Some basics on infectious diseases and infectious disease epidemiology

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Halle, 12.09.22, Summer School Modelling

HZI HELMHOLTZ Zentrum für Infektionsforschung

Learning aims

At the end of this session I would like you to be able to

- Have some understanding of the main epidemiological and clinical features that you should be able to look up for major infectious diseases

- Be able to hold a conversation with an (infectious disease) epidemiologist on common ground and give some insights on how we think

- Understand what epidemiologists mean, when they talk about a specific epidemiological study design

Agenda

1. Go through typical infectious disease measures using two infectious diseases with high burden of disease: TB and flu
2. Some further typical measures of disease transmission in infectious diseases
3. Main study types and infrastructures needed in infectious disease epidemiology

INTRODUCTION TO TUBERCULOSIS

Please think about the following

You have had some cough. You have been treated with antibiotics, but it did not go away.

When you are for the third time in the doctor`s office, you are not let in. You are given a mask to put over your mouth (no one else is wearing one). You then need to wait in front of the doctor`s office in a small room reserved for cleaning materials.

After 20 minutes you are let into the doctor`s room. She tells you: „We have found out that you have tuberculosis, a special infection of the lung.“

As the patient, **what would your feelings and thoughts be?**

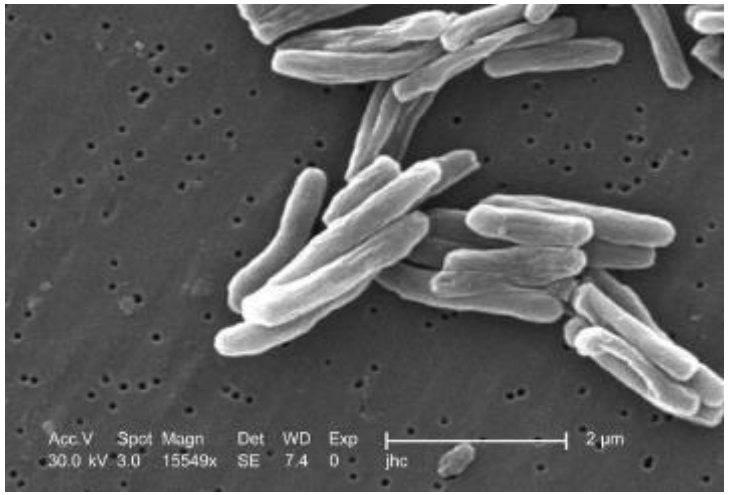
Mycobacterium tuberculosis complex

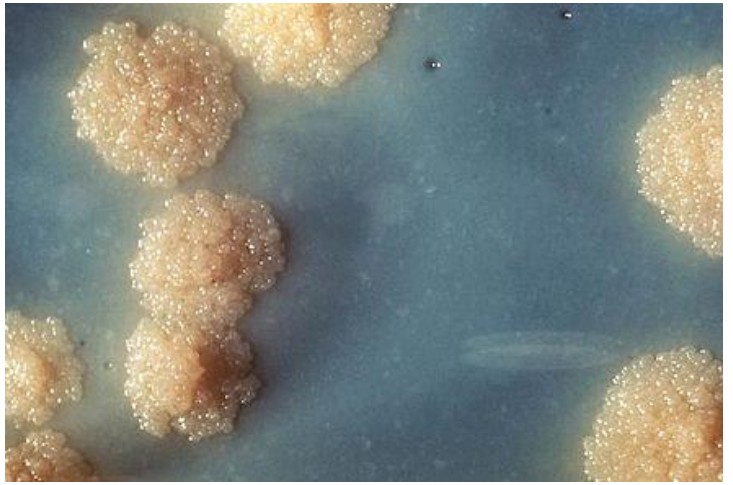
Microbiology

- Acid fast (does not absorb Gram stain, can be seen with e.g. Ziehl Neelsen)

- Pathogenic Mycobacteria vs opportunistic non-tuberculous mycobacteria

- Divides every 15-20 hours (slow growing)



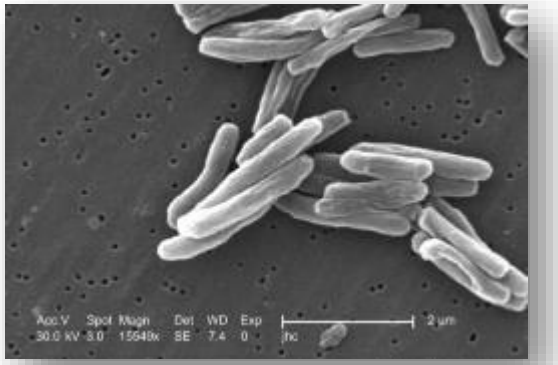


Tuberculosis

Transmission

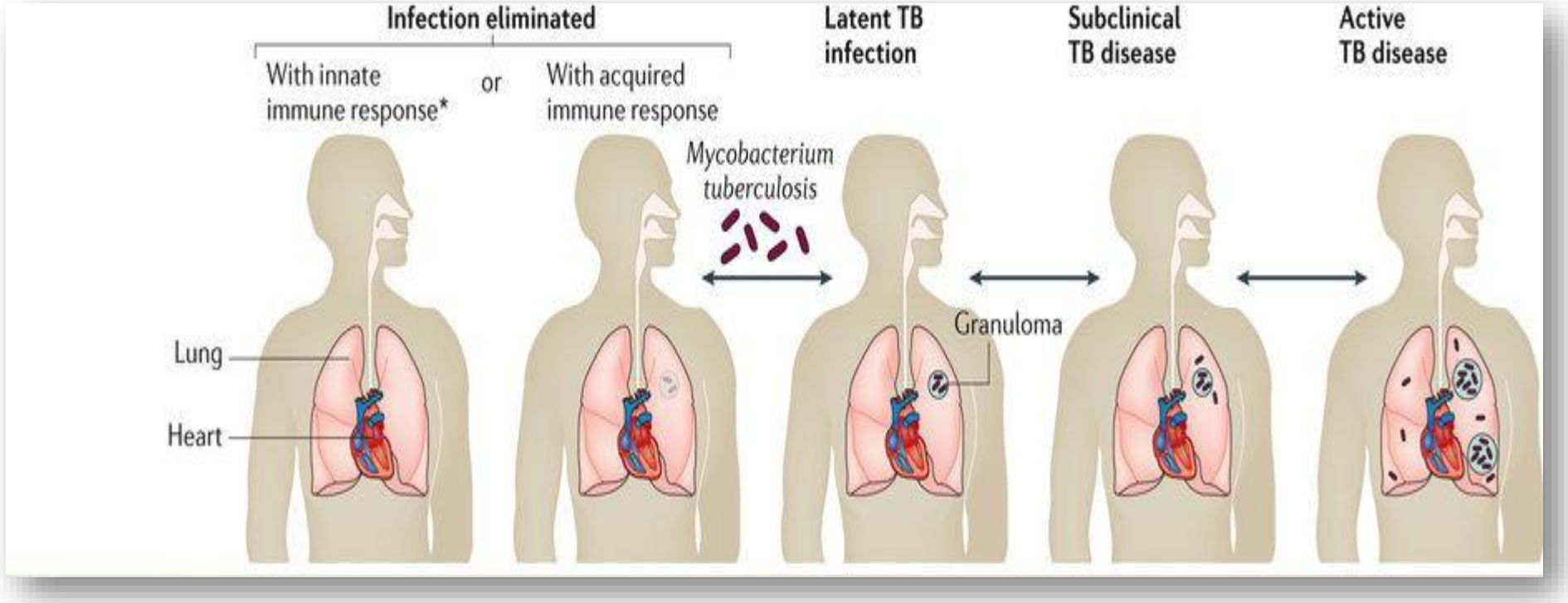
- Infection with *Mycobacterium tuberculosis*
  - Airborne, Droplet nuclei (1-5 µm)

- Infectivity depends on:
  - Exposure time
  - Concentration of organisms in the sputum
    - Cavernous tuberculosis is more infectious due to direct connection of cavern with bronchial system and upper airways
  - Amount of coughing
  - Duration of effective therapy
  - Distance to the person (5 meters)



Tuberculosis

Stages of Disease



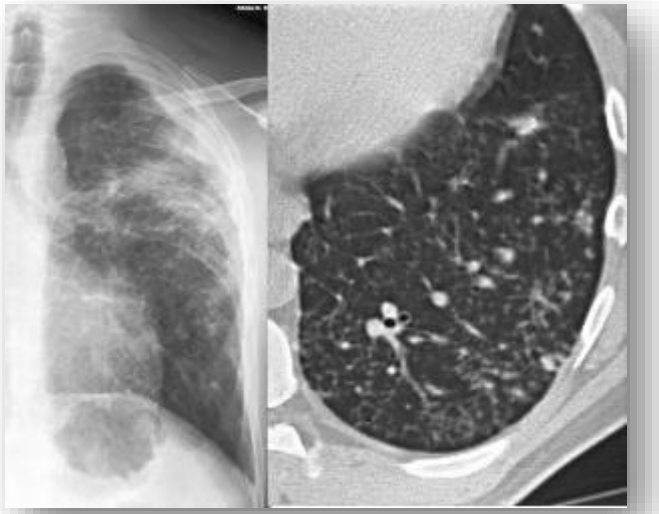
Pai et al. Tuberculosis. Nat Rev Dis Primers. 2016 Oct 27;2:16076.

Tuberculosis

The disease („active TB“)

Usually tuberculosis is a pulmonary disease

Leading to unspecific symptoms (cough, night sweats, weight loss, fever)



Upper lobe pneumonia

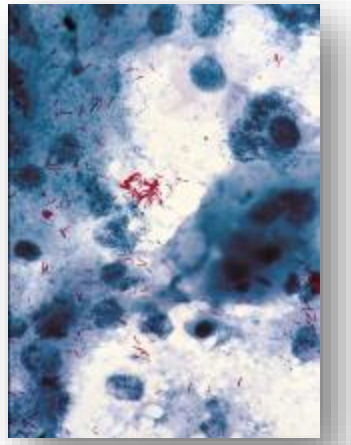
Cavitation

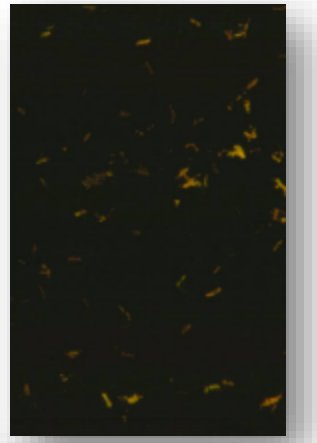
Extensive disease

Tuberculosis

Diagnostics active TB

- **Microscopy**
- staining of sputum (or bronchial lavage or gastric aspirates) 60-70% sensitivity
    - acid fast, Ziel-Neelsen;
    - Fluorecsence, Auramin (faster, higher sensitivity)
- **Culture – classic Goldstandard**
    - Liquid medium 2 weeks, otherwise 6 weeks
    - Biosaftey lab required
- **Molecular methods – increasingly Goldstandard**
    - Increasingly used as turn around of 1 day
    - Allows detection of resistances





Tuberculosis

Active TB treatment

Indication	Initial		Stabilisation	
	Duration	Medication	Duration	Medication
New microso culture posit				RMP
culture nega				RMP
INH-intoleran Resistenz				EMB
RMP-Intolera -Resistenz				EMB
PZA-Intoleranz -Resistenz		EMB		, RMP

