Principles of epidemiological thinking, design and methods

Guilherme Loureiro Werneck

Department of Epidemiology / State University of Rio de Janeiro
Institute for Public Health Studies / Federal University of Rio de Janeiro
Coordinator of the Program for the Development of Epidemiology in Health Services / Secretary of Health Surveillance, Brazilian Ministry of Health

gwerneck@iesc.ufrj.br / @guilhermewernec (Twitter) / @gwerneck12 (Threads)

Lecture objective

- To present principles of epidemiological thinking, design and methods, and how they might be used to generate and interpret data in the context of epidemics.

Lecture topics

- What is epidemiology?
- Epidemiologic reasoning and methods
- Basics of causal inference in epidemiology
- Covid-19 pandemic: descriptive epidemiology
- Use of surveys during Covid-19 pandemic
- Use of case-control studies for assessing vaccine effectiveness
- Challenges in carrying out epidemiological studies in the pandemic context

What is epidemiology?

Epidemiology – definition and domain

- A definition: The study of the occurrence and distribution of health-related events, states, and processes in specified populations, including the study of the determinants that influence such processes, and the application of this knowledge to control health problems.
- Plurality of practices and perspectives: reflecting theories, methods, values, and social commitments existing in different historical and geographical contexts
- Specific domain of interest: the population distribution of diseases, disabilities, deaths, health and their determinants and restraints, in space and time

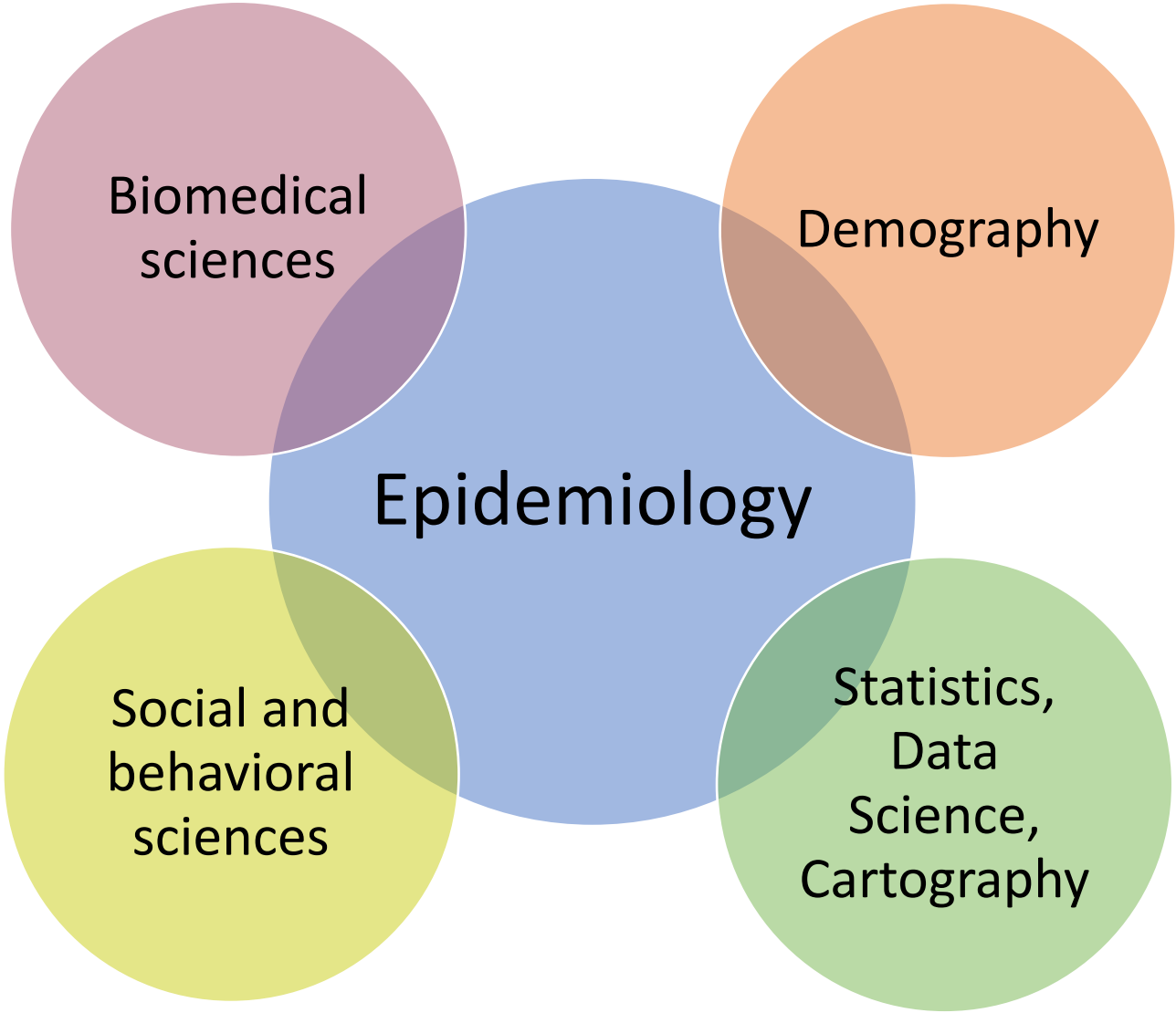
Porta M. A dictionary of epidemiology. 6a ed. New York: Oxford University Press; 2014.
Breilh J. Critical epidemiology and the people's health. New York, NY: Oxford University Press; 2021.
Krieger N. Commentary: society, biology, and the logic of social epidemiology. Int J Epidemiol. 2001; 30:44-46.
Krieger N. Epidemiology and the people's health: theory and context. New York: Oxford University Press; 2011.

Epidemiology – science and practice

- Epidemiological theories provide subsidies to think about and seek explanations about:
  - the mechanisms causing health events
  - the reasons that lead to spatial-temporal heterogeneities in the distribution of these events and their determinants.
- Epidemiology must be committed with the generation of knowledge that can be translated and applied to bring about changes that improve populations' health and quality of life, and reduce social inequalities in health.
- Viewing Epidemiology as a solely scientific activity implies a specific, naive, and idyllic conception of science devoid of moral values and political interests.

Krieger N. Epidemiology and the people's health: theory and context. New York: Oxford University Press; 2011.
Krieger N. Epidemiology and eb of causation: has anyone seen the spider? Soc Sci Med. 1994; 39:887-903
Krieger N. Questioning epidemiology: objectivity, advocacy, and socially responsible science. Am J Public Health. 1999; 89:1151-3.

Epidemiology – inherently multidisciplinary subject



Epidemiologic reasoning and methods

Epidemiology – Descriptive-Analytic Spectrum

- Descriptive epidemiology:
- Epidemiological studies and activities (e.g., surveillance) more concerned with
  - describing the occurrence of disease and other health-related characteristics in human populations (person, place and time)
  - exploring associations more than analyzing and explaining causal effects.
- Analytic epidemiology:
- Epidemiological studies conceived to examine hypothesized causal relationships and to make causal inferences.
  - can be conceptualized as etiological studies.
  - usually concerned with identifying or measuring the effects of risk factors or with the health effects of specific exposures or interventions.

Epidemiology – Observational-Experimental Dimensions

- Observational epidemiology:
  - The use of epidemiological reasoning, knowledge, and methods in studies and programs (e.g., surveillance) in which the main conditions (e.g., exposures) are not under the direct control of the researcher.
- Experimental epidemiology:
  - The application of epidemiological reasoning, knowledge, and methods to randomized controlled individual and community trials.
  - Clinical or community-based studies merit the term experiment or quasi-experiment only if it is possible to modify conditions (e.g., exposures) during the study.

Epidemiology - Study Designs

Experimental studies

- Clinical trials
- Field trials
- Community interventions and Cluster randomized trials

Non-experimental studies

- Cohort
- Case-control
- Cross sectional
- Proportional mortality
- Ecologic

Epidemiology – Measures

- Epidemiology uses a probabilistic approach to measure frequency of events and derive measures of association, effect and impact
- Frequency measures
  - Incidence (new cases): Cumulative (Proportion), Rate, Odds
  - Prevalence (existing cases): Proportion, Odds
- Association and effect measures
  - Ratio: risk ratio, rate ratio, odds ratio, prevalence ratio, prevalence odds ratio
  - Difference: risk difference (attributable risk), rate difference, odds difference, prevalence difference, prevalence odds difference
  - Mixed: attributable fraction (etiologic fraction, preventative fraction)
- Impact (potential), takes into account the % of the exposure in the population
  - Population attributable risk (rate): Population attributable risk (PAR), PAR percent

Epidemiology – Measures

- Two types of incidence measures defined by the type of population:
- (1) cumulative incidence (risk):
  - based on the number of persons at risk followed-up for a certain time
  - proportion of people who develop new disease during a specified period of time
  - need to refer it to a certain period of time (e. g., 2-year cumulative probability of death)
  - Expresses the average risk : probability of an individual developing a disease during a given period of time, subject to the absence of other risks related to other diseases
- (2) incidence rate (incidence density):
  - based on person-time units at risk of developing the disease
  - the occurrence of new cases of disease per unit of person-time

Epidemiology – Measures of frequency & association

Table 2 Findings from a hypothetical cohort study of 20 000 persons followed for 10 years

	Exposed	Non-exposed	Ratio
Cases	1813 (a)	952 (b)	
Non-cases	8187 (c)	9048 (d)	
Initial population size	10 000 (N_1)	10 000 (N_0)	
Person-years	90 635 (Y_1)	95 163 (Y_0)	
Incidence rate	0.0200 (I_1)	0.0100 (I_0)	2.00
Incidence proportion (average risk)	0.1813 (R_1)	0.0952 (R_0)	1.90
Incidence odds	0.2214 (O_1)	0.1052 (O_0)	2.11

$$Risk\ (incidence)\ among\ exposed\ = \frac{a}{N_1}$$

$$Risk\ (incidence)\ among\ non-exposed\ = \frac{b}{N_0}$$

$$Risk\ ratio = \frac{\frac{a}{N_1}}{\frac{b}{N_0}}$$

$$Odds\ ratio = \frac{\frac{a}{c}}{\frac{b}{d}} = \frac{\frac{a}{b}}{\frac{c}{d}} = \frac{ad}{bc}$$

$$Rate\ (incidence)\ among\ exposed\ = \frac{a}{Y_1}$$

$$Rate\ (incidence)\ among\ non-exposed\ = \frac{a}{Y_0}$$

$$Rate\ ratio = \frac{\frac{a}{Y_1}}{\frac{b}{Y_0}}$$

$$Risk\ difference = \frac{a}{N_1} - \frac{b}{N_0}$$

Pearce N. Classification of epidemiological study designs. Int J Epidemiol. 2012 Apr;41(2):393-7.

Epidemiology – Impact measures

Hypothetical Cohort Study of Cigarette Smoking and Lung Cancer, With Incidence Rates and Measures of Association

Cigarette exposure	Lung cancer		Person-years of observation	Incidence rates*
	Yes	No		
Yes	640	3,360	55,200	1,159
No	200	9,800	150,000	133

*Rates per 100,000 person-years

$$Rate\ ratio = \frac{\frac{640}{55{,}200}}{\frac{200}{150{,}000}} = \frac{1{,}159}{133} = 8.7$$

$$Risk\ difference\ (attributable\ rate) = 1{,}159 - 133 = 1{,}026\ per\ 100{,}000\ person - years$$

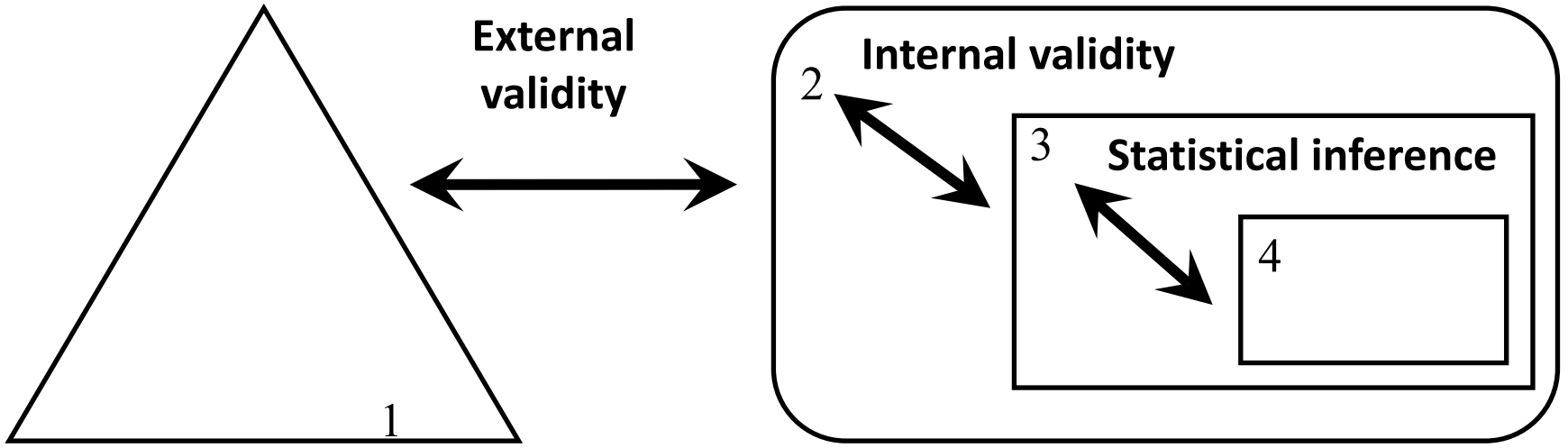
$$Attributable\ fraction\ (\%) = \frac{1{,}159 - 133}{1{,}159} = 88.5\%$$

$$Population\ Attributable\ Rate\ (PAR) = \frac{(640 + 200)}{(55{,}200 + 150{,}000)} - \frac{200}{150{,}000} = 276\ per\ 100{,}000\ person - years$$

$$Population\ Attributable\ Rate\ percent\ (\%) = \frac{PAR}{\frac{(640 + 200)}{(55{,}200 + 150{,}000)}} \times 100 = 67.4\%$$

Rockett IRH. Population and Health: An Introduction to Epidemiology. Population Bulletin. 1999;54(4):1-44.

