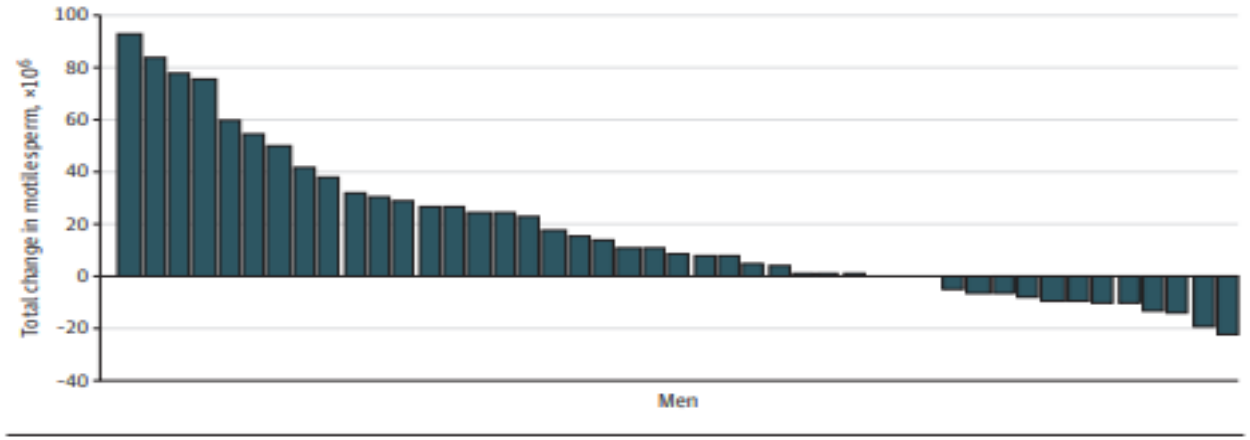
Sperm Parameters Before and After COVID-19 mRNA Vaccination

Table. Change in Semen Analysis Parameters Before and After COVID-19 Vaccination

Parameter	Normal value	Median (IQR)		*P* value
		Baseline	Follow-up	
No. of participants		45	45	
Volume, mL	>1.5	2.2 (1.5-2.8)	2.7 (1.8-3.6)	.01
Sperm concentration, million/mL	>15	26 (19.5-34)	30 (21.5-40.5)	.02
Total motility, %	>40	58 (52.5-65)	65 (58-70)	.001
TMSC, million	>9	36 (18-51)	44 (27.5-98)	.001

Abbreviations: IQR, interquartile range; TMSC, total motile sperm count.

Figure. Waterfall Plot Showing Changes in Total Motile Sperm Count Parameters Within Participants Before and After COVID-19 Vaccination



Each bar represents an individual participant.

- Semen was examined before and after vaccination to study the effect of mRNA vaccine on male infertility.
- Sperm volume and motility both improved after vaccination, and total motile sperm count (TMSC) increased!

Received: 28 January 2021 | Revised: 1 March 2021 | Accepted: 4 March 2021
DOI: 10.1002/jcp.30367

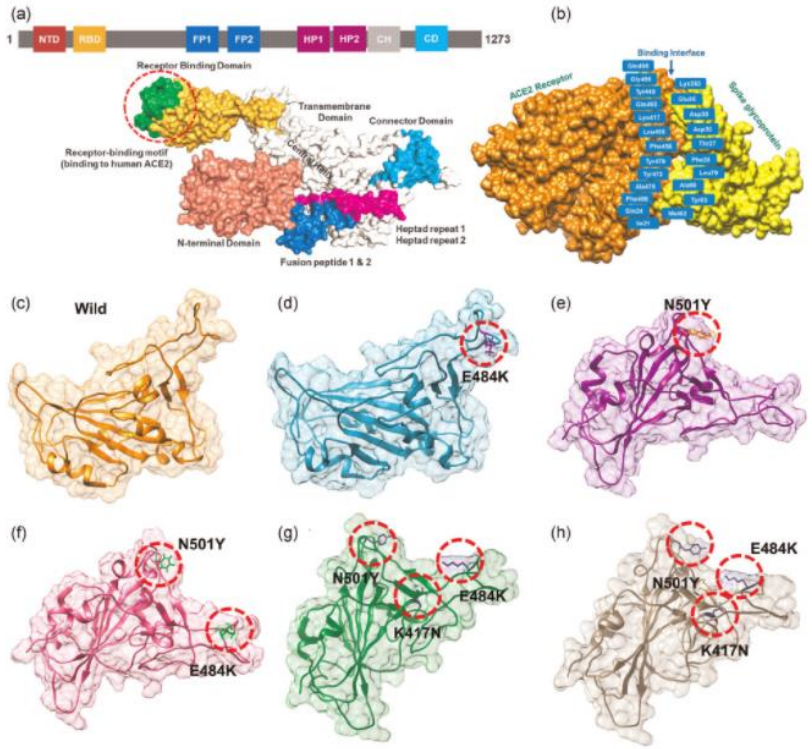
RESEARCH ARTICLE

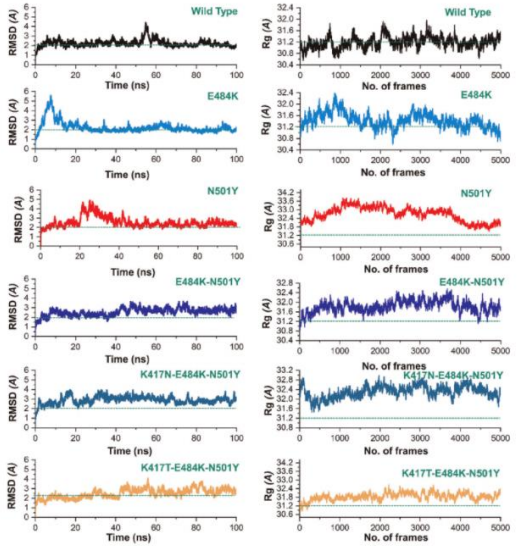
Journal of Cellular Physiology WILEY

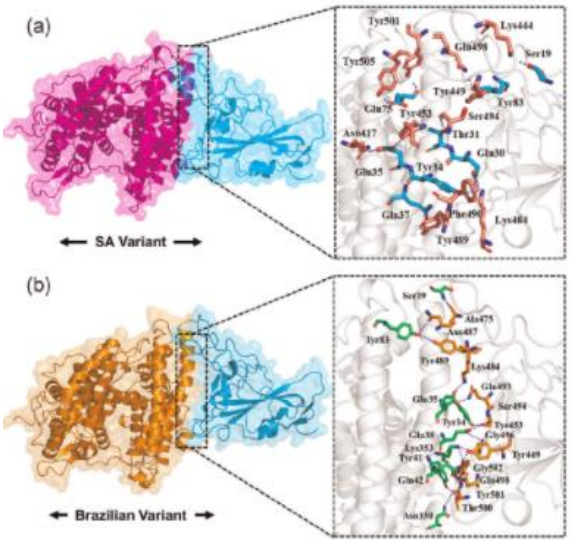
Higher infectivity of the SARS-CoV-2 new variants is associated with K417N/T, E484K, and N501Y mutants: An insight from structural data

Abbas Khan[1] | Tauqir Zia[2] | Muhammad Suleman[3] | Taimoor Khan[1] | Syed Shujait Ali[3] | Aamir Ali Abbasi[4] | Anwar Mohammad[5] | Dong-Qing Wei[1,6,7]

- The South African (K417N-E484K-N501Y) and Brazilian (K417T-E484K-N501Y) variants are more lethal than the UK variant (N501Y)
- May escape neutralizing antibodies induced by existing vaccines







The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

BNT162b2-Elicited Neutralization against New SARS-CoV-2 Spike Variants

May 12, 2021
DOI: 10.1056/NEJMc2106083

- ✓ The antibodies induced in Pfizer vaccine twice-vaccine recipients can neutralize a variety of mutant strains.
- ✓ At this time, the vaccine does not become ineffective when mutated strains appear.

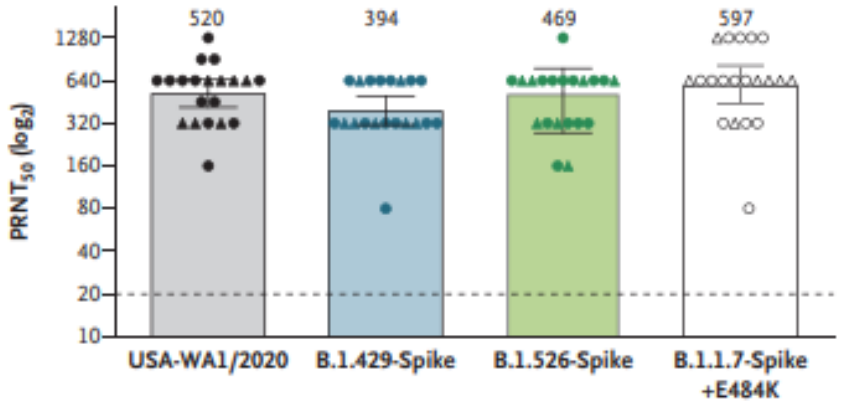


Figure 1. Serum Neutralization of New Variant Strains of SARS-CoV-2 after Two Doses of BNT162b2 Vaccine.

Shown are the results of 50% plaque reduction neutralization testing ($PRNT_{50}$) with the use of 20 samples obtained from 15 trial participants at 2 weeks (circles) or 4 weeks (triangles) after the administration of the second dose of the BNT162b2 vaccine. The mutant viruses were produced by engineering the complete *S* genes from the B.1.429 variant (B.1.429-spike), B.1.526 variant (B.1.526-spike), or B.1.1.7 variant plus an additional E484K mutation (B.1.1.7-spike+E484K) into USA-WA1/2020. Each data point represents the geometric mean $PRNT_{50}$ obtained with a serum sample against the indicated virus, including data from repeat experiments, as detailed in Table S1 in the Supplementary Appendix. The data for USA-WA1/2020 are from two experiments; the data for B.1.429-spike, B.1.526-spike, and B.1.1.7-spike+E484K viruses are from one experiment each. In each experiment, the neutralization titer was determined in duplicate assays, and the geometric mean was calculated. The heights of bars and the numbers over the bars indicate geometric mean titers. The I bars indicate 95% confidence intervals. The dashed line indicates the limit of detection. Statistical analysis was performed with the use of the Wilcoxon matched-pairs signed-rank test. The statistical significance of the difference between geometric mean titers in the USA-WA1/2020 neutralization assay and in each variant virus neutralization assay with the same serum samples are as follows: P=0.002 for B.1.429-spike; P=0.47 for B.1.526-spike; and P=0.04 for B.1.1.7-spike+E484K.

Article

BNT162b2-elicited neutralization of B.1.617 and other SARS-CoV-2 variants

https://doi.org/10.1038/s41586-021-03693-y

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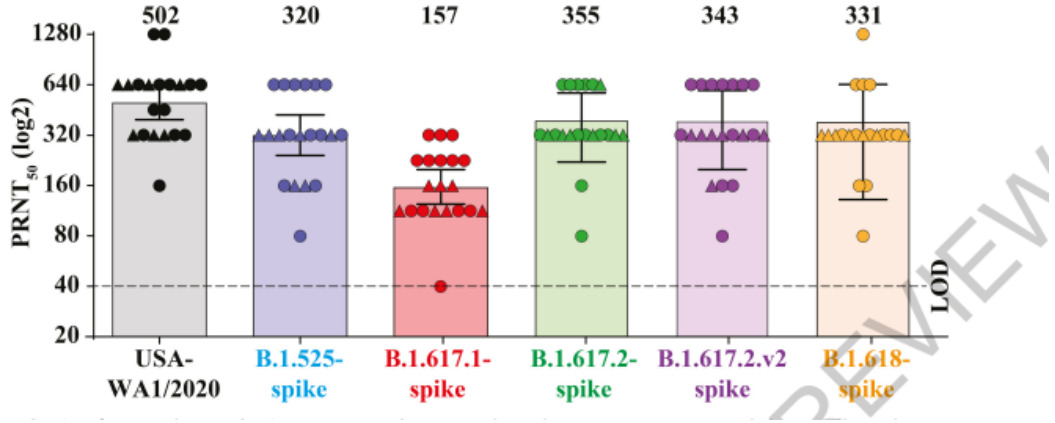
Accepted: 4 June 2021

Published online: 10 June 2021

Jianying Liu[1,2,9], Yang Liu[3,9], Hongjie Xia[3], Jing Zou[3], Scott C. Weaver[1,2,4,5,6], Kena A. Swanson[7], Hui Cai[7], Mark Cutler[7], David Cooper[7], Alexander Muik[8], Kathrin U. Jansen[7], Ugur Sahin[8]✉, Xuping Xie[3]✉, Philip R. Dormitzer[7]✉ & Pei-Yong Shi[2,3,4,5,6]✉

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to evolve around the world, generating new variants that are of concern based on their potential for altered transmissibility, pathogenicity, and coverage by vaccines and therapeutics[1–5]. Here we report that 20 human sera, drawn 2 or 4 weeks after two doses of BNT162b2, neutralize engineered SARS-CoV-2 with a USA-WA1/2020 genetic background (a virus strain isolated in January 2020) and spike glycoproteins from the newly emerged B.1.617.1, B.1.617.2, B.1.618 (all first identified in India) or B.1.525 (first identified in Nigeria) lineages. Geometric mean plaque reduction neutralization titers against the variant viruses, particularly the B.1.617.1 variant, appear lower than the titer against USA-WA1/2020 virus, but all sera tested neutralize the variant viruses at titers of at least 40. The susceptibility of these newly emerged variants to BNT162b2 vaccine-elicited neutralization supports mass immunization as a central strategy to end the coronavirus disease 2019 (COVID-19) pandemic across geographies.

Article



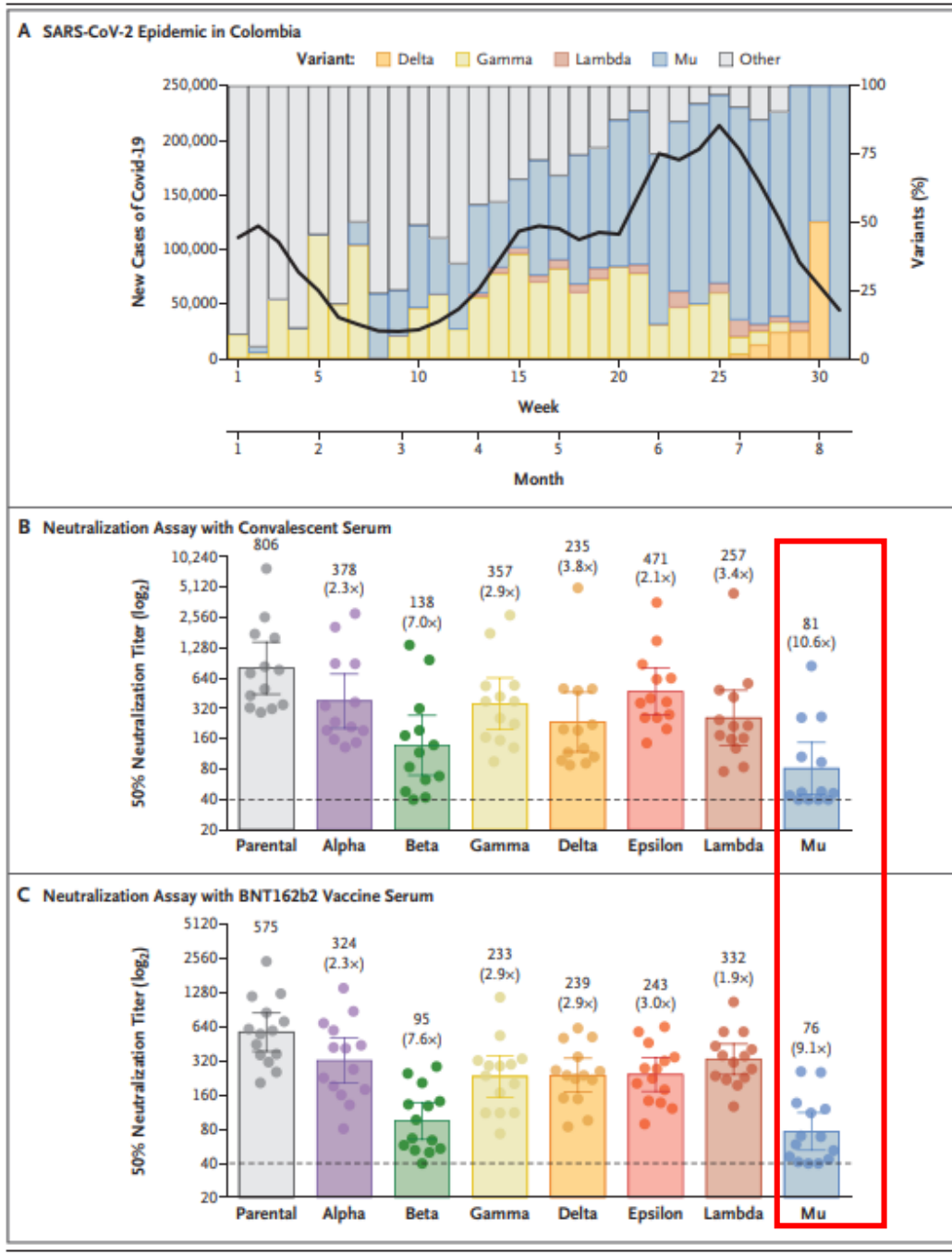
Sera from individuals who had completed two doses of Pfizer vaccine were neutralized against all virus strains tested, including the Indian delta and kappa strains and the Nigerian eta strain. (Nature 2021, Jun10)

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Neutralization of the SARS-CoV-2 Mu Variant by Convalescent and Vaccine Serum

- As of September 2021, the WHO reported four variants of concern (alpha [B.1.1.7], beta [B.1.351], gamma [P.1], and delta [B.1 .617.2 and AY]) and five notable variants (eta [B.1.525], iota [B.1.526], kappa [B.1.617.1], lambda[C.37], mu[B.1.621]).
- The mu strain was first isolated in Colombia on January 11, 2021, and the number of infected patients increased rapidly from March to July, with the gamma strain predominating in the early stages but becoming dominant in May and increasing in proportion thereafter
- Mu strains may have increased infection rates, virulence, and resistance to immune responses.
- Mu strains may pose a threat by developing significant resistance to antibodies induced by natural infection or by Pfizer vaccines.