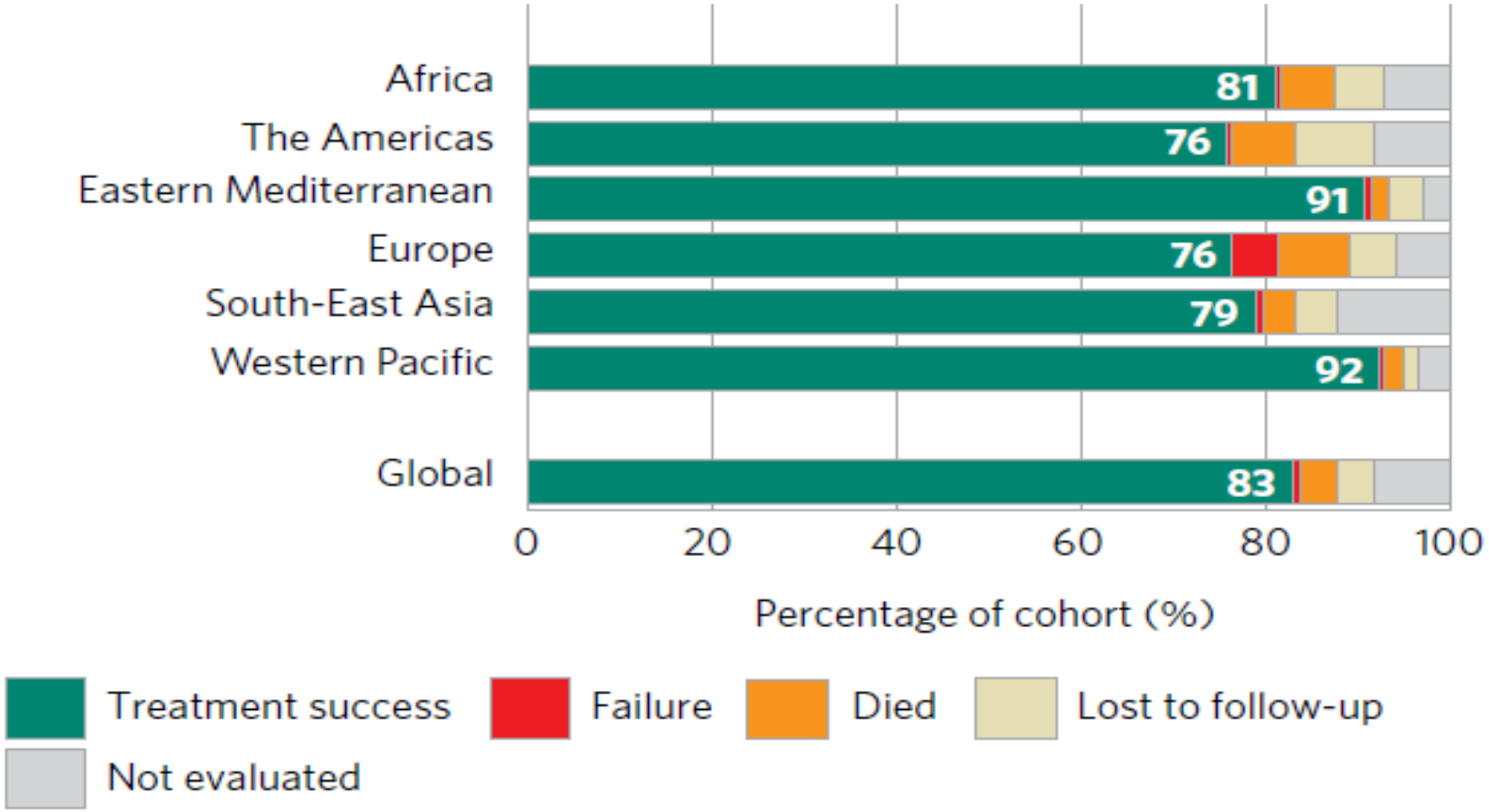
New short course treatment (4 months) now being established

https://www.nejm.org/doi/full/10.1056/NEJMoa2033400

Isoniazid (INH), Rifampicin (RMP), Pyrazinamide (PZA), Ethambutol (EMB), Streptomycin (SM)

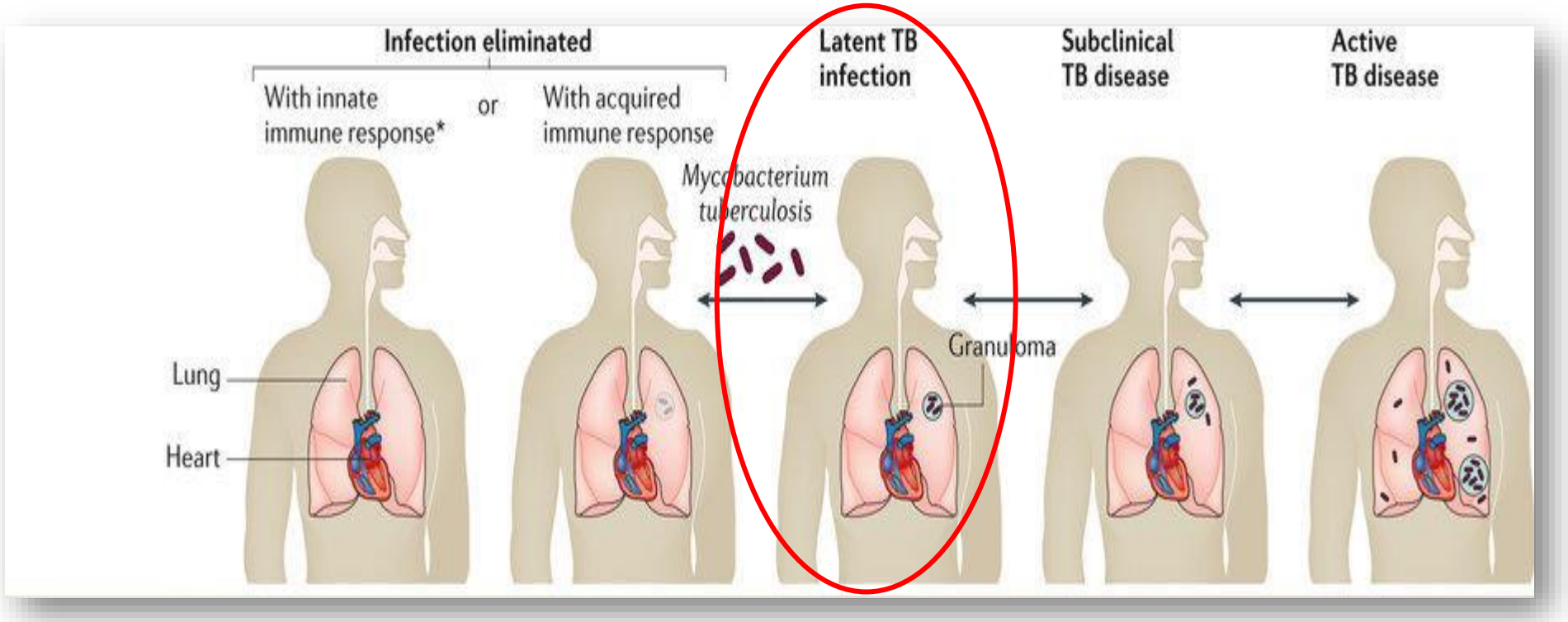
Tuberculosis

Treatment success



Tuberculosis

Stages of Disease

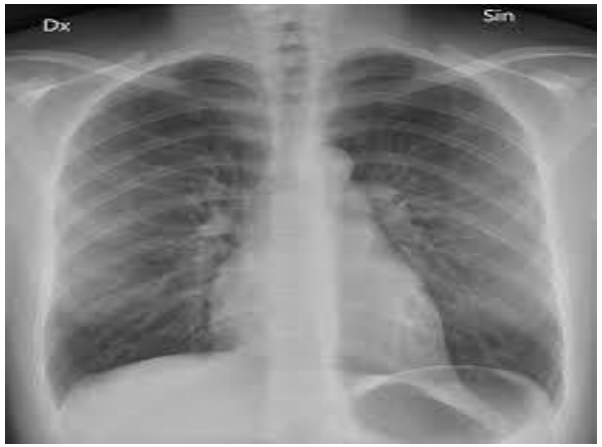


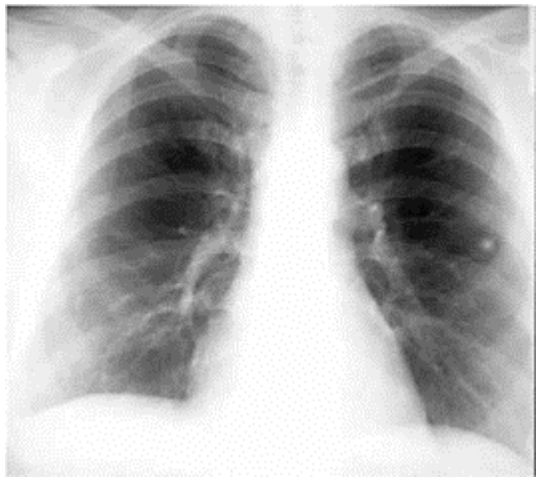
Pai et al. Tuberculosis. Nat Rev Dis Primers. 2016 Oct 27;2:16076.

Latent TB vs active TB very simply

„state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens with no evidence of clinically manifest active TB”