Epidemiology – Populations



(1) External population: group of individuals with no direct connection to the interests and procedures of the study, but to whom one may wish to extrapolate or generalize the results of this particular study.

(2) Target population: set of individuals that originated the actual population (not necessarily in a representative way) and about which we wish to make inferences.

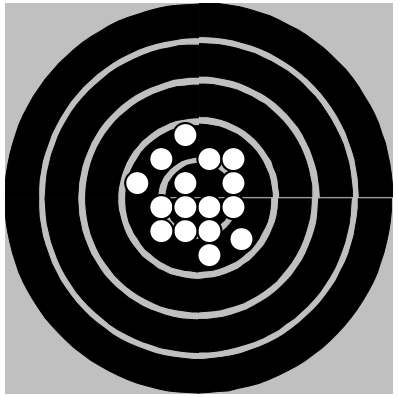
(3) Actual population: eligible individuals for the study (from which participants were sampled)

(4) Study population: the group of participants for whom we have collected data.

Kleinbaum DG, Kupper LL, Morgenstern H. Epidemiologic Research: Principles and Quantitative Methods. Belmont, CA: Lifetime Learning Publications, 1982.

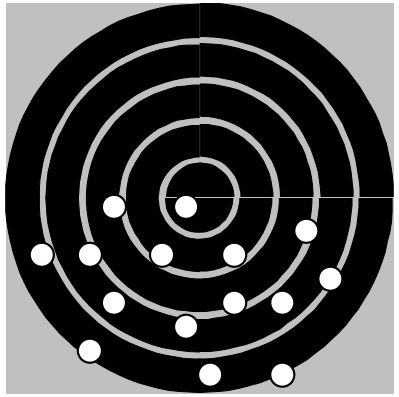
Validity vs Precision

- Validity: Lack of systematic error or bias
- Precision: Relative lack of random error



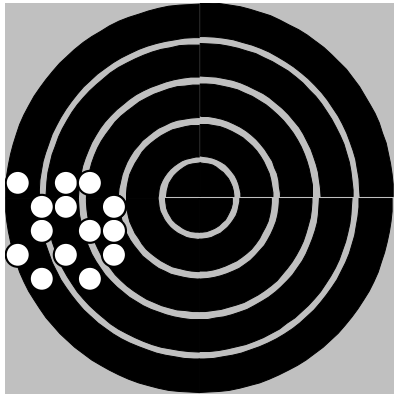
Unbiased

Reliable



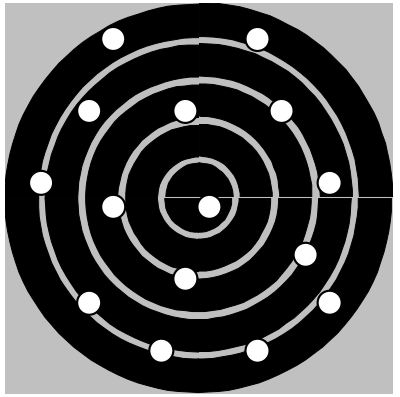
Biased

Unreliable



Biased

Reliable



Unbiased (!?)

Unreliable

Bias

- Selection bias: Bias in the estimated association or effect of an exposure on an outcome that arises from the procedures used to select individuals into the study or the analysis.
- Information bias (misclassification bias): Distortion of the effect estimate due to measurement errors of exposure, covariate, or outcome variables resulting in misclassification of individuals according to one or more variables.
- Confounding bias: Bias of the estimated effect of an exposure on an outcome due to the presence of common causes of the exposure and the outcome.

Basics of causal inference in epidemiology

The fundamental problem of causal inference

- At the individual level, it is not possible to observe the potential outcomes of an individual when she is, at the same time, exposed and not exposed
- The causal effect cannot be observed in a person (contrafactual reasoning)
- Epidemiology replaces the search for the individual causal effect by an estimate of a average causal effect at the population level
- Assuming a series of conditions, such as random allocation and no interference, the average causal effect can be estimated from the observed data

What about observational studies?

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell *BMJ* 2003;327:1459–61

HULTON/GETTY

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

What is already known about this topic

Parachutes are widely used to prevent death and major injury after gravitational challenge

Parachute use is associated with adverse effects due to failure of the intervention and iatrogenic injury

Studies of free fall do not show 100% mortality

What this study adds

No randomised controlled trials of parachute use have been undertaken

The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a "healthy cohort" effect

Individuals who insist that all interventions need to be validated by a randomised controlled trial need to come down to earth with a bump

Observational studies: Exchangeability

- Basic principle: comparison between two groups, one exposed to the potential “cause” and the other not exposed
- In order this comparison to be valid, the exposed and non-exposed groups should be (conditionally) similar in all aspects, except for exposure status.
- There is validity of comparison when the groups are interchangeable with each other.
- The idea of interchangeability is based on the assumption that the same results would be expected if the exposure status was exchanged between the two groups.

Epidemiological solution

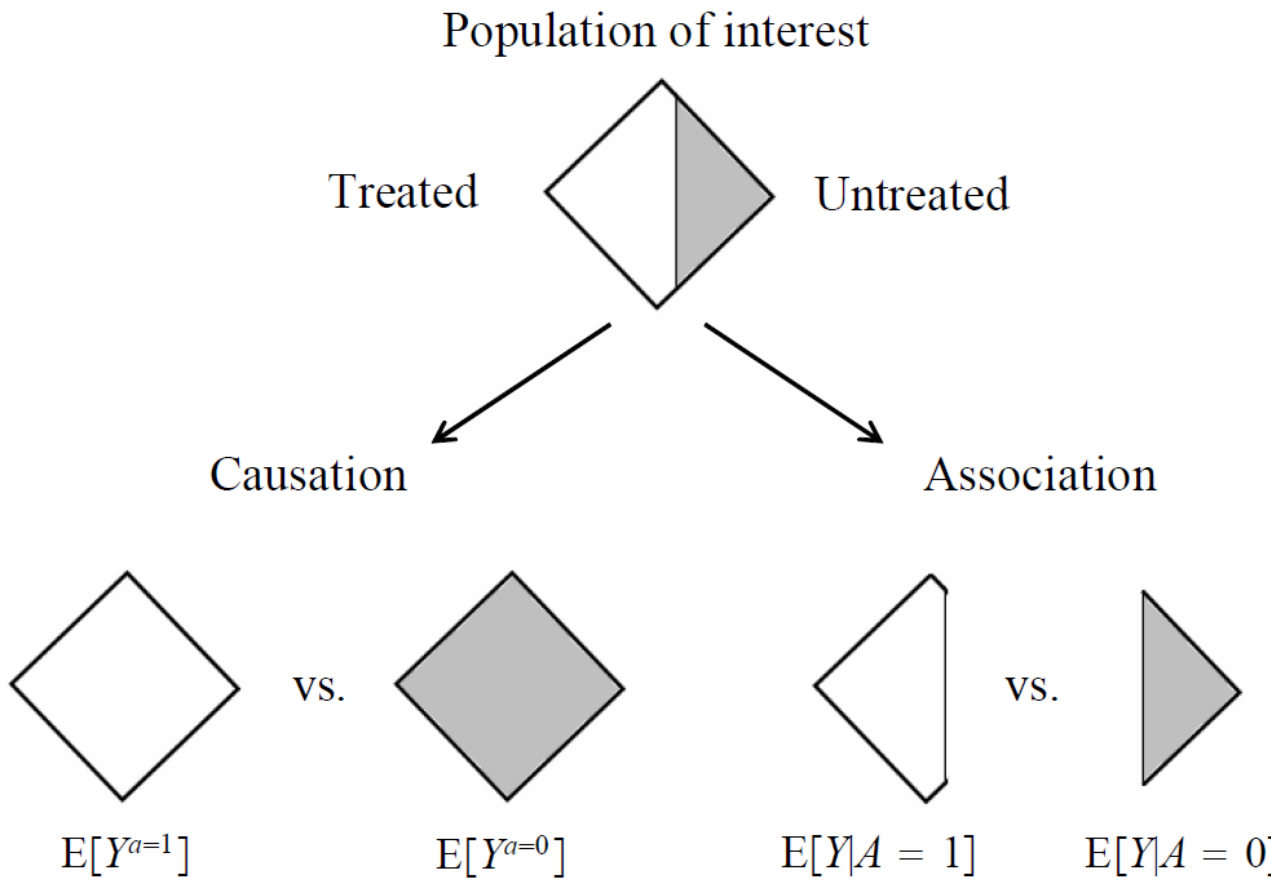
- Would it be possible to describe the occurrence of the outcome of interest between the exposed individuals, if they had not been exposed, from data obtained from the non-exposed people?
- In practice: substitute “the exposed when not exposed” by an individual not exposed
- Confounding is present if our “substitutes” imperfectly represent what our “originals” would have been under the counterfactual condition.

Maldonado G, Greenland S. Estimating causal effects. Int J Epidemiol. 2002 Apr;31(2):422-9.

Causality and association

- Statistical methods to identify associations between variables are the most frequently used strategies to estimate a causal parameter.

- Statistical association between two variables (X and Y) can reflect:
  - Random fluctuations
  - X is a cause of Y
  - Y is a cause of X
  - X and Y have a common cause
  - Association "induced" by methodological errors (eg, selection bias)
- Which of these possibilities is more consistent with the data available and the a priori knowledge?



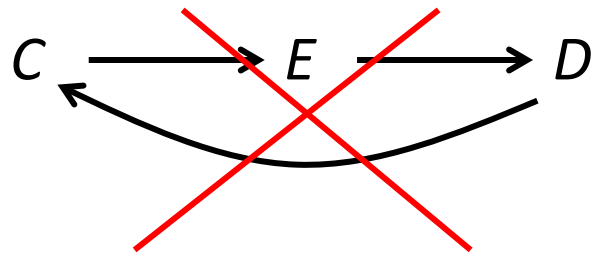
Hernán & Robins, Causal Inference, 2016

Causal diagrams

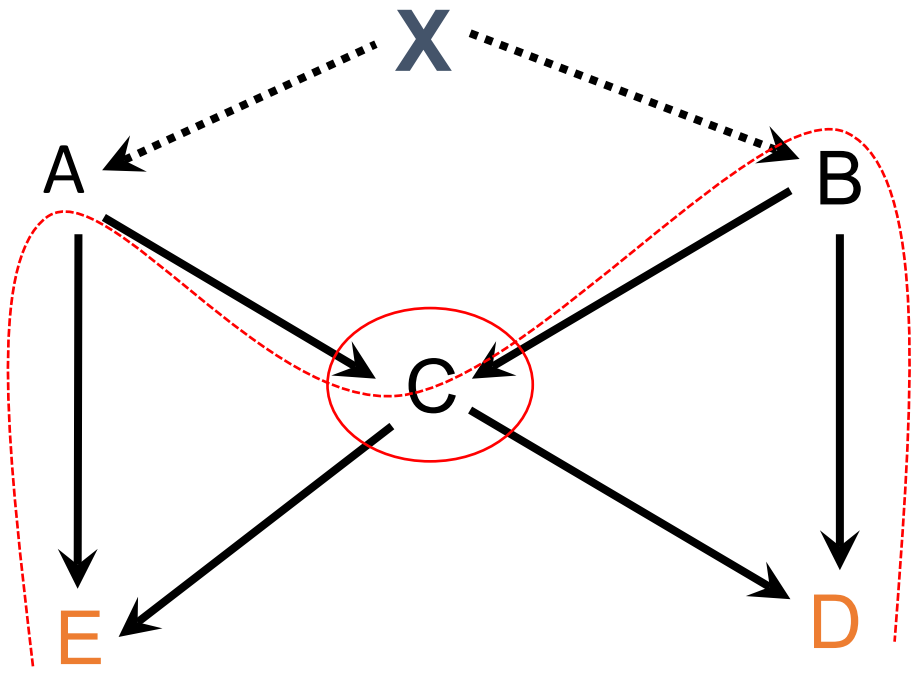
- Drawing up causal diagrams is one of the most commonly strategies used by epidemiologists to express their hypotheses about the relationships between variables that could explain the associations.
- The use graphic strategies requires that the assumptions about the hypothesized causal relationships be made explicit
- Given that the explicit causal model is correct and ignoring sample variation, these diagrams allow identifying:
  - if there is confounding
  - which variables need to be controlled in the analysis
  - which variables should not or do not need to be controlled in the analysis

