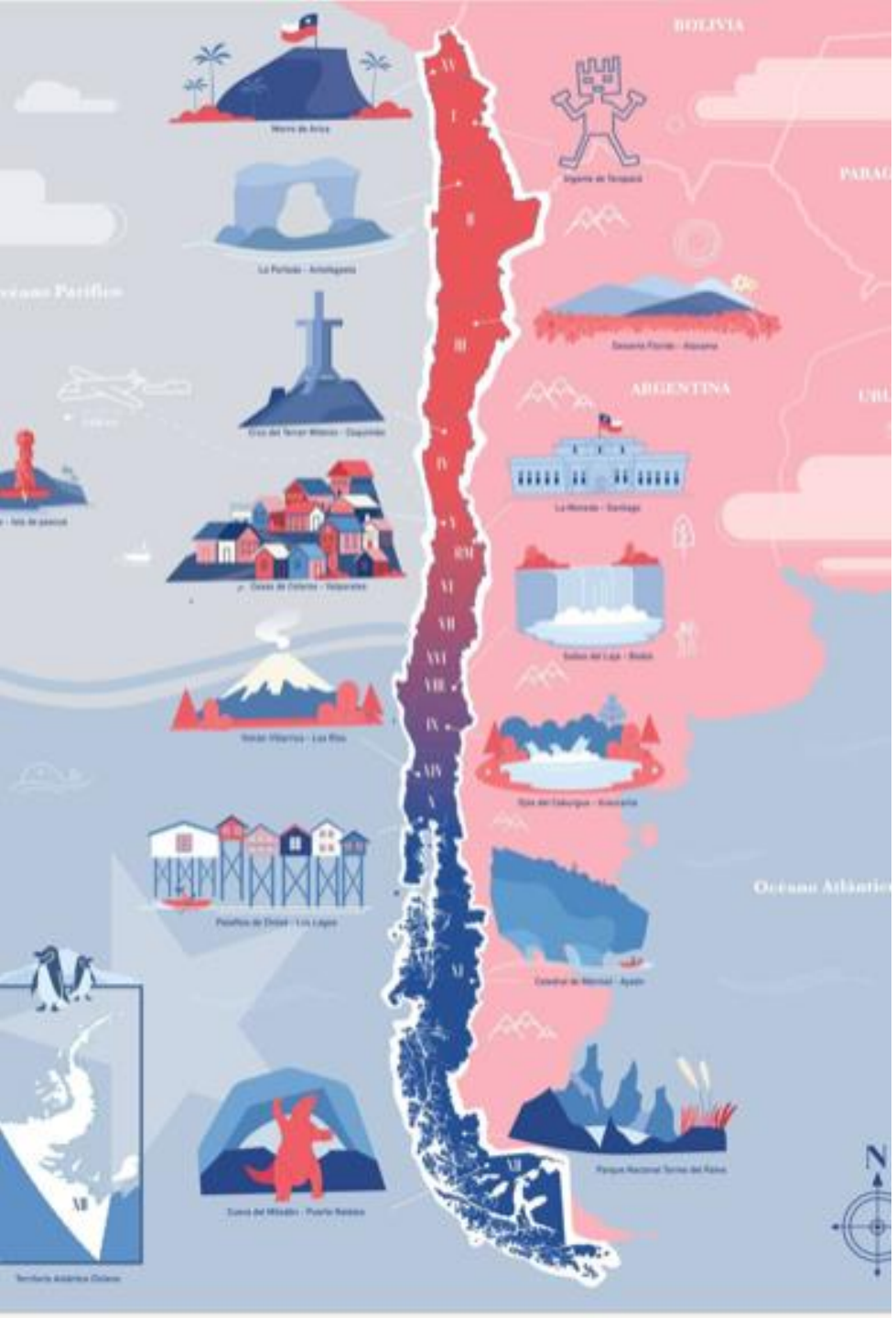
Research Ethics During the Pandemic: Experiences and Lessons from Chile. Research with pregnant women

Dr. Sofía P. Salas

Center for Bioethics, Faculty of Medicine
Clínica Alemana – Universidad del Desarrollo
Santiago, Chile



Initial declaration

1. As member of the IRB at the Faculty of Medicine, Universidad del Desarrollo (Santiago, CHILE), I have personal experience with the ethical review of research protocols during this pandemic.