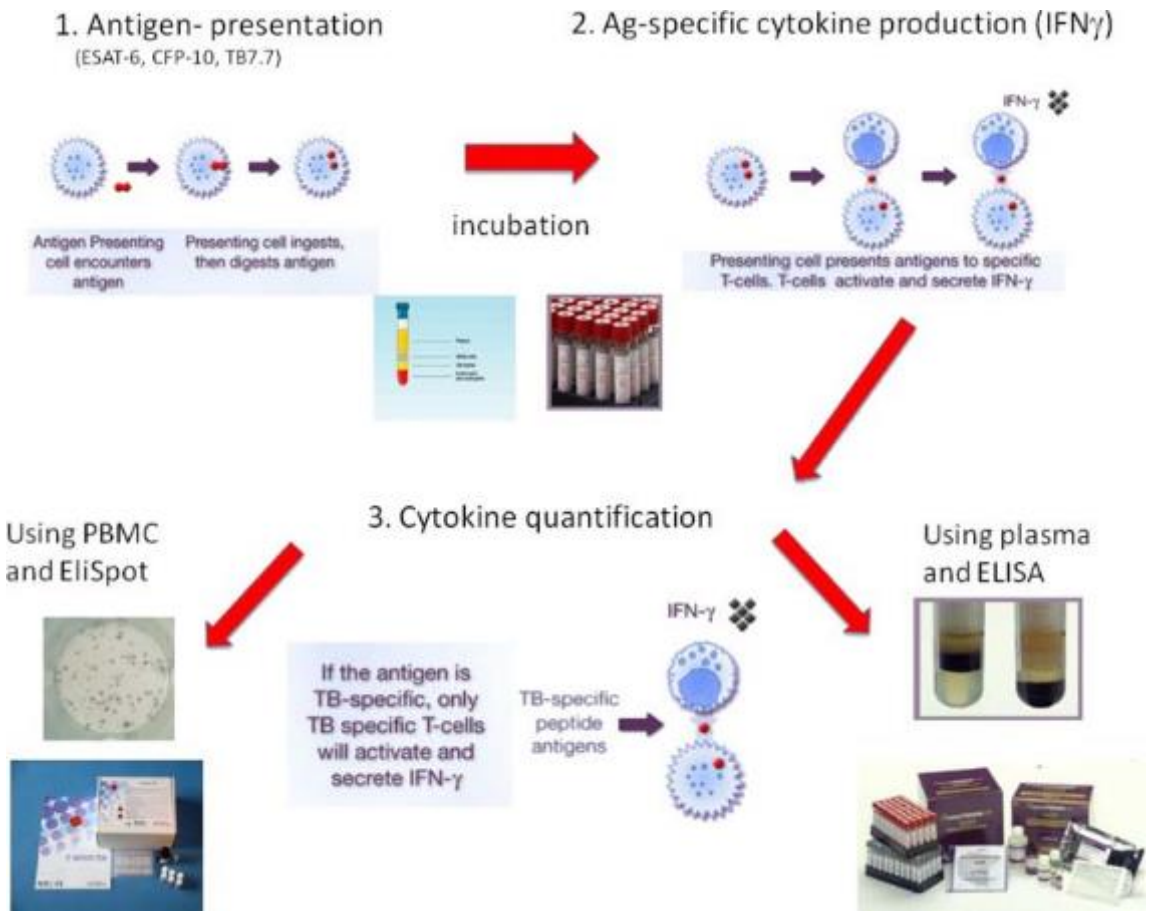
WHO, Latent Tuberculosis Guideline 2018





Not infected → Infection → LTBI → Progress (~10%) → Active TB

Assessing interferon gamma release to diagnose latent infection in tuberculosis



- Interferon-Gamma-Release Assays long established tool in Tuberculosis diagnostic for diagnosis of latent tuberculosis similar to Tuberculin Skin Test

Who should be tested and treated to prevent active disease LTBI guidelines 2018, WHO

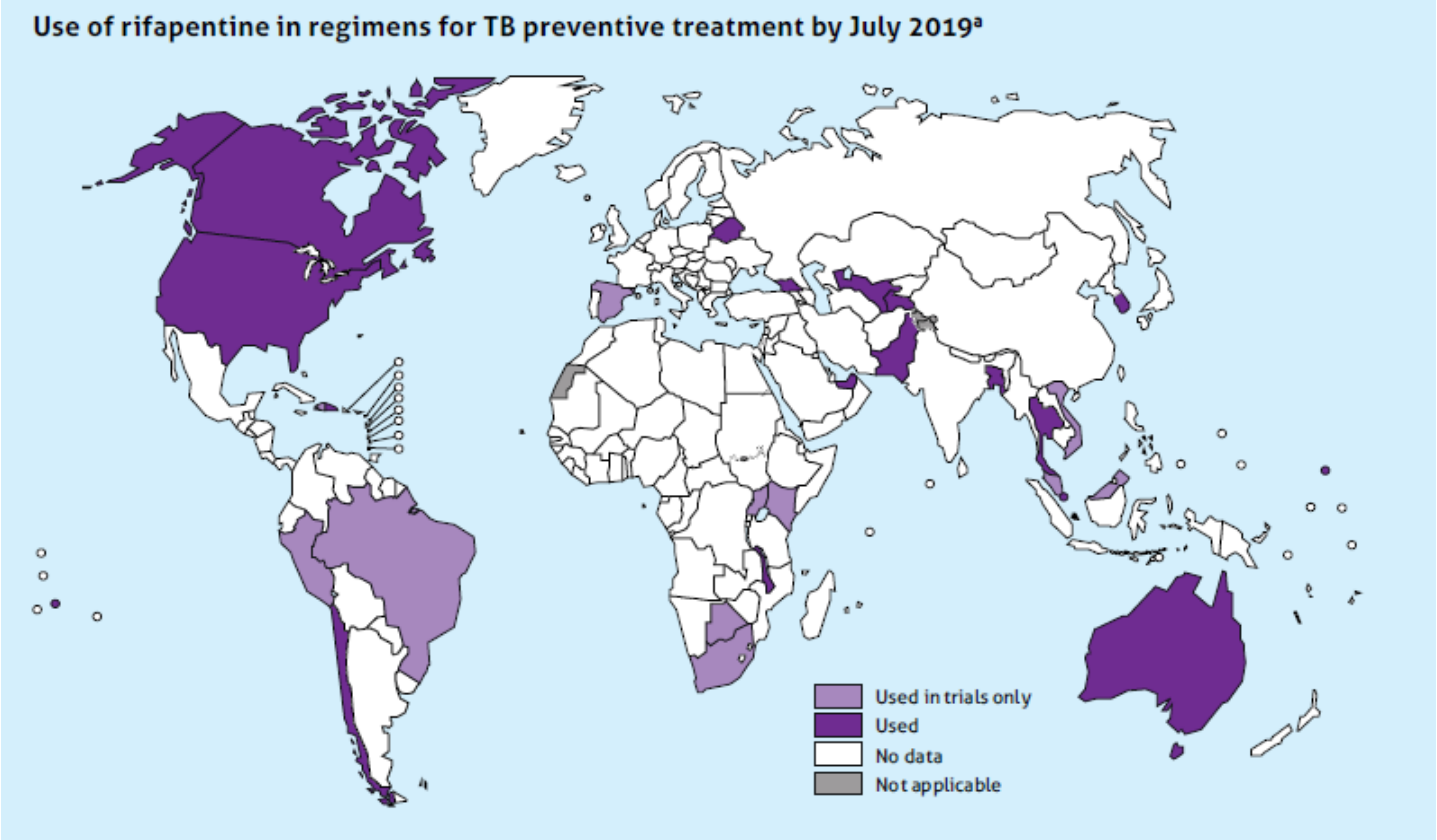
	Risikogruppe	Empfehlung	Evidenzgrad
Präventive Therapie	Kinder mit HIV	Strong	Low-moderate
	Kontakte < 5 Jahre	Strong	High
Testen			
	Kontakte in Niedriginzidenzländern	Strong	High-moderate
	Patienten vor Anti-TNF-alpha Therapie	Strong	low
	Dialysepatienten, Patienten vor Organtransplantationen, Patienten mit Silikose	Strong	Low-very low
Vielleicht testen	Gefangene, Gesundheitspersonal, Immigranten, Obdachlose, Drogenabusus in Niedriginzidenzländern	Conditional	Low-very low
Nicht testen	Diabetes, Alkohol, Rauchen, Untergewicht	Conditional	Very low quality

Latent TB Treatment

Rifapentin + INH für 3 Monate (wöchentlich)	Efficacy vs INH RR 0.44 (non-inferior) Hepatoxizität vs INH 0.16 Therapieadhärenz deutlich besser als INH!	Interaktionen: u.a. Efavirenz, Dolutegravir, Proteaseinhibitoren, Methadon, Cyclosporin, Marcumar
Rifa Mono für 3-4 Monate	Efficacy vs INH RR 0.78 (0.4-1.4) Hepatoxicity vs INH 6-mo: 0.03	
Rifa + INH für 3 Monate	Efficacy vs INH 0.89(0.7-1.2) Hepatoxicity vs INH 6-mo:0.89	
INH Monotherapie für 6 Monate	Efficacy 60-90% (vs Placebo) Serious adverse events 3-5%	Cave: Efavirenz, Benzodiazepine, SSRI

Getahun et al, NEJM 2015

Treatment with rifapentine….



You do not come from a biology or medicine background and did not at first know some of the words on the last slides?

- Make sure that you are up to basic microbiology, virology and immunology of the main infectious diseases

- Have at l
  - Mic
  - Imr
  - Clir

- It is easi e

- After that, e unknown) infectious diseases :
  - RKI
  - CDC
  - WHO

People will (very rightly so) expect you to be up to the microbiological, immunological, clinical and epidemiological basics of any disease you are modelling and those diseases similar – make sure you are

After you have read some textbooks on a new disease, what should you know about it?

- → Do also always consider the opposite:
- → The people you will be talking to will be experts on the above subjects
- → but not necessarily understand a lot of mathematics, modelling or infectious disease epidemiology.
- → And *they* will not have read basic textbooks on these subjects.
- → Make your reports understandable and usable to them….