Directed Acyclic Graphs (DAG)

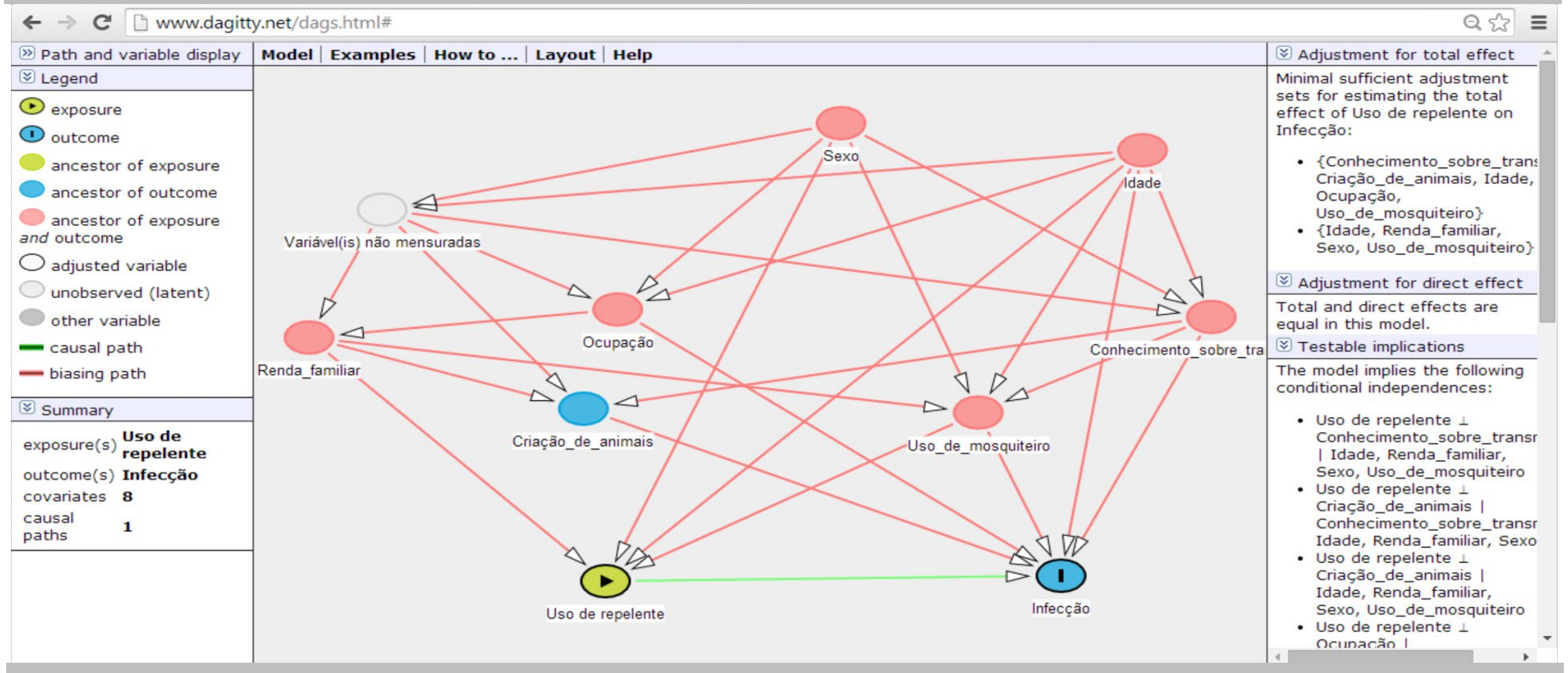
- Directed: All causal relationships have a direction (arrows).
- Acyclic: There is no circular path (causal loop)
- Backdoor paths: Any non-causal path linking E to D



- Blocked path: In graphic parlance, a collider is said to block a path through the backdoor preventing association from flowing through that collision point.
- Confounding: look for the existence of some backdoor unlocked pathway linking exposure to disease



Dagitty! (http://www.dagitty.net/)



Covid-19 pandemic: descriptive epidemiology

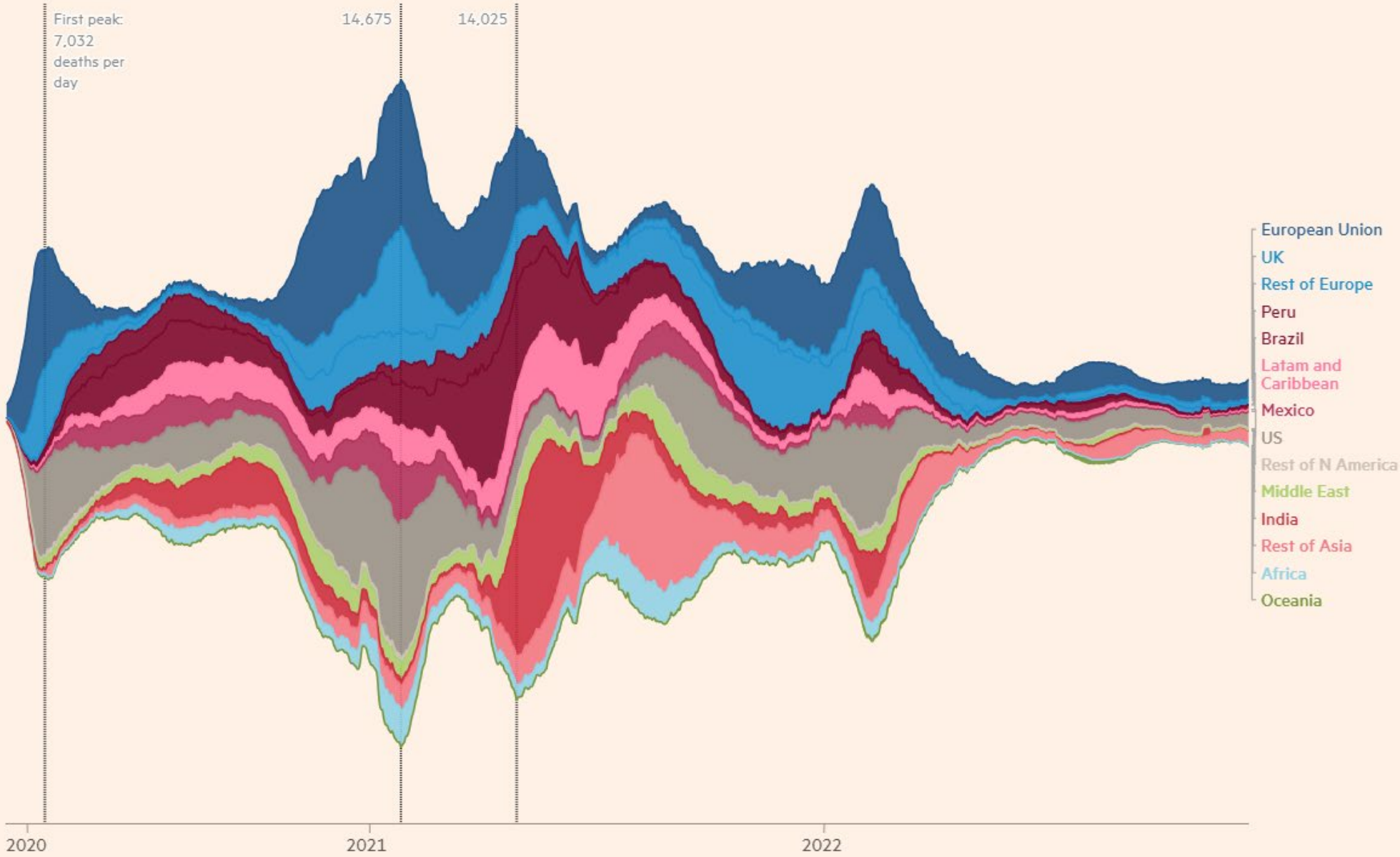
Covid-19 pandemic: the importance of descriptive epidemiology

- Descriptive approaches are often treated as “less scientific” and with a lower degree of analytical sophistication.
- The theoretical, conceptual and methodological issues involved in these studies are as or more challenging than those of other types of epidemiological approaches.
- Descriptive epidemiology is intended to designate the approach to the epidemiological characterization of the disease in the community, without this denomination connoting the description of phenomena lacking proper interpretation.

Barata RCB. The challenge of emergent diseases and the return to descriptive epidemiology. Rev Saude Publica. 1997 Oct;31(5):531-7.

More than 1,000 deaths each day are attributed to Covid-19

Daily deaths attributed to Covid-19 (7-day rolling average)



Source: Johns Hopkins CSSE, WHO, national sources, FT research • Excludes recent data covering less than 95% of global population
N America includes Canada, Bermuda, Greenland and St Pierre and Miquelon

FINANCIAL TIMES

EXCESS MORTALITY

Painel de análise do excesso de mortalidade por causas naturais no Brasil 2020-2022

*Painel sujeito a atualizações conforme dados fornecidos pelos Cartórios de Registro Civil do Brasil

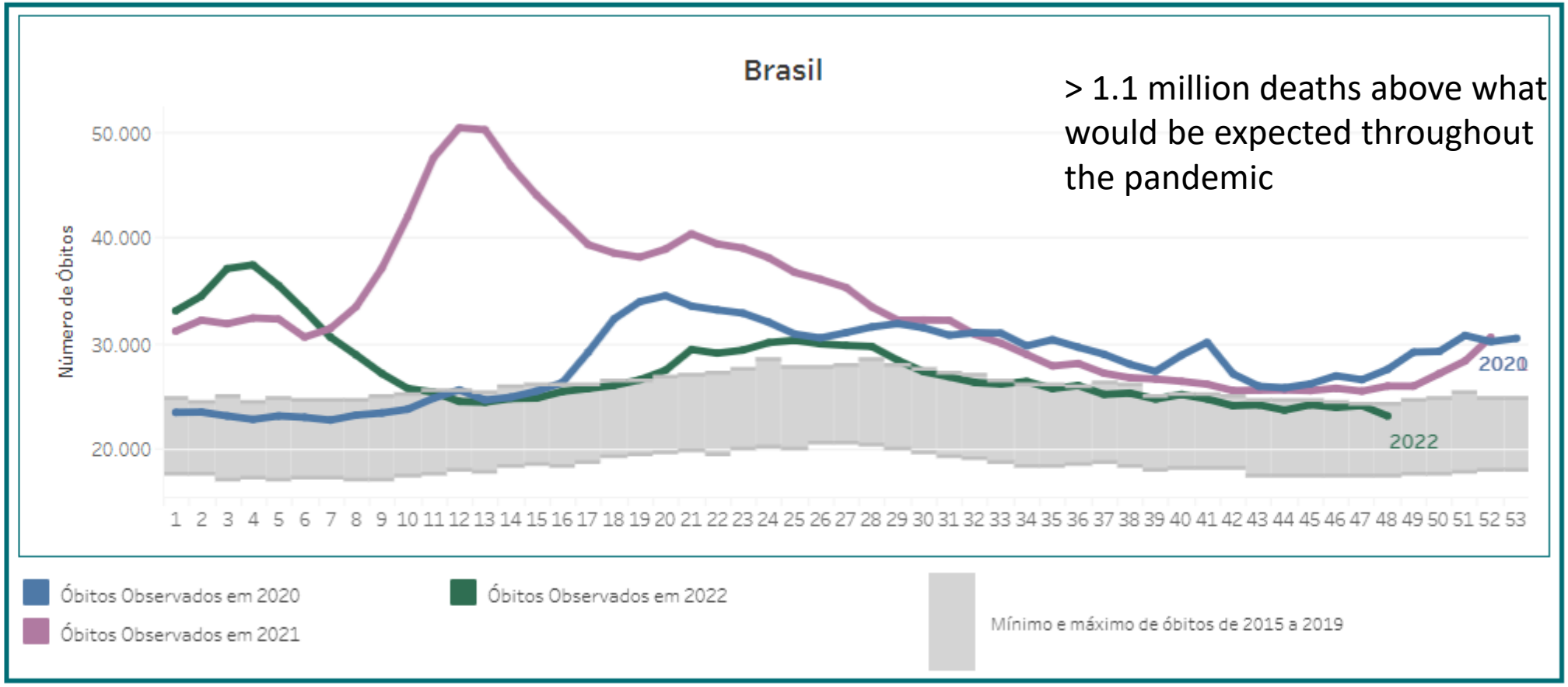
CONASS Conselho Nacional de Secretários de Saúde