2. However, I will maintain confidentiality regarding specific protocols I reviewed.

3. I have no conflict of interest to be declared.

Agenda

1. Brief information regarding Chile and its research organization
2. Ethical review of vaccine trials during the pandemic
3. Proposals for the ethical inclusion of pregnant women in vaccine trials

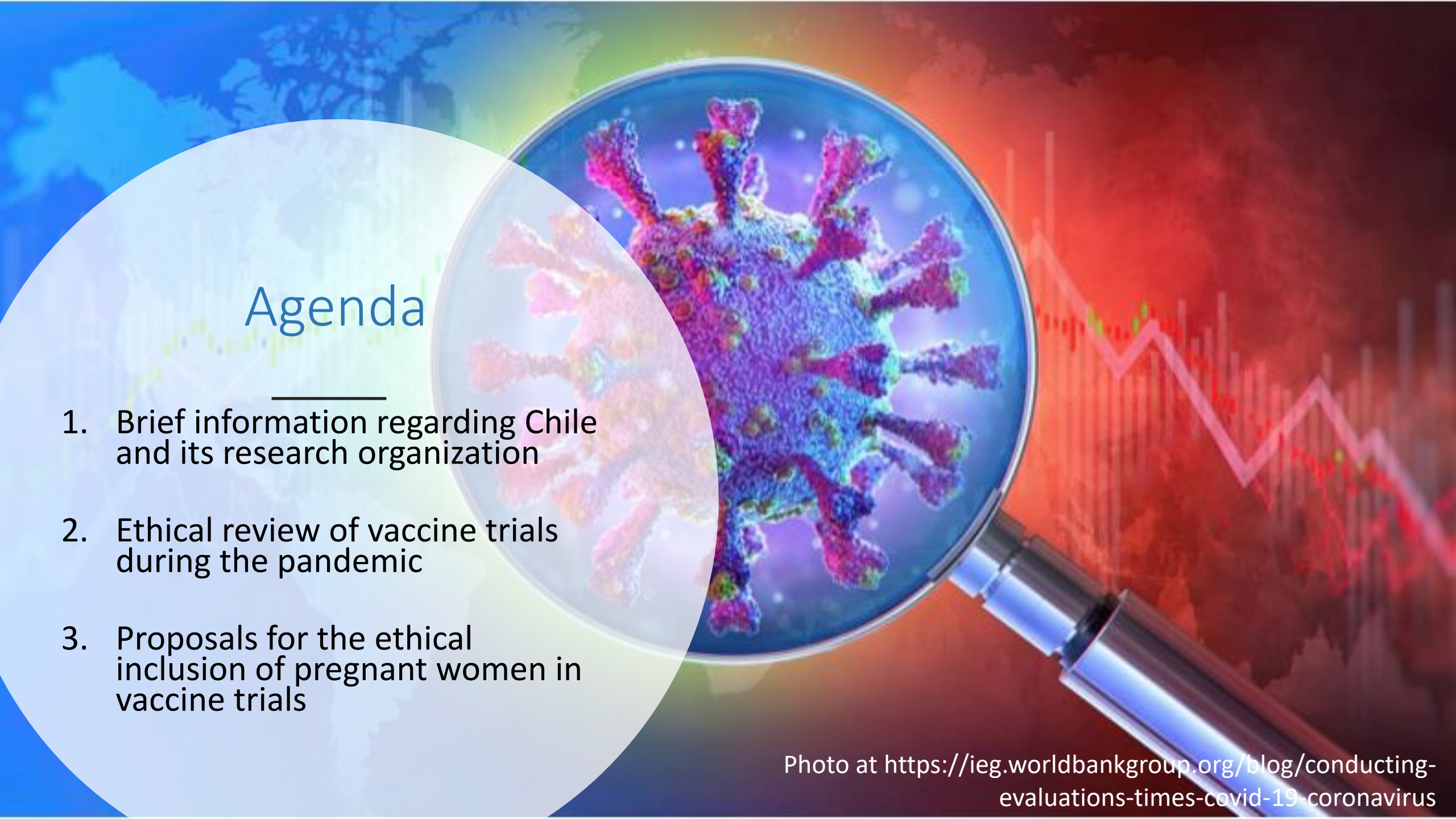


Photo at https://ieg.worldbankgroup.org/blog/conducting-evaluations-times-covid-19-coronavirus

Chile:

A cultural and ethnically diverse country

FACTS[1]:

- 19.458.000 hab
- 26 hab / km^2
- GDP € 11.376
- Health expenditure:
  - € 670 / hab
  - 5,88 % of the GDP

Genetic characterization[2]:

- 44.74 % Native
- 52.25 % European
- 3.01 % African

[1]https://datosmacro.expansion.com/paises/chile

[2]Eyheramendy, S.et al. Genetic structure characterization of Chileans reflects historical immigration patterns. *Nat Commun* **6,** 6472 (2015).

