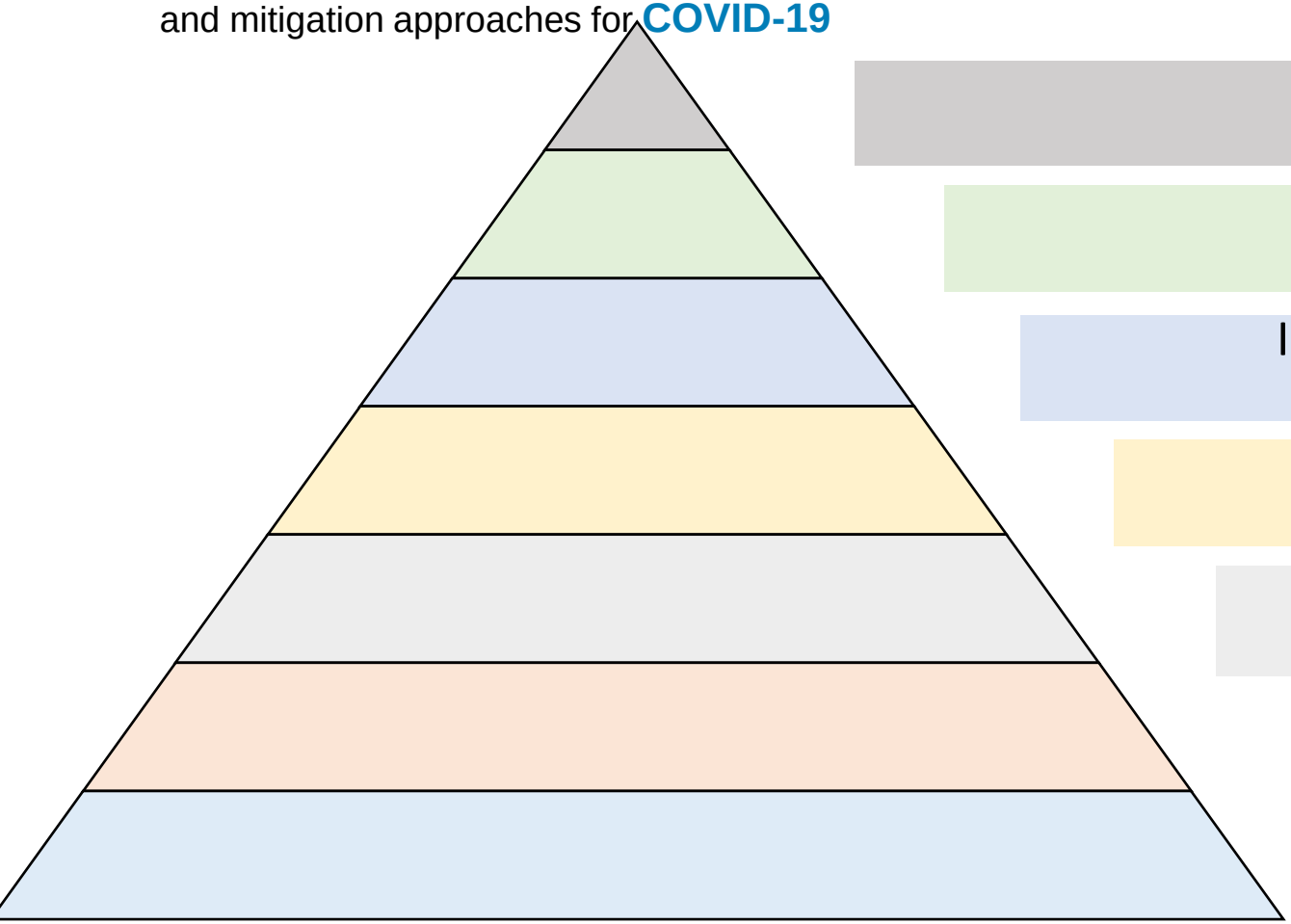
Case Study 2

Level of Evidence and Methods

- Case-control studies
- Cohort studies
- Systematic reviews
- Meta analyses and COVID-19

1 Level of Evidence

Has great **importance** for our interpretation of ”**what works**” also when we choose actions and mitigation approaches for **COVID-19**