Vital Strategies

ARPEN BRASIL Associação Nacional dos Registradores de Pessoas Naturais

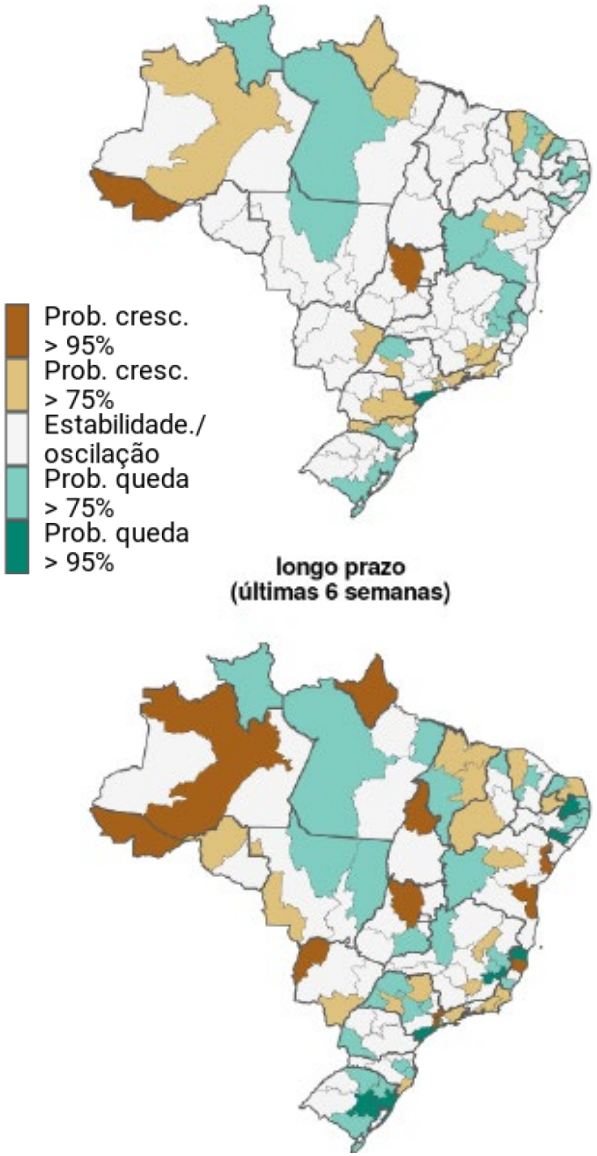
Data da última atualização 06/02/2023

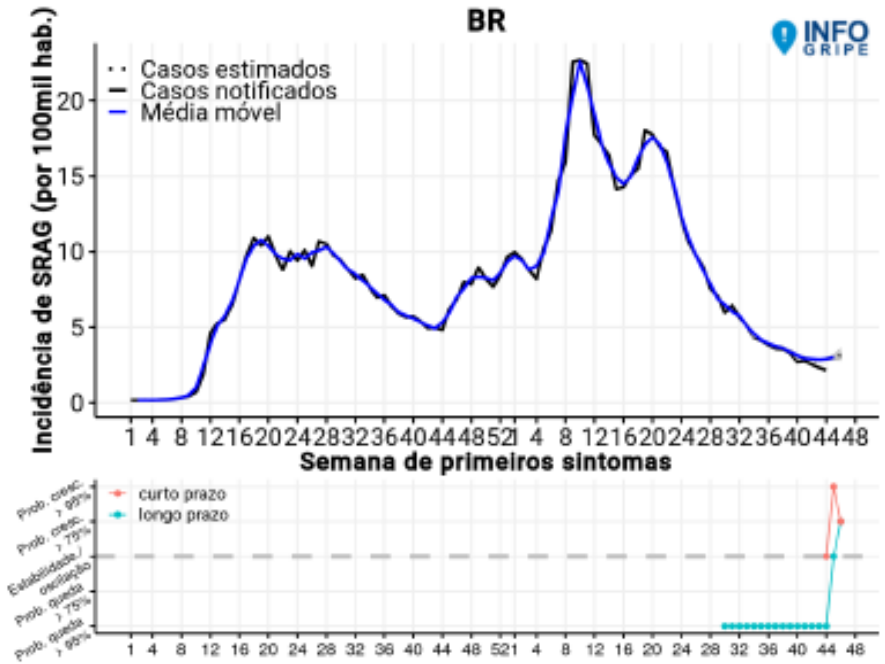
Curva de óbitos Esperados e Observados



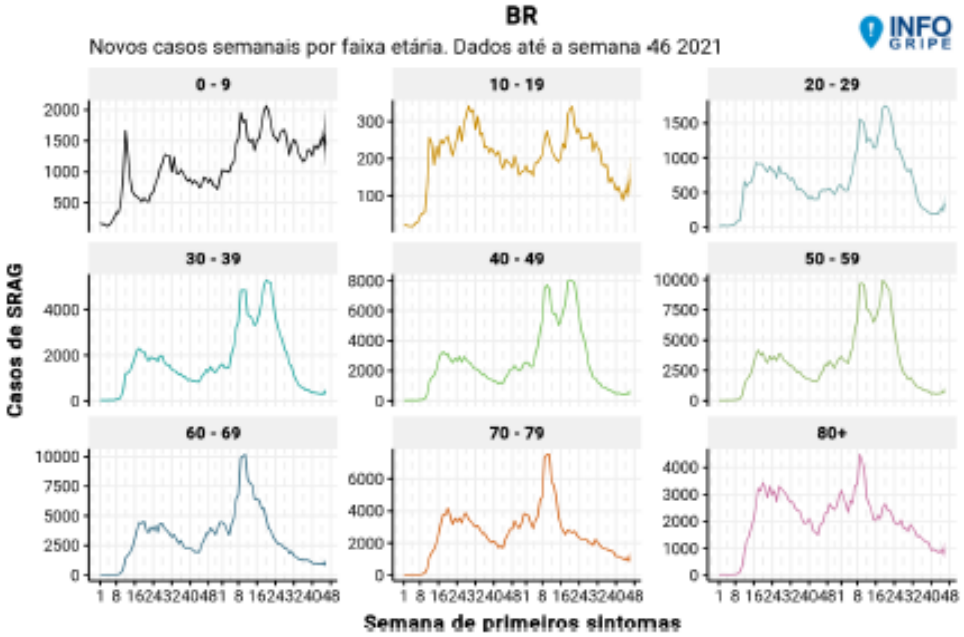
> 1.1 million deaths above what would be expected throughout the pandemic

Severe Acute Respiratory Infection (SARI)– EW 50





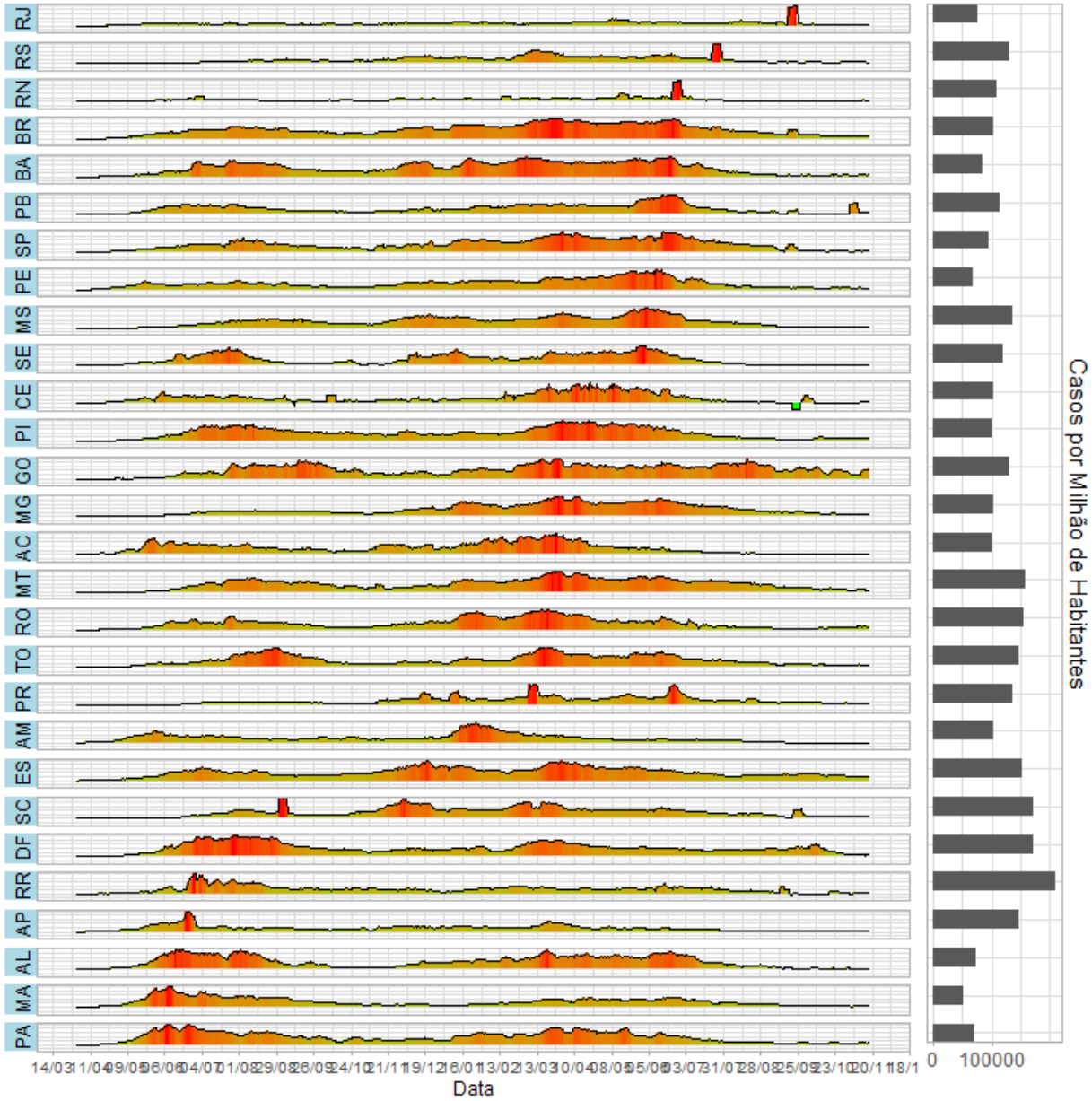
(a) Estimativa da incidência e análise de tendência atual para os casos de SRAG no Brasil.