Tuberculosis

Epidemiology

FIG. 13

Estimated TB incidence rates, 2020

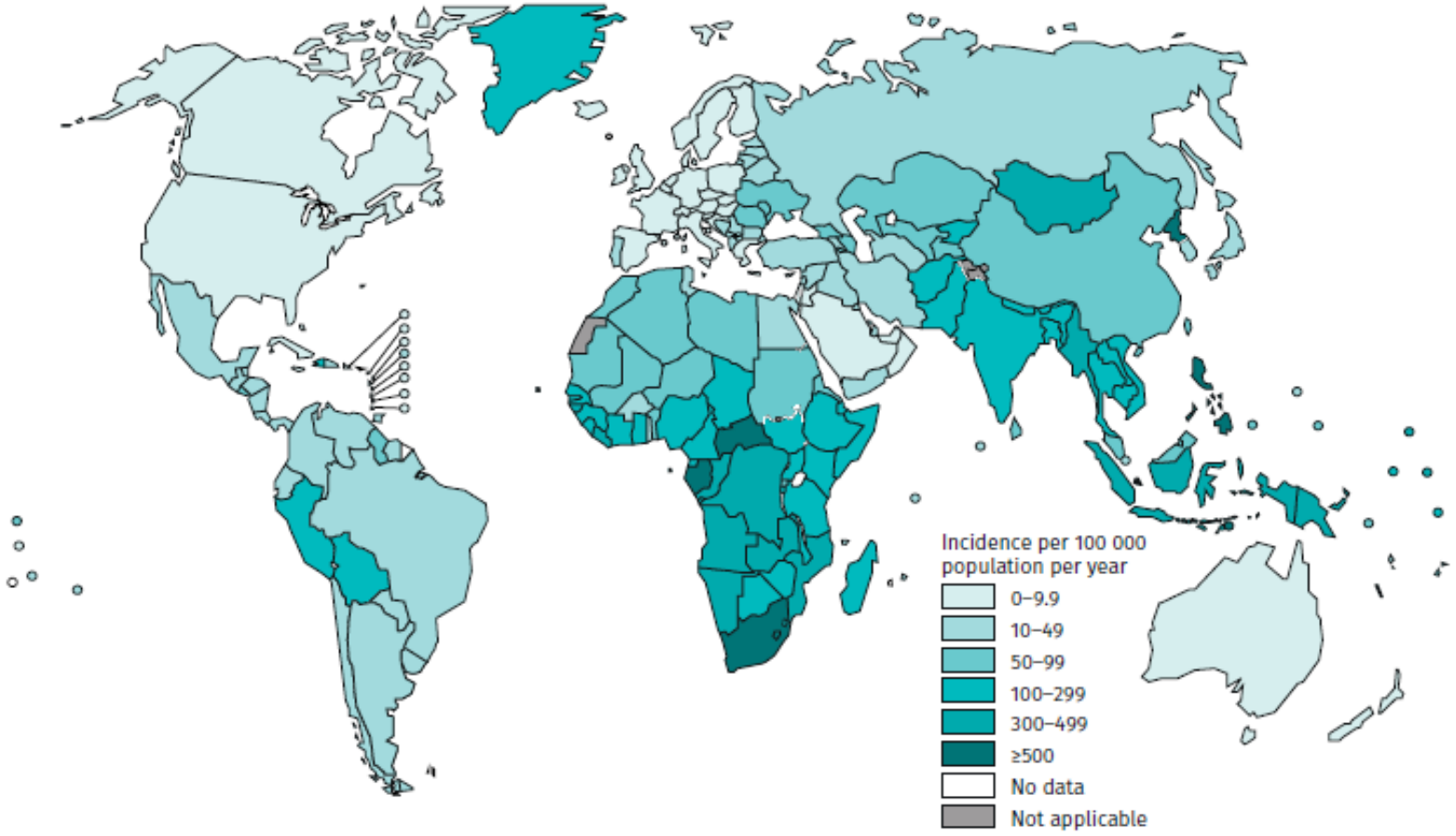


FIG. 14

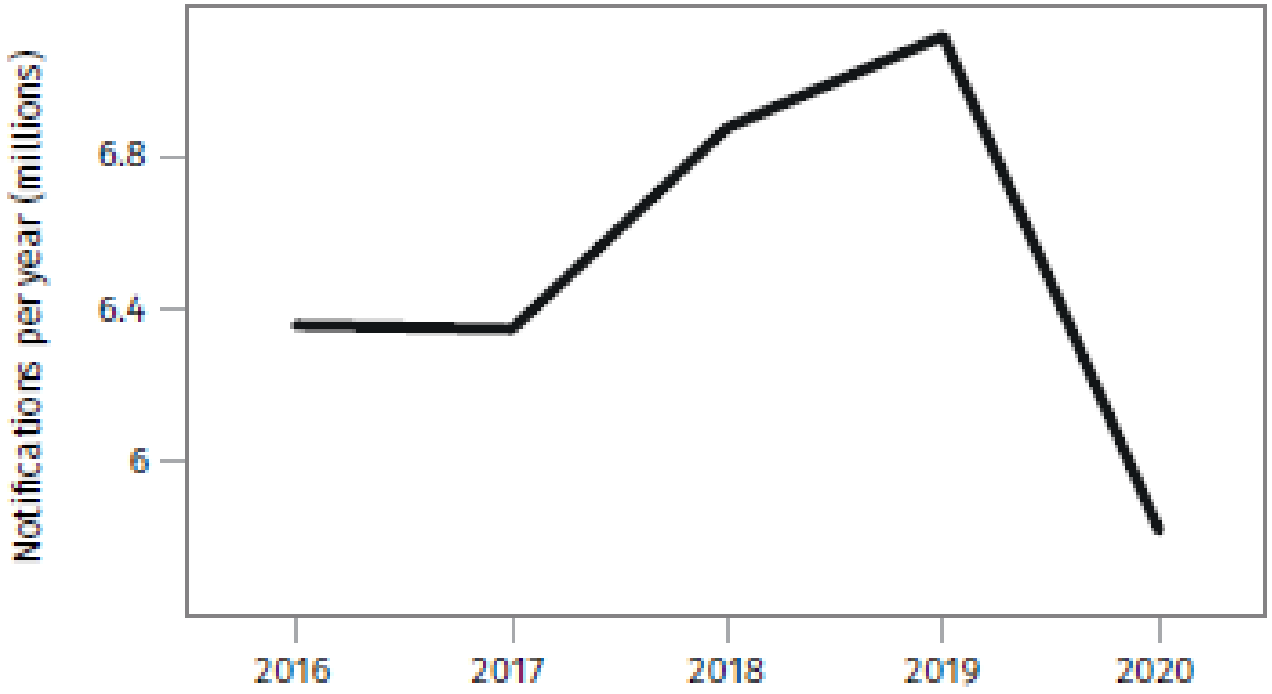
Global Tuberculosis Report 2015, 20th edition, World Health Organization, 18, figure 2.6

But 2020 was different …

Epidemiology

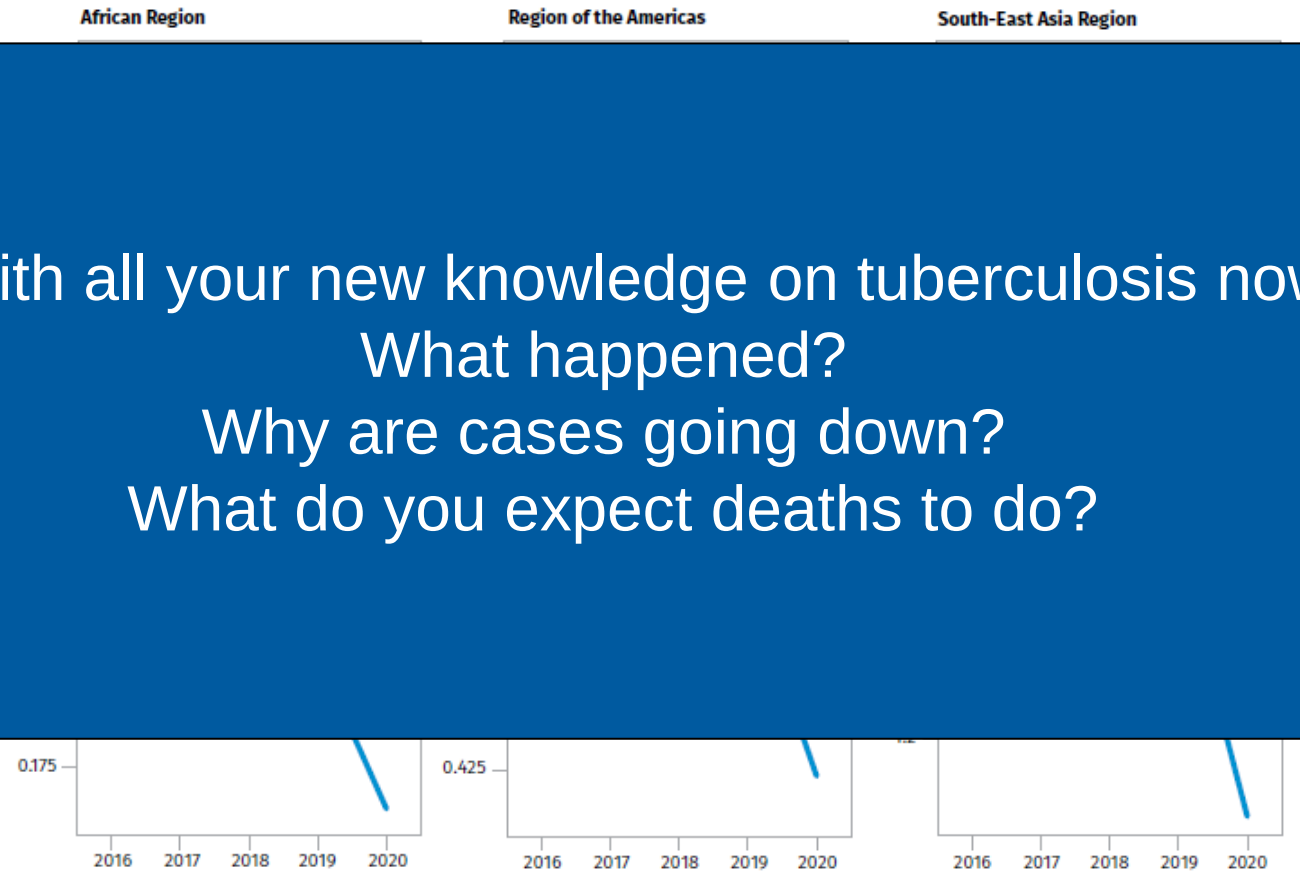
FIG. 1

Global trend in case notifications of people newly diagnosed with TB, 2016–2020



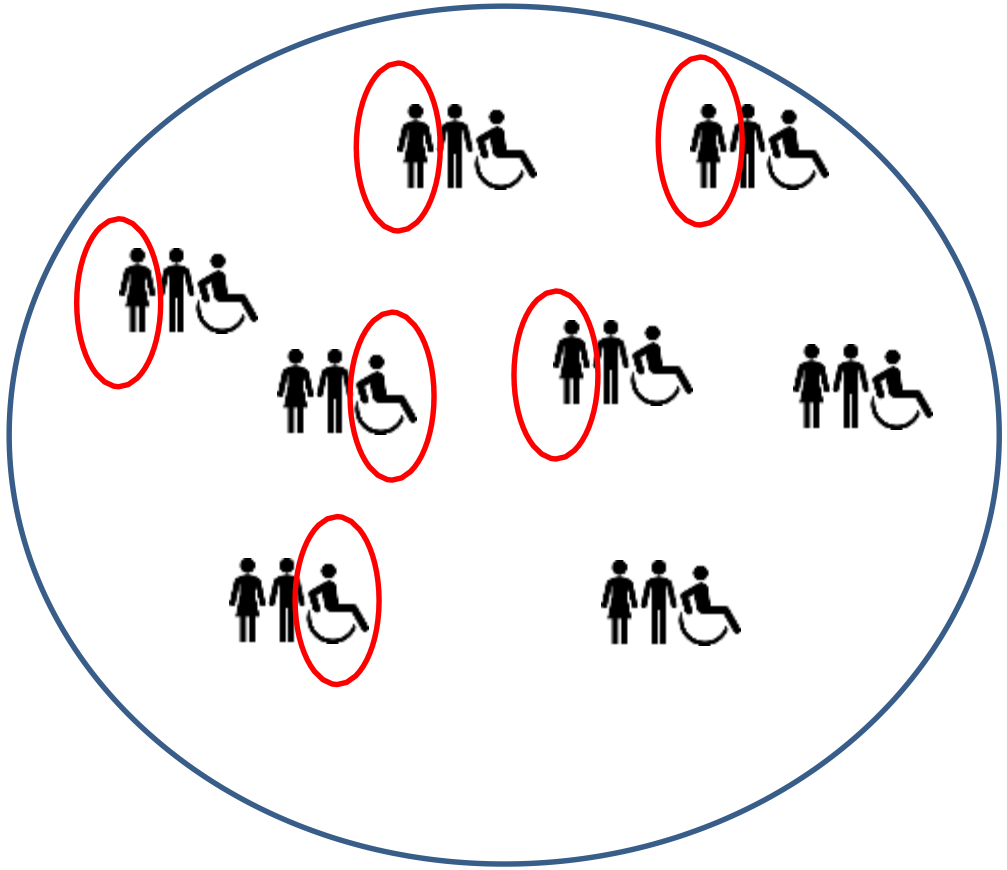
The trend is across regions

FIG. 2
Trends in case notifications of people newly diagnosed with TB by WHO region, 2016–2020



So with all your new knowledge on tuberculosis now:
What happened?
Why are cases going down?
What do you expect deaths to do?