Chilean laws related to research ethics

- Compulsory review of research projects with human subjects *(Law 20.120, 2006).*
- Accreditation of RECs/IRBs is mandated by law: 64 registered IRBs along the country *(Law 20.120, 2006).*
- Restrictions for research with subjects who are unable to provide informed consent due to physical or cognitive impairment *(Law 20.584, 2012, 2021).*
- Regulatory protections concerning compensation for research injuries *(Law 20.850, 2015).*
- Post-trial access to research treatments without cost as long as there is clinical indication *(Law 20.850, 2015).*

Trends in clinical trials (CT) in Chile

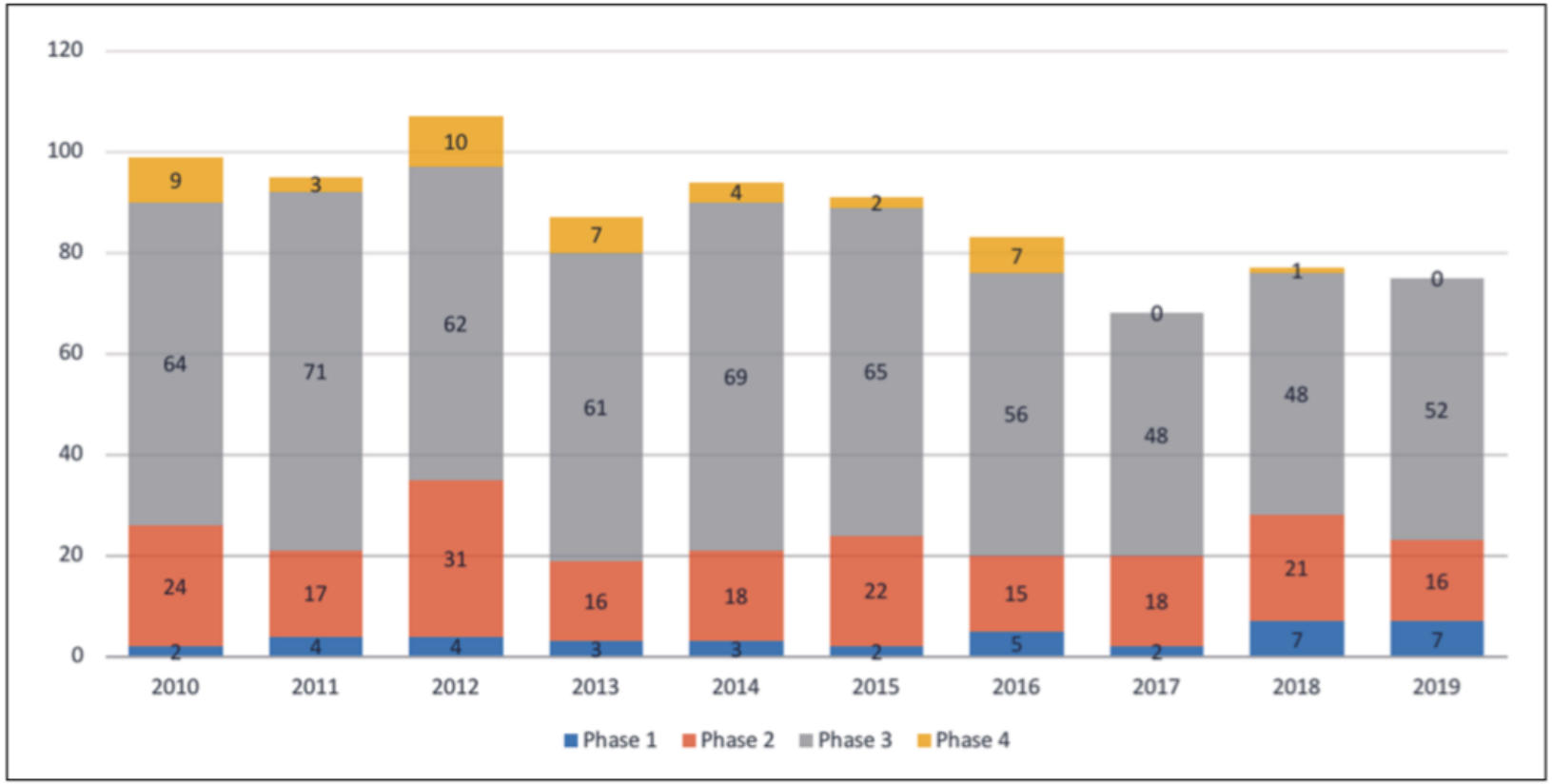


Figure 1. Total number of clinical trials registered in the Chilean Institute of Public Health (ISP) and their respective phases between 2010 and 2019 (n=876). Two trials from 2011 and one from 2017 were excluded because they were not reported as corresponding to phases 1-4.