Article

SARS-CoV-2 infection induces long-lived bone marrow plasma cells in humans

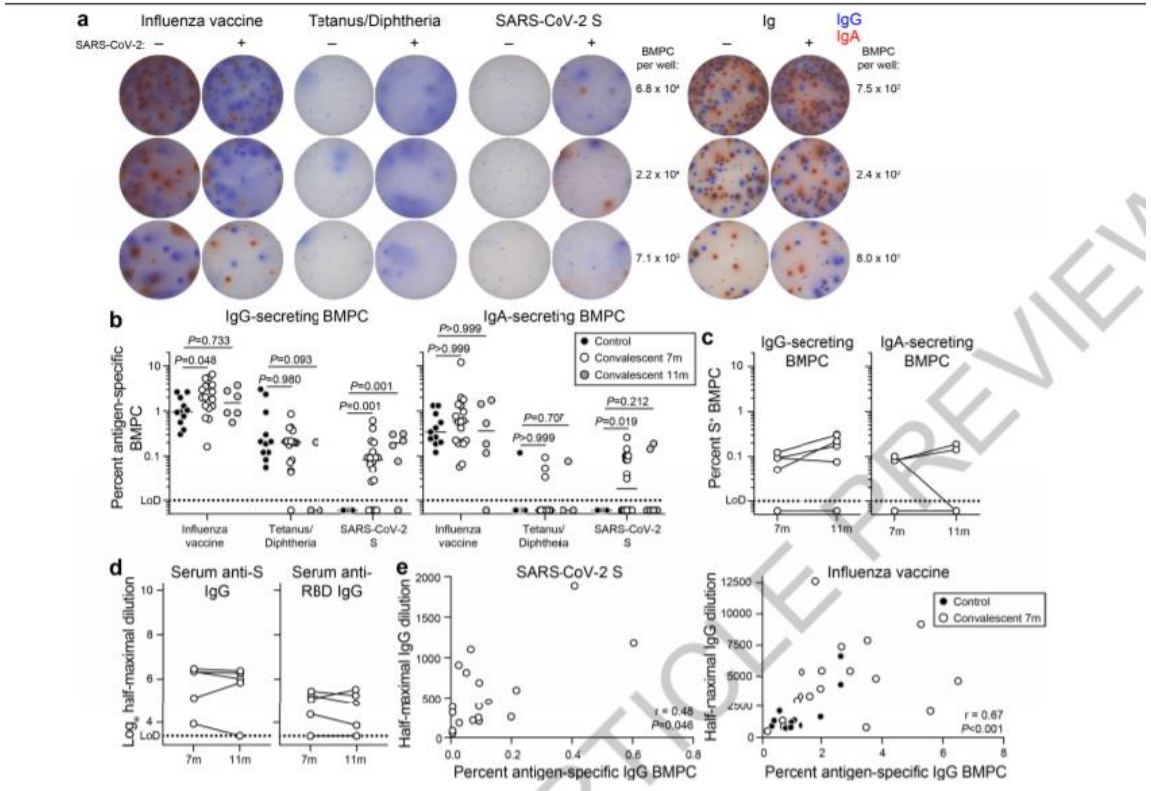
https://doi.org/10.1038/s41586-021-03647-4

Received: 20 December 2020

Accepted: 14 May 2021

Published online: 24 May 2021

Jackson S. Turner[1], Wooseob Kim[1], Elizaveta Kalaidina[2], Charles W. Goss[3], Adriana M. Rauseo[4], Aaron J. Schmitz[1], Lena Hansen[1,5], Alem Haile[6], Michael K. Klebert[6], Iskra Pusic[7], Jane A. O'Halloran[4], Rachel M. Presti[4,9] & Ali H. Ellebedy[1,8,9]



- Anti-SARS-CoV-2 antibodies are detectable up to 11 months after infection, although they rapidly decay in the first few months.
- SARS-CoV2 spike-specific plasmacytoid cells can be detected in bone marrow puncture fluid for a long time after inoculation.
- Memory B cells against S protein circulate and differentiate into plasma cells in recovering patients

Nature. May 24, 2021. (doi.org/10.1038/s41586-021-03647-4)

nature

https://doi.org/10.1038/s41586-021-03738-2

Accelerated Article Preview

SARS-CoV-2 mRNA vaccines induce persistent human germinal centre responses

Received: 8 March 2021

Accepted: 18 June 2021

Accelerated Article Preview Published online 28 June 2021

Cite this article as: Turner, J. S. et al. SARS-CoV-2 mRNA vaccines induce persistent human germinal centre responses. *Nature* https://doi.org/10.1038/s41586-021-03738-2 (2021).

Jackson S. Turner, Jane A. O'Halloran, Elizaveta Kalaidina, Wooseob Kim, Aaron J. Schmitz, Julian Q. Zhou, Tingting Lei, Mahima Thapa, Rita E. Chen, James Brett Case, Fatima Amanat, Adriana M. Rauseo, Alem Haile, Xuping Xie, Michael K. Klebert, Teresa Suessen, William D. Middleton, Pei-Yong Shi, Florian Krammer, Sharlene A. Teefey, Michael S. Diamond, Rachel M. Presti & Ali H. Ellebedy

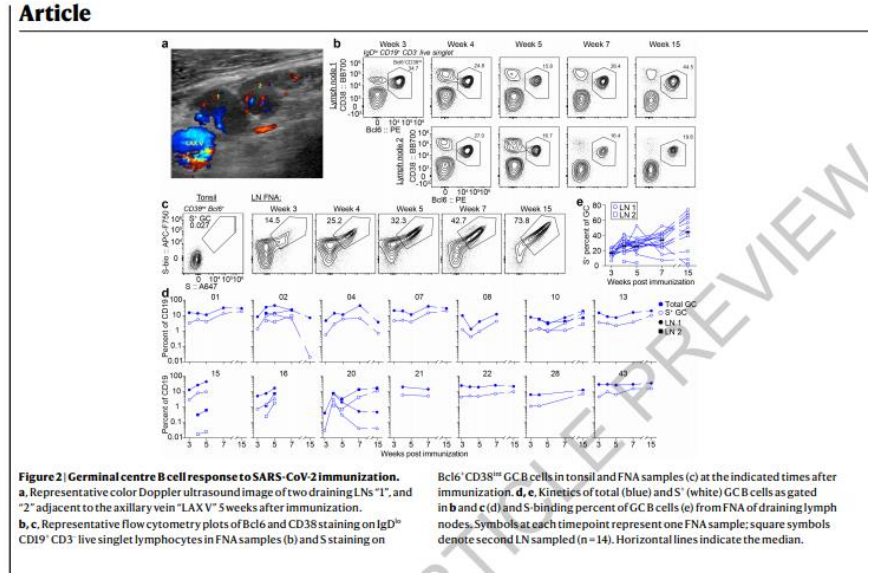
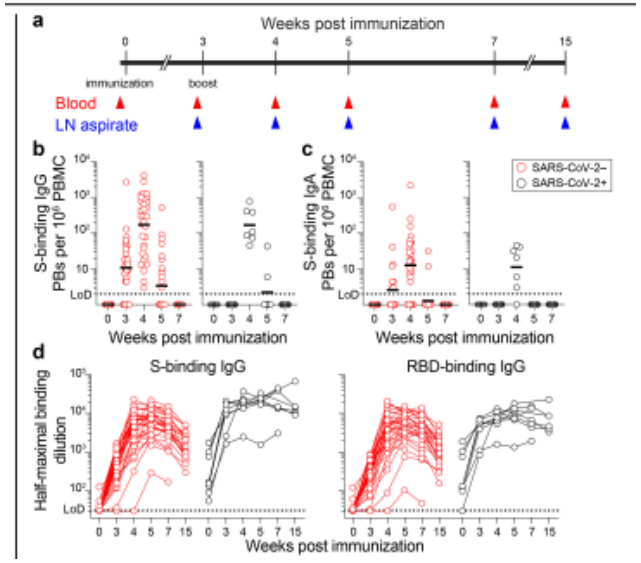


Figure 2 | Germinal centre B cell response to SARS-CoV-2 immunization. **a**, Representative color Doppler ultrasound image of two draining LNs "1", and "2" adjacent to the axillary vein "LAX V" 5 weeks after immunization. **b, c**, Representative flow cytometry plots of Bcl6 and CD38 staining on IgD^{lo} CD19^{+} CD3^{-} live singlet lymphocytes in FNA samples (b) and S staining on Bcl6^{+} CD38^{hi} GC B cells in tonsil and FNA samples (c) at the indicated times after immunization. **d, e**, Kinetics of total (blue) and S^{+} (white) GC B cells as gated in **b** and **c** (d) and S-binding percent of GC B cells (e) from FNA of draining lymph nodes. Symbols at each timepoint represent one FNA sample; square symbols denote second LN sampled (n = 14). Horizontal lines indicate the median.



- Peripheral blood B cells secreting IgG and IgA targeting the S protein reached a peak one week after the second immunization and then declined.
- In contrast, needle aspirates (FNA) of axillary lymph nodes, GC B cells binding to the S protein remained high for at least 12 weeks after booster immunization.
- In addition, clones of cross-reactive B cells had higher levels of somatic hypermutation than clones that recognized only the S protein of ARS-CoV-2.

New Results

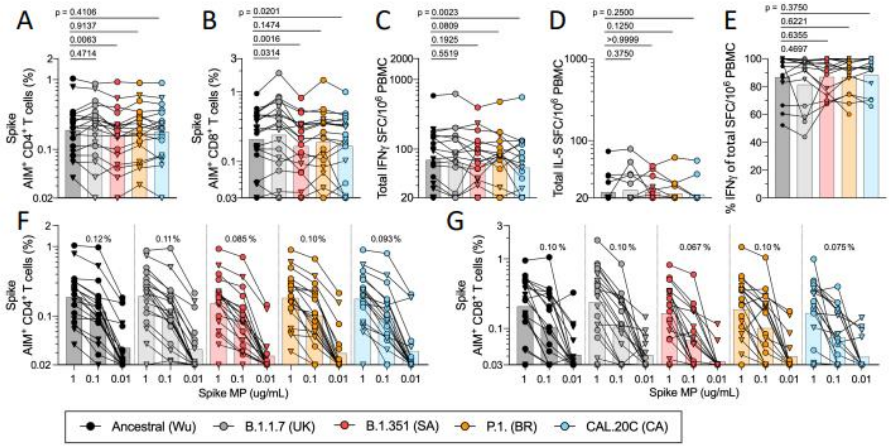
Comments (10)

Negligible impact of SARS-CoV-2 variants on CD4+ and CD8+ T cell reactivity in COVID-19 exposed donors and vaccinees

Alison Tarke, John Sidney, Nils Methot, Yun Zhang, Jennifer M. Dan, Benjamin Goodwin, Paul Rubiro, Aaron Sutherland, Ricardo da Silva Antunes, April Frazier, Stephen A. Rawlings, Davey M. Smith, Bjoern Peters, Richard H. Scheuermann, Daniela Weiskopf, Shane Crotty, Alba Grifoni, Alessandro Sette

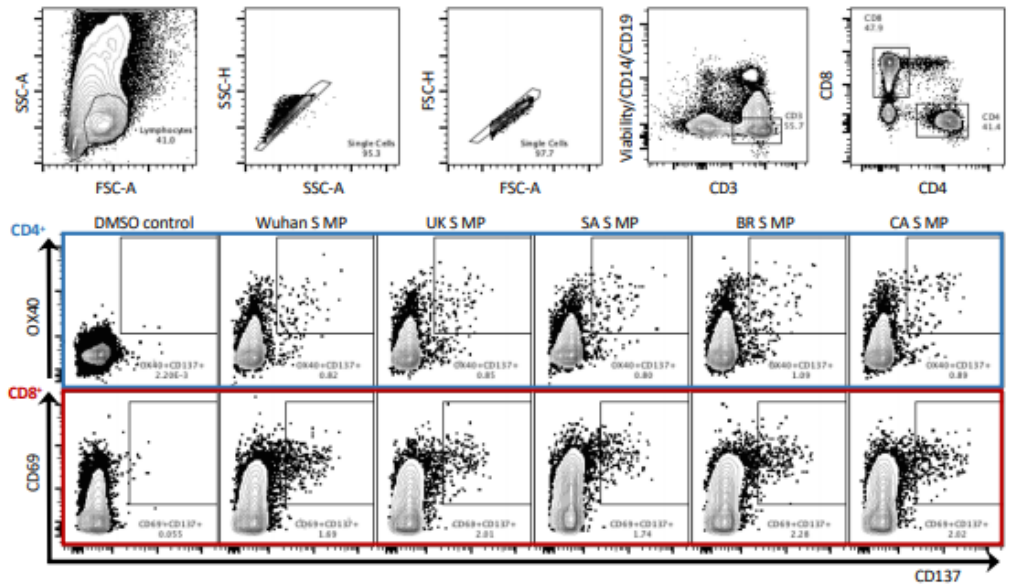
doi: https://doi.org/10.1101/2021.02.27.433180

Fig. 3



- The CD4+ and CD8+ T-cell responses of patients recovering from COVID-19 and those who received two doses of vaccine were virtually unaffected by the mutant strains.

Fig. S3



Immunity

ARTICLE | ONLINE NOW

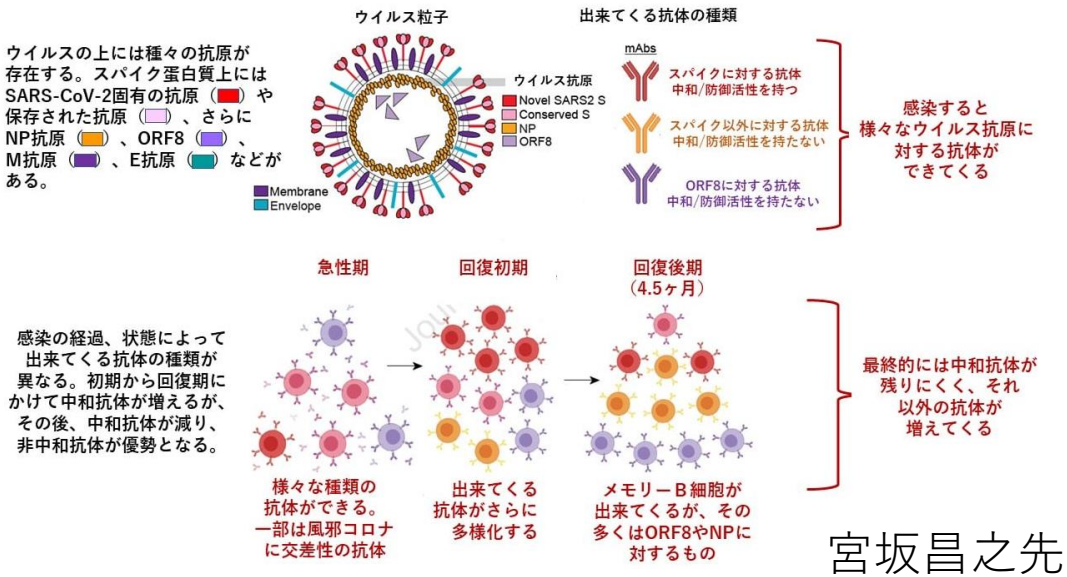
Profiling B cell immunodominance after SARS-CoV-2 infection reveals antibody evolution to non-neutralizing viral targets

Haley L. Dugan [14] • Christopher T. Stamper [14] • Lei Li [14] • ... Daved H. Fremont • Yoshihiro Kawaoka • Patrick C. Wilson [15] • Show all authors • Show footnotes

Published: May 06, 2021 • DOI: https://doi.org/10.1016/j.immuni.2021.05.001

Highlights

- Simultaneous capture of B cell transcripts, BCR sequence, and specificity in COVID-19
- ASCs reactive to HCoV dominate the early response to severe acute infection
- MBCs targeting NP and ORF8 adapt over time and are increased in older patients
- Anti-NP and ORF8 mAbs given prophylactically in animal infection models do not protect



宮坂昌之先生のFBより

- Early antibodies are partly cross-reactive antibodies to common cold coronaviruses, neutralizing antibodies to spike proteins, and non-neutralizing antibodies to other proteins.
- In the early stages of recovery, neutralizing antibodies increase and a variety of antibodies are produced.
- Later, neutralizing antibodies decrease and other antibodies increase relatively.
- In the case of natural infection, neutralizing antibodies temporarily increase, but decrease over time, and non-neutralizing antibodies increases.
- In the case of vaccination, the production of neutralizing antibodies lasts longer and T-cell activation is sustained, thus reducing the risk of reinfection.

Cold Spring Harbor Laboratory

bioRxiv

THE PREPRINT SERVER FOR BIOLOGY

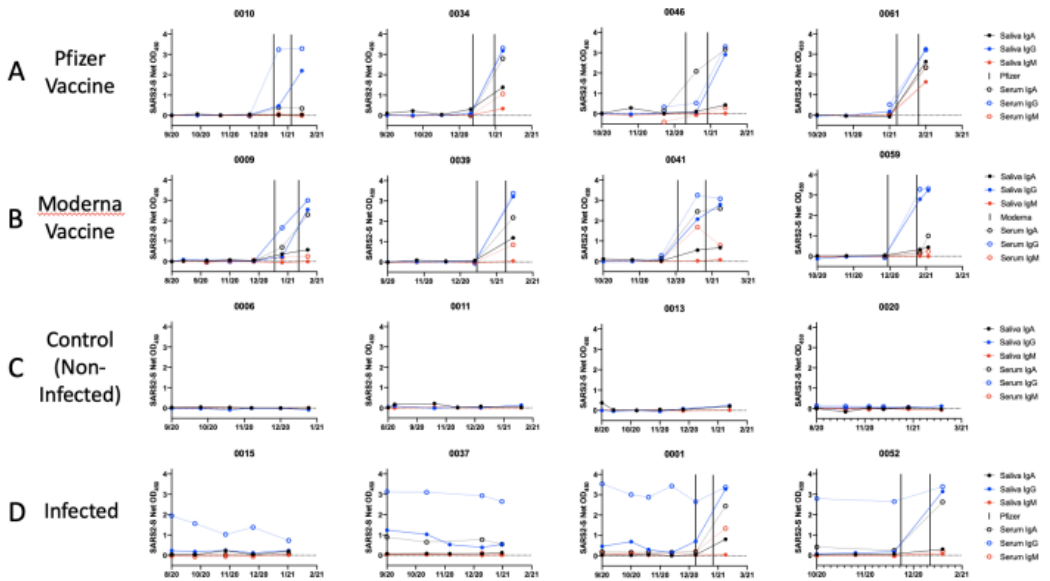
New Results

Antibody responses to SARS-CoV-2 mRNA vaccines are detectable in saliva

Thomas J. Ketas, Devidas Chaturbhuj, Victor M Cruz-Portillo, Erik Francomano, Encouse Golden, Sharanya Chandrasekhar, Gargi Debnath, Randy Diaz-Tapia, Anila Yasmeen, Wilhem Leconet, Zhen Zhao, Philip J.M. Brouwer, Melissa M. Cushing, Rogier W. Sanders, Albert Cupo, P. J. Klasse, Silvia C. Formenti, John P. Moore

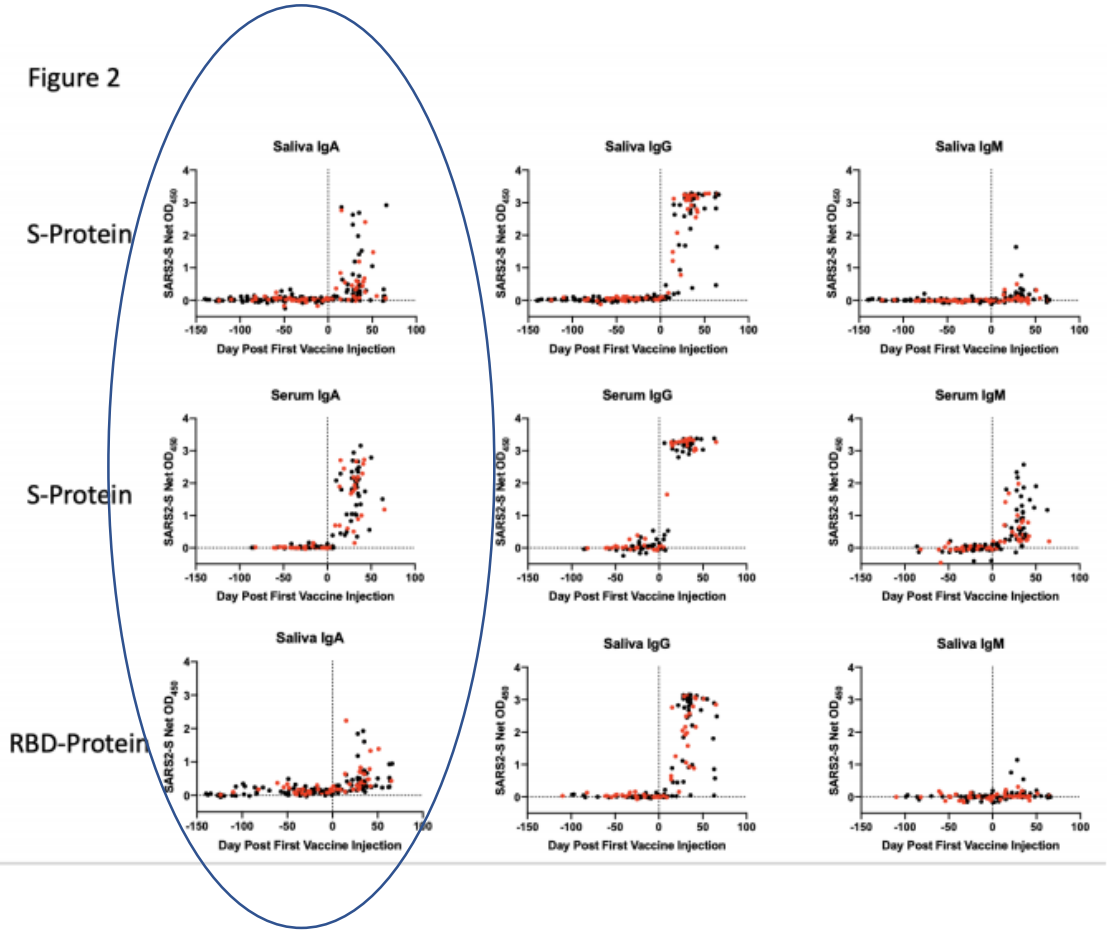
doi: https://doi.org/10.1101/2021.03.11.434841