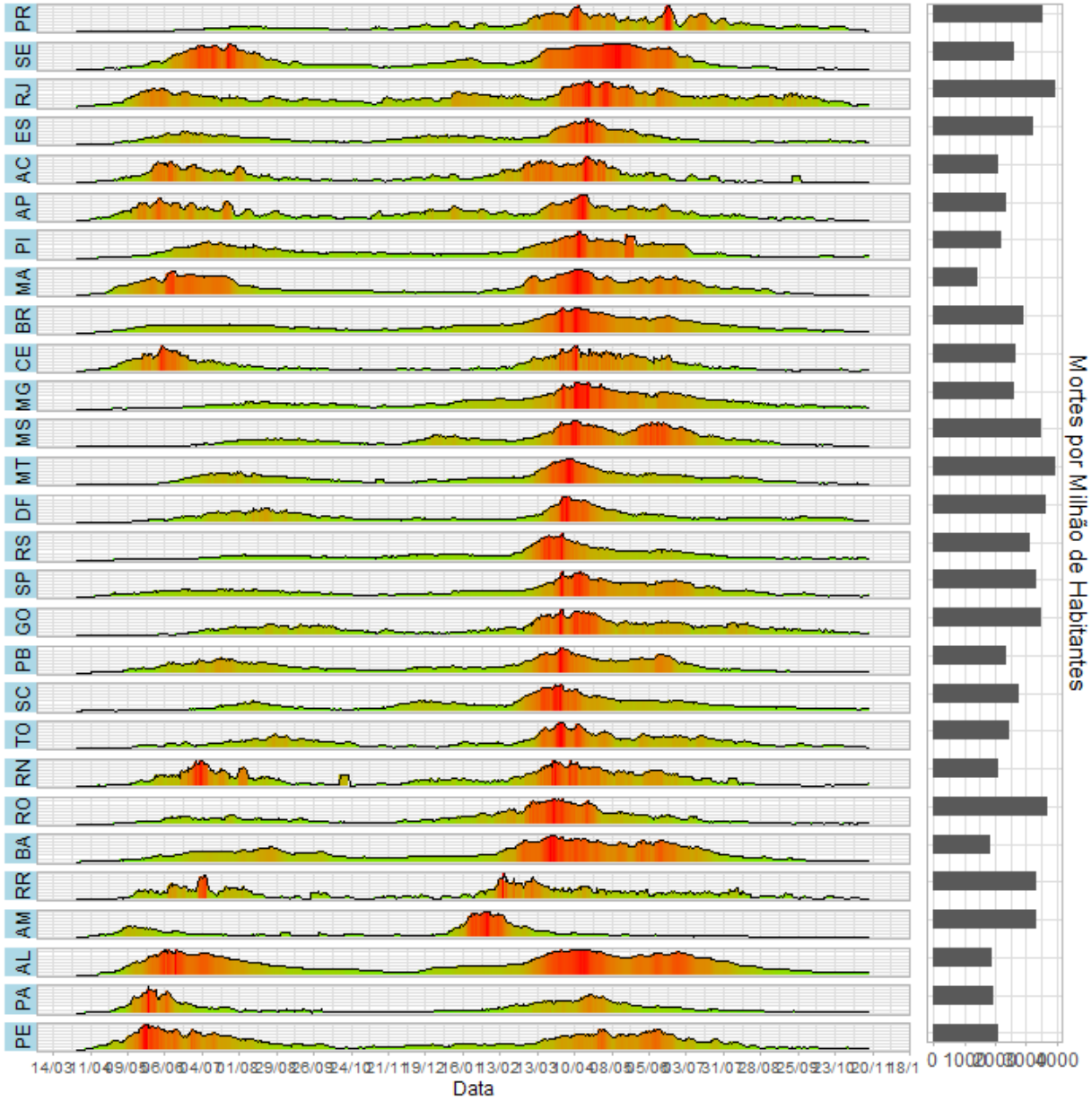


(b) Estimativa de novos casos semanais de SRAG no Brasil, por faixa etária.

http://info.gripe.fiocruz.br/

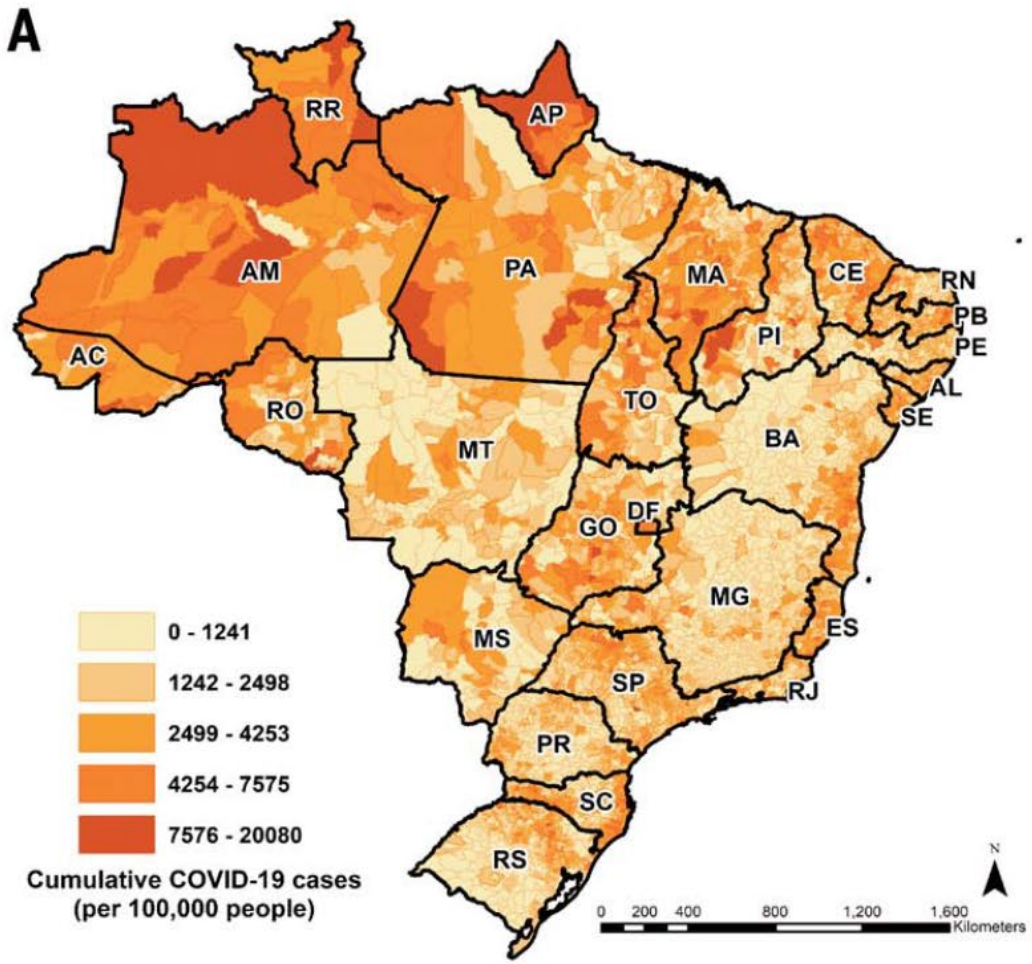
Heterogeneity and quasi-synchronicity: cases and deaths

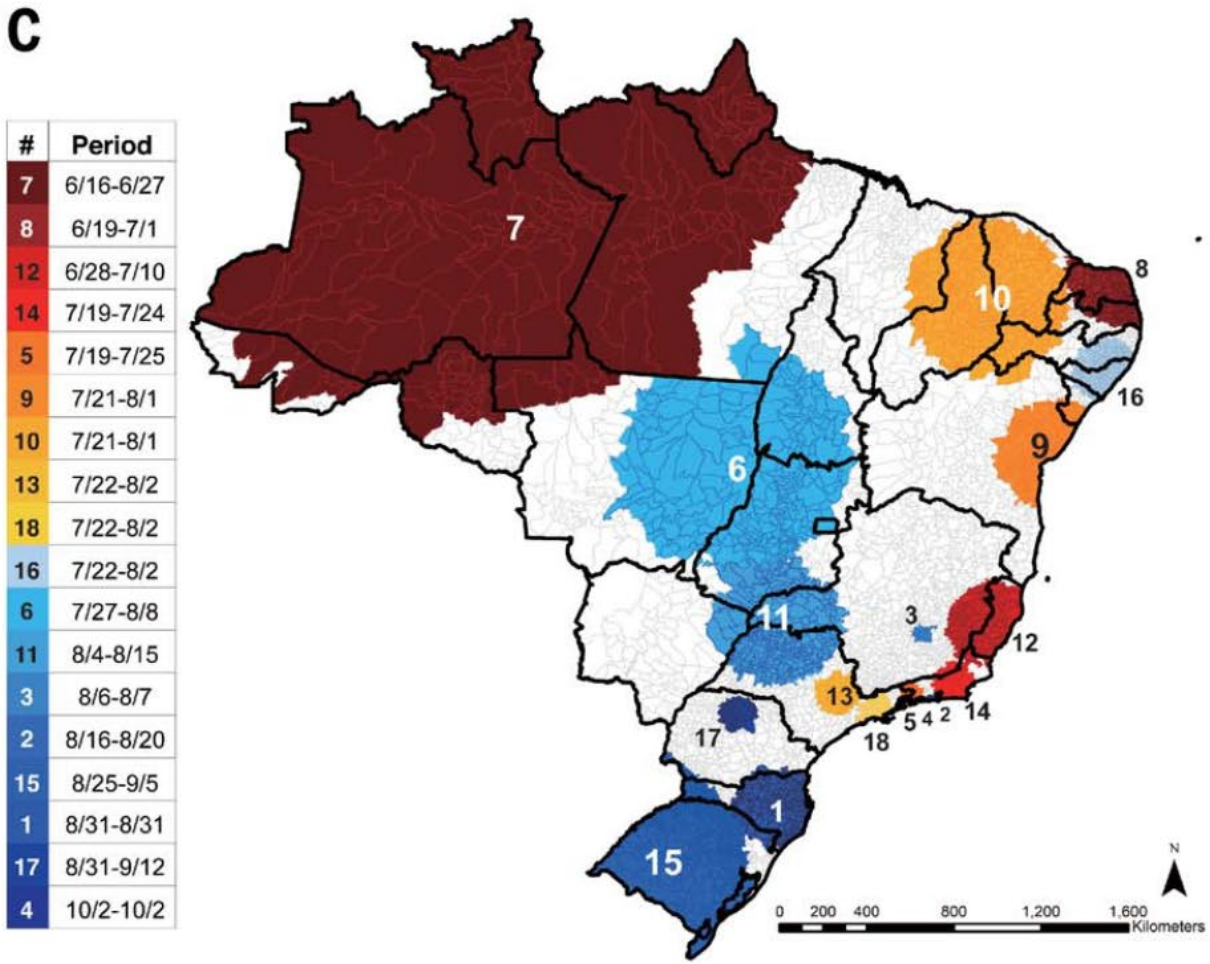




https://covid19analytics.com.br/

Spatiotemporal heterogeneity of the pandemic





Science AAAS

Castro MC, Kim S, Barberia L, Ribeiro AF, Gurzenda S, Ribeiro KB, Abbott E, Blossom J, Rache B, Singer BH. Spatiotemporal pattern of COVID-19 spread in Brazil. Science. 2021;372(6544):821-826. doi: 10.1126/science.abh1558.

Use of surveys during Covid-19 pandemic

Main uses of surveys in Covid-19

- Evaluate markers of infection
- Evaluate adherence to non-pharmacological measures and their effects at the population level
- Estimate vaccine coverage, vaccine hesitancy and associated factors
- Identify the effects of the pandemic on access to and use of health services
- Assess social inequalities in the context of the pandemic
- Characterize the direct and indirect effects of the pandemic on the health of the population for health planning

Winter & Hedge (2020) The important role of serology for COVID-19 control. doi: 10.1016/S1473-3099(20)30322-4
Lipsitch M et al. (2020). Defining the epidemiology of Covid-19 – studies needed. doi: 10.1056/NEJMp2002125.

Using population surveys to estimate infection fatality rate

Table 6. Estimated number of infections, excess deaths, and infection fatality rates of SARS-CoV-2 by sex and age groups, state of Maranhão, Brazil, 2020. N=3156

Sex	Age Group, years	SARS-CoV-2 seroprevalence, % (95%CI)	Estimated number of infections	Number of deaths (estimate based on excess deaths due to natural causes)[a]	Infection fatality rate, % (95%CI)
Male					
	0–59	36.38 (30.54–42.22)	1,149,733	1366	0.12 (0.10–0.14)
	≥ 60	39.85 (32.74–46.95)	133,937	3903	2.91 (2.43–3.49)
	Total	37.18 (31.81–42.55)	1,299,992	5270	0.41 (0.35–0.47)
Female					
	0–59	44.05 (38.71–49.40)	1,415,266	563	0.04 (0.03–0.05)
	≥ 60	36.02 (24.46–47.58)	146,117	2278	1.56 (1.13–2.15)
	Total	42.37 (36.11–48.63)	1,533,005	2840	0.19 (0.16–0.22)
Overall					
	0–59	41.26 (36.84–45.69)	2,629,556	1929	0.07 (0.07–0.08)
	≥ 60	37.54 (29.24–45.85)	278,482	6181	2.22 (1.78–2.77)
	Total	40.44 (35.57–45.32)	2,877,454	8110	0.28 (0.25–0.32)

IFR: infection fatality rate; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.
[a] Fonte: Conselho Nacional de Secretários de Saúde. Painel de análise do excesso de mortalidade por causas naturais no Brasil em 2020. Brasília, DF: CONASS; 2020 [cited 2020 Sept 21]. Available from: https://www.conass.org.br/indicadores-de-obitos-por-causas-naturais/

Silva AAMD et al. (2020) Population-based seroprevalence of SARS-CoV-2 and the herd immunity threshold in Maranhão. doi: 10.11606/s1518-8787.2020054003278.

Variation in the prevalence of infection according to adherence to protective measures for Covid-19 in Maranhão, 2020

Table 2. Prevalence of antibodies against SARS-CoV-2 according to adherence to non-pharmaceutical interventions at the beginning of the pandemic and in the last month, state of Maranhão, Brazil, 2020.