The common unknown: The actual number of infections



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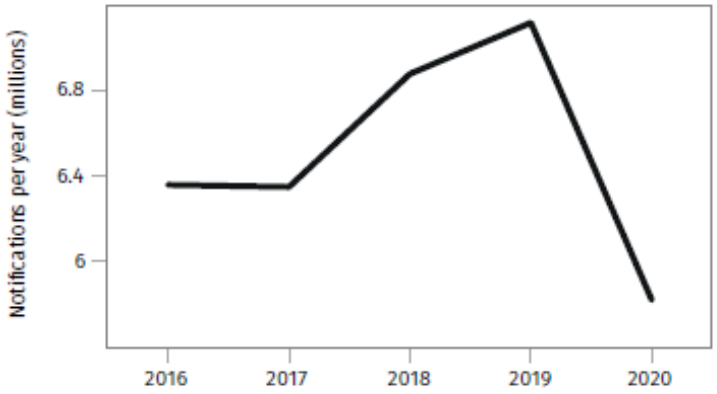
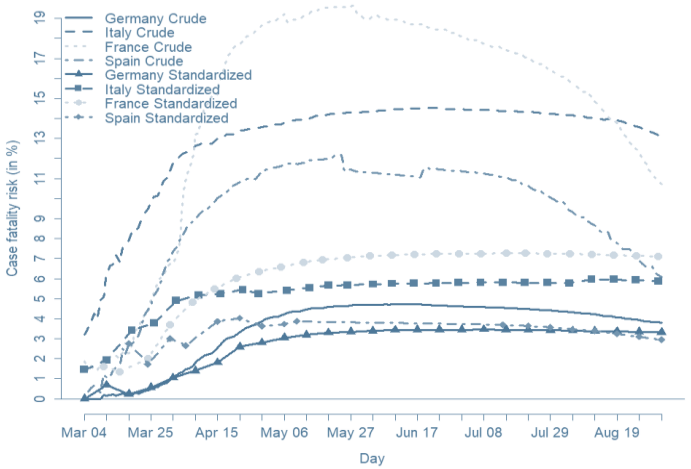
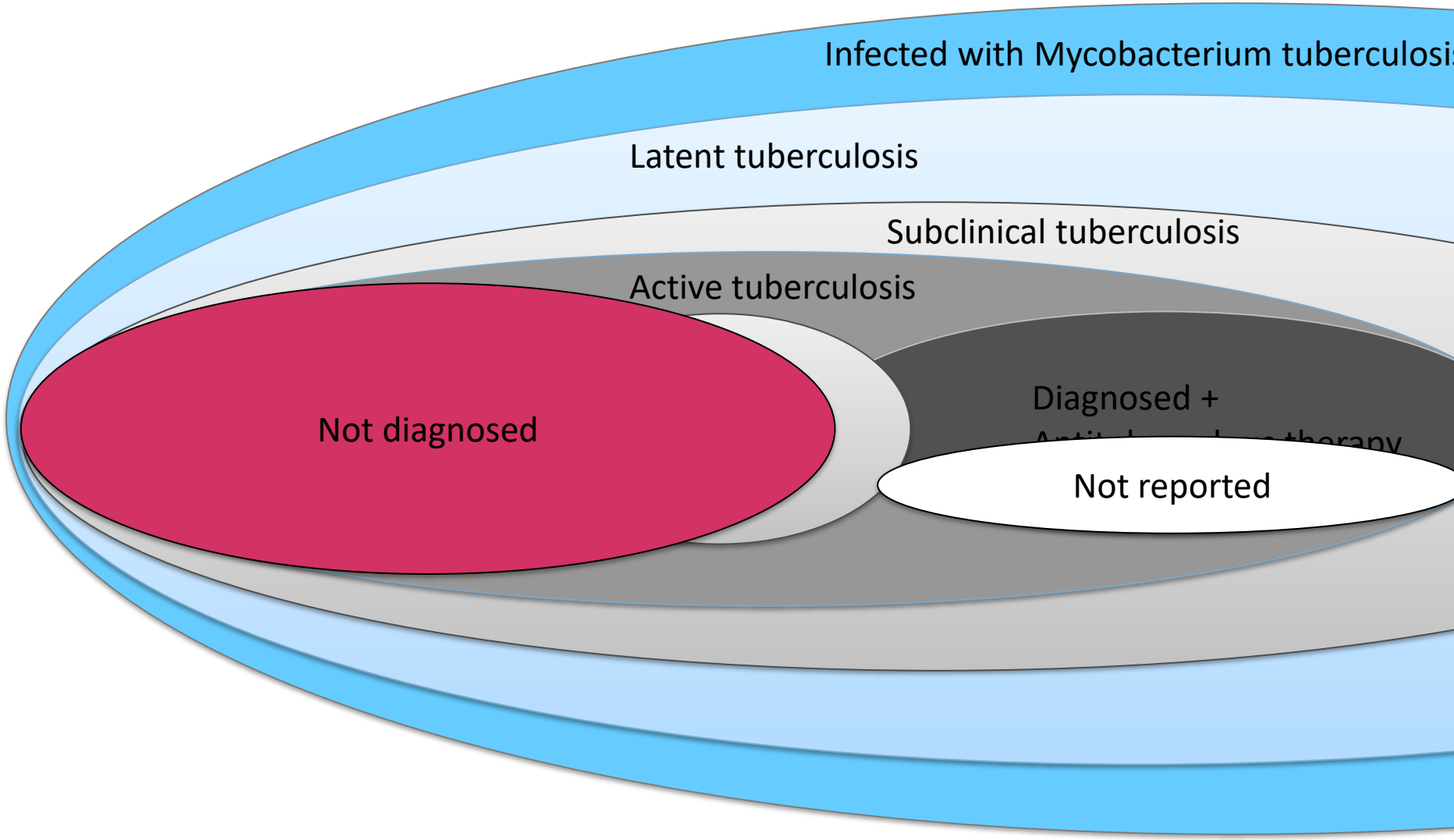
Global trend in case notifications of people newly diagnosed with TB, 2016–2020





Undercoverage using the example of tuberculosis



This leads to different solutions

Without additional data collection

Linking different data sources

- Capture-recapture
- Inventory studies

Inference from data on more severe courses such as hospitalisations or deaths to infections

- Only works if deaths are not also subject to significant under-reporting

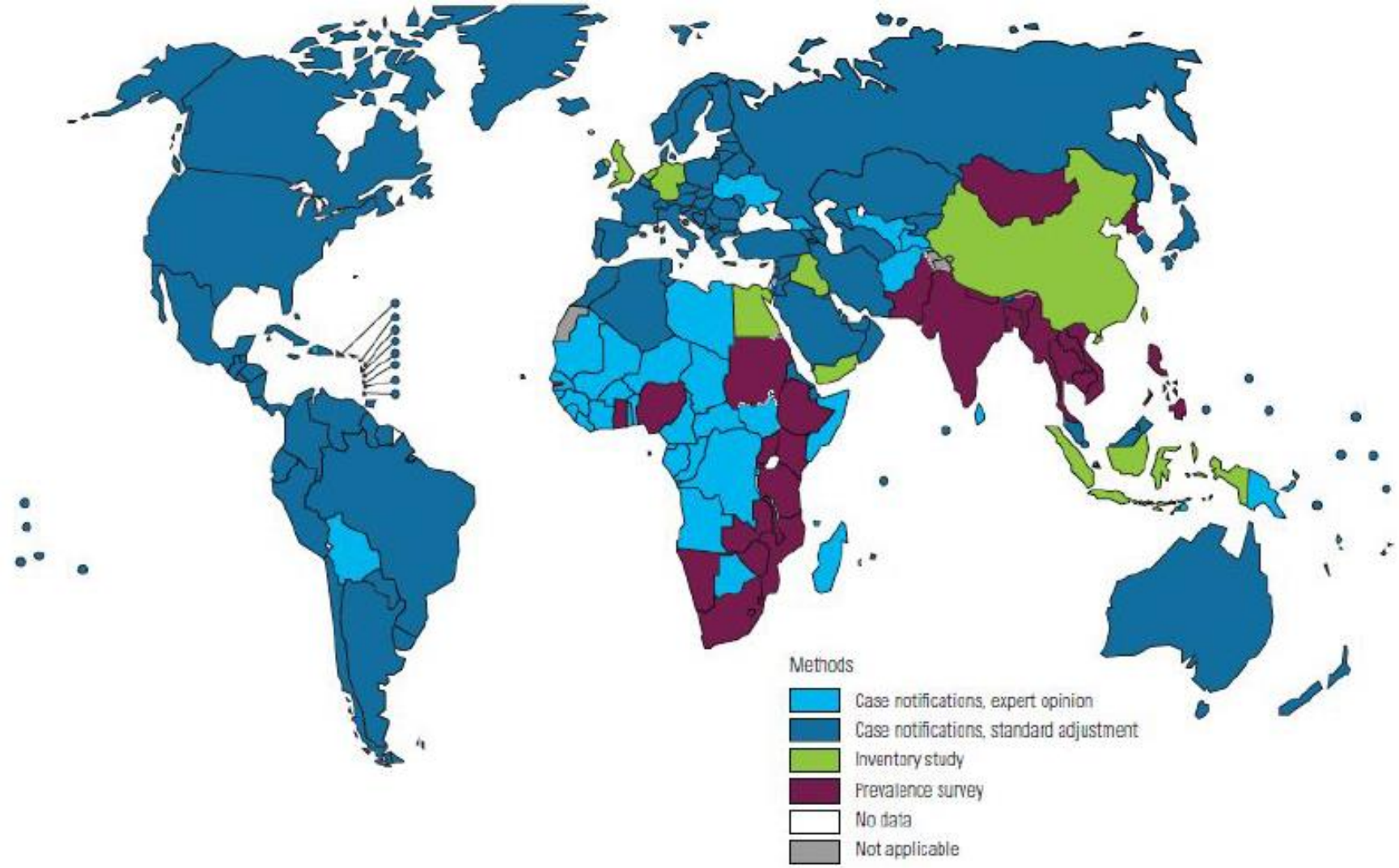
Inference from data on the number of diagnostics and test positivity

- Works especially well when data are not skewed with respect to pretest probability or specific population groups

With additional data collection

- New reporting rules
- Population-based prevalence studies
- Prevalence studies in specific population groups