FACTS:

- 96.5% of CT in drugs were sponsored by international pharmaceutic companies.
- 73% of CT were phases III/IV.
- Reduction in number of CT after year 2015.

Aguilera B. *Rev Med Chile 2021; 149: 110-118*

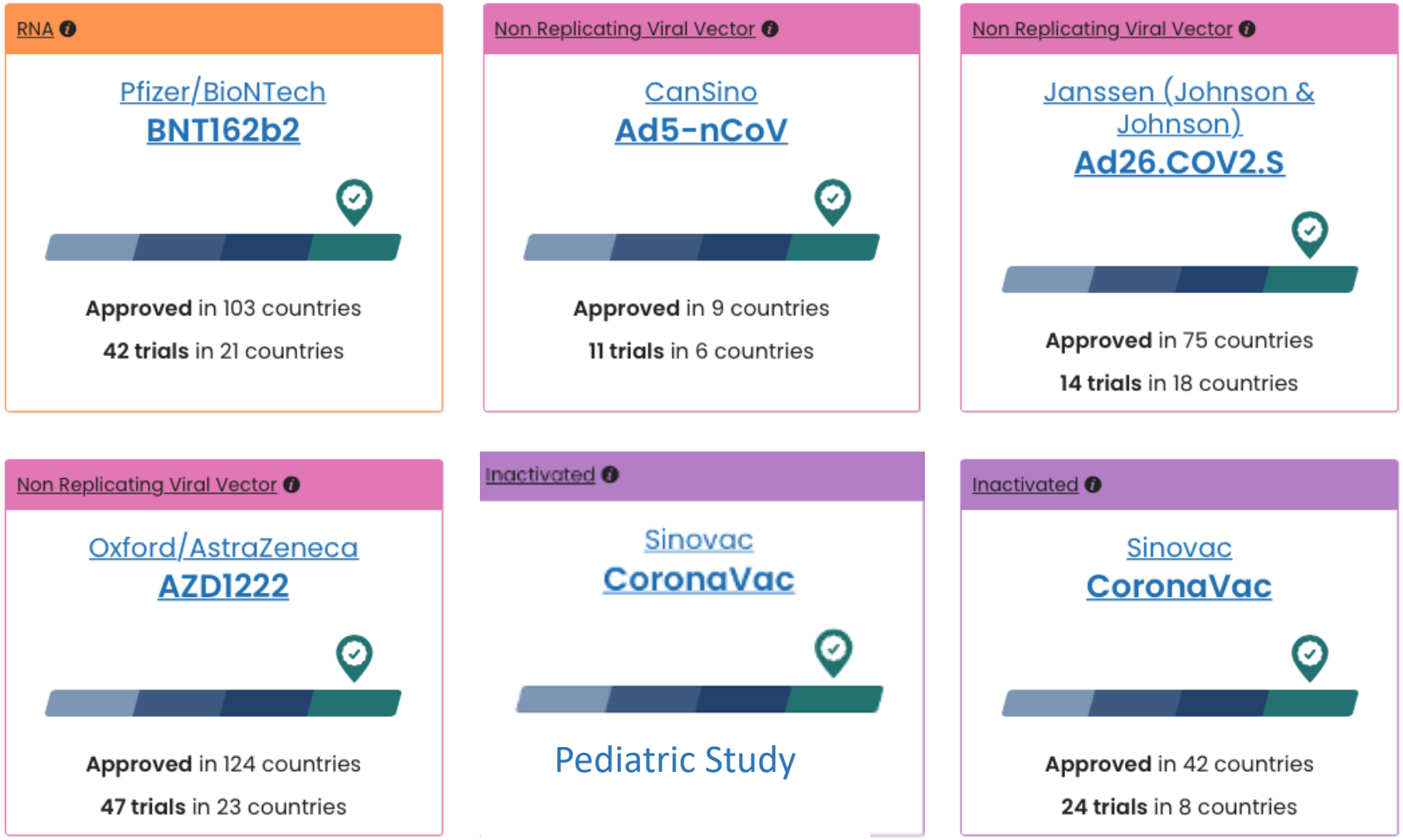
Photo at Ciencia UNAM

Ethical challenges of new vaccines during pandemic

Why are vaccine trials during pandemic so special?