Meta-analysis and systematic reviews

Randomized, blinded and placebo controlled trials

Interventional study with open label/non-randomized methodology

Observational study: prospective longitudinal cohort

Cross-sections case-control studies

Case series/case reports

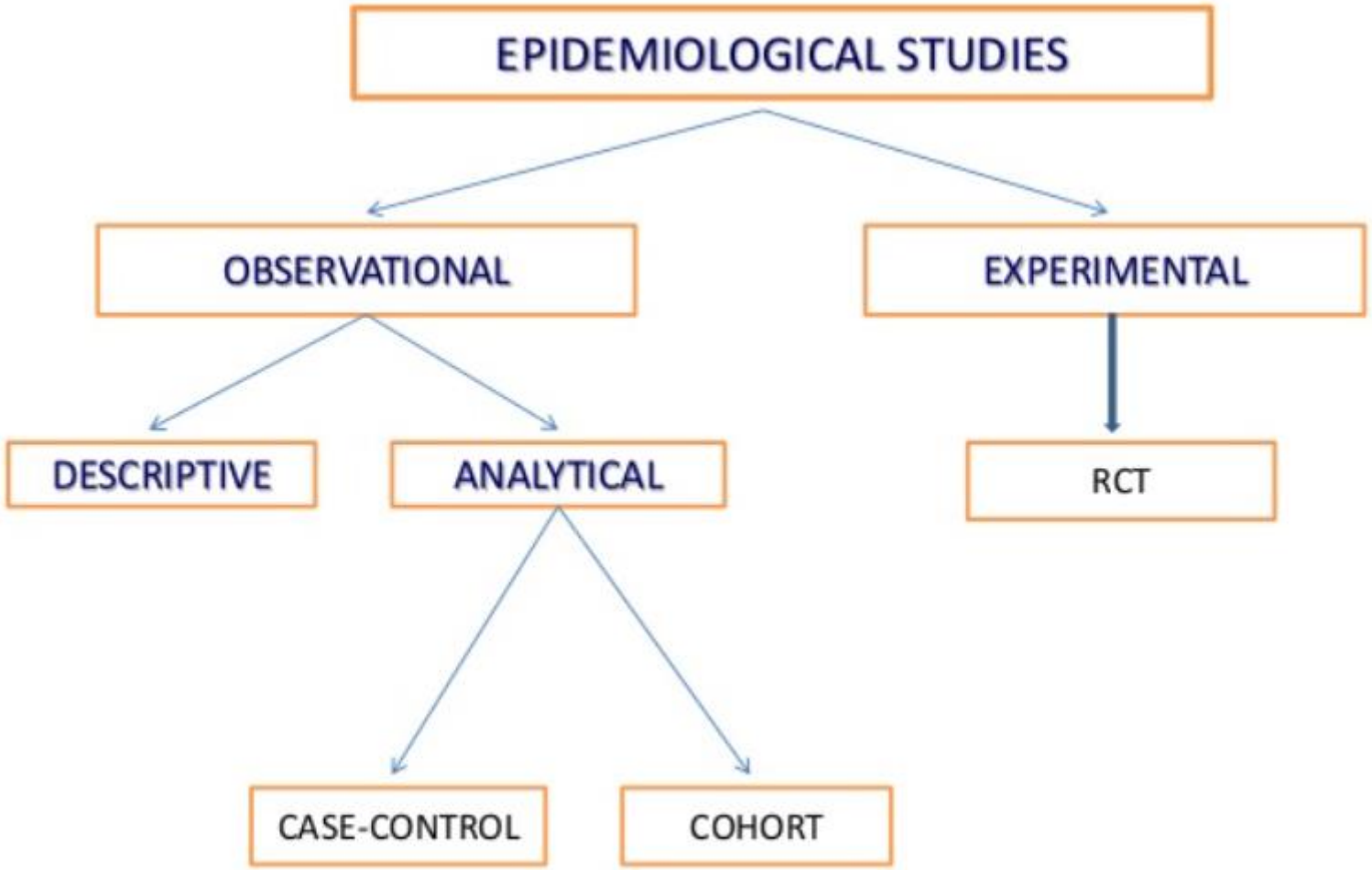
Expert opinion

Literature Review

Miscellaneous

2 Methods

How to test if methods (innovations) for containment of an epidemic or pandemic truly works?
How can we assess what is causing risk?