Figure 1



Specific secretory IgA in saliva detected in 59% (22/37) of vaccine recipients with Pfizer's vaccine and 88% (7/8) with Moderna's vaccine

Figure 2



nature

https://doi.org/10.1038/s41586-021-04186-8

Accelerated Article Preview

Pre-existing polymerase-specific T cells expand in abortive seronegative SARS-CoV-2

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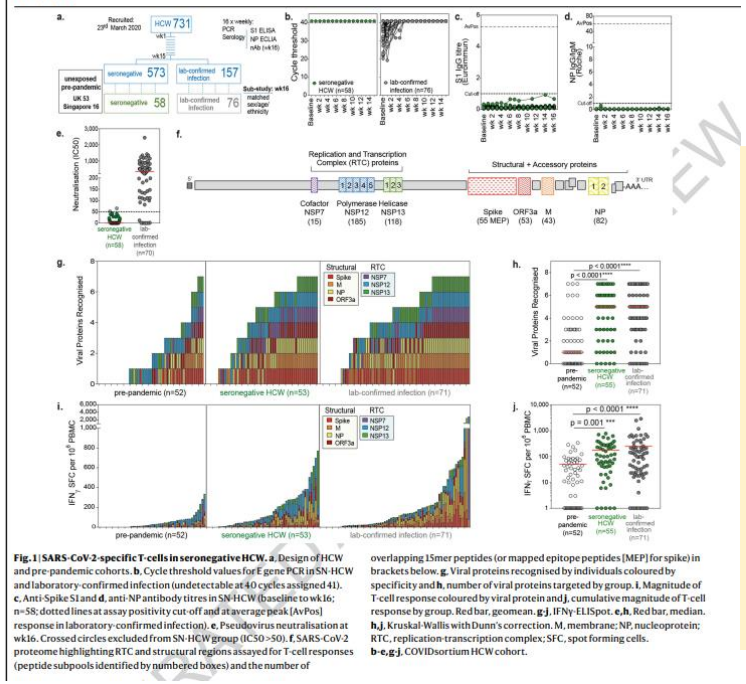
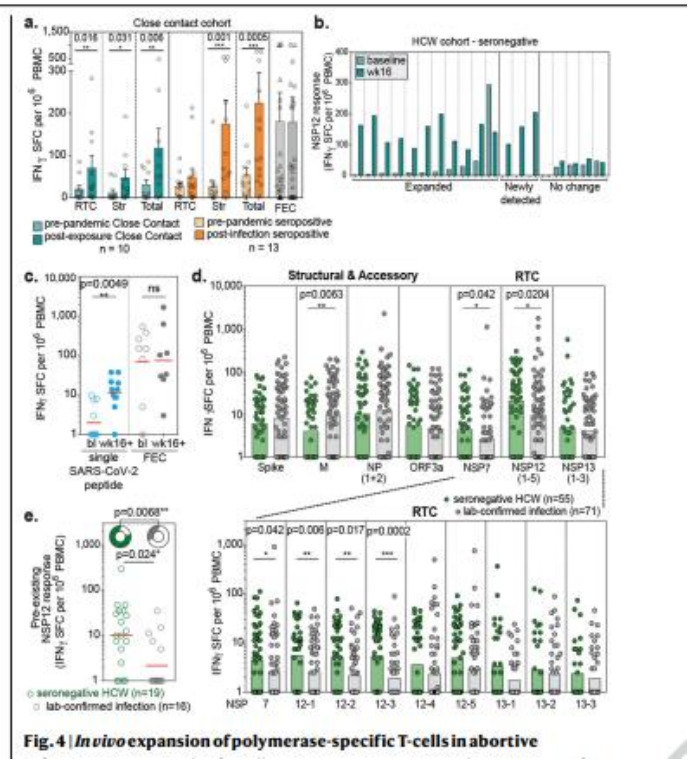
Leo Swadling, Mariana O. Diniz, Nathalie M. Schmidt, Oliver E. Amin, Aneesh Chandran, Emily Shaw, Corinna Pade, Joseph M. Gibbons, Nina Le Bert, Anthony T. Tan, Anna Jeffery-Smith, Cedric C. S. Tan, Christine Y. L. Tham, Stephanie Kucykowicz, Gloryanne Aidoo-Micah, Joshua Rosenheim, Jessica Davies, Marina Johnson, Melanie P. Jensen, George Joy, Laura E. McCoy, Ana M. Valdes, Benjamin M. Chain, David Goldblatt, Daniel M. Altmann, Rosemary J. Boyton, Charlotte Manisty, Thomas A. Treibel, James C. Moon, COVIDsortium investigators, Lucy van Dorp, Francois Balloux, Áine McKnight, Mahdad Noursadeghi, Antonio Bertoletti & Mala K. Maini





- T cell responses to previously infected coronaviruses control infection
- In particular, SARS-CoV-2 reactive T cells, including responses to replication transcription complexes (RTCs)12,13, are important and are not necessarily accompanied by elevated neutralizing antibody titers.

Article

Untimely TGFβ responses in COVID-19 limit antiviral functions of NK cells

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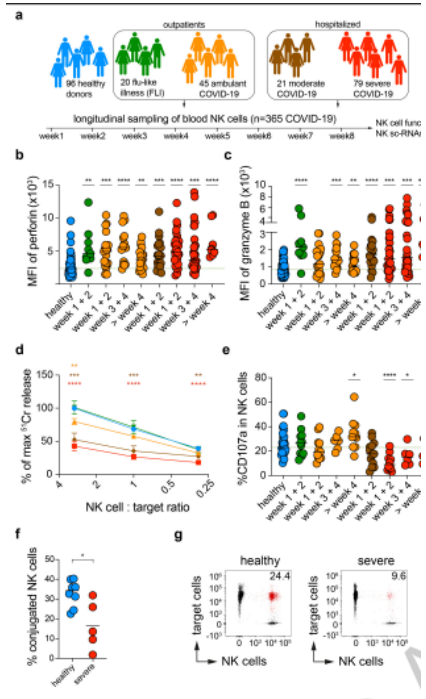
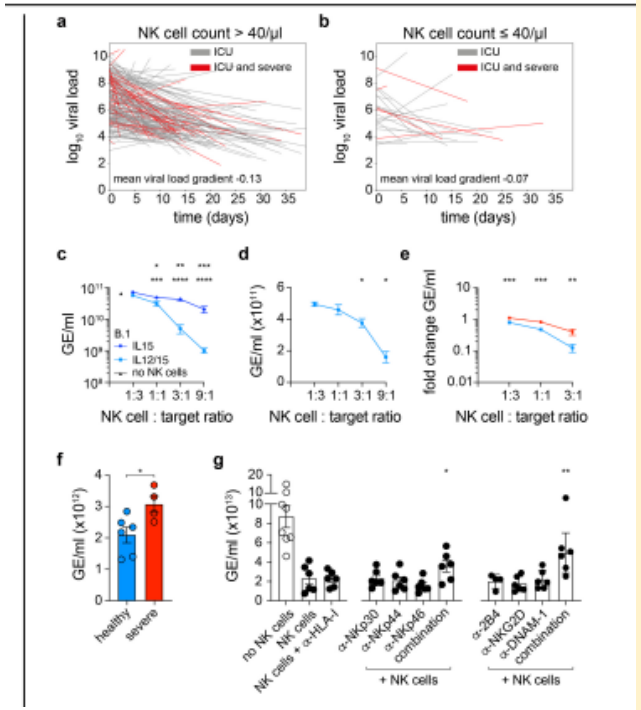
Published online: 25 October 2021

Mario Witkowski[1,2,3,26], Caroline Tizian[1,2,26], Marta Ferreira-Gomes[4,26], Daniela Niemeyer[5,6], Terry C. Jones[5,6,7], Frederik Heinrich[4], Stefan Frischbutter[8], Stefan Angermair[9], Thordis Hohnstein[1,2], Irene Mattiola[1,2], Philipp Nawrath[1,2], Sophie Mc Ewen[1,2], Silvia Zocche[10], Edoardo Viviano[11], Gitta Anne Heinz[4], Marcus Maurer[8], Uwe Kölsch[12], Robert Lorenz Chua[13], Tom Aschman[14], Christian Meisel[12], Josefine Radke[14], Birgit Sawitzki[15], Jobst Roehmel[16], Kristina Allers[17], Verena Moos[17], Thomas Schneider[17], Leif Hanitsch[15], Marcus A. Mall[16,18], Christian Conrad[13], Helena Radbruch[14], Claudia U. Duerr[19], Joseph A. Trapani[20], Emanuela Marcenaro[21], Tilmann Kallinich[4,18,22], Victor M. Corman[5,6], Florian Kurth[23], Leif Erik Sander[23], Christian Drosten[5,6], Sascha Treskatsch[9], Pawel Durek[4], Andrey Kruglov[4,24,25], Andreas Radbruch[4], Mir-Farzin Mashreghi[4,18,25,27] & Andreas Diefenbach[1,2,3,27]





- ✓ TGFβ is inappropriately increased in severe COVID-19 early in infection, inhibiting NK cell function and early viral defense
- ✓ Decreased viral load in COVID-19 correlates with NK cell status, and NK cells can control SARS-CoV-2 replication by recognizing infected target cells.
- ✓ In severe COVID-19, NK cells show marked defects in virus control, cytokine production, and cytotoxicity, despite high expression of cytotoxic effector molecules
- ✓ Single-cell RNA analysis of NK cells in all stages of COVID-19 revealed unique gene expression.
- ✓ In severe COVID-19, serum levels of TGFβ peak within 2 weeks of infection, resulting in a significant TGFβ-dependent impairment of NK cell function.
- ✓ In patients with mild disease, TGFβ increased only slightly after 3 weeks of infection.
- ✓ Suppression of TGFβ may prevent the development of severe disease.

Nature. Oct 25, 2021. (doi.org/10.1038/s41586-021-04142-6)

Maternal-neonatal transfer of SARS-CoV-2 immunoglobulin G antibodies among parturient women treated with BNT162b2 messenger RNA vaccine during pregnancy

Omer Nir, MD; Anat Schwartz, MD; Shlomi Toussia-Cohen, MD; Leah Leibovitch, MD; Tzipi Strauss, MD; Keren Asraf, PhD; Ram Doolman, PhD; Sivan Sharabi, MSc; Carmit Cohen, DVM, PhD; Yaniv Lustig, PhD; Gili Regev-Yochay, MD, MPH; Yoav Yinon, MD

- Efficient transfer of SARS-CoV-2 immunoglobulin G across the placenta in women, vaccinated with the BNT162b2
- A positive correlation between maternal serum and cord blood antibody concentrations.
- Positive correlation between blood and breast milk.
- In addition to maternal protection against COVID-19, the vaccine may also provide neonatal humoral immunity.

C

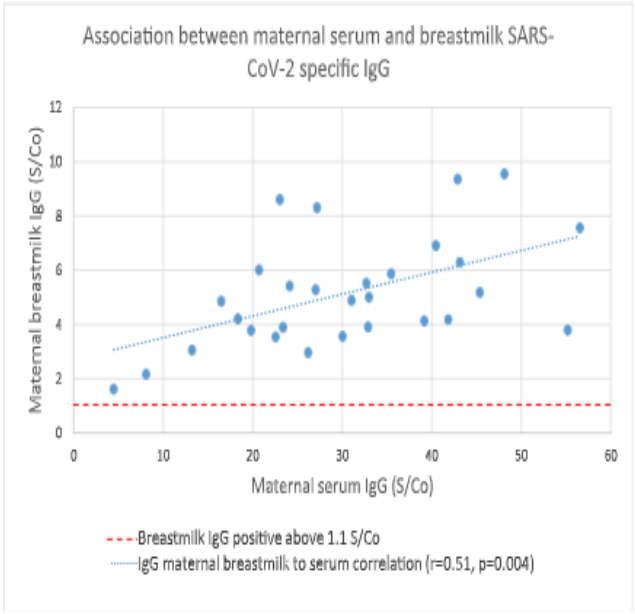
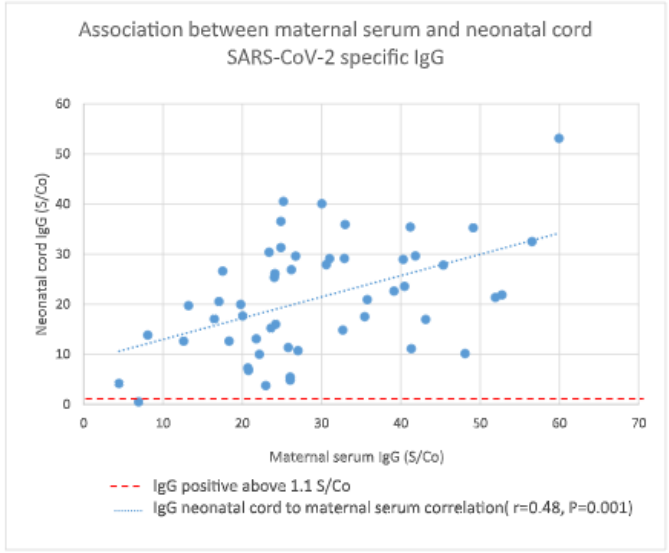
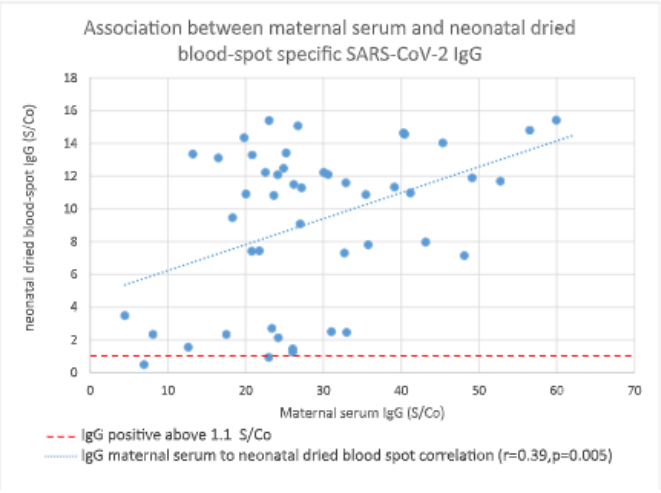


FIGURE 1
Association between maternal and neonatal SARS-CoV-2 IgG

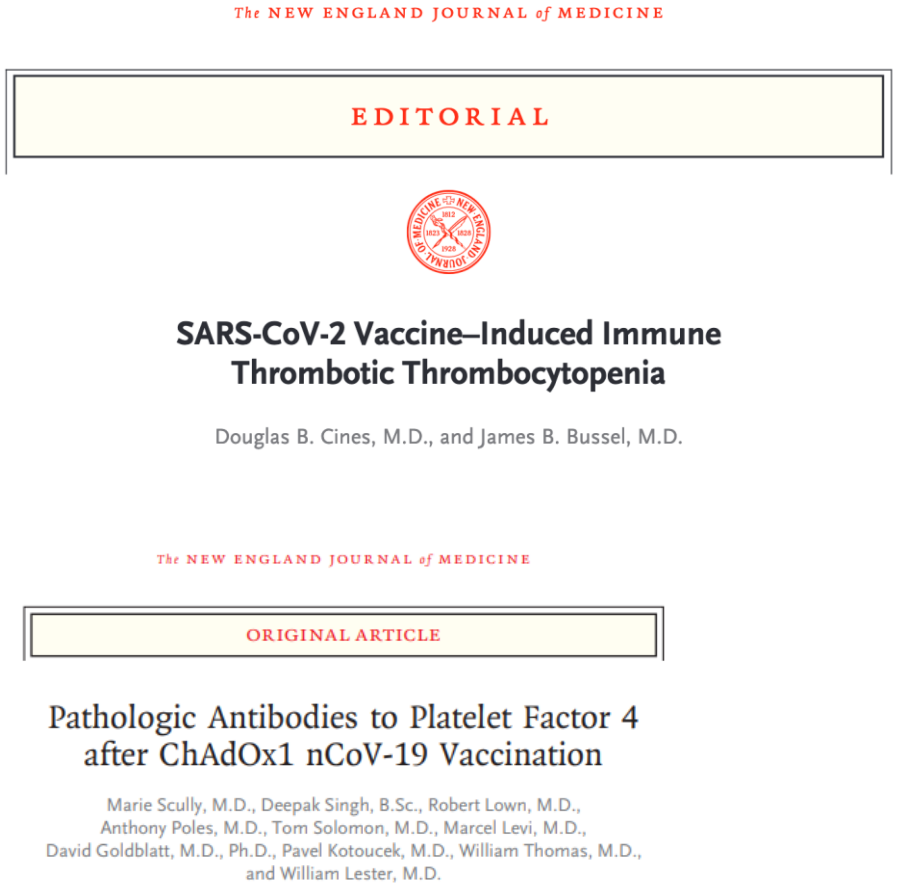
A



B



•. Am J Obstet Gynecol MFM 2021 Sep 20;4(1):100492.



The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

SARS-CoV-2 Vaccine–Induced Immune Thrombotic Thrombocytopenia

Douglas B. Cines, M.D., and James B. Bussel, M.D.

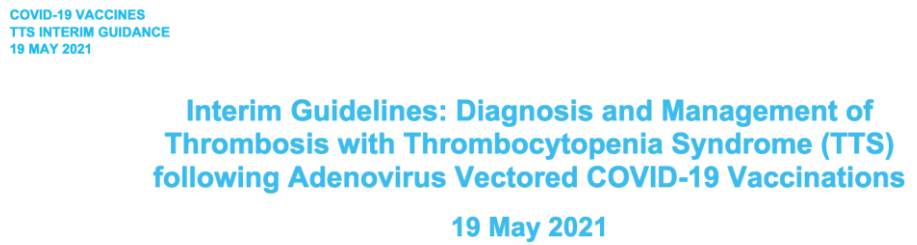
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination

Marie Scully, M.D., Deepak Singh, B.Sc., Robert Lown, M.D., Anthony Poles, M.D., Tom Solomon, M.D., Marcel Levi, M.D., David Goldblatt, M.D., Ph.D., Pavel Kotoucek, M.D., William Thomas, M.D., and William Lester, M.D.