- Healthy population
- Fast results
- Frequent new data
- Global impact

Clinical Trials new vaccines in Chile



Most CT were multicentre, in different cities and regions.

Additional trials:

- Booster trial after two doses of Sinovac (Sinovac, Pfizer, Astrazeneca & Placebo arms)
- Pediatric trial with Sinovac vaccine.

https://covid19.trackvaccines.org/vaccines/ November 5th, 2021

Need of an *ad-hoc* REC

- We were receiving various protocols of new vaccine candidates, at different centers.
- There were no uniform criteria for review and / or approval.
- Even though the law authorizes multicenter studies to be reviewed by a single REC, that is insufficient for follow-up.
- There was a need to make general recommendations that could be applied across different IRBs.

Ad-hoc Committee for COVID-19 vaccine trials

- Representatives of all accredited RECs that would review COVID-19 vaccines protocols.
- Members of the National Advisory Committee for Research Ethics.
- A community representative.
- Met every other week.
- Protocol presented by the local PI or the Chair of the REC

CREA COMISIÓN ASESORA DENOMINADA "COMITÉ ÉTICO CIENTÍFICO CONSULTOR AD – HOC PARA INVESTIGACIÓN CIENTÍFICA RELATIVA A VACUNAS COVID -19".

SANTIAGO, 24 SEP 2020

EXENTA Nº 805

Recommendations from the ad-hoc Committee

Situation	Recommendations
Participant's selection	Adequate description of participants selection criteria Rationale for exclusion of some groups Careful review of recruitment Ads
Consent form	Fair description of adverse events Ways of providing information regarding new vaccines Meaning of a placebo arm Measures at the end of the study: will placebo arm receive a vaccine?
R/B in pregnancy & lactation	Clarity about unknown fetal effects Need of safe & effective contraceptive methods Clear information about eventual follow-up of newborn
Insurance policy	With coverage at a national level
Quality of the centre	Registered with the corresponding authority
External data monitoring	Independent data monitoring should be clearly specified
Researchers' qualifications	To ensure participants protection

Additional challenges for RECs/IRBs in LMICs

1. IRBs generally do not evaluate “community engagement” as part of the review process.
2. IRBs are more interested in reviewing the consent document rather than the consent process.
3. IRBs do not consider as part of their duty to engage in public campaigns or to foster relationships with different stake holders.

Pregnant women and COVID-19

Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status

What is added by this report?

- In 400,000 women aged 15–44 years with symptomatic COVID-19, pregnant women had higher risk of:
  - ✓ intensive care unit admission,
  - ✓ invasive ventilation,
  - ✓ extracorporeal membrane oxygenation,
  - ✓ and death.

What are the implications for public health practice?

- Pregnant women should be counseled about the risk for severe COVID-19–associated illness including death.
- These findings can inform clinical practice, risk communication, and resource allocation.

MMWR Morb Mortal Wkly Rep. 2020 Jun 26; 69(25): 769–775.

Coronavirus Disease 2019 (COVID-19) Pandemic and Pregnancy Outcomes in a U.S. Population

- Retrospective cohort study that compared outcomes between those PW who tested positive for SARS-CoV-2 infection *vs* those with negative test results or no SARS-CoV-2 diagnosis.
- N = 108.647 PW;
- 7.432 with Sars-Cov-2 + test (6.9%).

Results indicated no significant differences in pregnant women who were + vs – to Sars-Cov-2 test:

- preterm birth (8.5% vs 7.6%)
- stillbirth (0.4% vs 0.4%)
- small for gestational age (6.4% vs 6.5%)
- large for gestational age (7.7% vs 7.7%)
- hypertensive disorders of pregnancy (16.3% vs 15.8%)
- caesarean birth (31.2% vs 29.4%)
- postpartum haemorrhage (3.4% vs 3.1%)

Son, Moeun et al. Obstetrics & Gynecology: August 9, 2021

Although present data might be not conclusive about how COVID-19 affects mother and baby…

- Pregnant women (PW) live in community (family members, kids, work-place), so they can get infected as others do.
- If infected, PW at least have similar (not lower) risks than non-pregnant women.
- Among PW, there are some high-risk groups (underlying medical conditions, some ethnic minorities, health-care workers), that most probably will benefit from safe & effective vaccines.
- At least initially, regulators offered conflicting recommendations about whether PW should be offered the jab.
- Because of the lack of data, WHO “could not provide a broad recommendation for vaccination of PW”!