3 Analytical Epidemiological Studies

These studies are used to analyze the relationship between health status and other variables

The objective is to test a hypothesis

Subjects of interest are individuals, but with inference applied to population

Types

1. Case-control studies (also known as Case-reference studies)
2. Cohort studies, aka Follow-up studies

At the top of the pyramid of evidence in medical sciences:

1. Randomized, controlled trials
2. Systematic reviews and
3. Meta-analyses

CASE-CONTROL STUDIES

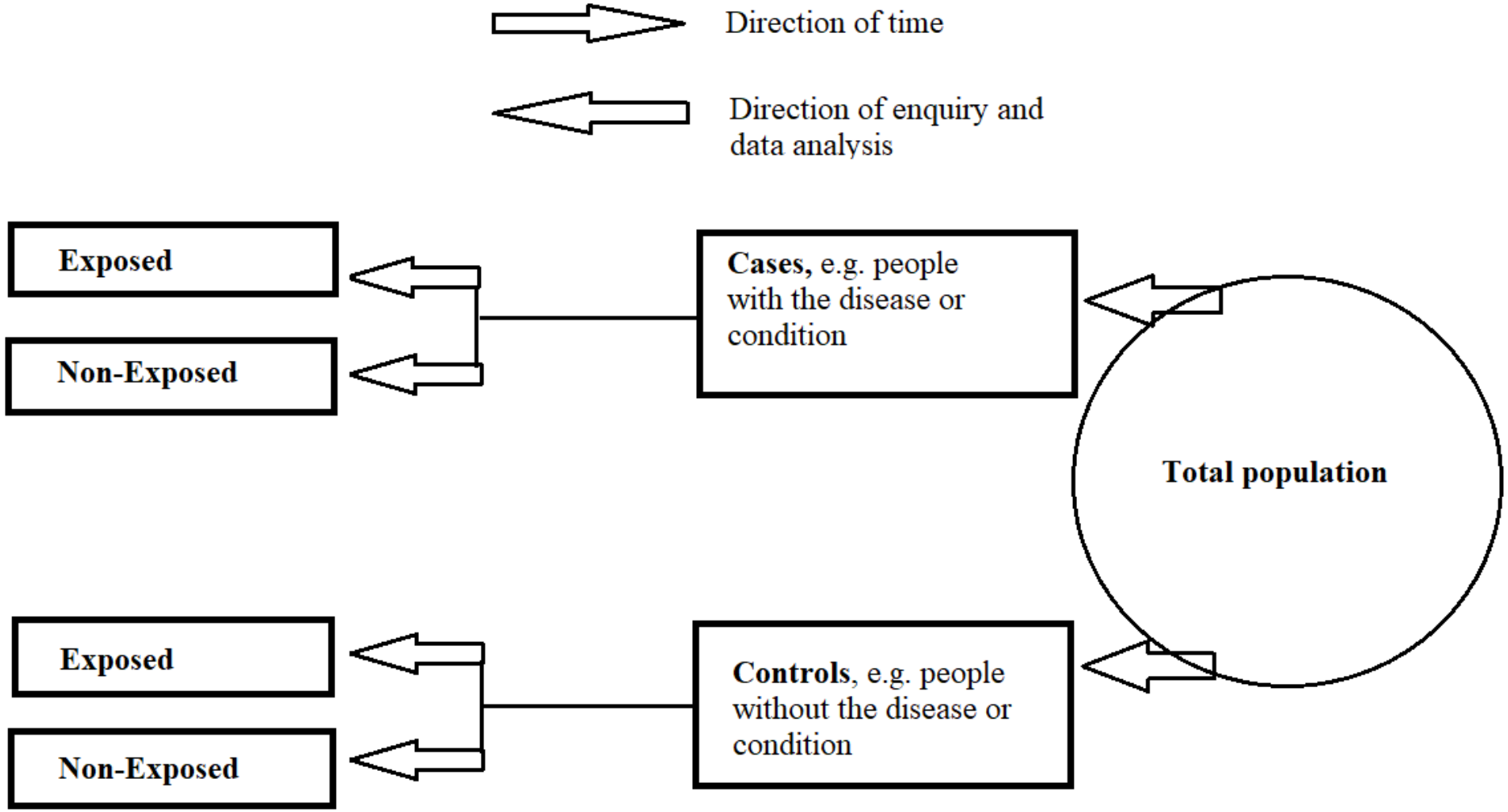
4 The Case-control Study

The Case-control study is usually the first approach to testing a hypothesis about disease causality, especially for rare diseases