How WHO is measuring underdetection for tuberculosis in their reports



Tuberculosis

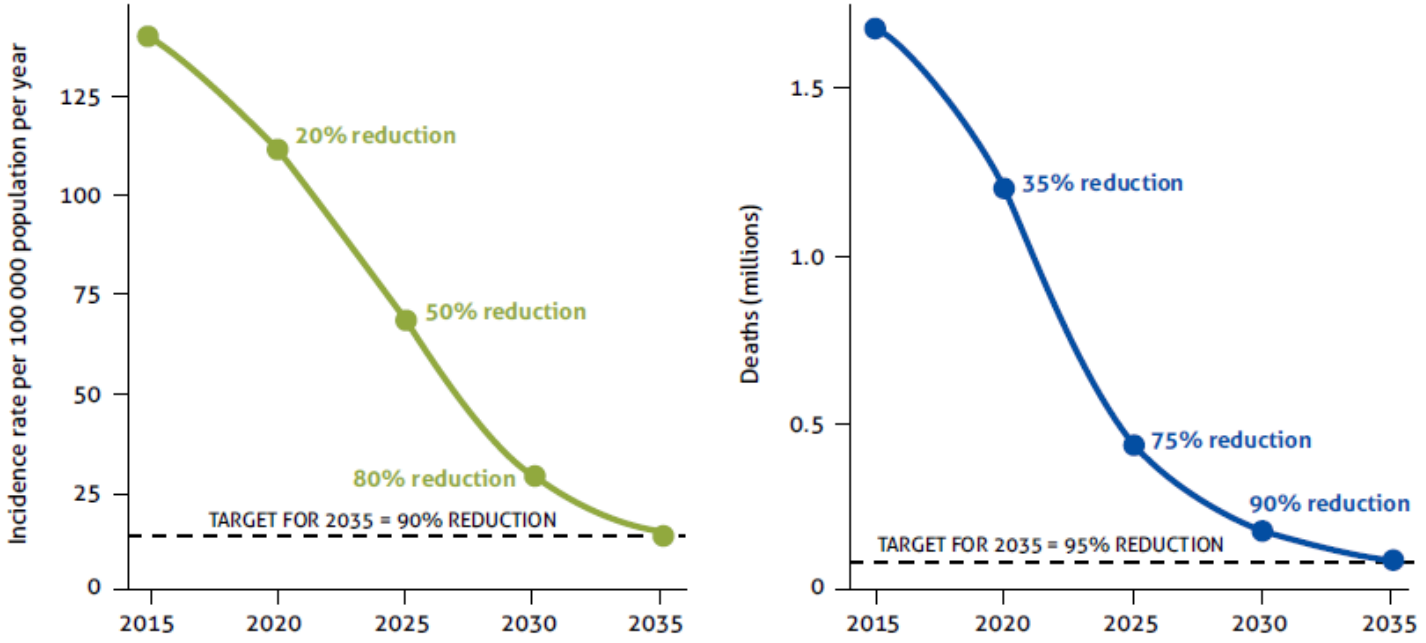
End TB Strategy

VISION	**A WORLD FREE OF TB** — zero deaths, disease and suffering due to TB			
GOAL	**END THE GLOBAL TB EPIDEMIC**			
INDICATORS	**MILESTONES**		**TARGETS**	
	2020	**2025**	**SDG 2030***	**END TB 2035**
Percentage reduction in the absolute number of TB deaths *(compared with 2015 baseline)*	35%	75%	90%	95%
Percentage reduction in the TB incidence rate *(compared with 2015 baseline)*	20%	50%	80%	90% (approximately 10 per 100 000 population)
Percentage of TB-affected households experiencing catastrophic costs due to TB *(level in 2015 unknown)*	0%	0%	0%	0%

Projected incidence reduction required

FIG. 2.1

Projected incidence and mortality curves that are required to reach End TB Strategy targets and milestones, 2015–2035

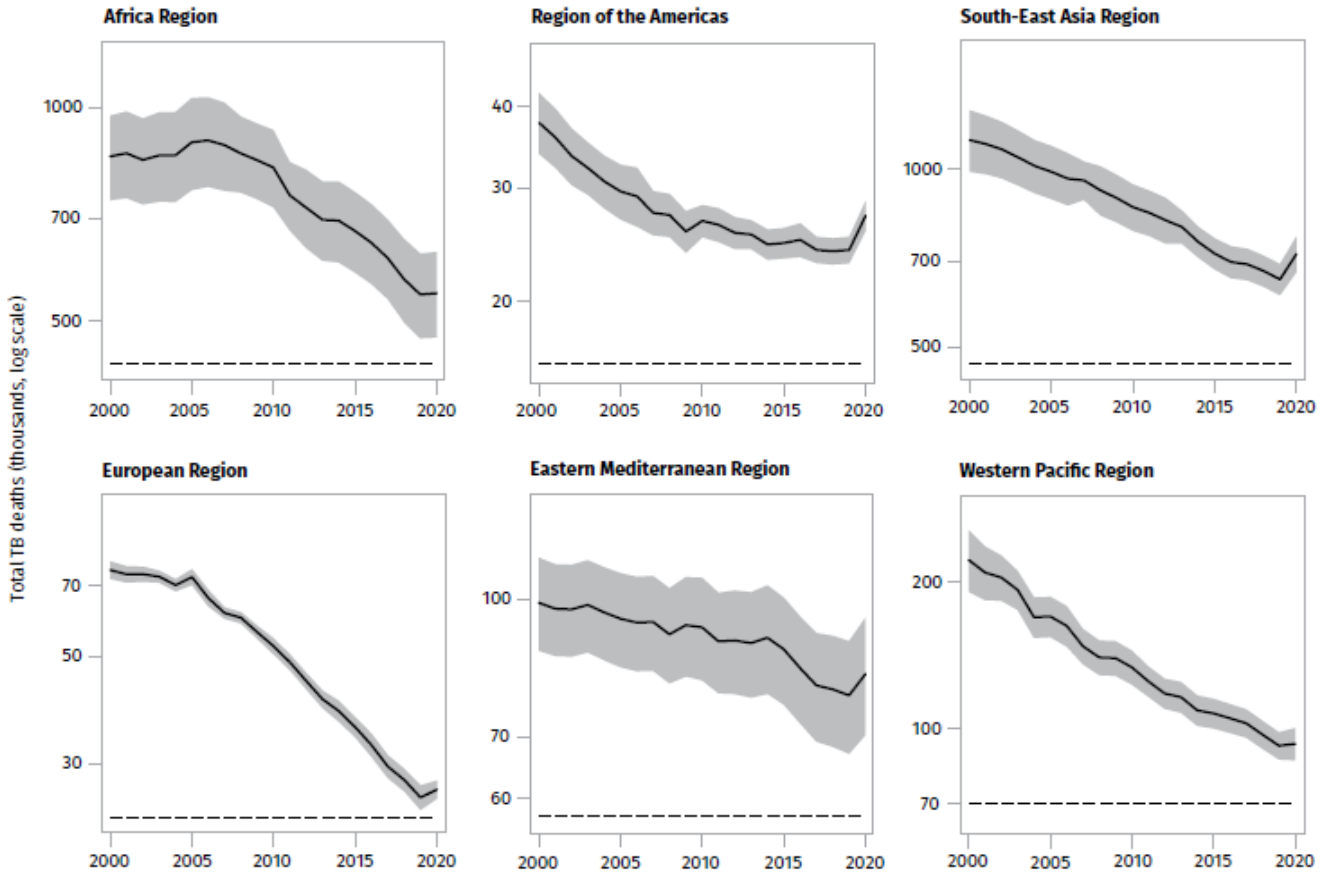


Unfortunately – not only – due to the pandemic we are far from that

FIG. 8

Trends in the estimated absolute number of TB deaths (HIV-positive and HIV-negative) by WHO region, 2000–2020

Shaded areas represent uncertainty intervals. The horizontal dashed line shows the 2020 milestone of the End TB Strategy.



Summary

Tuberculosis is …

… after COVID the infectious disease that kills most people around the world

…. Labelled LTBI if IGRA or TST is positive and no sign of active disease

…. Around ¼ of the global population has LTBI but most of these (90%) will never have active TB disease

…. Diagnosed via either microscopy/culture or molecular methods in pulmonary (e.g. sputum) or extrapulmonary samples **if active** and via TST/IGRA **if latent**

…. Well treatable if DS, less well (and more expensive) if DR

…. Hopefully being eliminated as planned in the WHO endTB strategy (but with caveats…)

Back to being the patient at the beginning

You have had some cough. You have been treated with antibiotics, but it did not go away.

W…e, you
…ur
…d to

**We can treat it well,
and you will be fine if we work
together on your treatment
over the next few months**

;-)

…he
…ulosis,

…ghts

be?

As the doctor, **what is your next sentence?**

INTRODUCTION TO INFLUENZA

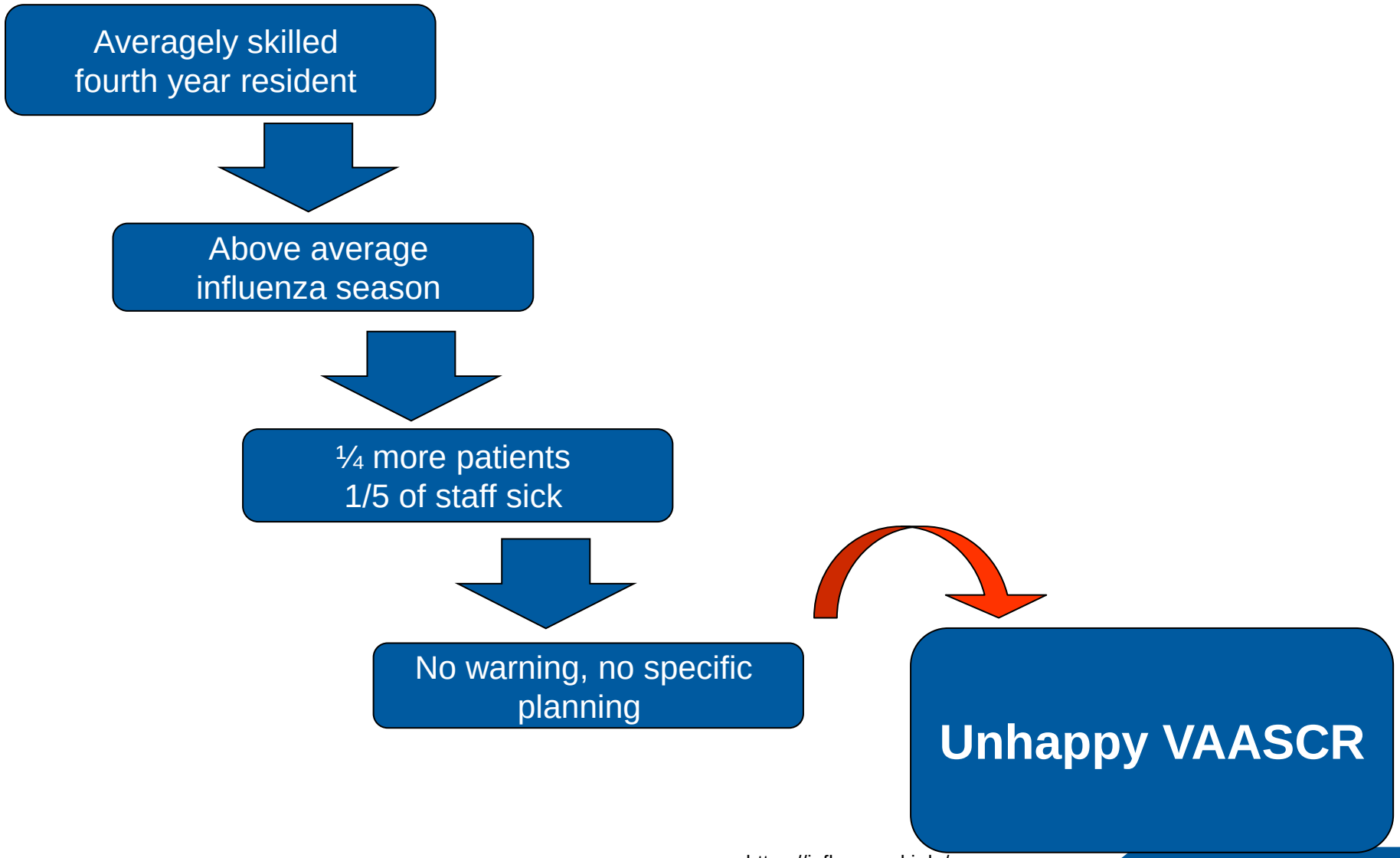
One day…

In February of 2015 – into the third month of an until that point in time smoothly-running A&E rotation…

Unhappy VAASCR

a very anonymous averagely skilled clinical resident (VAASCR) suddenly felt …

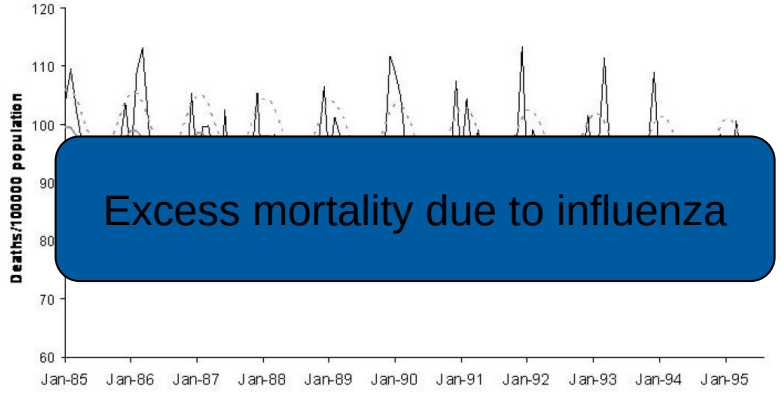
What had happened?