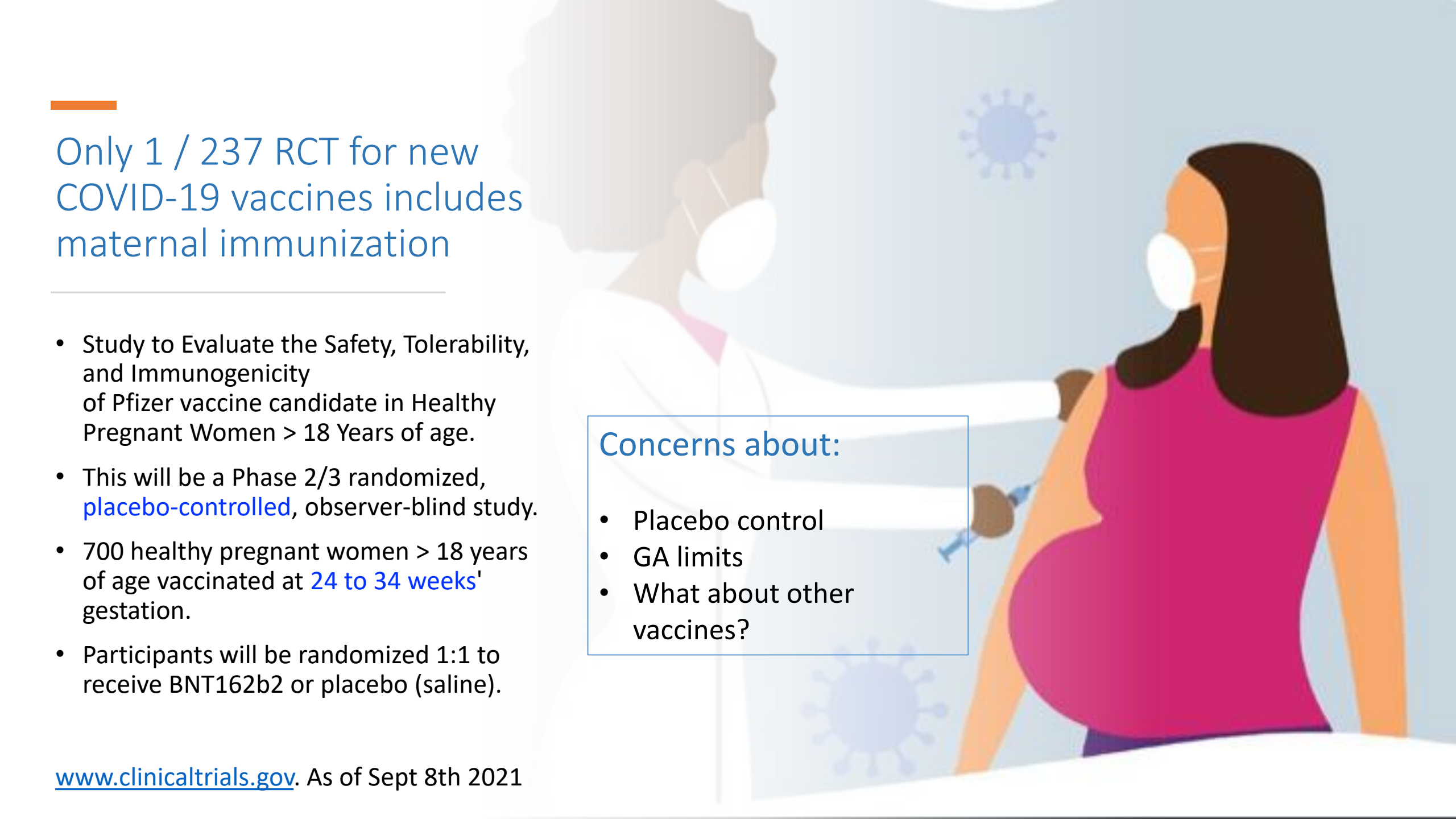
Subbaranam, Nature, March 2021

Why we need Covid-19 vaccine trials in pregnant women

Only 1 / 237 RCT for new COVID-19 vaccines includes maternal immunization

- Study to Evaluate the Safety, Tolerability, and Immunogenicity of Pfizer vaccine candidate in Healthy Pregnant Women > 18 Years of age.
- This will be a Phase 2/3 randomized, placebo-controlled, observer-blind study.
- 700 healthy pregnant women > 18 years of age vaccinated at 24 to 34 weeks' gestation.
- Participants will be randomized 1:1 to receive BNT162b2 or placebo (saline).

www.clinicaltrials.gov. As of Sept 8th 2021



Concerns about:

- Placebo control
- GA limits
- What about other vaccines?