- In the AZ and J&J vaccines, autoantibodies against platelet factor-4 (PF4) polymerize and produce antibodies against PF4, which is known as heparin-induced thrombosis, and clotting occurs by the same mechanism as platelet activation.
- If thrombosis is suspected in the range of 4-20 days post-vaccination, we have to suspect vaccine-induced thrombosis (VIPIT), low platelets, elevated D-dimer, and if possible, antibodies against PF4-heparin with high concentration immunoglobulin.
- Never use heparin, but give danaparoid to prevent coagulation, fibrinogen to compensate for low fibrinogen, and concentrated immunoglobulin.



COVID-19 VACCINES
TTS INTERIM GUIDANCE
19 MAY 2021

Interim Guidelines: Diagnosis and Management of Thrombosis with Thrombocytopenia Syndrome (TTS) following Adenovirus Vectored COVID-19 Vaccinations

19 May 2021

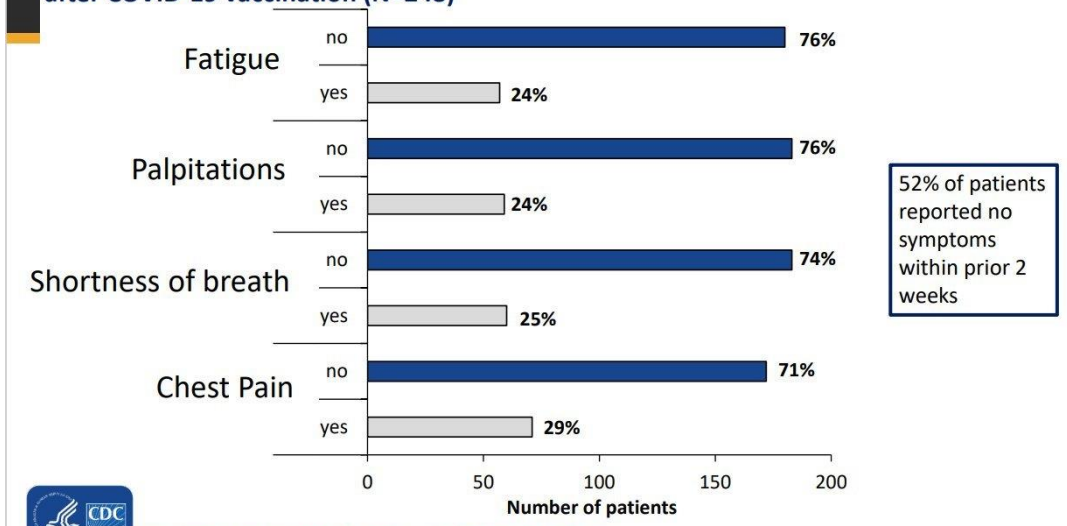
Post-vaccine myocarditis

- After 3 months , patients who visited the outpatient clinic at least once after myocarditis, 40% had no symptoms.
- While 24-29% still had <u>shortness of breath, chest pain, and /or fatigue.</u>

Vaccine Safety Datalink Confirmed Myocarditis/pericarditis 0-21 Days after Any Dose of mRNA Vaccine by Age Group/Product: 3 month follow-up review of Cases with at least 1 follow-up visit since initial episode

3-month chart review status (not mutually exclusive)	12-17 Year-Olds (Pfizer-BioNTech) N=16	18-39 Year-Olds (Pfizer-BioNTech) N=14	18-39 Year-Olds (Moderna) N=18
Recovered, no medication, without exercise restrictions or symptoms	5 (31%)	6 (43%)	9 (50%)
Still symptomatic	4 (25%)	5 (36%)	3 (17%)
Still on medication (primarily NSAIDS, colchicine)	2 (13%)	4 (29%)	7 (39%)
Still on exercise/physical activity restrictions	7 (44%)	2 (14%)	1 (6%)

Patient self-report of symptoms within prior 2 weeks at 3-month follow-up of myocarditis after COVID-19 vaccination (N=248)



https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myo-outcomes.html

20

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-11-2-3/04-COVID-Oster-508.pdf

12.Nov CDC

nature medicine

BRIEF COMMUNICATION

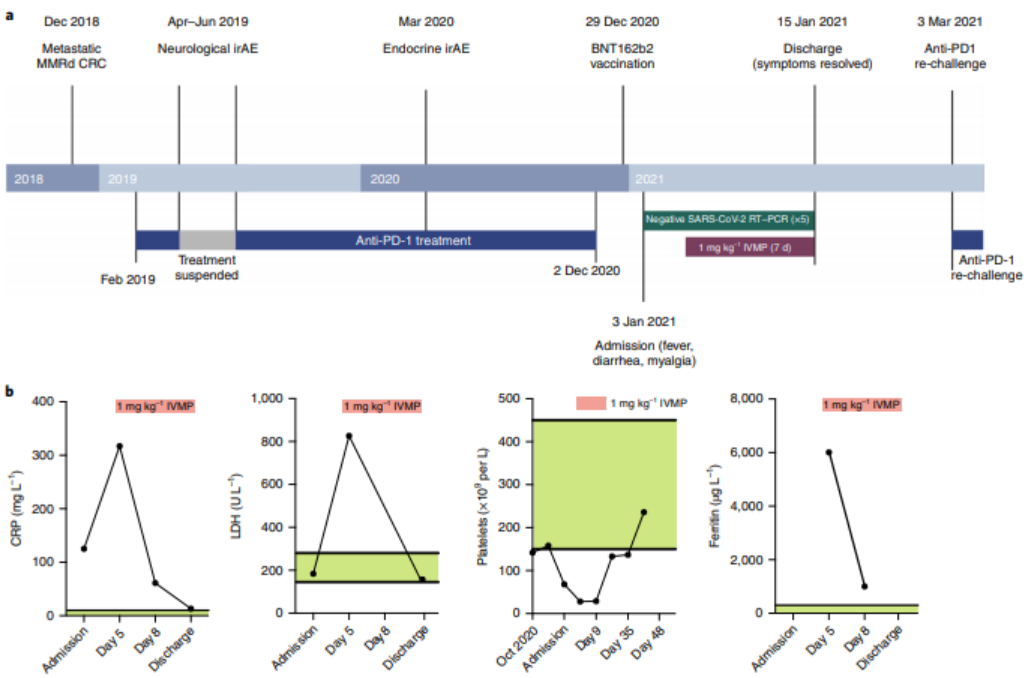
https://doi.org/10.1038/s41591-021-01387-6

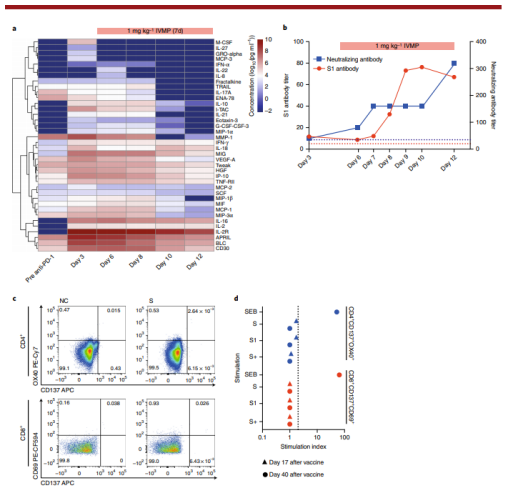
Check for updates

OPEN

Cytokine release syndrome in a patient with colorectal cancer after vaccination with BNT162b2

Lewis Au[1,2,15], Annika Fendler[1,15], Scott T. C. Shepherd[1,2], Karolina Rzeniewicz[1], Maddalena Cerrone[3,4], Fiona Byrne[1], Eleanor Carlyle[2], Kim Edmonds[2], Lyra Del Rosario[2], John Shon[5], Winston A. Haynes[5], Barry Ward[1], Ben Shum[1,2], William Gordon[1], Camille L. Gerard[1,6], Wenyi Xie[1], Nalinie Joharatnam-Hogan[2], Kate Young[2], Lisa Pickering[2], Andrew J. S. Furness[2], James Larkin[2], Ruth Harvey[7], George Kassiotis[8], Sonia Gandhi[9,10], Crick COVID-19 Consortium*, Charles Swanton[11], Charlotte Fribbens[12,13], Katalin A. Wilkinson[3], Robert J. Wilkinson[3,4], David K. Lau[13], Susana Banerjee[14], Naureen Starling[13], Ian Chau[13], CAPTURE Consortium* and Samra Turajlic[1,2]





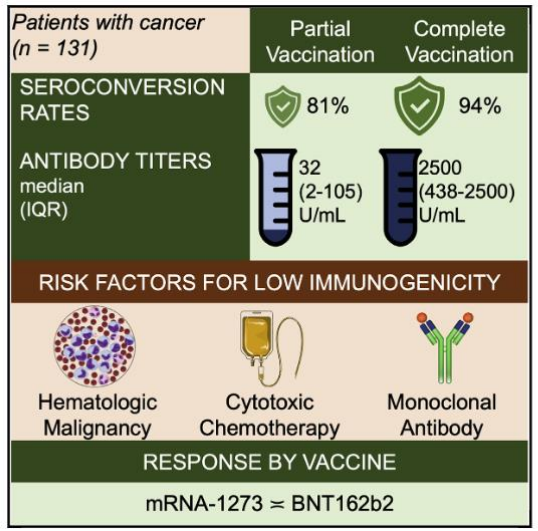
- On the fifth day of the first vaccine in a colorectal cancer patient receiving checkpoint inhibitor therapy, generalized muscle pain, diarrhea, and fever of 38.4° C.
- The patient was admitted a diagnosis of cytokine storm. He was treated with intravenous methylprednisolone.
- His symptoms rapidly improved and was discharged 7 days after treatment.
- Since 5 days after vaccination coincided with the time of immune response, T cells specific for the spike were releasing cytokines to develop cytokine storm.

Cancer Cell

Article

Immunogenicity of SARS-CoV-2 messenger RNA vaccines in patients with cancer

Graphical abstract



Authors

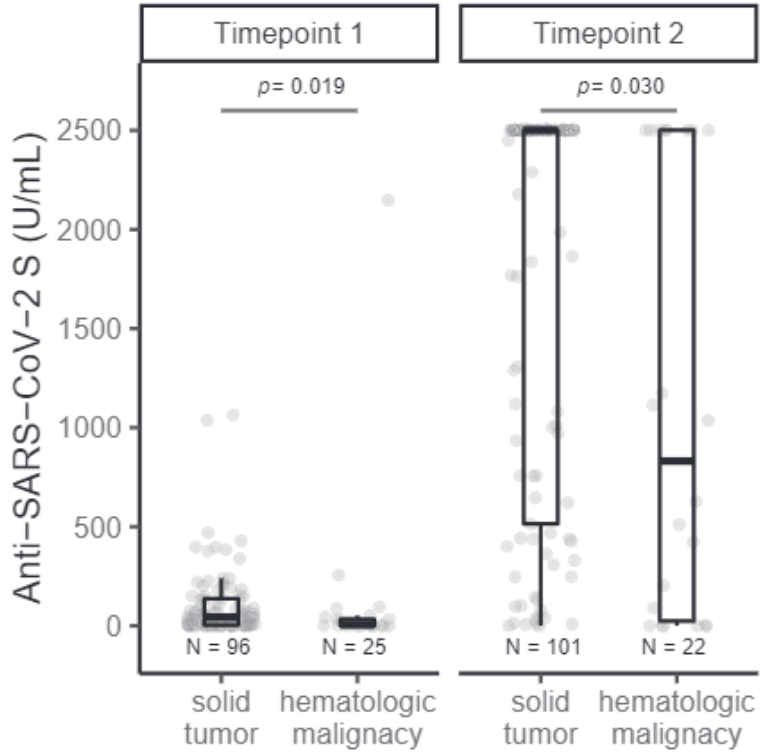
Alfredo Addeo, Pankil K. Shah, Natacha Bordry, ..., Kate Lathrop, Nicolas Mach, Dimpy P. Shah

Correspondence

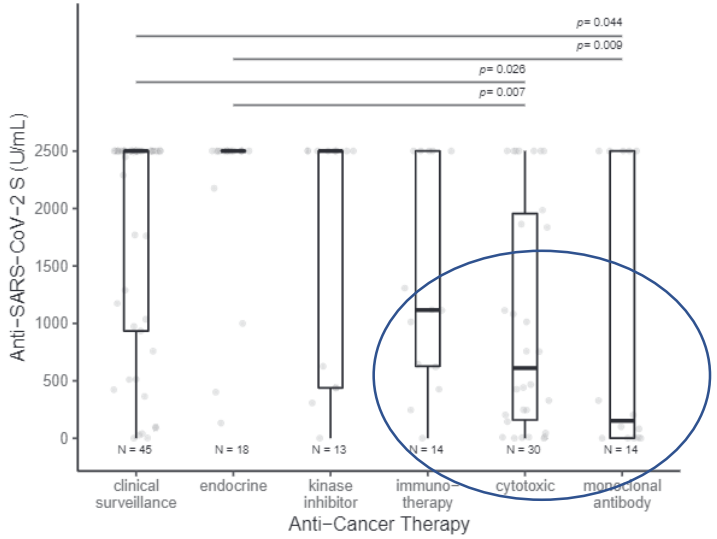
alfredo.addeo@hcuge.ch (A.A.), shahdp@uthscsa.edu (D.P.S.)

In brief

Addeo et al. show patients with cancer have poor antibody response after one dose and excellent antibody response at 3 weeks after two doses with mRNA COVID-19 vaccines. A subset of immunocompromised patients (i.e., those receiving anti-CD20), are at high risk for not developing antibodies post-vaccination.



- mRNA vaccination causes high seroconversion in carriers
- A second dose of vaccine is important to increase antibody levels.
- Patients with hematologic malignancies are more likely to fail to respond to the vaccine.
- <u>Patients receiving rituximab (anti CD20) did not develop antibodies after two doses of vaccine</u>.



Article

Untimely TGFβ responses in COVID-19 limit antiviral functions of NK cells

https://doi.org/10.1038/s41586-021-04142-6

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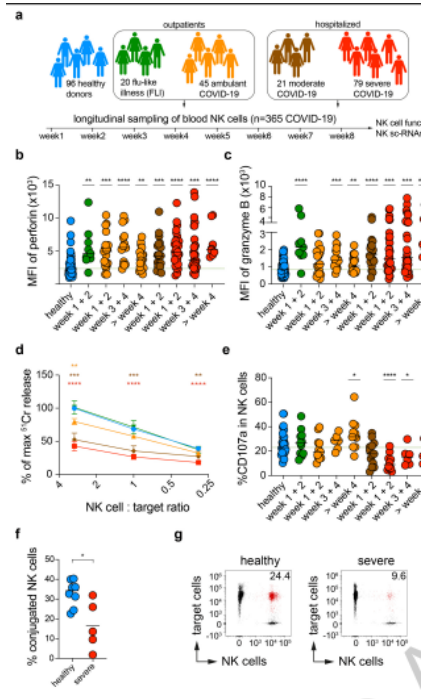

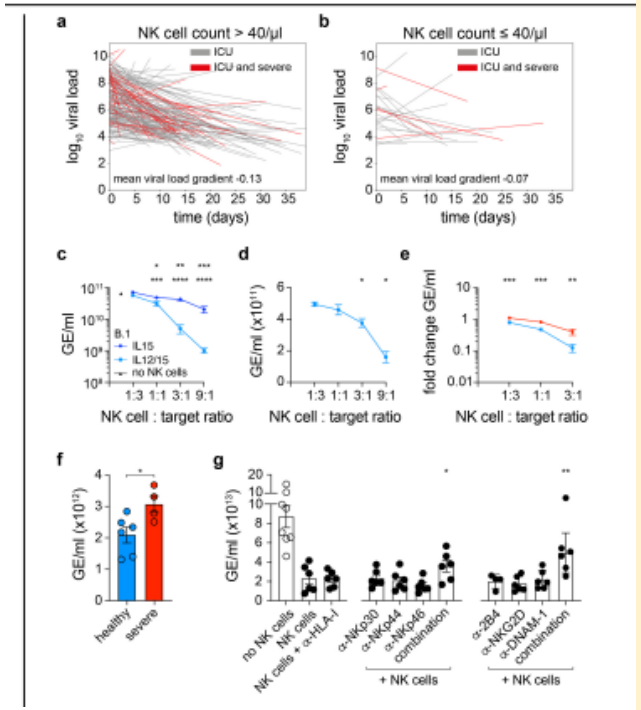

- ✓ TGFβ is inappropriately increased in severe COVID-19 early in infection, inhibiting NK cell function and early viral defense
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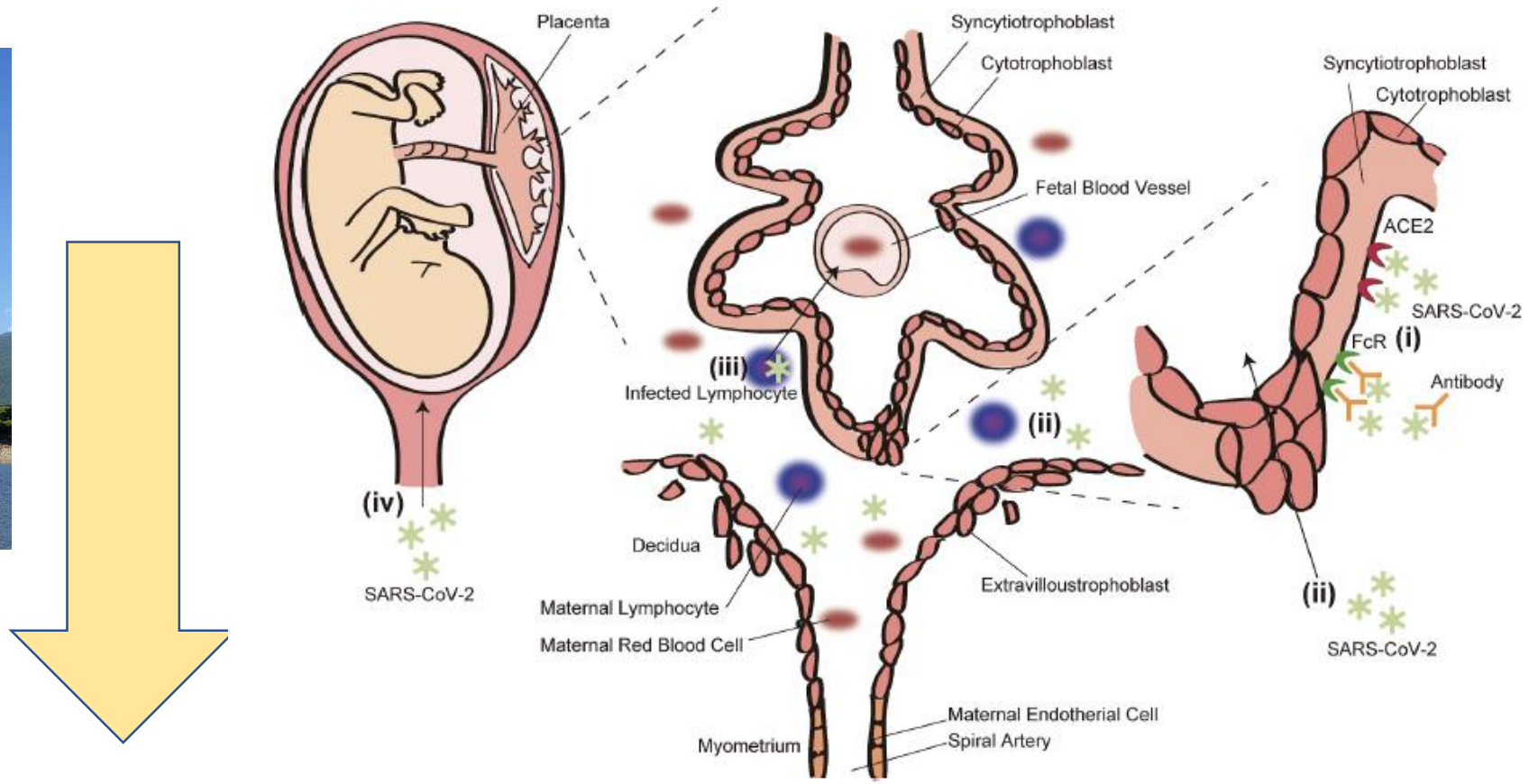
Nature. Oct 25, 2021. (doi.org/10.1038/s41586-021-04142-6)