Non-pharmaceutical interventions	n	% weighted	f infected	% infected weighted (95%CI)	p
Last month					
Social distancing					0.015
No	1875	62.6	757	44.3 (39.6–49.0)	
Yes[a]	1281	37.4	410	34.0 (26.5–41.4)	
Wearing of face masks					0.036
No	1310	44.5	517	45.9 (40.6–51.3)	
Yes[b]	1846	55.5	650	36.0 (29.1–43.0)	
Hand hygiene					0.095
No	1557	51.6	612	44.4 (39.1–49.7)	
Yes[c]	1599	48.4	555	36.2 (28.7–43.8)	
Physical distancing					0.030
No	1817	61.0	710	43.3 (38.0–48.6)	
Yes[d]	1339	39.0	457	35.9 (29.7–42.2)	

95%CI: 95% confidence interval; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

[a] Never leaves home or seldom goes out, with a maximum of one outing every fifteen days.

[b] Uses mask on all exits and does not remove or seldom removes the mask from the face.

[c] Sanitizes the hands ≥ 6 times per turn (morning, afternoon, and night) with soap or alcohol gel.

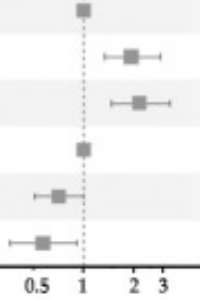
[d] Never or hardly ever comes within 1.5 m of other people.

Silva AAMD et al. (2020) Population-based seroprevalence of SARS-CoV-2 and the herd immunity threshold in Maranhão. doi: 10.11606/s1518-8787.2020054003278.

Fatores associados à hesitação vacinal, Salvador, 11/20 a 01/21

Prevalência de hesitação vacinal = 18.6%; 95% CI 17.1–20.1% (N=2521)

Associated factors according to sex	Response	OR for COVID-19 vaccine hesitancy	OR (95% CI)	p value
Male group				
Received influenza vaccine in 2020	No		Reference	
	Yes		0.59 (0.39 – 0.88)	0.01
Currently working	No		Reference	
	Yes		0.59 (0.39 – 0.89)	0.01
Comorbidities [1]	No		Reference	
	Yes		0.56 (0.34 – 0.89)	0.02
Female group				
Received influenza vaccine in 2020	No		Reference	
	Yes		0.56 (0.43 – 0.72)	< 0.001
Years of formal education	>12		Reference	
	10 to 12		1.93 (1.33 – 2.89)	< 0.001
	0 to 9		2.17 (1.45 – 3.30	< 0.001
COVID-19 risk perception [2]	Not probable		Reference	
	Slightly or moderately probable		0.71 (0.51 – 1.00)	0.04
	Very probable		0.57 (0.36 – 0.90)	0.02



Nery N Jr et al. (2021). COVID-19 vaccine hesitancy and associated factors according to sex: A population-based survey in Salvador, Brazil. doi: 10.1371/journal.pone.0262649.

Trust in scientists in times of pandemic

Individual trust and willingness to be vaccinated

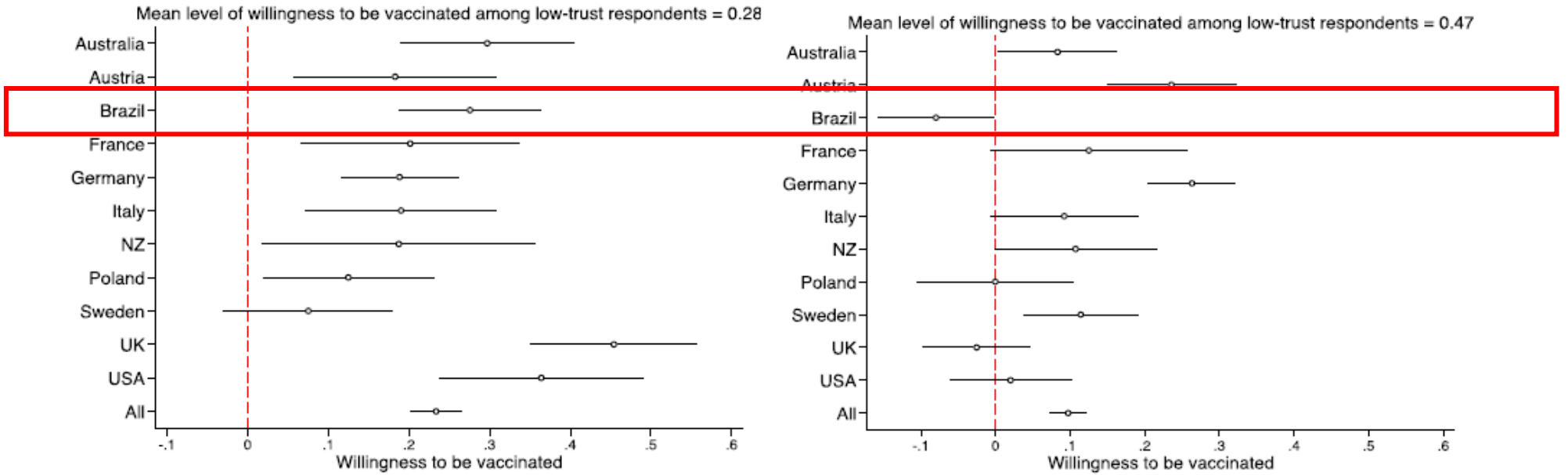


Fig. S5a. Trust in scientists

Fig. S5b. Trust in government

https://www.pnas.org/content/pnas/suppl/2021/09/21/2108576118.DCSupplemental/pnas.2108576118.sapp.pdf

Impact of Covid-19 – outpatient care

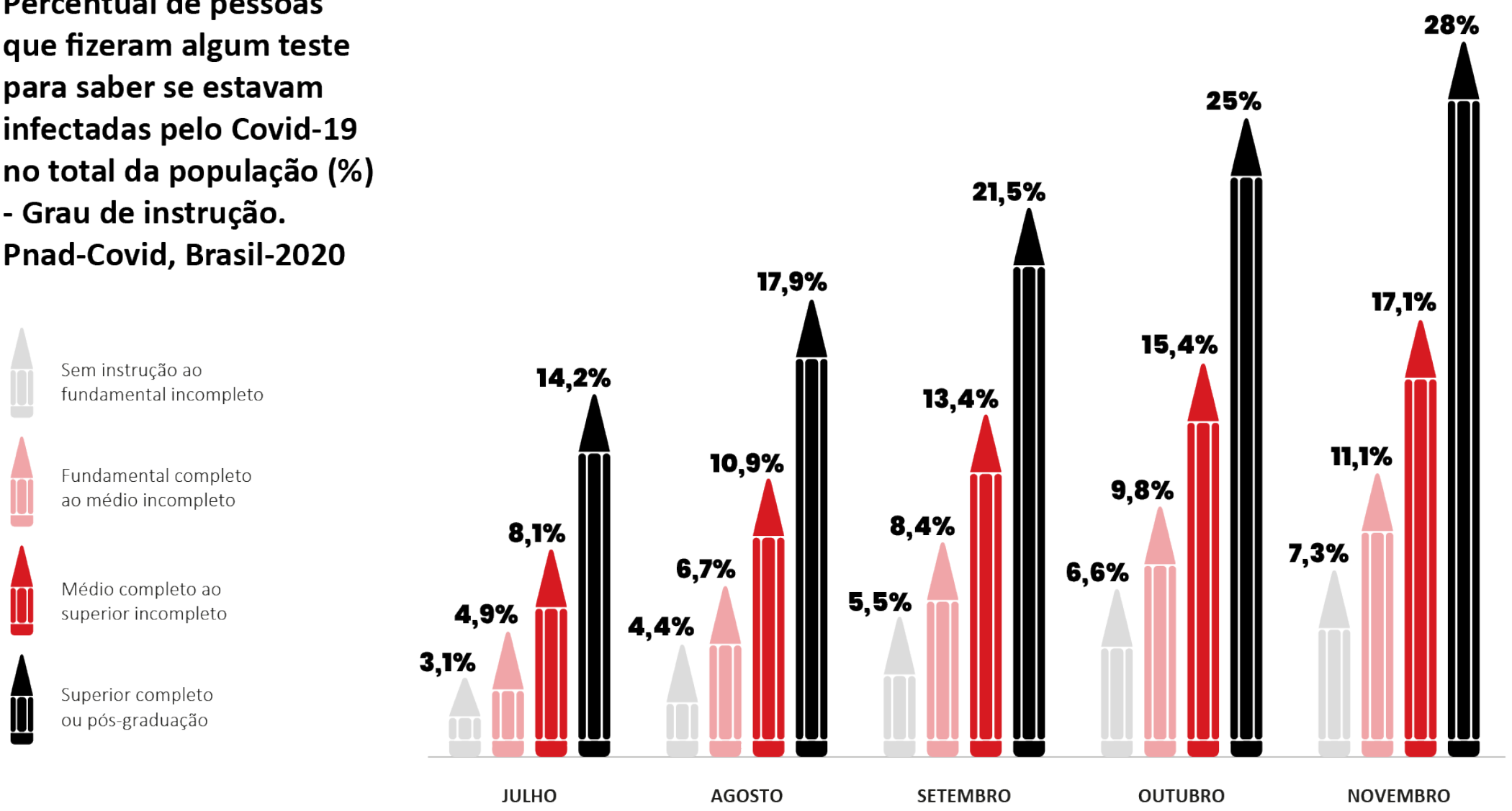
Proportion of subjects who failed to seek health care, or missed a routine or screening examination.	% (95%CI)
Since March 2020, had a health problem and failed to seek health care	11.8 (11.4-12.1)
Since March 2020, failed to attend to a health service for a routine or screening examination	17.3 (16.9-17.7)
Main reason for not seeking health care	
Health service was closed	21.4 (20.4-22.5)
Fear of getting COVID-19 infection	45.9 (44.6-47.1)
Considered unnecessary	10.3 (9.6-11.0)
Other	22.4 (21.5-23.5)

Since March 2020,	had a health problem and failed to seek health care		failed to attend to a health service for a routine or screening examination	
	%	PR (95%CI)	%	PR (95%CI)
Wealth quintiles		p < 0.001 **		p < 0.001 **
Poorest	14.1	1.64 (1.48-1.81)	18.8	1.18 (1.09-1.28)
2nd	12.7	1.47 (1.32-1.64)	18.0	1.13 (1.04-1.23)
3rd	11.8	1.38 (1.23-1.54)	16.3	1.02 (0.94-1.11)
4th	10.7	1.25 (1.11-1.40)	17.0	1.06 (0.98-1.16)
Richest	8.6	1.00 (Reference)	15.9	1.00 (Reference)
Region of Brazil		p < 0.001 *		p < 0.001 *
North	17.2	2.04 (1.83-2.26)	20.9	1.56 (1.43-1.71)
Northeast	13.4	1.58 (1.43-1.75)	18.7	1.40 (1.29-1.53)
Southeast	9.1	1.07 (0.96-1.20)	16.3	1.22 (1.12-1.33)
South	8.5	1.00 (Reference)	13.4	1.00 (Reference)
Central-West	9.9	1.17 (1.02-1.34)	15.8	1.18 (1.06-1.31)
Race/Skin color		p < 0.001 *		p < 0.001 *
White	9.9	1.00 (Reference)	16.0	1.00 (Reference)
Mixed-race	12.9	1.31 (1.22-1.40)	17.7	1.10 (1.04-1.17)
Black	12.0	1.22 (1.11-1.35)	18.1	1.13 (1.05-1.22)
Asian	14.9	1.51 (1.28-1.78)	21.1	1.31 (1.15-1.50)
Indigenous	14.8	1.50 (1.21-1.86)	20.3	1.26 (1.05-1.52)

Horta BL et al. COVID-19 and outpatient care: a nationwide household survey. Cad Saude Publica. 2022 Apr 15;38(4):e00194121. doi: 10.1590/0102-311X00194121.