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

- "V-safe is a new CDC smartphone-based active-surveillance system developed for the Covid-19 vaccination program" (35,691 pregnant women provided data). [1]
- "Preliminary findings did not show obvious safety signals among pregnant persons who received mRNA Covid-19 vaccines". [1]
- "However, more longitudinal follow-up, including follow-up of large numbers of women vaccinated earlier in pregnancy, is necessary to inform maternal, pregnancy, and infant outcomes". [1]
- Any risk estimate would need to account for gestational week–specific risk of spontaneous abortion. [2]

[1]Shimabukuro et al, N Engl J Med 2021; 384:2273-2282
[2] Shimabukuro et al. NEJM 2021; 385:1536

Social media post misrepresents preliminary data on miscarriages and COVID-19 vaccines

Facebook posts https://www.politifact.com/factchecks/2021/jul/09/facebook-posts/post-misrepresents-preliminary-data-miscarriages-a/

stated on July 6, 2021 in an Instagram post:

> **A study found an "82% miscarriage rate" among women between 30 days and 20 weeks pregnant who got an mRNA COVID-19 vaccine.**

Until all the pregnancies are evaluated and more authoritative data is released, any statistic on this topic should be considered preliminary.
Future studies should stratify data according to the gestational age the shot is received (1st vs 2nd or 3rd trimester).

No link with spontaneous abortion

Spontaneous Abortion Following COVID-19 Vaccination During Pregnancy

COVID-19 infection during pregnancy can be associated with severe maternal morbidity.[1] In the United States, 1 COVID-19 vaccine has been approved and 2 have been authorized for use for pregnant women. To date, data on maternal COVID-19 vaccine safety come primarily from passive surveillance, and studies lack an unvaccinated comparison group.[2,3] Spontaneous abortion has been identified as a priority outcome in studies of maternal vaccine safety,[4] and concerns regarding risks of spontaneous abortion may be a barrier to vaccination during pregnancy. We present findings from case-control surveillance of COVID-19 vaccination during pregnancy and spontaneous abortion.

Supplemental content

- Case-control surveillance study of COVID-19 vaccination during pregnancy and spontaneous abortion (n= 105 446 unique pregnancies).
- Spontaneous abortions did not have an increased odds of exposure to a COVID-19 vaccination in the prior 28 days compared with ongoing pregnancies (adjusted odds ratio, 1.02; 95% CI, 0.96-1.08).
- Despite limitations, these data can be used to inform vaccine recommendations and to counsel patients.