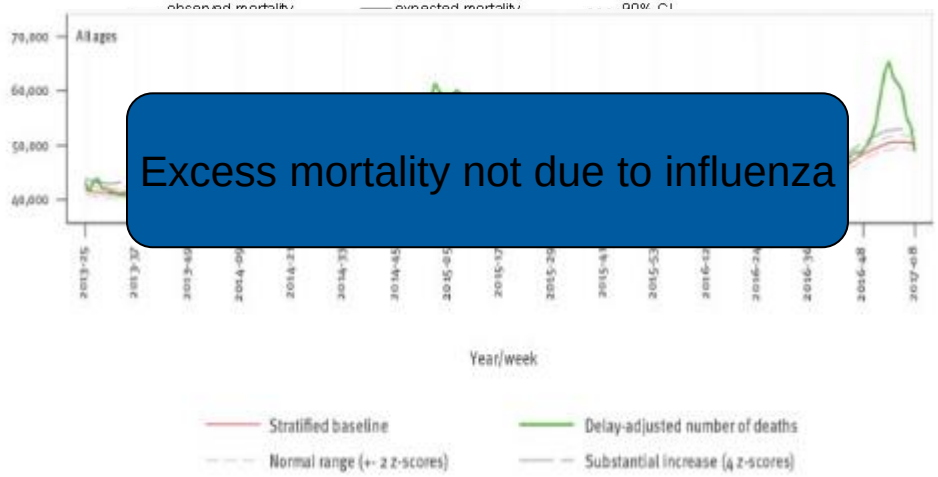
https://influenza.rki.de/

berit.lange@helmholtz-hzi.de

nhappy VAASC



Excess mortality due to influenza



Excess mortality not due to influenza

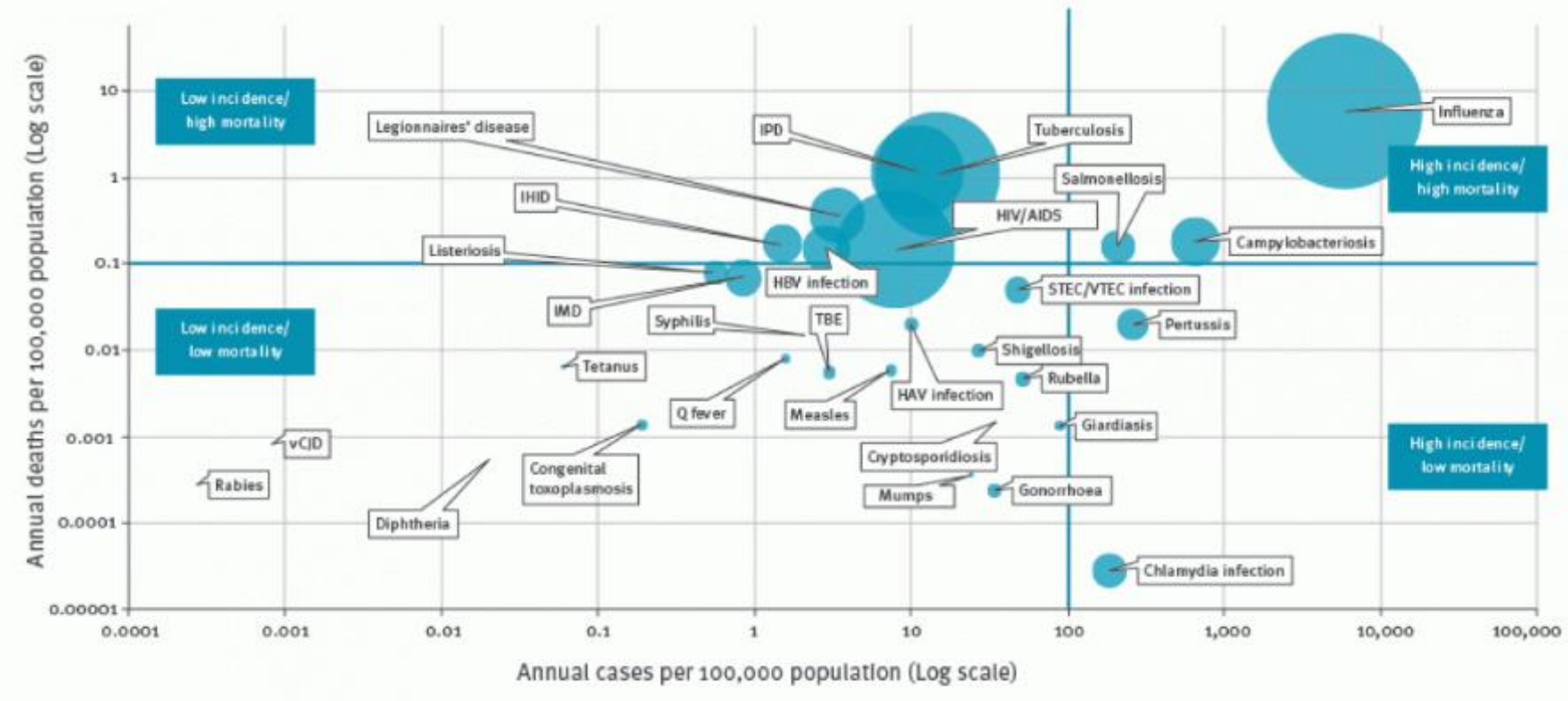
Economic costs

https://ecdc.europa.eu/en/seasonal-influenza/surveillance-and-disease-data

Vestergaard LS et al *Euro Surveill*. 2017

gerard.krause@helmholtz-hzi.de

Influenza burden in comparison to other Infectious disease burdens - ECDC



www.ecdc.eu

So how what should influenza surveillance tell to whom?

What?

- When to start/continue vaccinating
- When to start planning for influenza season
- When to expect an extraordinarily severe influenza season
- What burden to expect in what region

To whom?

- Health providers
- Public health system
- Schools/Universities
- The general public

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Basic facts about influenza

- RNA Virus
- Seasonal variation of strains and subtypes
- Incomplete / non lasting immunity after exposure /vaccination
- Vaccines need to be given every season
- Transmission primarily via droplets
- 8 – 44 excess deaths per 100.00 population per season (ECDC 2014)

Influenza Viruses

Classified into types A, B, and C

- Types A and B cause significant disease worldwide
- Types B and C limited to humans
- Type A viruses
  - More virulent
  - Wild waterfowl reservoir
  - Affect many species

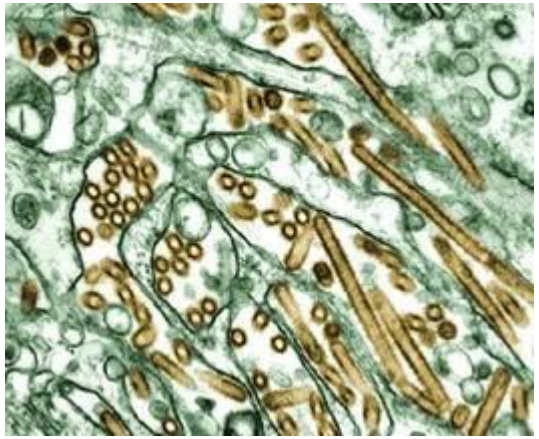
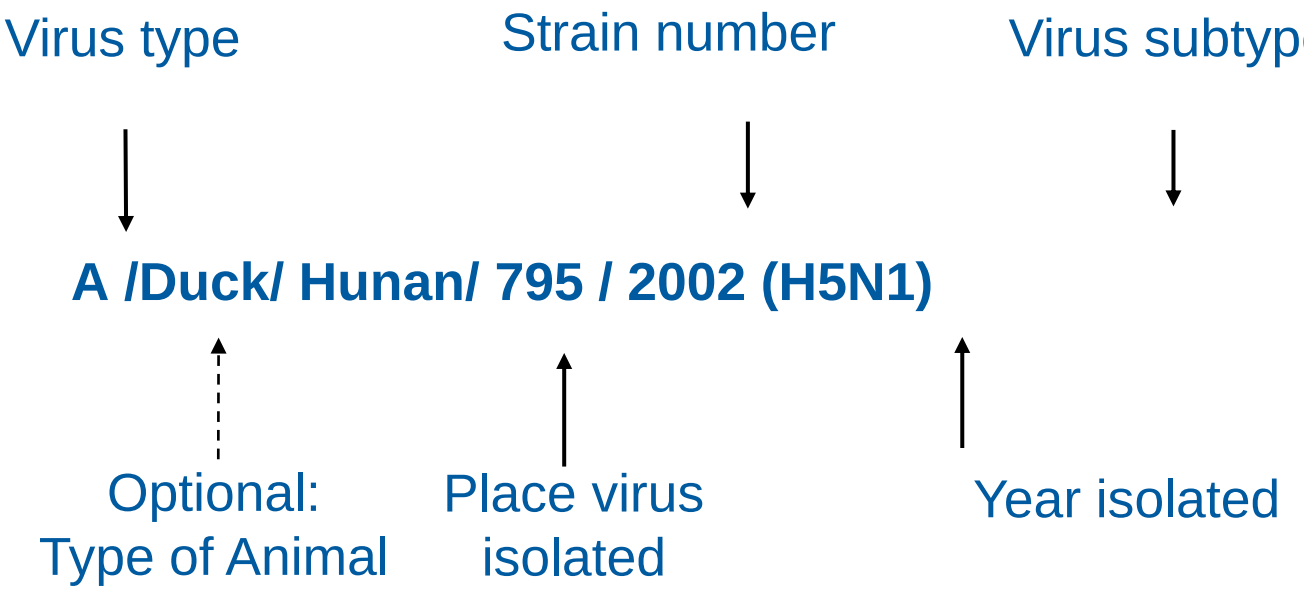


Photo: Cynthia Goldsmith, CDC

Nomenclature of Influenza Viruses



Influenza Vaccination

Developed from 3 circulating strains (2 Type A and 1 Type B strain)

Seasonal “flu shot” only works for 3 influenza subtypes and will not work on pandemic strains

Inactivated, intramuscular vaccine injection for persons 6 months and older

Live, intranasal spray vaccine for healthy non-pregnant persons (2 – 49 years old)