Three features

a. Both exposed and outcome (disease) has already occurred, usually data is extracted from databases
b. Study proceeds backwards in time, from effect (disease) to cause
c. It uses control groups to support or refute, deny or contradict a hypothesis of inference

5 Design of a Case-control Study



	Cases With Lung cancer	Controls Without Lung cancer	Total
Smokers	A = 33	B=55	(a+b)=88
Non-smokers	C=2	D=27	(c+d)=29
Total	A+C =35	B+D=82	N=a+b+c+d

6 The Term: Odds Rate (OR)

The OR gives an estimation of risk of disease associated with the exposure

It measures strength of association of risk factor and the outcome, here disease

ODDS RATIO = AxD / B x C

In the example above: OR = 33 x 27 / 55 x 2 = 8,1

Conclusion: Smokers have a risk of developing lung cancer which is 8,1 times higher than non-smokers

Now, conduct the same analysis for matched groups, either with (i) using face-mask or (ii) not wearing face-mask, OR, travelling to work or work from home, with the outcome parameter: Rate of COVID-19.

	Cases With COVID-19	**Controls Without COVID-19**	**Total**
Going to work	A =	B=	(a+b)=
Work at home	C=	D=	(c+d)=
Total:	A+C =	B+D=	N=a+b+c+d

For the Odds Ratio to be a good approximation, the cases and the controls must be **representative** of the general population with respect to exposures.

However, **notice that** if the incidence of disease is unknown, the relative risk cannot be calculated

COHORT STUDIES

7 The Cohort Study

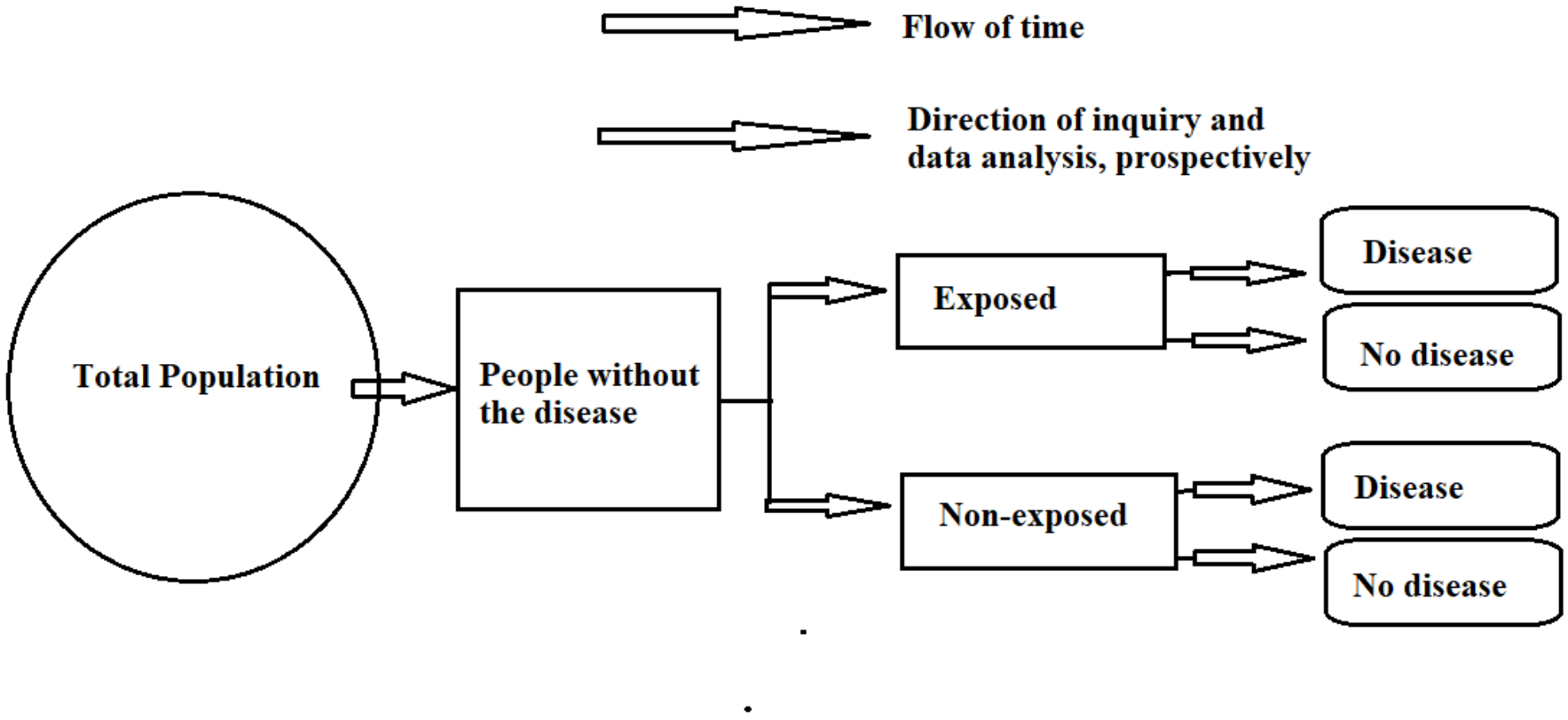
Cohort is a group of people, where all have similar characteristics