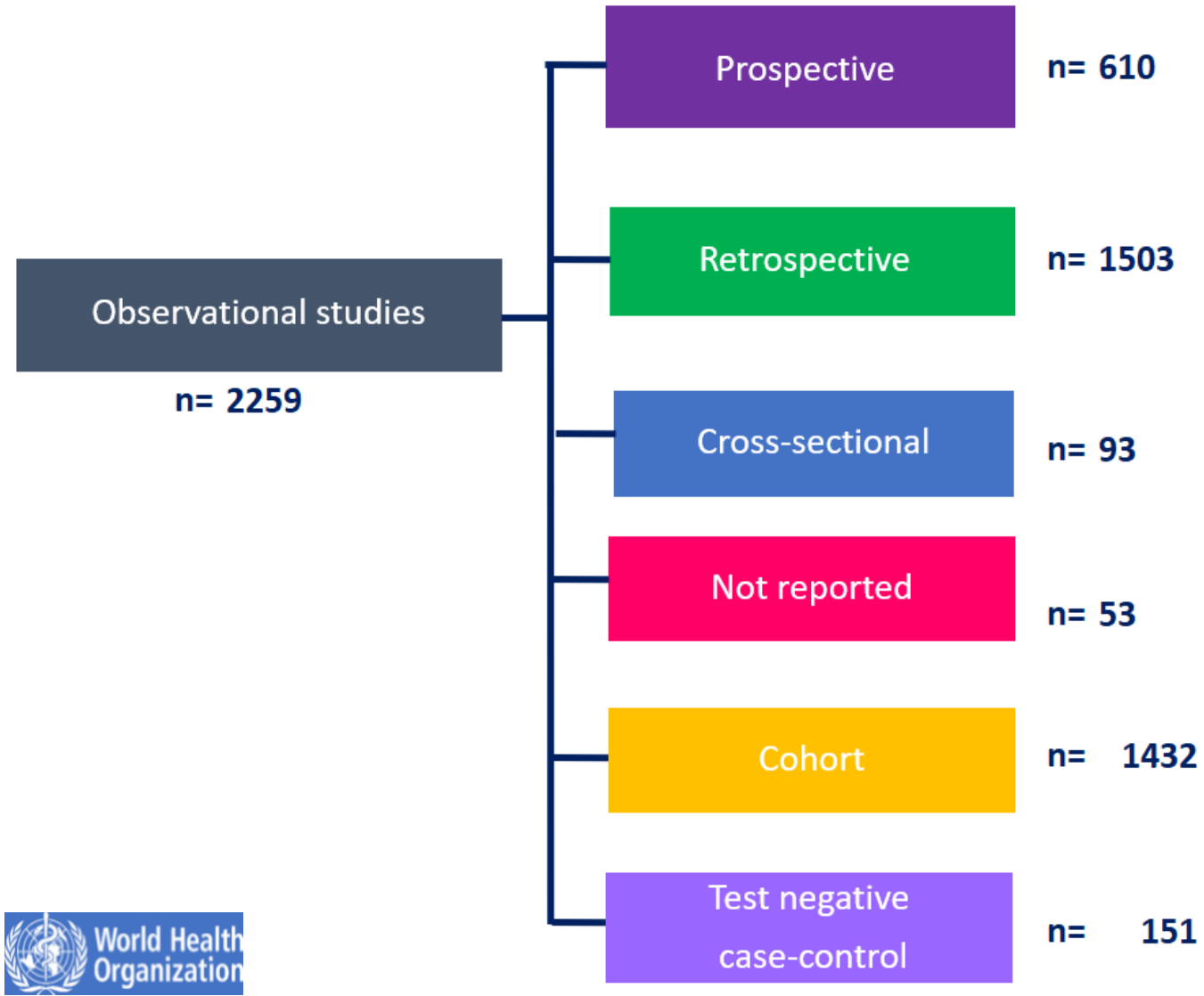
Inequalities in testing for Covid-19 in Brazil, 2020

Percentual de pessoas que fizeram algum teste para saber se estavam infectadas pelo Covid-19 no total da população (%) - Grau de instrução. Pnad-Covid, Brasil-2020



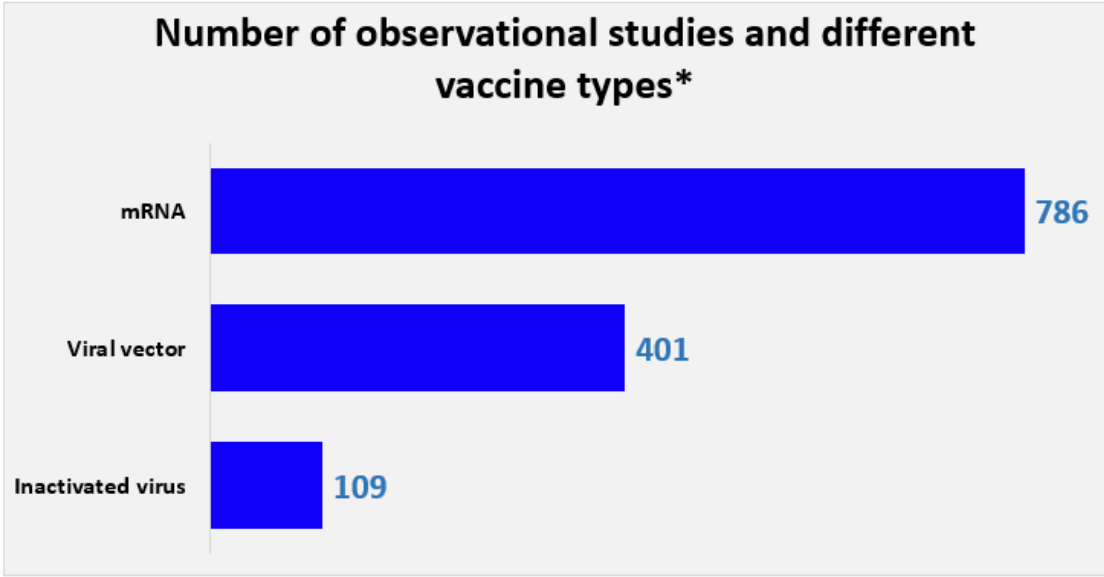
Use of case-control studies for assessing vaccine effectiveness

Landscape of observational studies on the effectiveness of COVID-19 vaccination



Number of Observational studies on variants

Types of variants	# studies
Variants of concern	1294
Alpha	996
Beta	457
Gamma	434
Delta	1410
Omicron	767



** These numbers are an estimate, as some studies have not reported the vaccine type, and many studies that have assessed multiple vaccines*

https://www.who.int/publications/m/item/draft-landscape-of-observational-study-designs-on-the-effectiveness-of-covid-19-vaccination

World Health Organization

Test-negative case-control study

- Problems in studies with cases presenting diagnostic test +:
  - It is a selected group that presents
    - Symptoms
    - Motivation (health-seeking behavior) + Access to take the test
  - Controls randomly selected from the population → selection bias
- Controls with negative test:
  - Have symptoms and have gone through a similar selection process (health-seeking behavior + access)

Table 1. Calculation of Unadjusted Vaccine Effectiveness among Patients with Covid-19–like Illness in a Study with a Test-Negative Design.*

Vaccination Status	Patients Who Sought Medical Care		Patients Who Did Not Seek Medical Care	
	Positive SARS-CoV-2 Test	Negative SARS-CoV-2 Test	Positive SARS-CoV-2 Test	Negative SARS-CoV-2 Test
Vaccinated	Stratum A, 600 patients	Stratum B, 20,000 patients	Stratum C	Stratum D
Not vaccinated	Stratum E, 4000 patients	Stratum F, 16,000 patients	Stratum G	Stratum H

* Shown are the strata of a full population before sampling and the numbers of patients in a hypothetical sample. This test-negative design involves data from patients who sought medical care for coronavirus disease 2019 (Covid-19)–like illness and had a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test result. The remaining information on the patients who did not seek medical care is not observed. Unadjusted vaccine effectiveness (VE) is estimated as 1 minus the odds ratio for vaccine effectiveness among patients who sought medical care for Covid-19–like illness and had a SARS-CoV-2 test result, calculated as VE=1−(A/E) divided by (B/F), or 1−(600÷4000)÷(20,000÷16,000)=88%. In order for the VE odds ratio to be a valid measure of effectiveness in the full population, it must be assumed that VE is the same for patients who sought medical care for Covid-19–like illness and those who did not. This implies equivalence between the odds ratios (A/E) divided by (B/F) and (C/G) divided by (D/H). To adjust for confounders that are observed, an adjusted odds ratio, estimated with case weighting or regression, is used in place of the unadjusted odds ratio. Adapted from Jackson and Nelson.[4]

Condition for extrapolation of vaccine effectiveness estimates for the population that did not seek health services and/or did not have access to testing:

$$\frac{A/E}{B/F} = \frac{C/G}{D/H}$$

Dean, Hogan, and Schnitzer

VIGVAC

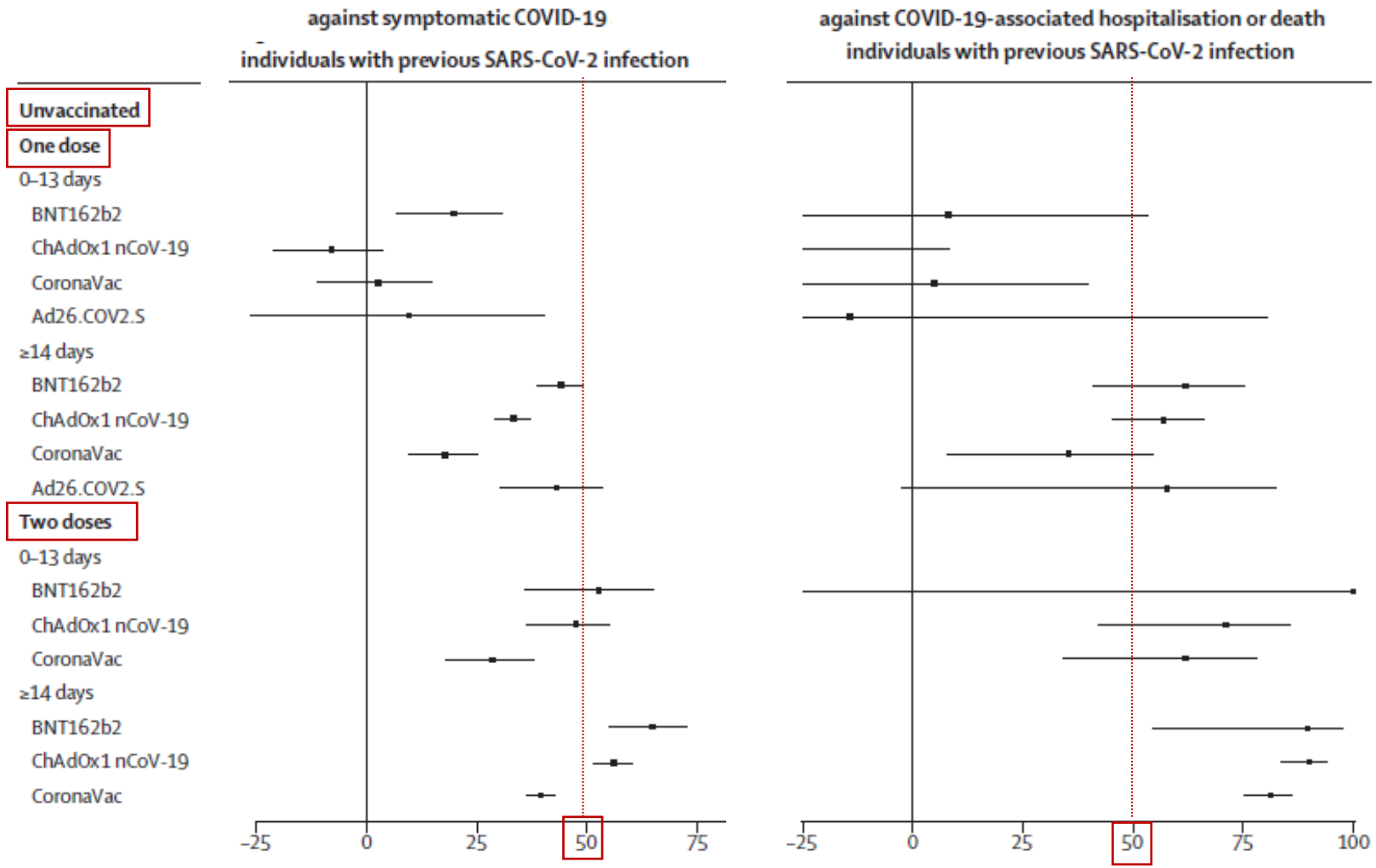
MONITORING THE IMPACT OF COVID-19 VACCINATION IN BRAZIL

VIGIVAC COVID-BR

VIGIVAC COVID-BR - https://vigivac.fiocruz.br/

Effectiveness and prior infection

- Increased protection to avoid infection and, mainly, hospitalization and death, of people who had already been infected before being vaccinated.
- Among those who had already been infected before vaccination, the effectiveness of the vaccine against hospitalization or death 14 or more days after completion of the vaccine series was 81.3% for CoronaVac, 89.9% for AstraZeneca, 57, 7% for Janssen and 89.7% for Pfizer.



Cerqueira-Silva T, Andrews JR, Boaventura VS, Ranzani OT, de Araújo Oliveira V, Paixão ES, Júnior JB, Machado TM, Hitchings MDT, Dorion M, Lind ML, Penna GO, Cummings DAT, Dean NE, Werneck GL, Pearce N, Barreto ML, Ko AI, Croda J, Barral-Netto M. Effectiveness of CoronaVac, ChAdOx1 nCoV-19, BNT162b2, and Ad26.COV2.S among individuals with previous SARS-CoV-2 infection in Brazil: a test-negative, case-control study. Lancet Infect Dis. 2022 Jun;22(6):791-801. doi: 10.1016/S1473-3099(22)00140-2..