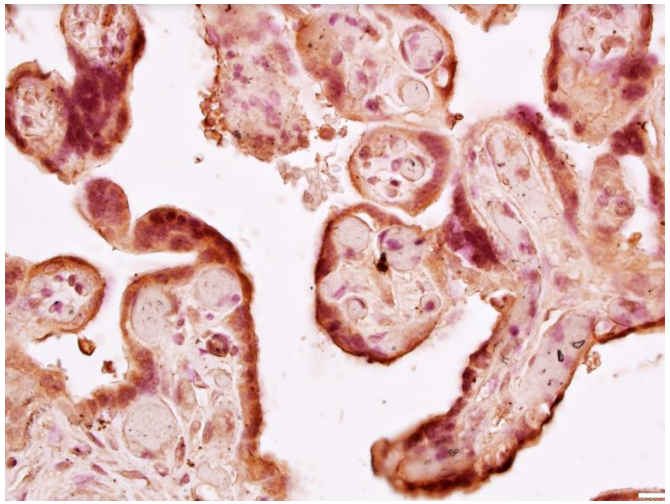
Most **fetuses are protected** from in utero infection



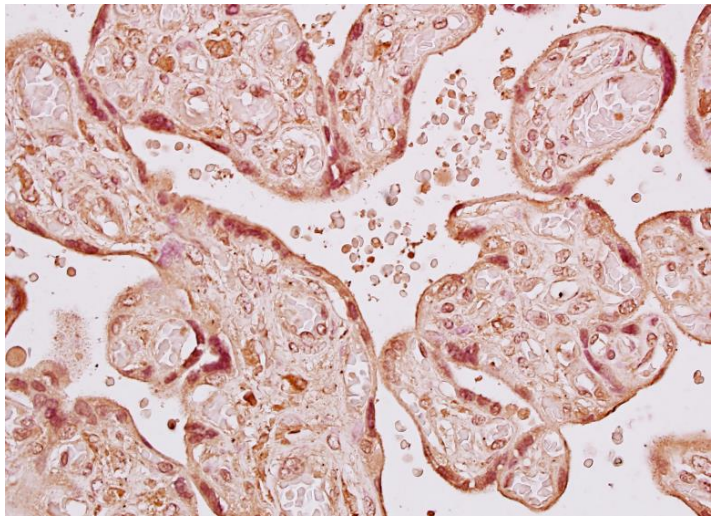
Placental fortress against SARS-CoV-2

Komine-Aizawa S, Takada K, Hayakawa S.
Placenta, 2020

A case of intrauterine fetal death at 35 weeks of pregnancy



Stillbirth placenta



Control placenta

Fetal organs obtained by autopsy

- ✓Lung PCR(-)
- ✓Kidney PCR(-)
- ✓Liver PCR(-)
- ✓Intestine PCR(-)
- ✓Lymph nodes PCR(-)
- ✓Spleen PCR (-)

Twin delivery (29 weeks of gestation) emergent Caesarean section for acute fetal distress

- Cord Blood

neonate 1 PCR(-) IgG Ab(-) IgM Ab(-)

neonate 2 PCR(-) IgG Ab(-) IgM Ab(-)

- Maternal blood

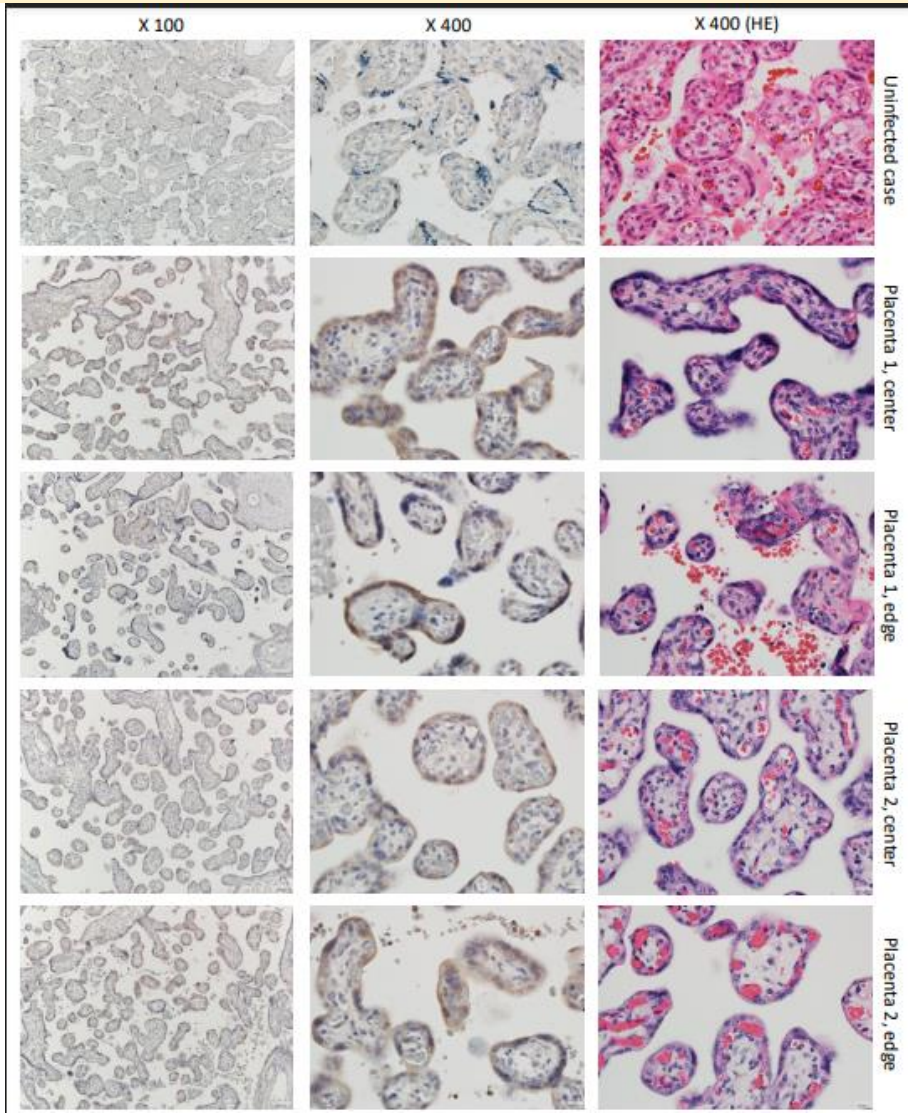
PCR(+) IgG Ab(+) IgM Ab(+)

- Placenta

PCR(++) Antigen(++)

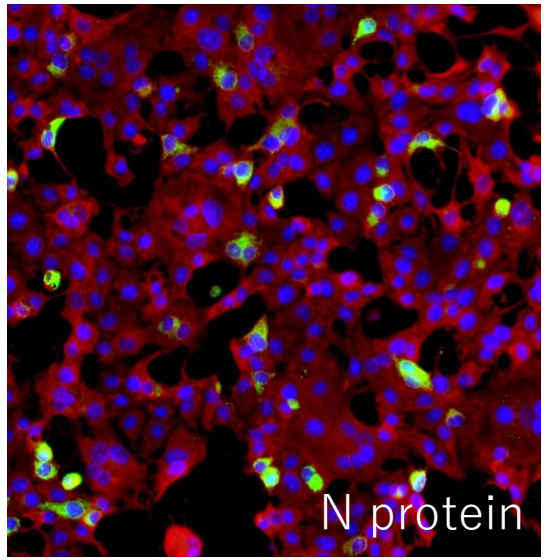
- Breast Milk

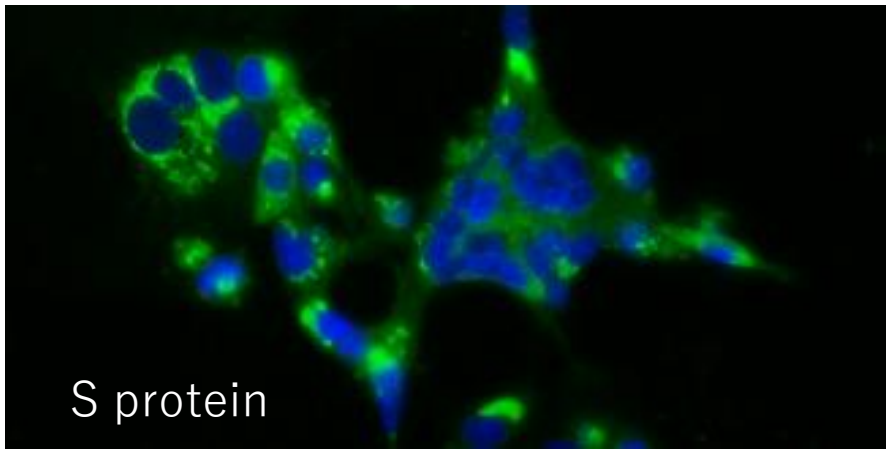
PCR(-)



Molecular and immunohistochemical localization of SARS-CoV-2 genes or antigens in placenta

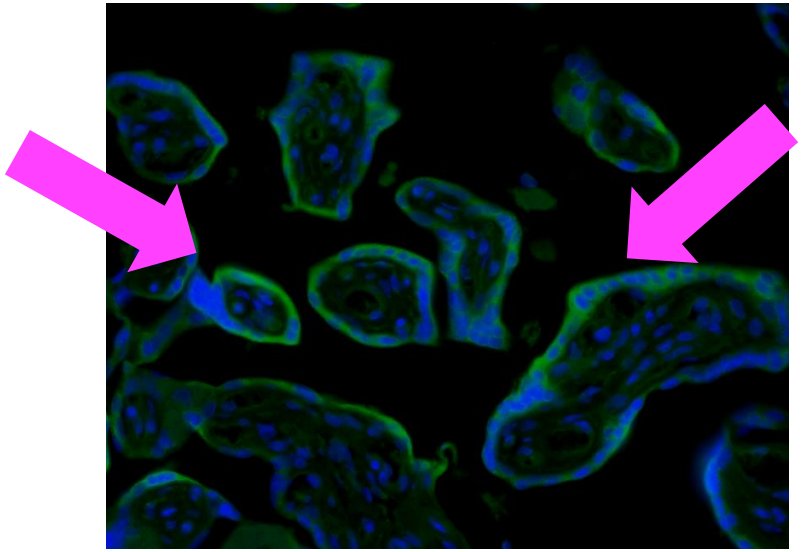
- Placental sampling by Caesarean section or vaginal delivery
- PCR detection of viral genome and immunohistochemistry (immunofluorescent or Enzymatic detection)
- Routine pathological examinations



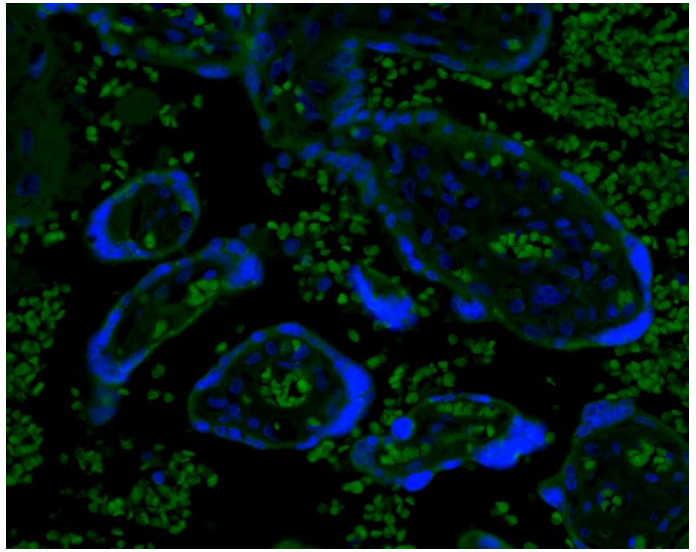


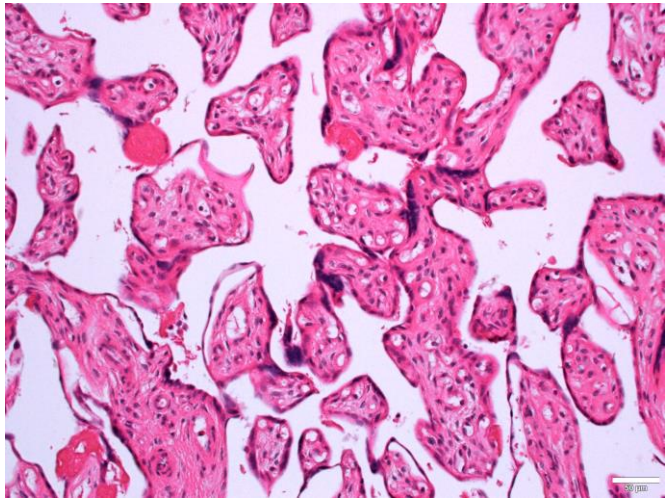
Localization of SARS-CoV-2 spike protein in the placenta collected from a COVID-19 infected mother term C/S

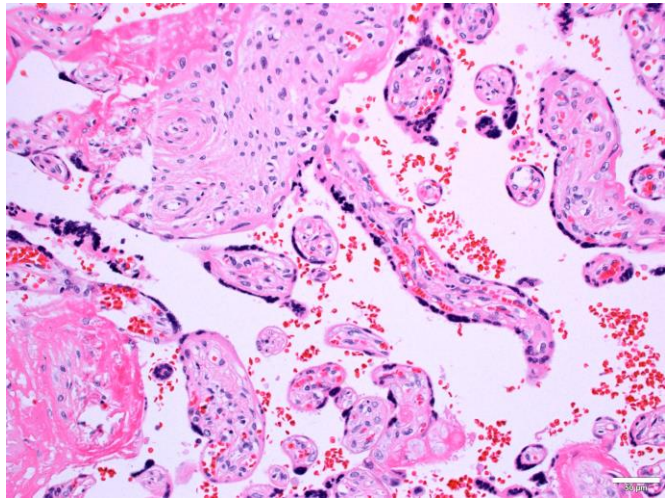
COVID-19 (+)



COVID-19 (-)







Fortunately, the neonate was COVID-19 negative

GFP: SARS-CoV-2 spike protein
DAPI: nuclei

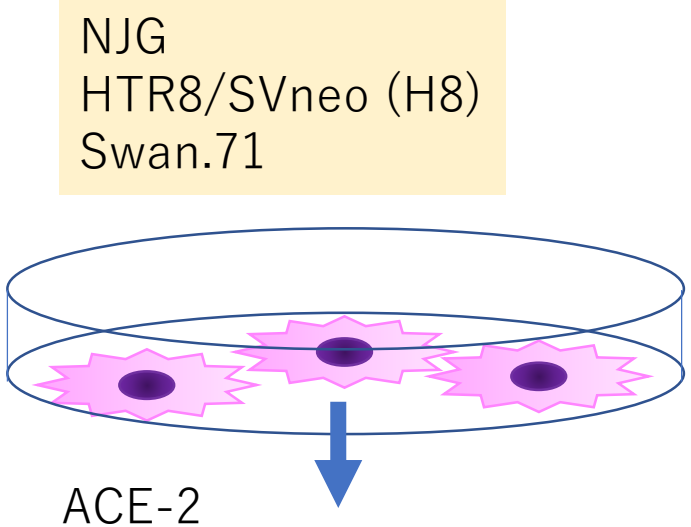
Materials and Methods

- VeroE6/TMPRSS2

- Trophoblast cell lines

Bewo
JEG-3
NJG
HTR8/SVneo (H8)
Swan.71

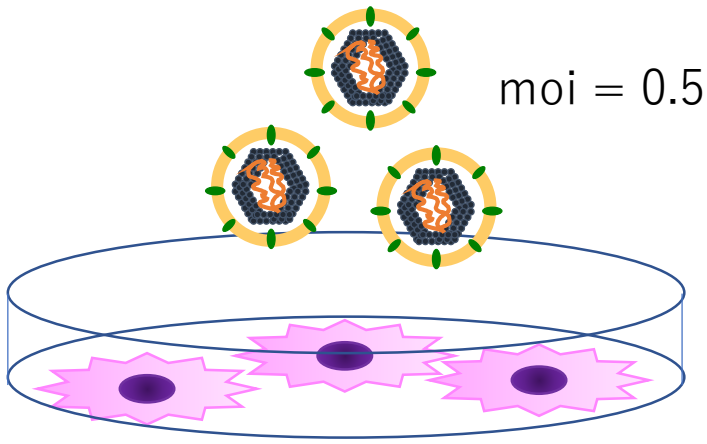
Forskolin



ACE-2
TMPRSS2

- WB
  - anti-ACE-2 antibody (abcam)
  - anti-TMPRSS2 antibody (abcam)

SARS-CoV-2
(WK-521)



moi = 0.5 to 1

multiplicity of infection (moi)