This is also called a prospective follow-up study

It starts with people who are free of the disease

Whole cohort is followed up prospectively, it often follows the cohort into the future, to see the effect of an exposure or to see the effect of measures to reduce exposures

Design of a Cohort Study



Example of Cohort study analysis, with application to assess causative association of smoking as cause of lung cancer

Smoking	Developed Lung Cancer	Did NOT develop Lung cancer	Total
Yes	A: 70	B: 6930	A+B = 7000
No	C: 3	D: 2997	C+D=3000

Incidence among smokers = 70/7000 = 10 per 1000 smokers
Incidence among non-smokers = 3/3000 = 1 per 1000

9 Attributable Risk (AR) or Risk Difference

Attributable Risk (AR) is the difference in incidence rates, between exposed and non-exposed groups.

AR = (Incidence Rate among exposed – Incidence Rate among non-exposed, divided by Incidence among the exposed) x 100

Example: AR = (10-1 / 10) x 100 = 90% in the previous example

AR is the proportion of disease which is due to a particular exposure risk factor. From the given example, 90 % of the lung cancers are due to smoking. In this case this would mean that most of the disease would be eliminated, if the risk-factor is eliminated.

Now apply this approach to the **COVID-19 pandemic**, using (if available) data on exposure rates from your home country. Do you have data on different exposures? Could we estimate how much % of COVID-19 could be prevented if 50% of the people stayed at home and away from exposure instead of travel to work?

Daily use of face mask	**Developed COVID-19**	**Did NOT develop COVID-19**	**Total**
Yes	A:	B:	A+B =
No	C:	D:	C+D=

10 Population Attributable Risk

Population AR = (Incidence rate in total population minus Incidence Rate among non-exposed, divided by Incidence rate in total population) x 100

Population Attributable Risk is a useful concept as it **gives the magnitude of disease that can be reduced, from the population if the suspected risk factor is reduced** or modified (*social distancing, Face-mask, work from home instead of travel to work etc*).

Applied to COVID-19, using national data from your country, measured or estimated, what can we conclude, from using estimated incidence rates among people with modified risk-exposure, such as use of face-masks, social distancing or other?

11 Comparison of Case-control vs. Cohort Studies

Case-control study	Cohort study
From effect to cause	From cause to effect
Starts with disease	Starts with people exposed to risk factors
Test whether the suspected risk-factor is associated more with disease	Tests whether disease occur more in those exposed to risk factor
First approach to testing the hypothesis	To precisely formulate hypothesis
Few subjects needed	Large number of subjects needed
Suitable for rare diseases	Inappropriate when exposure is rare
Only estimates Odds Ratio (OR)	Yields measurements of risk, IR, RR, AR
Less expensive and requiring less work to conduct	More expensive and work intense to conduct

Comparison

What can be concluded from a Case-control study or from a Cohort study?

Understanding this is key to make correct conclusions from study-reports.

This is vital to allow managers and decision-makers draw the right conclusions and make correct decisions.

12 Case-study Material

Case-study material for readingrreports using the key epidemiological terms and concepts presented in the webinars 1-3.