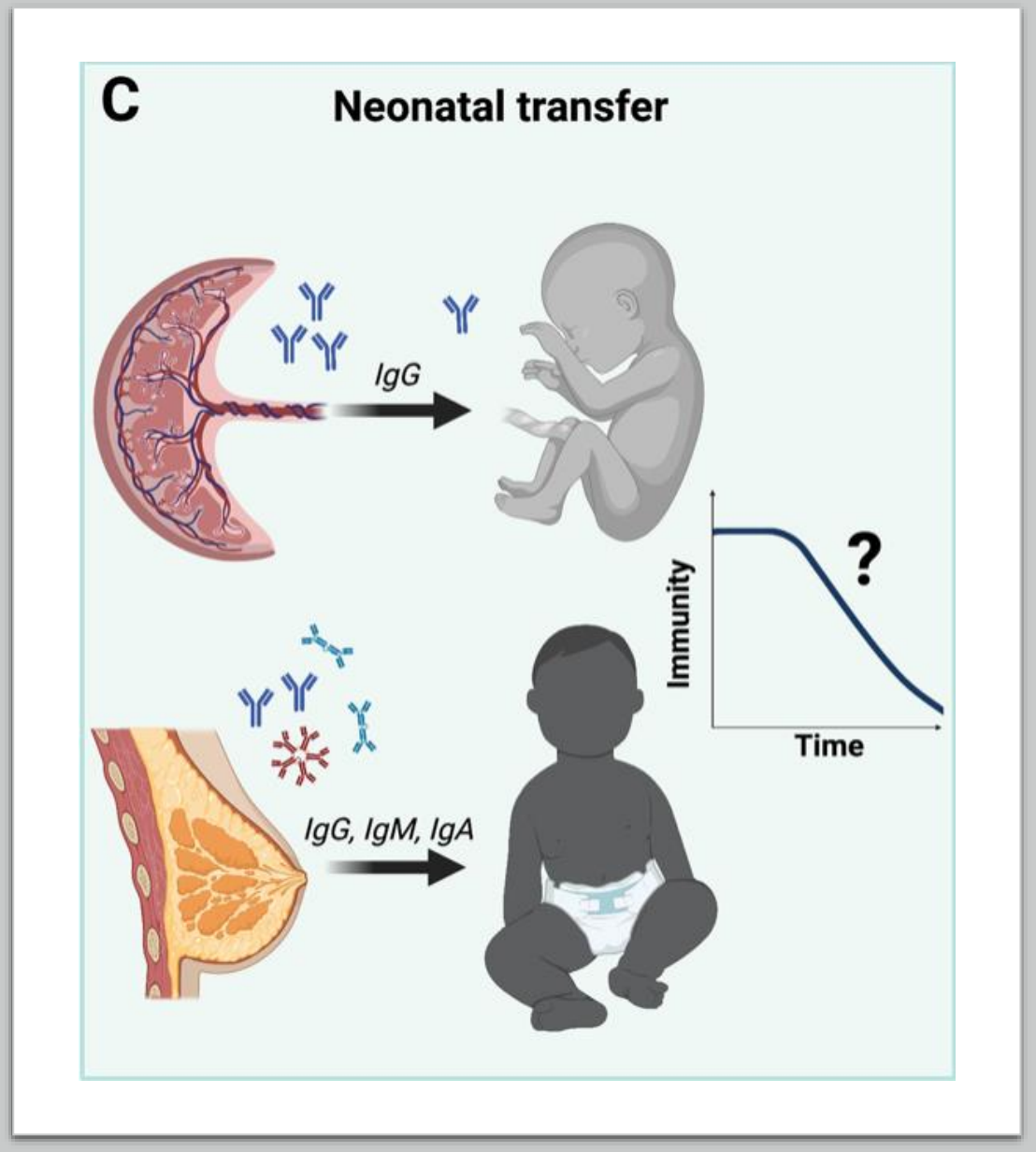
Kharbanda E, *JAMA*. Published online September 8, 2021.

Additional advantages if pregnant and lactating women get the vaccine

There is evidence of antibody in cord blood and breast-milk, which may offer protection to infants through passive immunity:

- Neutralizing anti-Spike IgG is transplacentally transferred from mother to fetus.
- IgG, IgM and IgA are transferred through breastmilk.

Duration of the protection is still unknown.



Shook LL et al Front. Cell. Infect. Microbiol., 16 September 2021

Ethical inclusion of pregnant women in vaccine trials

Women susceptible to and becoming pregnant (WoSuP)

- Main reason to exclude WoSuP in RCT is the potential risk to the unborn.
- When fertile women are included in RCT, they need to be under contraception, but they DO became pregnant.
- There is need to include appropriate R/B analysis for their safe inclusion in RCT.

PLOS Neglected Tropical Diseases. June 2020

Some issues to be considered when reviewing CT

- Evidence from developmental and reproductive toxicology studies.
- Type of vaccine being studied.
- Evidence from inadvertently exposed pregnancies during vaccine clinical trials.
- Potential risks to pregnancy of vaccine reactogenicity.
- Timing of vaccination during pregnancy.
- Risk of COVID-19 complications due to pregnancy and the pregnant person's underlying conditions.

Obstet Gynecol. 2021 Mar; 137(3): 408–414.

A possible way for safe inclusion of WoSuP in RCT of new vaccines

- The needs of WoSuP and the offspring should be fairly addressed.
- Relevant data to maternal, obstetric, & newborn health outcomes should be recorded to inform PH response.
- There is need of evidence-based strategies to promote confidence about new vaccines.
- Possible use of vaccines in WoSuP should guide the development of new vaccine platforms, for example, requesting adequate toxicology studies.

PREVENT. Ethics guidance for preparedness, research & response. Sept 2018.

In conclusion

- Pregnant women are to be included in vaccine R&D.
- The burden of proof, both scientific and ethical, falls on those who argue for their exclusion.
- The “presumption of inclusion” corresponds to a fundamental shift in the way pregnant women are viewed in the field of vaccines.

PREVENT. Ethics guidance for preparedness, research & response. Sept 2018.

Gracias
Thanks
Merci
Vielen Dank
Grazie
Salamat

sofiasalas@udd.cl