- RT-qPCR

  N set

N_Sarbeco_F1	CACATTGGCACCCGCAATC
N_Sarbeco_R1	GAGGAACGAGAAGAGGCTTG
N_Sarbeco_P1	FAM-ACTTCCTCAAGGAACAACATTGCCA-BHQ

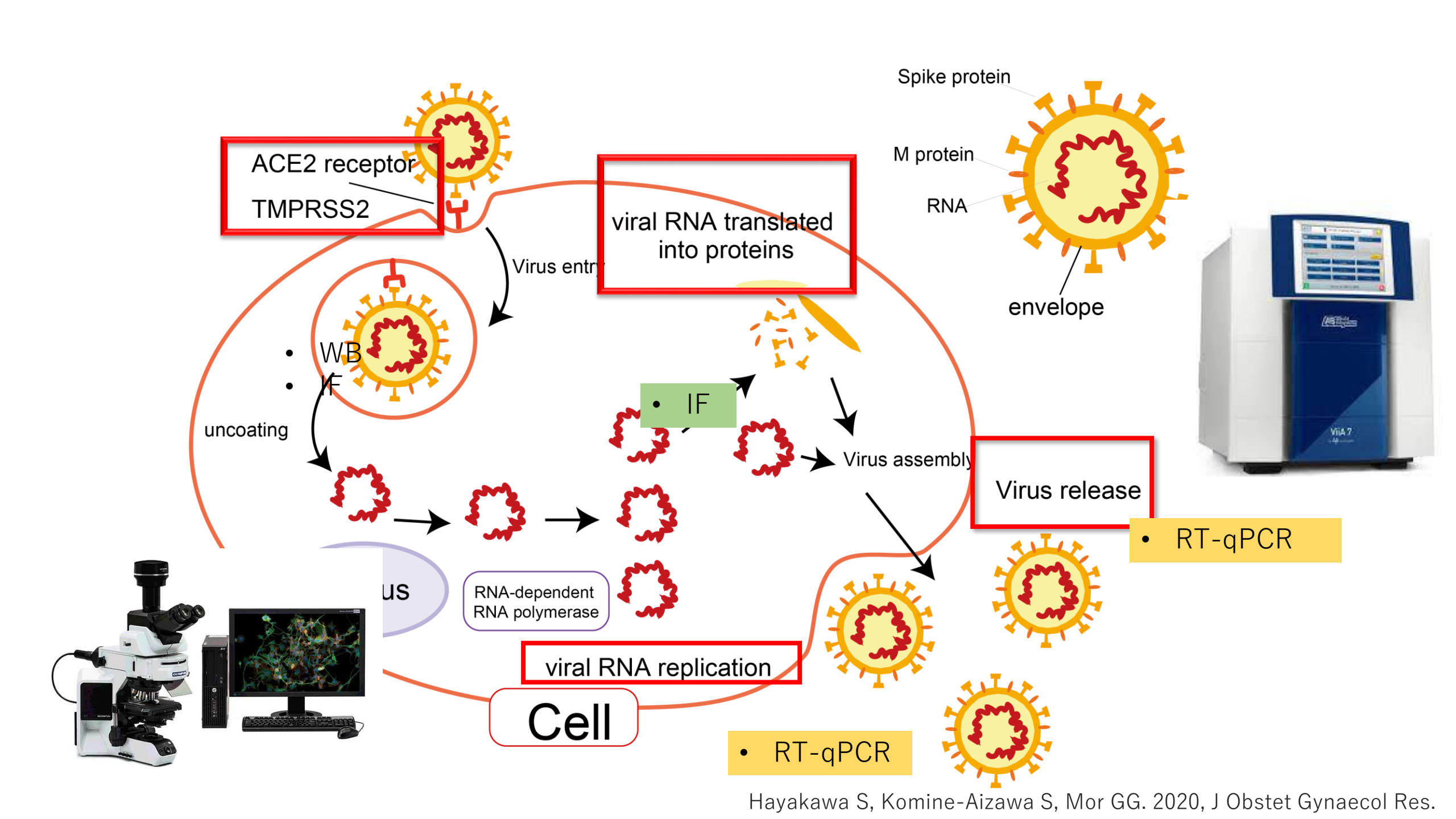
  N2 set

NIID_2019-nCOV_N_F2	AAATTTTGGGGACCAGGAAC
NIID_2019-nCOV_N_R2	TGGCAGCTGTGTAGGTCAAC
NIID_2019-nCOV_N_P2	FAM-ATGTCGCGCATTGGCATGGA-BHQ

- IF

  anti-spike protein antibody (Abcam)

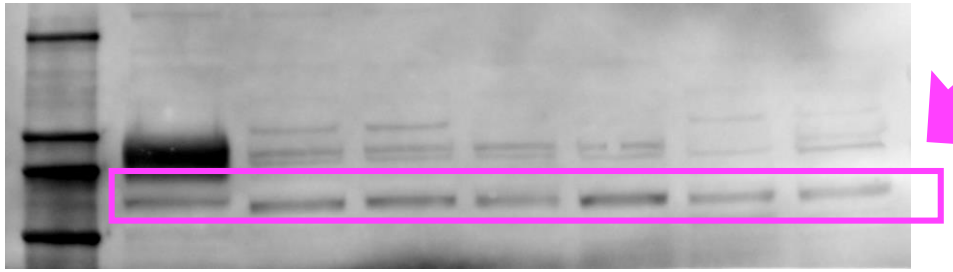
Ethical committee approval number: RK-200512-9, P20-22-0
Bio-risk management and control committee approval number: 2020-5-0



Hayakawa S, Komine-Aizawa S, Mor GG. 2020, J Obstet Gynaecol Res.

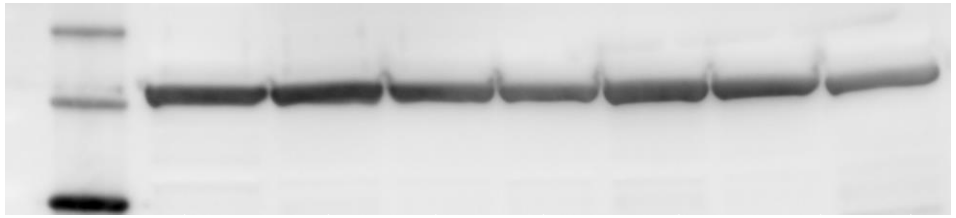
Trophoblast cell lines express ACE 2 and TMPRSS2

ACE 2(90 kDa)



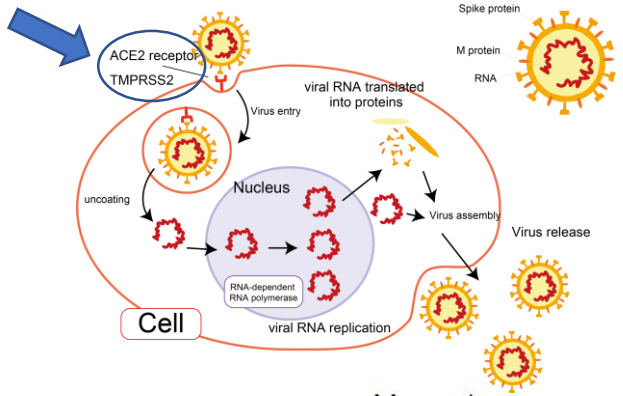
TMPRSS2(54 kDa)

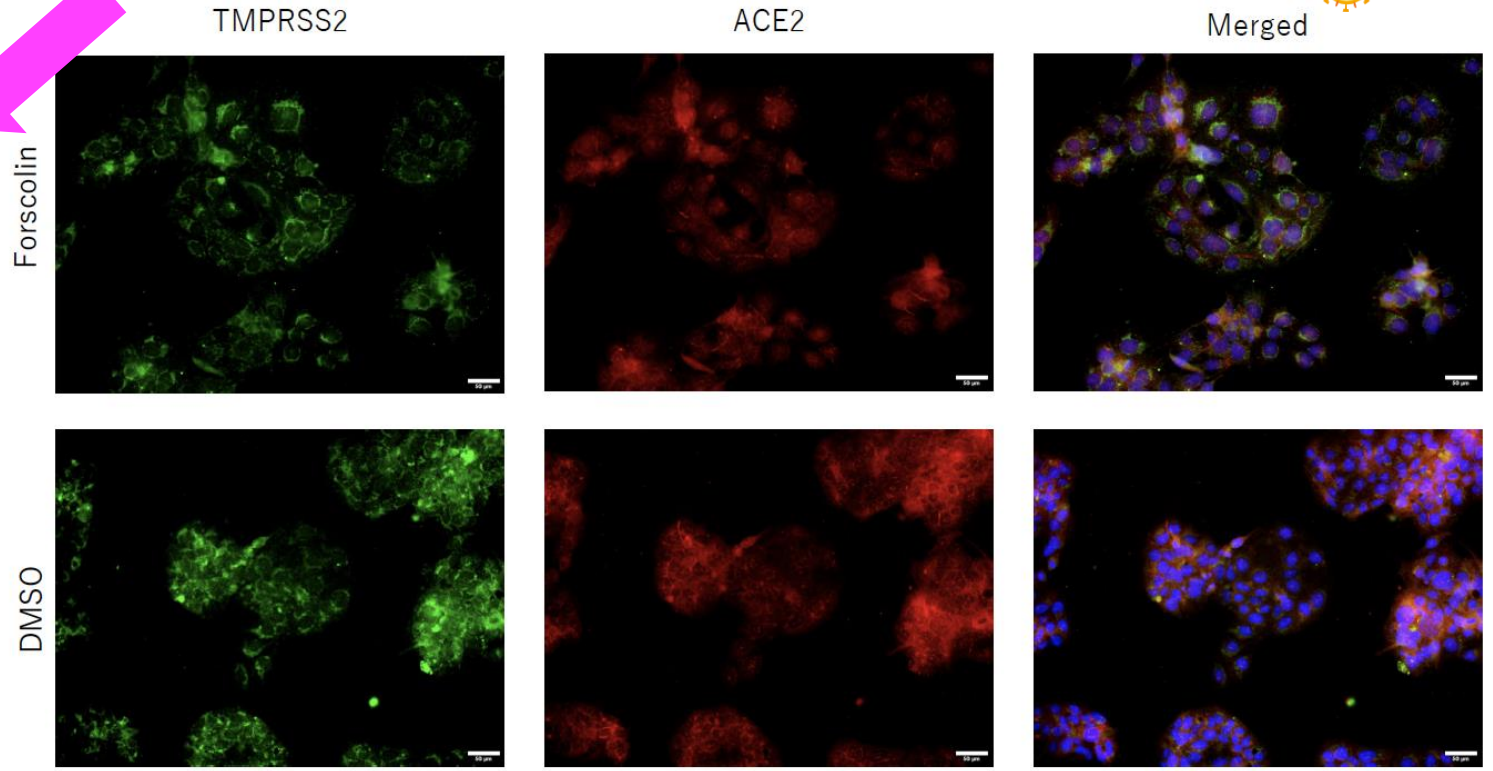
α-tubulin(50 kDa)



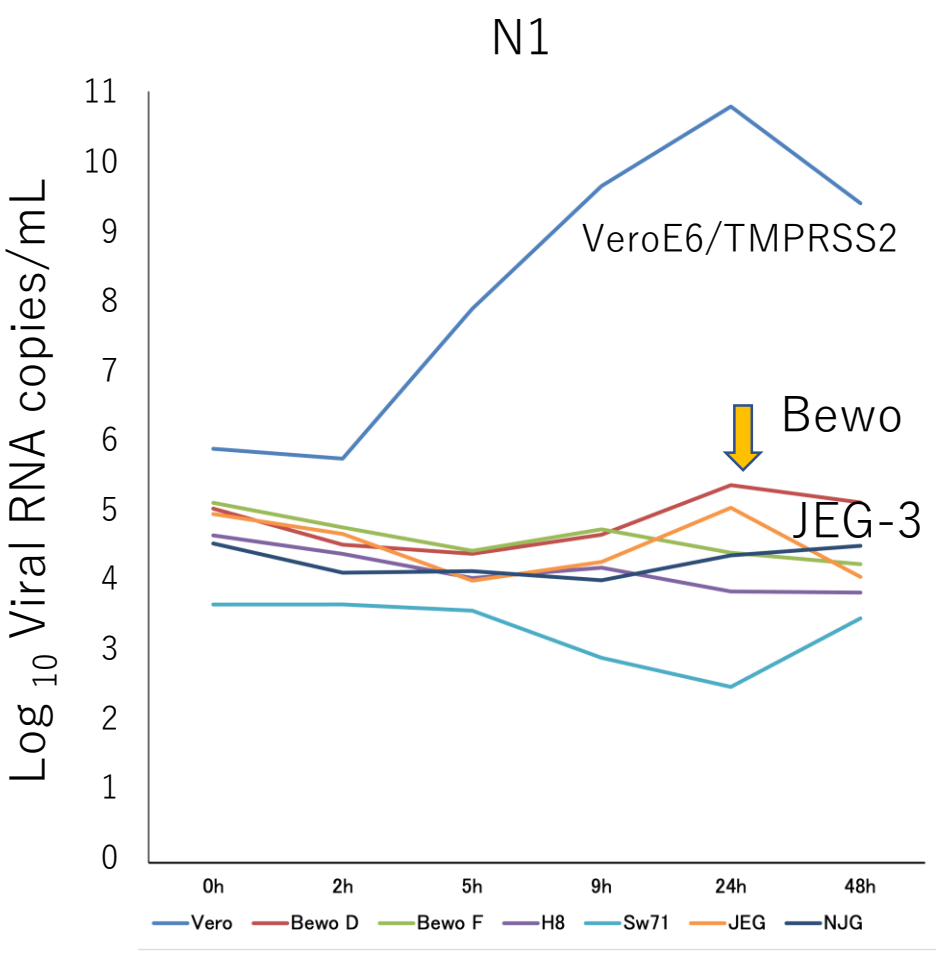
VeroE6/ TMPRSS2 | Bewo D | Bewo F | HTR8/ SVneo | Sw.71 | JEG-3 | NJG

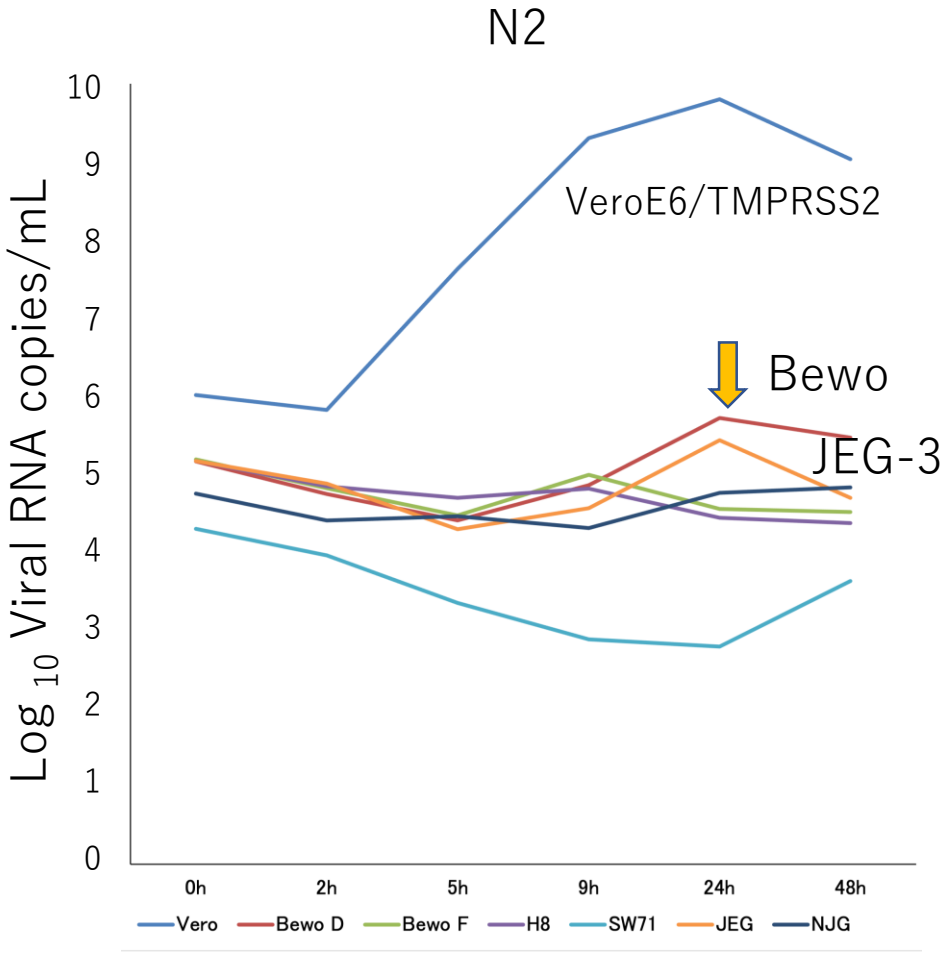
Bewo

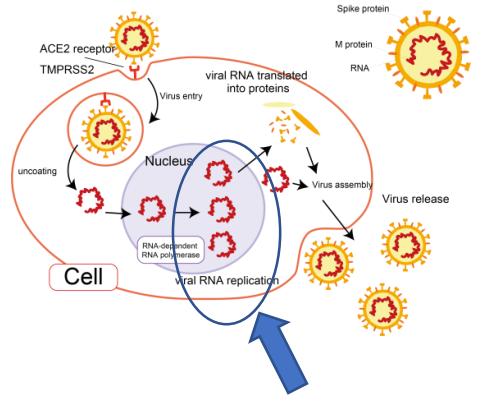




The replications of SARS-CoV-2 in trophoblast cell lines were limited comparing VeroE6/TMPRSS2 cells.







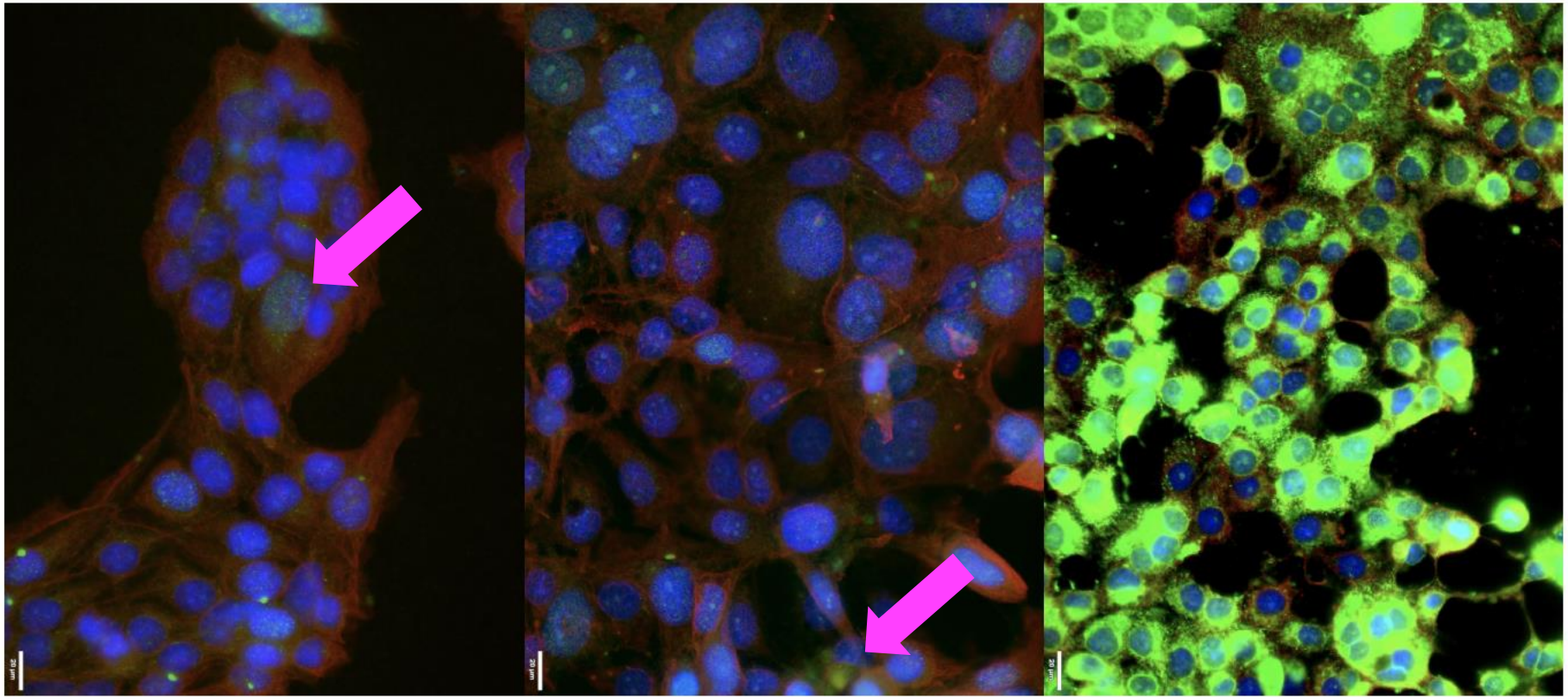
Intracellular localization of the SARS-CoV-2 spike protein

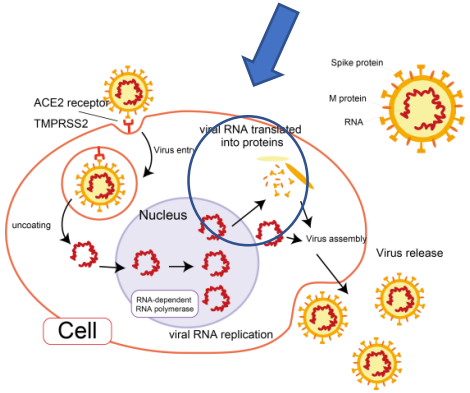
Bewo

Forskolin (-)