WHO Update on OMICRON
https://www.who.int/news/item/28-11-2021-update-on-omicron
COVID-19 Breaking News: Cross-Sectional Case Control Studies
https://www.eanpages.org/2022/01/10/covid-19-breaking-news-cross-sectional-case-control-studies-part-1/
Effectiveness of COVID-19 vaccines against the Omicron (B.1.1.529) variant of concern
https://khub.net/documents/135939561/430986542/Effectiveness+of+COVID-19+vaccines+against+Omicron+variant+of+concern.pdf/f423c9f4-91cb-0274-c8c5-70e8fad50074
Association Between 3 Doses of mRNA COVID-19 Vaccine and Symptomatic Infection Caused by the SARS-CoV-2 Omicron and Delta Variants
https://jamanetwork.com/journals/jama/fullarticle/2788485
Analysis: A meta-analysis of Early Results to predict Vaccine efficacy against Omicron
https://www.medrxiv.org/content/10.1101/2021.12.13.21267748v1.full.pdf
Effect of Covid-19 Vaccination on Transmission of Alpha and Delta Variants
https://www.nejm.org/doi/full/10.1056/NEJMoa2116597?query=featured_coronavirus

Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection (Review)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8078597/pdf/CD013705.pdf
Cohort study presentation: Statistical analysis reveals less severe COVID-19 outcome due to Omicron variant
https://www.news-medical.net/news/20220105/Statistical-analysis-reveals-less-severe-COVID-19-outcome-due-to-Omicron-variant.aspx
Cohort study in The Lancet: Reduced Risk of Hospitalisation Associated With Infection With SARS-CoV-2 Omicron Relative to Delta: A Danish Cohort Study
https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4008930
Cohort study: Severity of Omicron variant of concern and vaccine effectiveness against symptomatic disease: national cohort with nested test negative design study in Scotland
https://www.research.ed.ac.uk/en/publications/severity-of-omicron-variant-of-concern-and-vaccine-effectiveness-
Cohort study: Three-dose vaccination elicits neutralising antibodies against omicron.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)00092-7/fulltext

13 COVID-19 Cross-Sectional Case Control Studies

January, 2022.

- BNT162b2 Vaccine Booster and Mortality Due to COVID-19
- Protection against COVID-19 by BNT162b2 Booster across Age Groups
- Two-dose ChAdOx1 nCoV-19 vaccine protection against COVID-19 hospital admissions and deaths over time: a retrospective, population-based cohort study in Scotland and Brazil
- Heterologous ChAdOx1 nCoV-19 and BNT162b2 prime-boost vaccination elicits potent neutralizing antibody responses and T cell reactivity against prevalent SARS-CoV-2 variants
- Risk of venous thrombotic events and thrombocytopenia in sequential time periods after ChAdOx1 and BNT162b2 COVID-19 vaccines: A national cohort study in England
- Disentangling post-vaccination symptoms from early COVID-19
- Severity of Illness in Persons Infected With the SARS-CoV-2 Delta Variant vs Beta Variant in Qatar
- Omicron extensively but incompletely escapes Pfizer BNT162b2 neutralization
- Striking Antibody Evasion Manifested by the Omicron Variant of SARS-CoV-2
- Report 49: Growth, population distribution and immune escape of Omicron in England
- Effectiveness of mRNA-1273 against delta, mu, and other emerging variants of SARS-CoV-2: test negative case-control study