Heterologous protection (Coronavac + Pfizer) –Ômicron

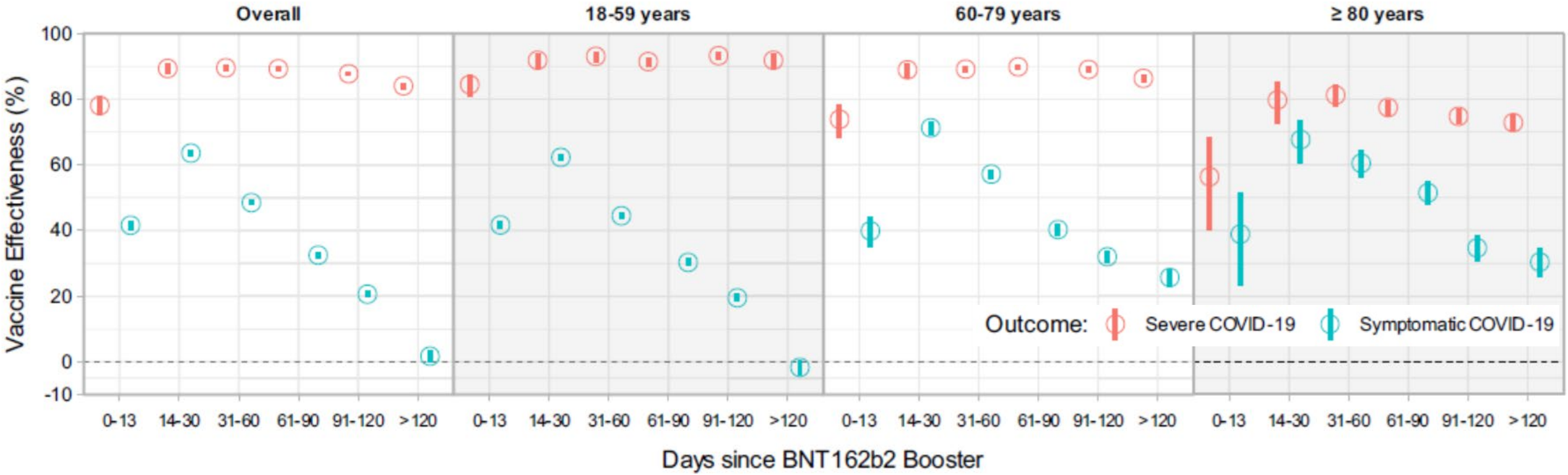


Fig. 3 Vaccine Effectiveness against symptomatic and Severe COVID-19. According to days after booster dose during the Omicron dominance period, stratified by age group. Point estimates are adjusted vaccine effectiveness (1- adjusted odds ratio), with error bars indicating the corresponding 95% Wald's C.I. Blue represents adjusted VE against symptomatic infection, and red adjusted VE against severe outcomes. All models the comparison group is unvaccinated.

- No significant protection against symptomatic infection
- Except for subjects aged ≥80 years, CoronaVac plus a booster dose of BNT162b2 offered high and durable protection against serious outcomes due to Omicron.

Cerqueira-Silva T et al. Duration of protection of CoronaVac plus heterologous BNT162b2 booster in the Omicron period in Brazil. Nat Commun. 2022 Jul 18;13(1):4154. doi: 10.1038/s41467-022-31839-7.

Pregnancy

Table 2 Effectiveness of CoronaVac against symptomatic and severe COVID-19, among pregnant women aged 18–49 years in Brazil (comparison of symptomatic and severe cases with test-negative controls)

Sinovac-CoronaVac

Vaccination status	Unadjusted odds ratio (95% CI)	Unadjusted[#] odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Adjusted* VE% (95% CI)	*p*-value
Symptomatic COVID-19					
Unvaccinated	Ref	Ref	Ref	Ref	
One dose < 13 days	0.94 (0.77–1.14)	1.35 (1.10–1.66)	1.35 (1.09–1.68)	–	0.006
Partially vaccinated (one dose ≥ 14 days)	0.64 (0.53–0.77)	1.00 (0.82–1.22)	0.94 (0.76–1.18)	5.02 (–18.22– 23.69)	0.645
Two doses ≥ 14 days	0.42 (0.35–0.50)	0.69 (0.57–0.83)	0.59 (0.47–0.72)	40.97 (27.07– 52.22)	< 0.001
Severe COVID-19					
Unvaccinated	Ref	Ref	Ref	Ref	
One dose < 13 days	1.38 (0.87–2.19)	1.64 (1.01–2.65)	1.42 (0.83–2.43)	–	0.192
Partially vaccinated (one dose ≥ 14 days)	0.30 (0.13–0.69)	0.38 (0.16–0.87)	0.32 (0.13–0.80)	67.74 (20.00–87.00)	0.015
Two doses ≥ 14 days	0.15 (0.06–0.37)	0.20 (0.08–0.50)	0.14 (0.05–0.40)	85.39 (59.44– 94.80)	< 0.001

VE Vaccine effectiveness

* Adjusted for: Age, race, co-morbidities, region of residency, IBP and time

Adjusted for time

- A complete CoronaVac regimen in pregnant women was effective in preventing symptomatic COVID-19 and highly effective against severe forms in an environment that combined high disease burden and maternal deaths related to COVID-19.

Paixao ES, Wong KLM, Alves FJO, de Araújo Oliveira V, Cerqueira-Silva T, Júnior JB, Machado TM, Junior EPP, Boaventura VS, Penna GO, Werneck GL, Rodrigues LC, Pearce N, Barreto ML, Barral-Netto M. CoronaVac vaccine is effective in preventing symptomatic and severe COVID-19 in pregnant women in Brazil: a test-negative case-control study. BMC Med. 2022 Apr 5;20(1):146. doi: 10.1186/s12916-022-02353-w.

Challenges in carrying out epidemiological studies in the pandemic context

Challenges in carrying out epidemiological studies in the pandemic context

Table 1 Basic characteristics of COVID-19-related, peer-reviewed original articles

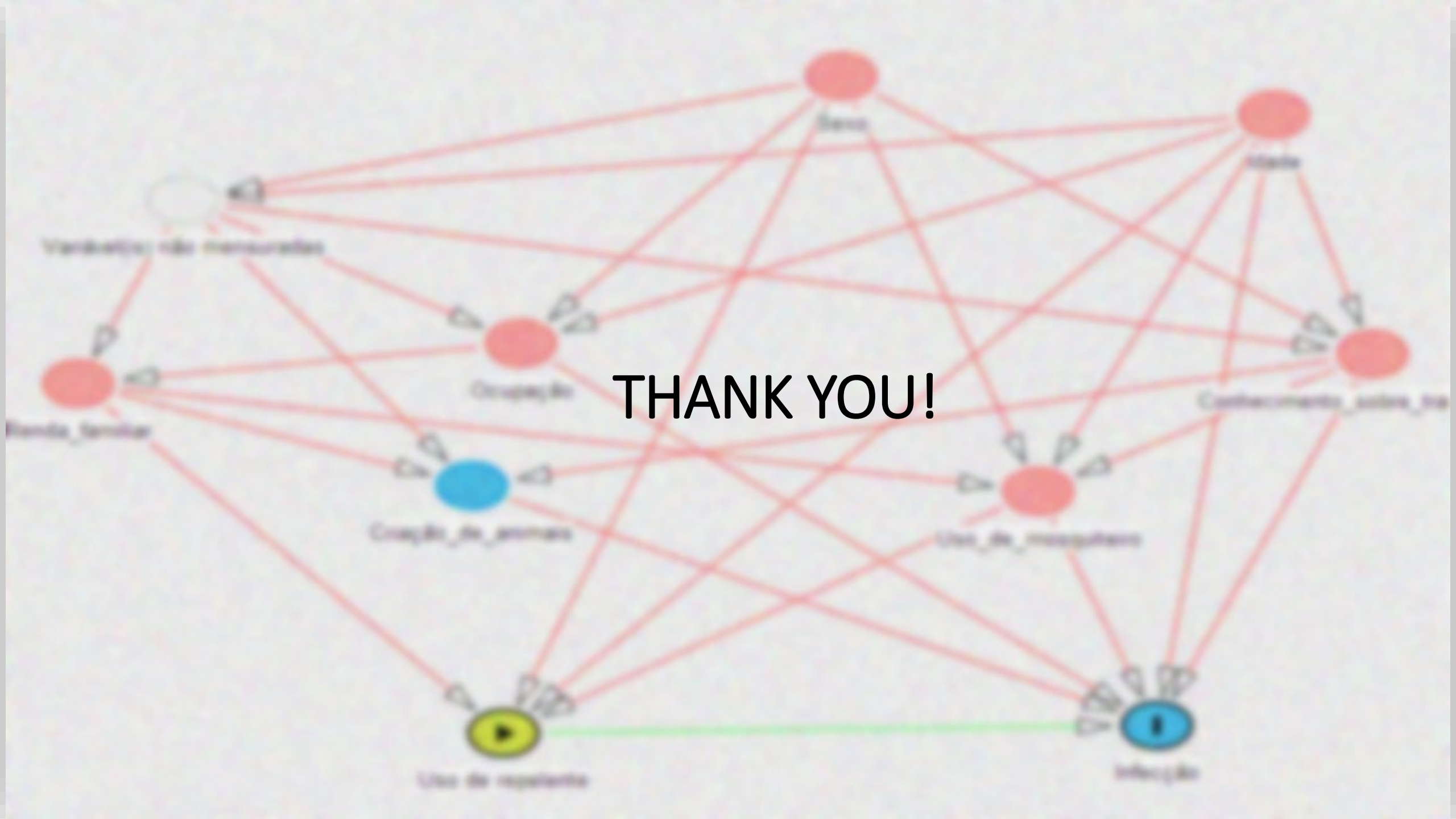
Type of original article studies involving patients	Number of studies (%)	Number of patients Median (IQR)	Number of studies at risk of bias (%)			Patient consent			
			Low	Intermediate	High	Written informed consent N (%)	Oral consent N (%)	Open data N (%)	No consent N (%)
Case-control	68 (9.5)	108 (62–211)	11 (16.2)	25 (36.7)	32 (47.1)	22 (32.4)	2 (2.9)	2 (2.9)	42 (61.8)
Cohort	50 (7.0)	110 (54–327)	7 (14.0)	20 (40.0)	23 (46.0)	15 (30.0)	1 (2.0)	4 (8.0)	30 (60.0)
Cross-sectional	306 (42.9)	217 (80–730)	10 (3.3)	43 (14.0)	253 (82.7)	89 (29.1)	18 (5.9)	75 (24.5)	112 (40.5)
Case series	129 (18.1)	18 (9–53)	9 (6.9)	26 (20.2)	94 (72.9)	24 (18.6)	15 (11.6)	3 (2.3)	87 (67.4)
Diagnostic	37 (5.2)	84 (49–215)	0 (0)	0 (0)	37 (100.0)	3 (8.1)	0 (0)	0 (0)	34 (91.9)
Prognostic	8 (1.1)	143 (66–217)	3 (37.5)	1 (12.5)	4 (50.0)	0 (0)	0 (0)	0 (0)	8 (100.0)
Simulation	185 (25.9)	1428 (14–40,696)	16 (8.6)	47 (25.4)	122 (66.0)	3 (1.6)	1 (0.5)	131 (70.8)	50 (27.0)
Non-randomized trial	8 (1.1)	35 (29–58)	1 (12.5)	1 (12.5)	6 (75.0)	4 (50.0)	0 (0)	0 (0)	4 (50.0)
Randomized controlled trial	4 (0.6)	56 (29–111)	0 (0)	2 (50.0)	2 (50.0)	2 (50.0)	0 (0)	0 (0)	2 (50.0)

This table displays the basic characteristics of the 713 clinical, peer-reviewed, COVID-19-related, original articles we critically appraised based on several risk of bias tools, according to the type of studies. Eighty-two studies were assessed using two tools, to better reflect their design. Shown are the number of studies, the median number of patients, the overall risk of bias after quality assessment, and how patient consent was addressed by authors

Raynaud et al. (2021). COVID-19-related medical research: a meta-research and critical appraisal. doi: 10.1186/s12874-020-01190-w

Challenges in carrying out epidemiological studies in the pandemic context

- Measurement
- Selection
- Representativeness
- Epidemic dynamics
- Social dynamics and volatility of feelings, perceptions and attitudes
- Statistical inference
- Causal inference
- Quality of reports (STROBE)
- Online surveys (Checklist for Reporting Results of Internet E-Surveys (CHERRIES)


Sexo
Idade
Variável(is) não mensuradas
Ocupação
Renda_familiar
Coação_de_animais
Uso_de_mosquiteiro
Uso de repelente
Infecção

THANK YOU!