Forskolin (+)

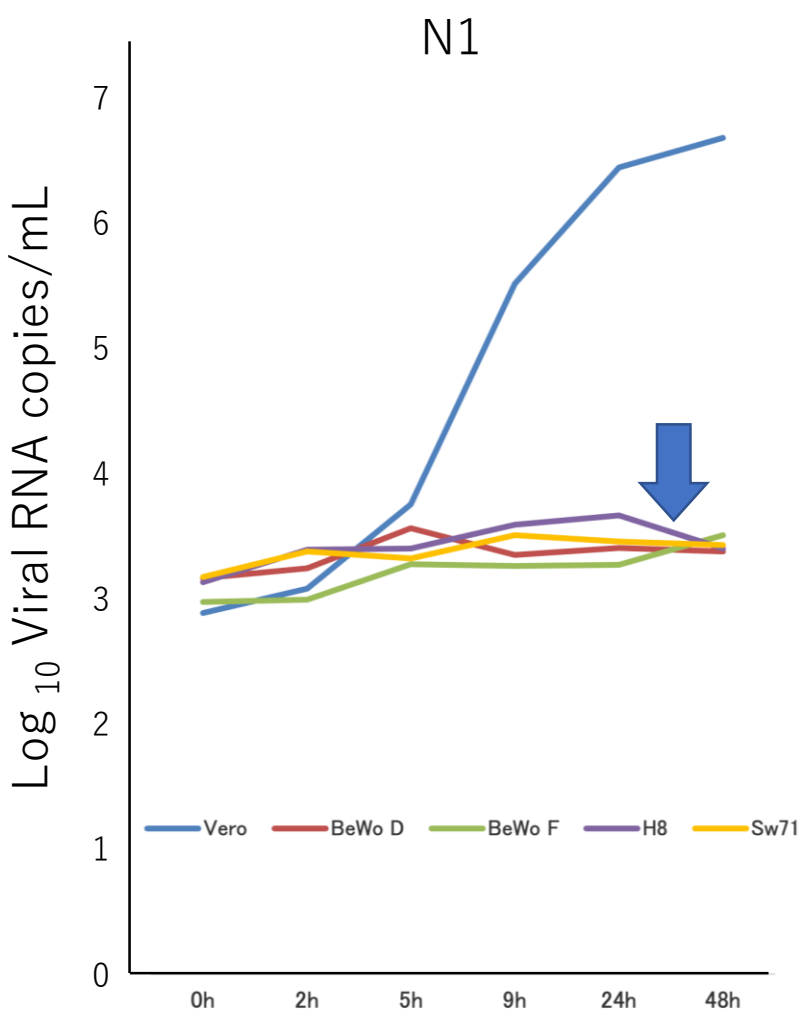
VeroE6/TMPRSS2

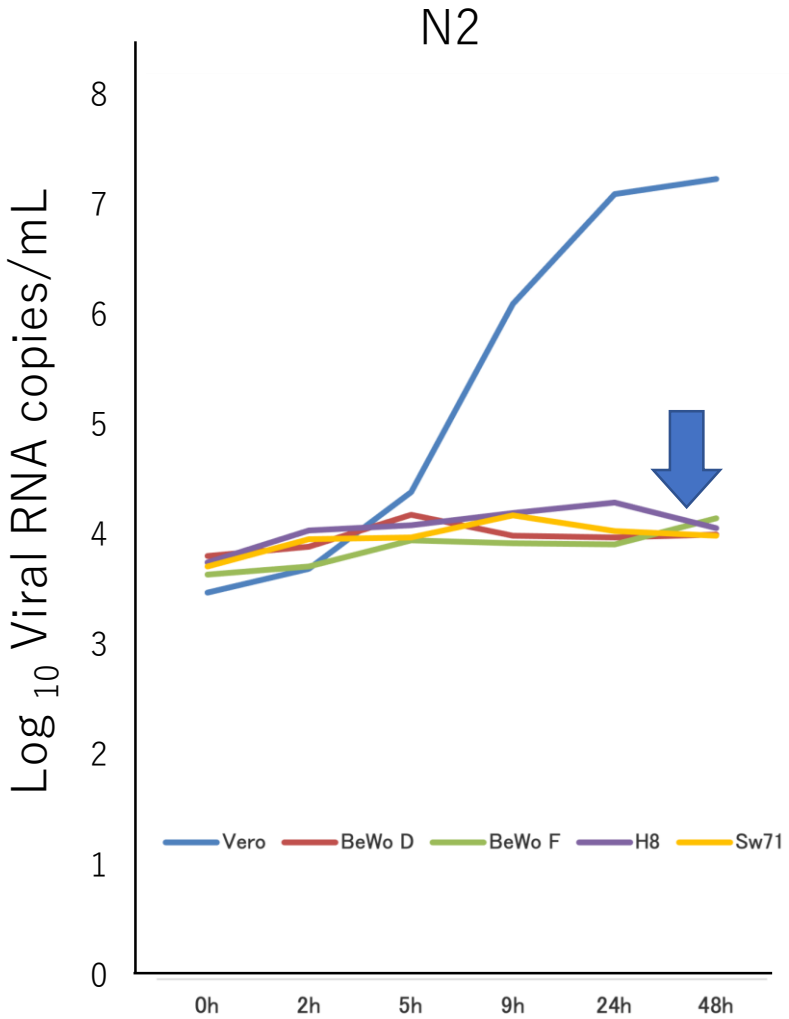


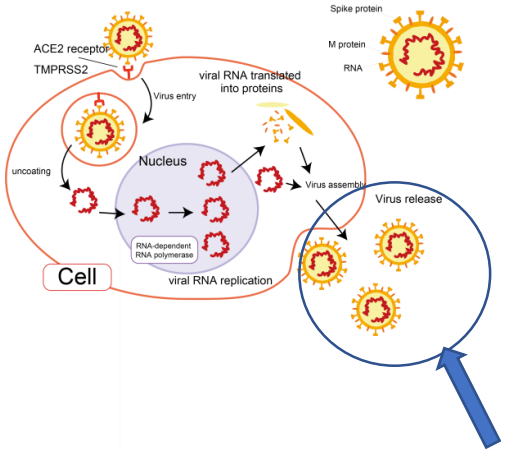


Green: SARS-CoV-2 spike protein
Red: cytokeratin
Blue: nuclei

SARS-CoV-2 release from trophoblast cell lines were limited comparing highly proliferative VeroE6/TMPRSS2 cells.

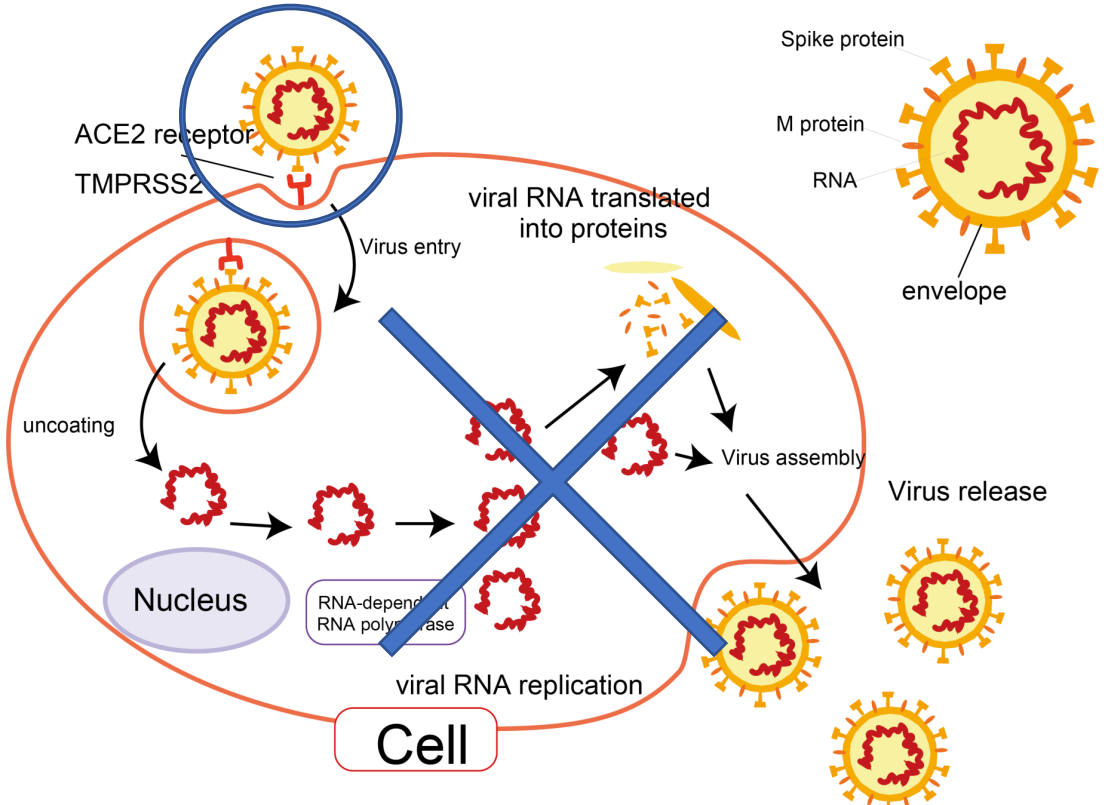






Results

- Trophoblast cell lines expressed ACE 2 and TMPRSS2.
- The viral RNA replication was repressed in most trophoblast cell lines.
- Forskolin induced differentiation of Bewo cells might increase SARS-CoV-2 susceptibility but does not induce viral release



Syncytial trophoblasts can be infected with SARS-CoV-2 scarcely, but it is an abortive infection

Pathogens and the Placental Fortress

Jennifer R. Robbins[1,2,4] and **Anna I. Bakardjiev**[1,2,3]

[1]Department of Pediatrics, University of California, San Francisco, California, USA

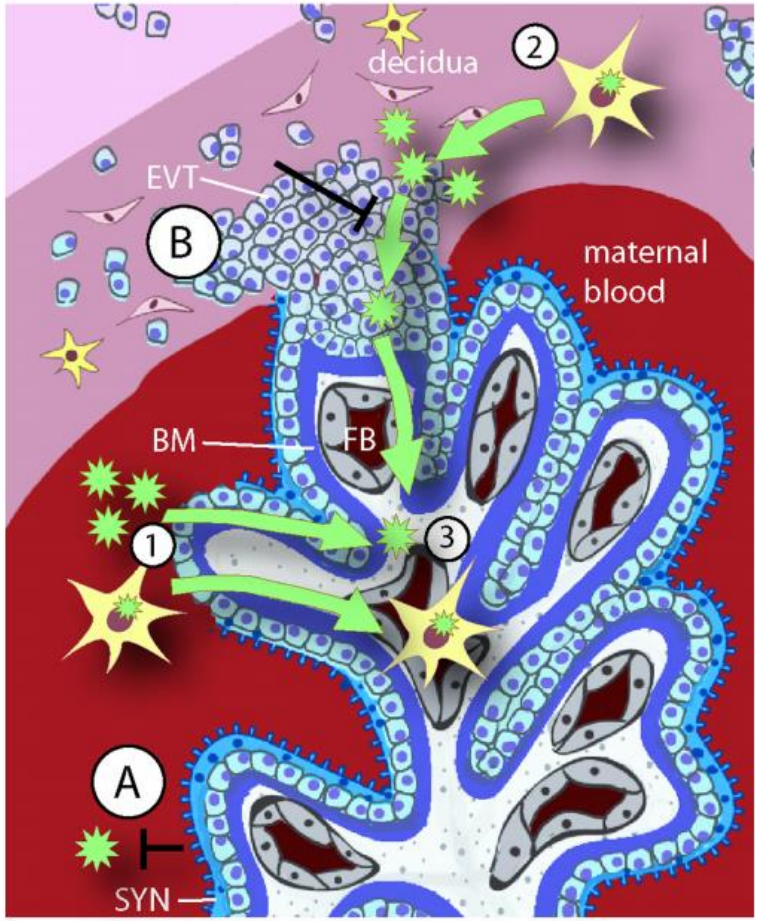
[2]Program in Microbial Pathogenesis and Host Defense, University of California, San Francisco, California, USA

[3]Biomedical Sciences Program, University of California, San Francisco, California, USA

[4]Department of Biology, Xavier University, Cincinnati, Ohio, USA

Curr Opin Microbiol
2012 Feb;15(1):36-43

- The placenta presents multiple defenses against pathogens
- The syncytiotrophoblast lacks intercellular junctions that contribute to pathogen resistance
- The uterine-trophoblast environment is rich in innate cellular defenses
- The few pathogens that can circumvent these barriers have intracellular life cycles



H11/HSPB8 Restricts HIV-2 Vpx to Restore the Anti-Viral Activity of SAMHD1

*Ayumi Kudoh[1], Kei Miyakawa[1], Satoko Matsunaga[1], Yuki Matsushima[2], Isao Kosugi[3], Hirokazu Kimura[4], Satoshi Hayakawa[5], Tatsuya Sawasaki[6] and Akihide Ryo[1]**

- Among 620 protein kinases, we have identified H11/HSPB8 as a Vpx-binding protein that negatively regulates the stability and function of Vpx
- Targeted knockdown of H11/HSPB8 in human trophoblast cells, restored the expression and function of Vpx and subsequent replication of HIV-2

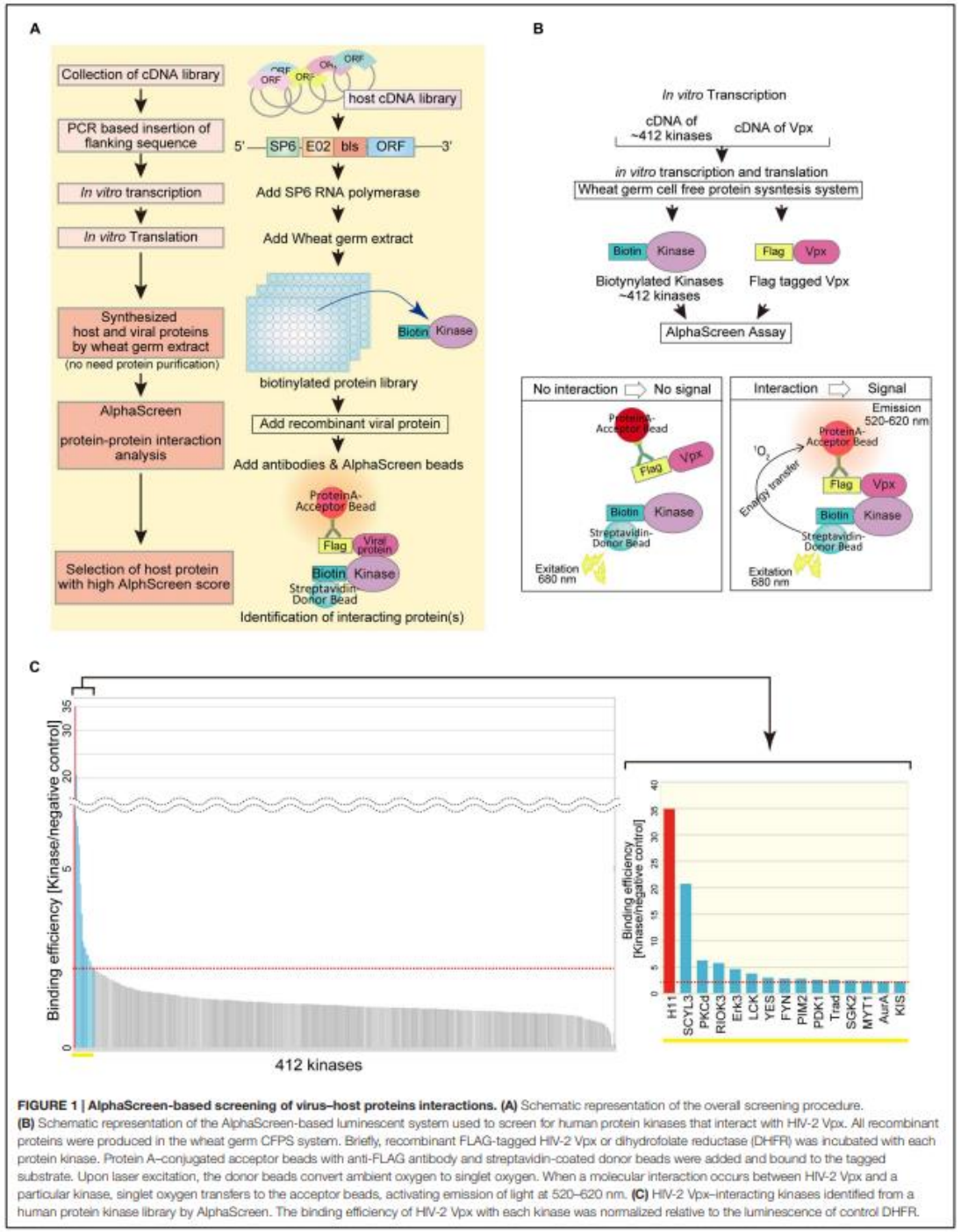


FIGURE 1 | AlphaScreen-based screening of virus–host proteins interactions. (A) Schematic representation of the overall screening procedure. **(B)** Schematic representation of the AlphaScreen-based luminescent system used to screen for human protein kinases that interact with HIV-2 Vpx. All recombinant proteins were produced in the wheat germ CFPS system. Briefly, recombinant FLAG-tagged HIV-2 Vpx or dihydrofolate reductase (DHFR) was incubated with each protein kinase. Protein A–conjugated acceptor beads with anti-FLAG antibody and streptavidin-coated donor beads were added and bound to the tagged substrate. Upon laser excitation, the donor beads convert ambient oxygen to singlet oxygen. When a molecular interaction occurs between HIV-2 Vpx and a particular kinase, singlet oxygen transfers to the acceptor beads, activating emission of light at 520–620 nm. **(C)** HIV-2 Vpx–interacting kinases identified from a human protein kinase library by AlphaScreen. The binding efficiency of HIV-2 Vpx with each kinase was normalized relative to the luminescence of control DHFR.