14 Systematic Review and Meta-analysis on Effects of Lockdown on Excess Mortality

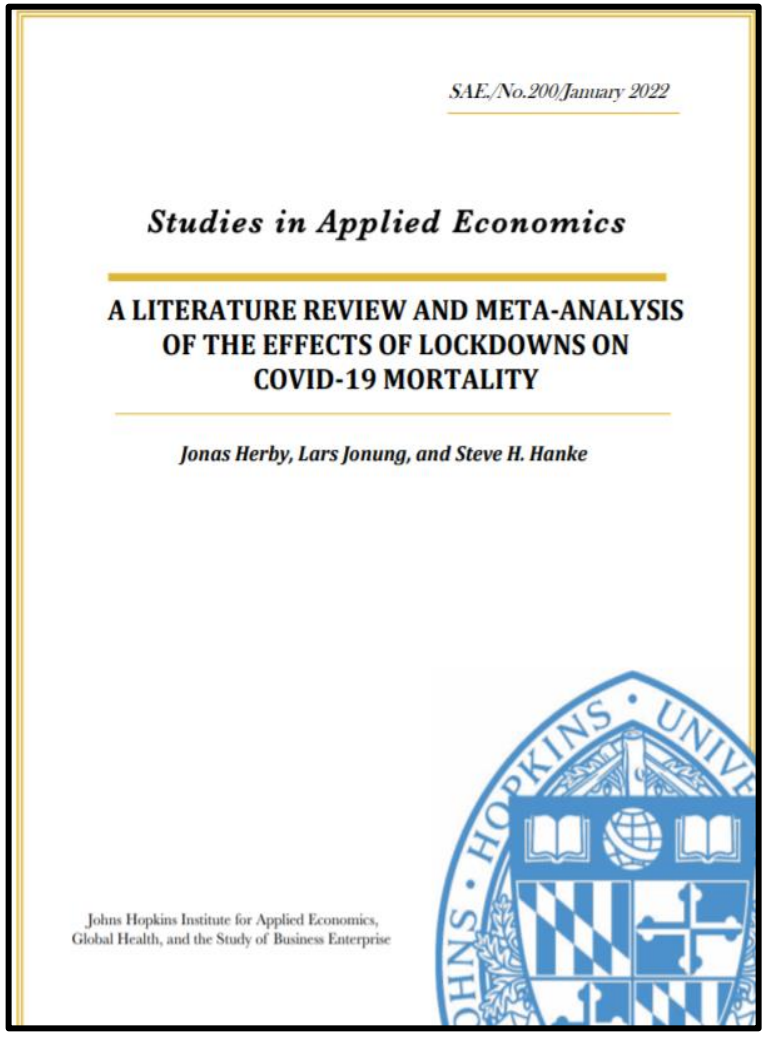
January, 2022.

Study conclusion: Large scale lock-downs in Europe and USA did in reality not save any lives.

The statistical Meta analysis covered in all 18590 studies, whereof only 24 were found to meet criteria to ensure elimination of bias etc.

In summary: Lockdowns in Europe gave only marginal effect against excess mortality with on average 0,2%. This according to studies which meet criteria for validity and appropriate methodology.

The effect of lockdowns is thus marginal and not in proportion to the high cost associated with the lockdowns. In addition to economic costs, other costs must also be considered such as negative impacts on health, quality of life and social consequences. The effect of lockdowns on mortality may even be the opposite, if negative health related effects of lost quality of life are included.



Reading material: https://sites.krieger.jhu.edu/iae/files/2022/01/A-Literature-Review-and-Meta-Analysis-of-the-Effects-of-Lockdowns-on-COVID-19-Mortality.pdf

The study revealed a positive correlation between the degree of lockdowns and mortality in Europe: The more stringent lockdown, the higher excess mortality.

The report concluded that the reason behind was likely due to lockdowns being politically motivated, and not based on evidence of proven efficacy of lockdowns as method against mortality.

One example of interest is the case of the UK where the political decisions for lock-down was prompted by a report from Imperial college in London. That report presented premature conclusions which forecast of 510,000 possible deaths. This prompted one of the most stringent lockdowns in all of Europe.

The effect on the lock-down on the economy was disastrous but the effect against mortality was slight.

Meanwhile Sweden launched far less stringent measures, no lockdown and instead emphasis on advice for social distancing. On short term, COVID-19 deaths in Sweden first appeared to run high, but over time cumulative excess mortality in Sweden landed below the excess mortality in other European countries.

What has worked:

Vaccination, Social distancing advice to flatten the curve and boost healthcare capacity

15 Participant Discussion

When the Covid-19 pandemic hit us world-wide, many countries launched strict lock-down procedures, closed businesses etc.

By now, several epidemiological systematic review reports have concluded that social distancing and other **public health measures can slow down and reduce the transmission rate but large scale lock-down have NOT been effective to save lives.**

Discuss what these data means for further planning of prevention and launch of countermeasures in your country.

10 Lockdowns

Already in 2006, this team wrote about social lockdowns:

It is difficult to identify circumstances in the past half-century when large-scale quarantine has been effectively used in the control of any disease.

The negative consequences of large-scale quarantine are so extreme.. that this mitigation measure should be eliminated from serious consideration.

They also discussed other mitigations like school closures, social distancing, etc.

It is well-worth to return to read this, in the perspective of experiences gained during the Covid-19 pandemic, and results from the recent Meta-analysis of lockdown lack of effect on mortality.