Front Microbiol 2016 Jun 13;7:883

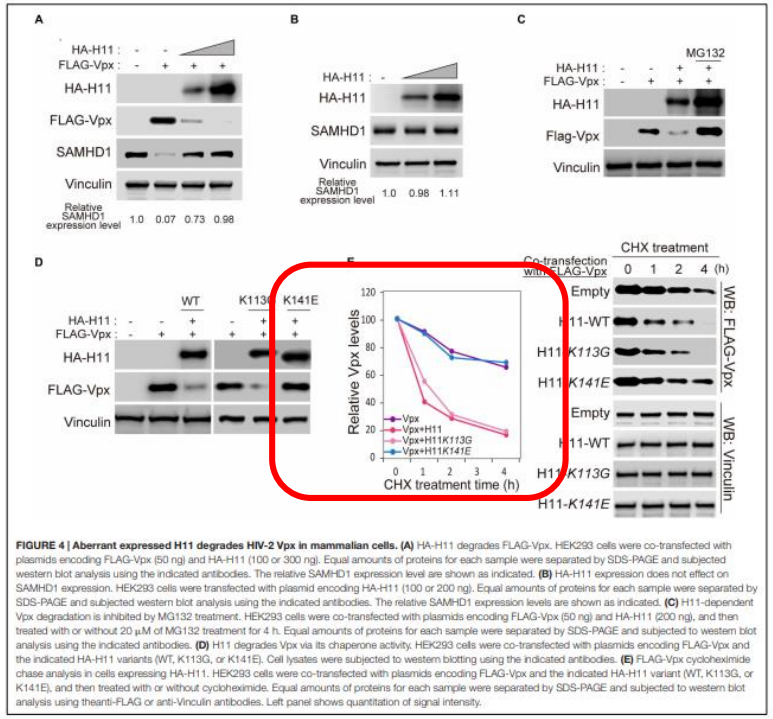


FIGURE 4 | Aberrant expressed H11 degrades HIV-2 Vpx in mammalian cells. (A) HA-H11 degrades FLAG-Vpx. HEK293 cells were co-transfected with plasmids encoding FLAG-Vpx (50 ng) and HA-H11 (100 or 300 ng). Equal amounts of proteins for each sample were separated by SDS-PAGE and subjected western blot analysis using the indicated antibodies. The relative SAMHD1 expression level are shown as indicated. **(B)** HA-H11 expression does not effect on SAMHD1 expression. HEK293 cells were transfected with plasmid encoding HA-H11 (100 or 200 ng). Equal amounts of proteins for each sample were separated by SDS-PAGE and subjected western blot analysis using the indicated antibodies. The relative SAMHD1 expression levels are shown as indicated. **(C)** H11-dependent Vpx degradation is inhibited by MG132 treatment. HEK293 cells were co-transfected with plasmids encoding FLAG-Vpx (50 ng) and HA-H11 (200 ng), and then treated with or without 20 μM of MG132 treatment for 4 h. Equal amounts of proteins for each sample were separated by SDS-PAGE and subjected to western blot analysis using the indicated antibodies. **(D)** H11 degrades Vpx via its chaperone activity. HEK293 cells were co-transfected with plasmids encoding FLAG-Vpx and the indicated HA-H11 variants (WT, K113G, or K141E). Cell lysates were subjected to western blotting using the indicated antibodies. **(E)** FLAG-Vpx cycloheximide chase analysis in cells expressing HA-H11. HEK293 cells were co-transfected with plasmids encoding FLAG-Vpx and the indicated HA-H11 variant (WT, K113G, or K141E), and then treated with or without cycloheximide. Equal amounts of proteins for each sample were separated by SDS-PAGE and subjected to western blot analysis using theanti-FLAG or anti-Vinculin antibodies. Left panel shows quantitation of signal intensity.

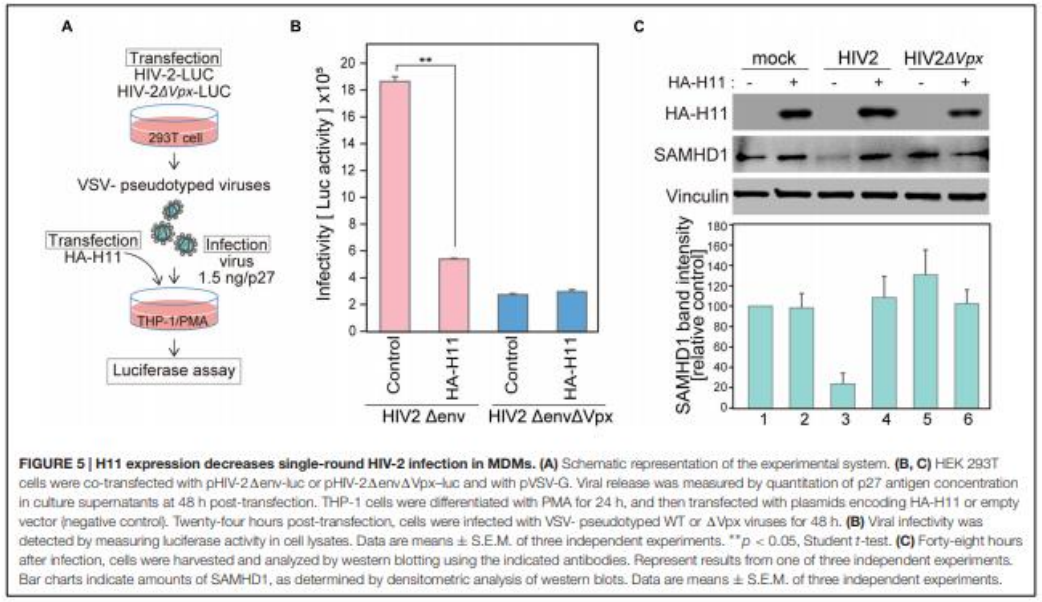
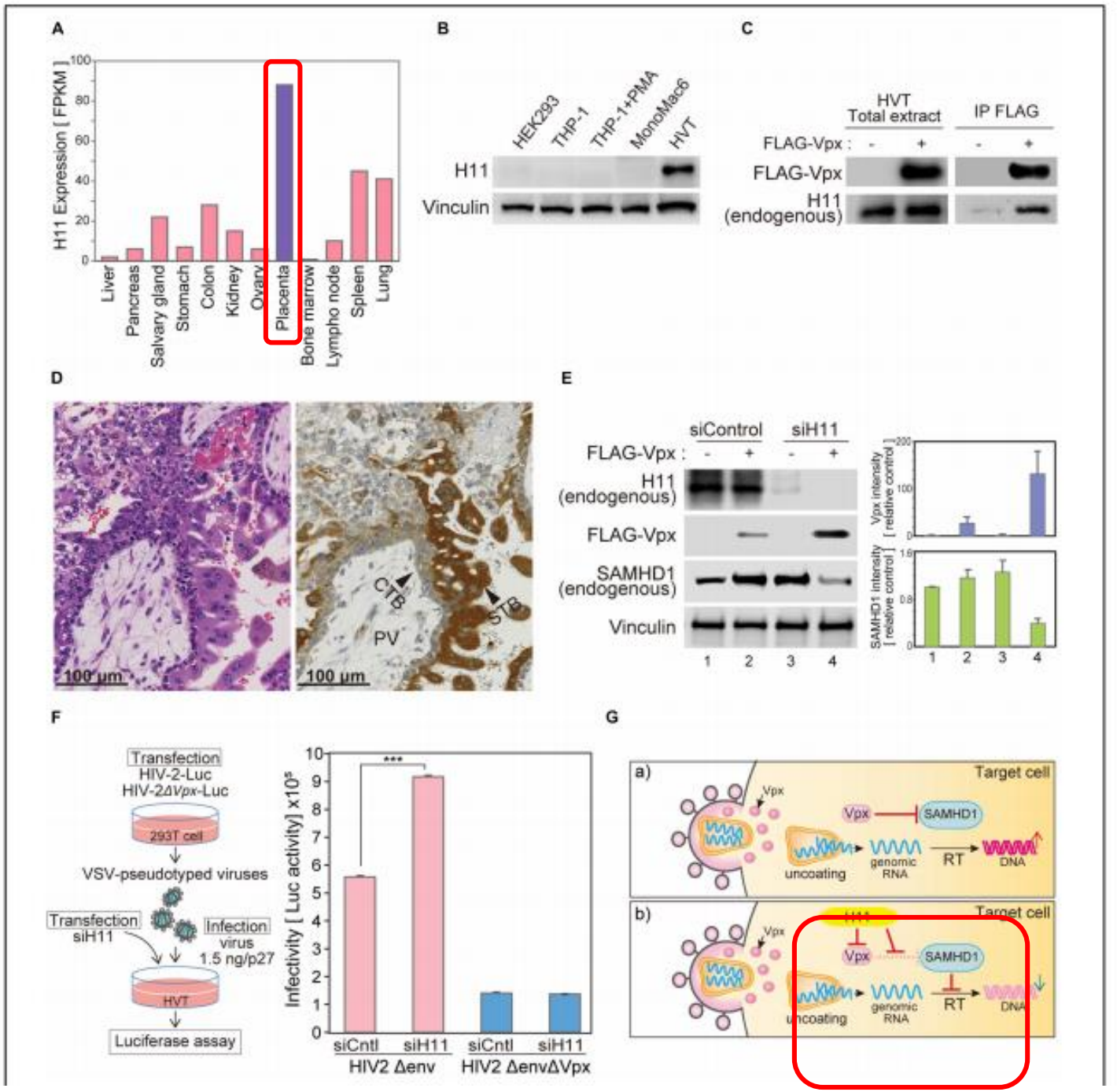


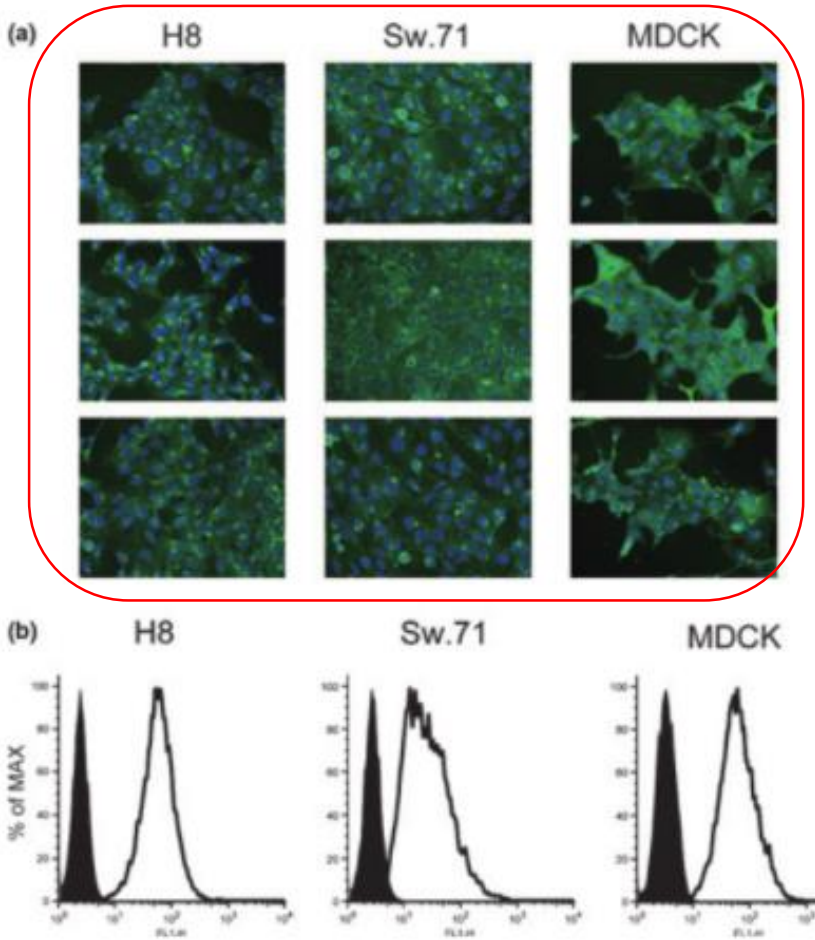
FIGURE 5 | H11 expression decreases single-round HIV-2 infection in MDMs. (A) Schematic representation of the experimental system. **(B, C)** HEK 293T cells were co-transfected with pHIV-2Δenv-luc or pHIV-2ΔenvΔVpx-luc and with pVSV-G. Viral release was measured by quantitation of p27 antigen concentration in culture supernatants at 48 h post-transfection. THP-1 cells were differentiated with PMA for 24 h, and then transfected with plasmids encoding HA-H11 or empty vector (negative control). Twenty-four hours post-transfection, cells were infected with VSV- pseudotyped WT or ΔVpx viruses for 48 h. **(B)** Viral infectivity was detected by measuring luciferase activity in cell lysates. Data are means ± S.E.M. of three independent experiments. $^{**}p < 0.05$, Student *t*-test. **(C)** Forty-eight hours after infection, cells were harvested and analyzed by western blotting using the indicated antibodies. Represent results from one of three independent experiments. Bar charts indicate amounts of SAMHD1, as determined by densitometric analysis of western blots. Data are means ± S.E.M. of three independent experiments.

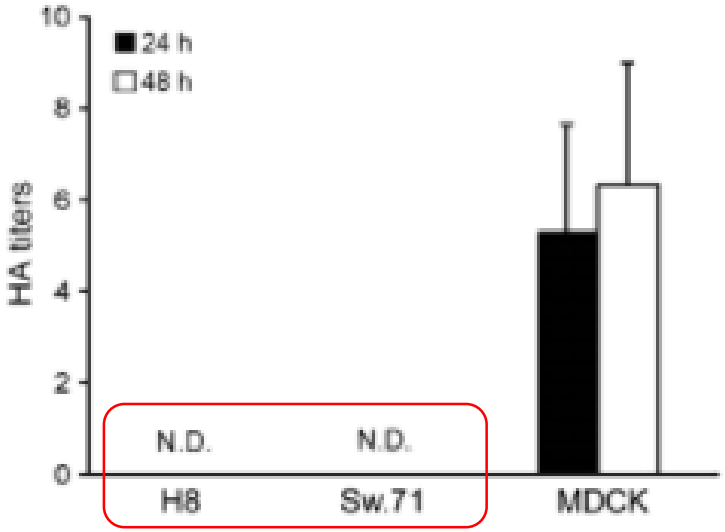


H1N1/09 Influenza A Virus Infection of Immortalized First Trimester Human Trophoblast Cell Lines

Shihoko Komine-Aizawa*, Ai Suzaki, Quang D. Trinh, Yasuyuki Izumi, Toshikatsu Shibata, Kazumichi Kuroda, Satoshi Hayakawa

Division of Microbiology, Department of Pathology and Microbiology, Nihon University School of Medicine, Tokyo, Japan





- ✓Two trophoblast cell lines Swan71 and HTR8 are susceptible to H1N1/09 influenza A virus.
- ✓However, viral release was not detected.
- ✓ Abortive infection of H1N1/09 influenza A virus might protect fetus from vertical transmission

Am J Reprod Immunol. 2012 Sep;68(3):226-32.

microorganisms

MDPI

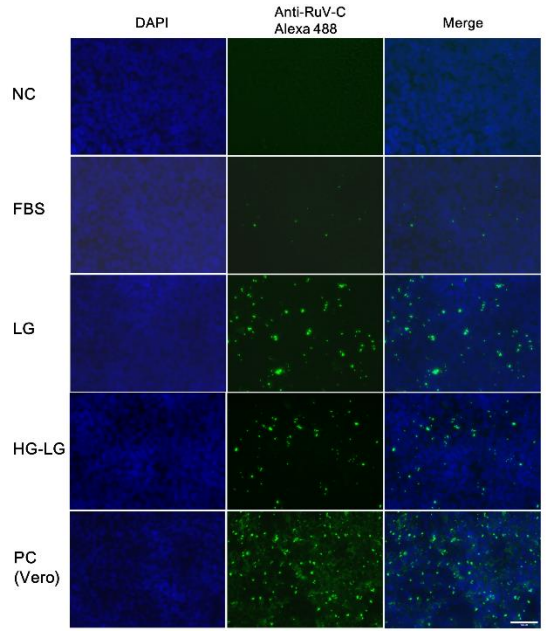
Article

Rubella virus infection in immortalized human first trimester trophoblasts under endoplasmic reticulum stress conditions

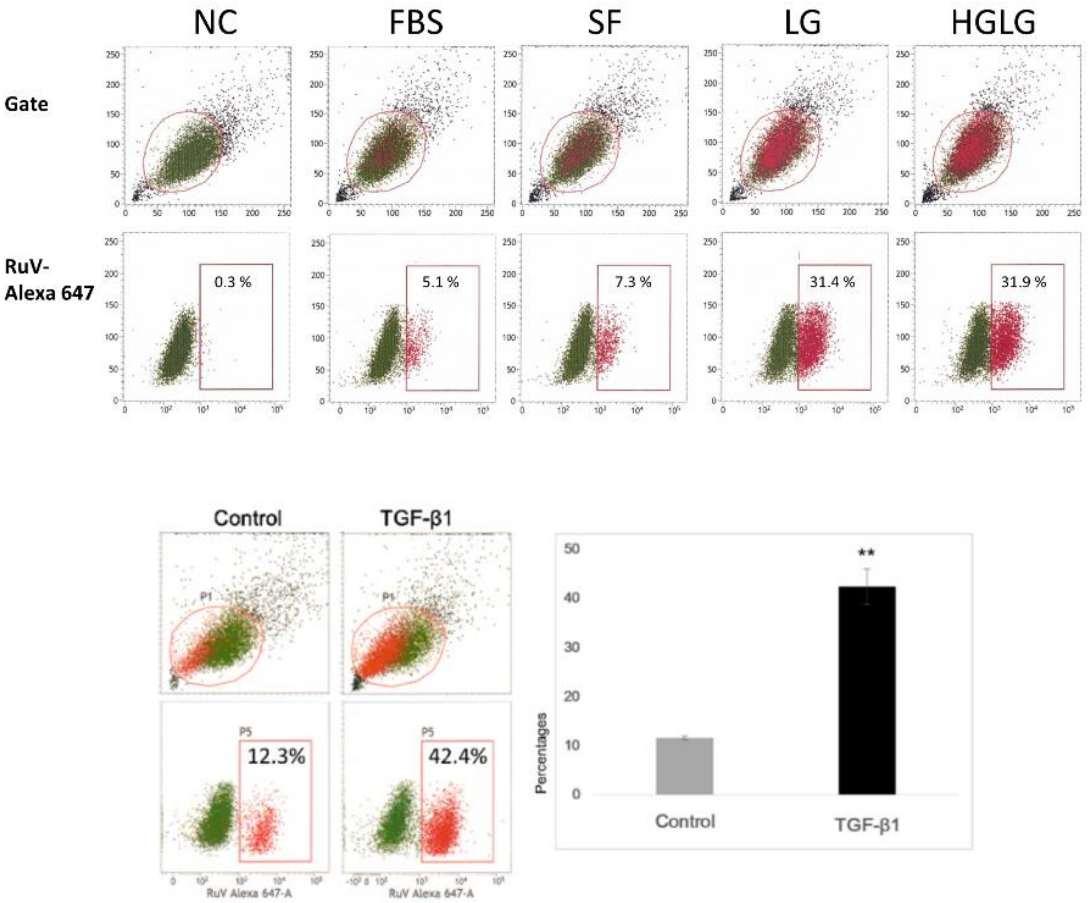
Quang Duy Trinh[1], Kazuhide Takada[1], Ngan Thi Kim Pham[1], Chika Takano[1], Takahiro Namiki[2], Ryo Ikuta[3], Shingo Hayashida[2], Shoko Okitsu[1], Hiroshi Ushijima[1], Shihoko Komine-Aizawa[1,*] and Satoshi Hayakawa[1,*]

[1] Division of Microbiology, Department of Pathology and Microbiology, Nihon University School of Medicine, Tokyo, Japan
[2] Nihon University School of Medicine, Tokyo, Japan
[3] Department of Pediatric Surgery, Nihon University School of Medicine
* Correspondence: aizawa.shihoko@nihon-u.ac.jp (S.K.A.); hayakawa.satoshi@nihon-u.ac.jp (S.H.)

Abstract: Rubella virus (RuV) infections in pregnant women, especially first-trimester infections, can lead to severe complications for the developing fetus, namely, congenital rubella syndrome



HTR-8/SVneo細胞



Pham et al. Microorganisms. 2021　　in press

Take Home message

- Pregnant women infected with COVID-19 often become severely ill in late pregnancy.
- There is no teratogenicity.
- Transplacental infection is less frequent.
- Vaccination can be given at any stage of pregnancy.
- The vaccines do not cause fetal or reproductive toxicity.
- However, there are several adverse reactions such as anaphylaxis, myocarditis, and thrombosis.
- Pregnant women often become anxious, thus adequate communication is important.
- The small number of infected and severely ill people in Asian countries may be due to cross-reactions with other coronaviruses.

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- Yoshiyasu Hirata

Osaka University

- Tadashi Kimura

Wayne University

Gil G Mor

Thank you for your attention

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