Vaccine efficacy varies with season and population in between 20-50%

U.S. Centers for Disease Control and Prevention

Definitions

ARI = acute respiratory illness

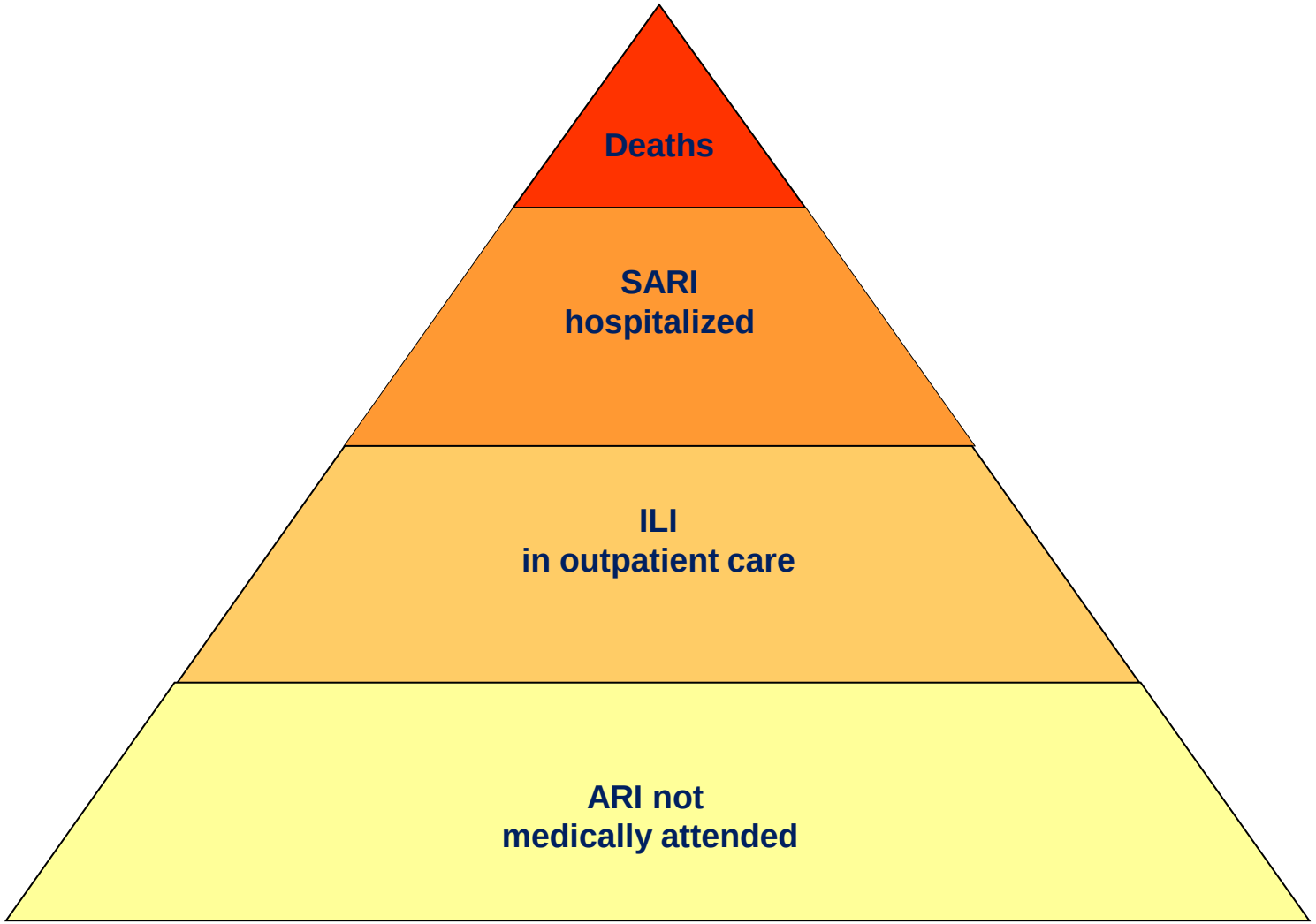
ILI = Influenza-like-Illness

- Acute illness with fever > 38°C *AND*
- cough or sore throat

SARI = Severe Acute Respiratory Infection

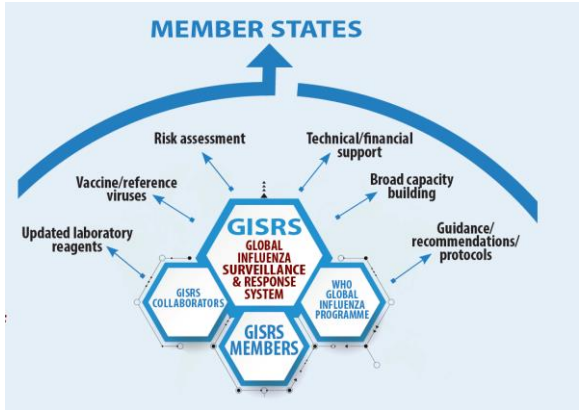
- Temperature > 38ºC *AND*
- Cough or sore throat *AND*
- Shortness of breath or difficulty breathing *AND*
- Requiring hospitalization

Distribution of influenza within the population



Influenza surveillance systems

Global Influenza Surveillance and Response System (GISRS)



Joint ECDC/WHO Europe surveillance

Flu News Europe

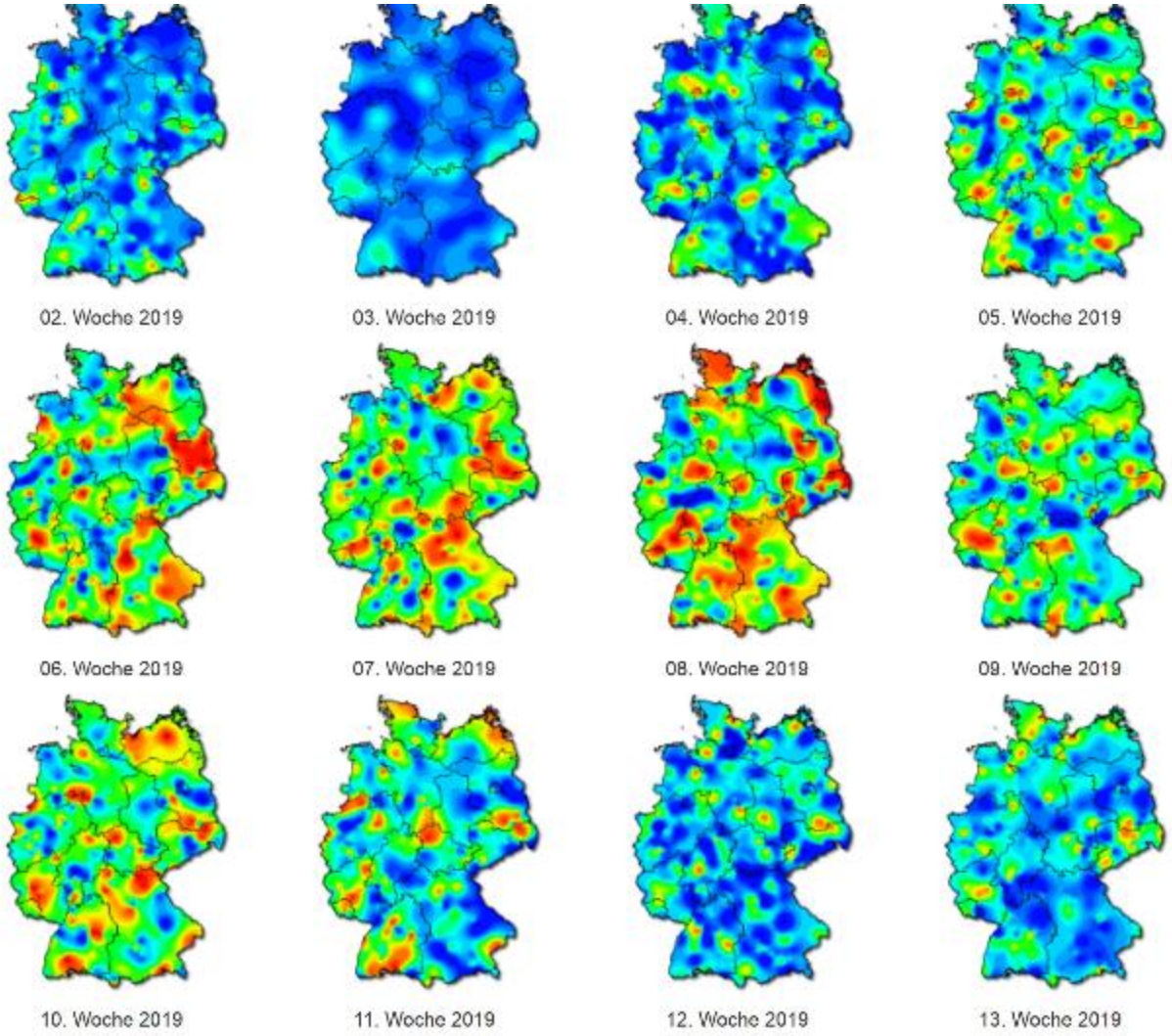
ecdc World Health Organization Europe

Surveillance in Germany

Arbeitsgemeinschaft Influenza

Berit.lange@helmholtz-hzi.de

Timely, by region info



https://influenza.rki.de/

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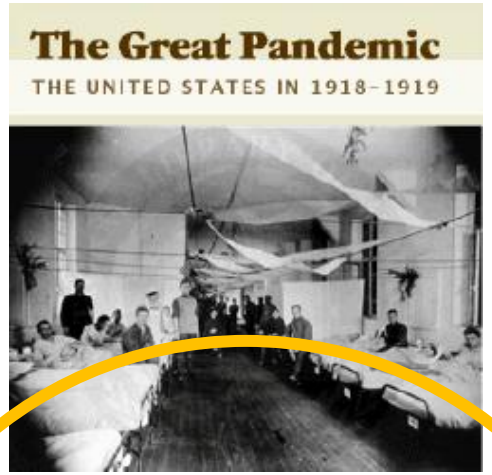
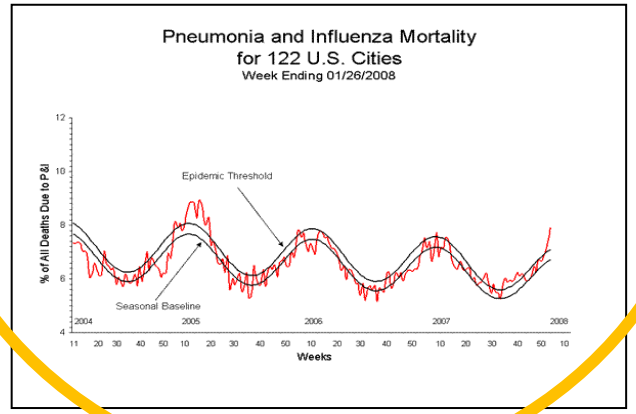
Pandemic



Seasonal



http://www.pandemicflu.gov/
http://www.cdc.gov/flu/weekly/

Influenza is

- An RNA virus with seasonal variation of strains and subtypes
- Has seasonally varying moderately effective vaccination
- comes with high but seasonally varying morbidity, direct and non-direct mortality as well as capacity to overburden health care systems

Surveillance systems of influenza aim to

- Provide isolates for identification of virus strains (for composition of vaccine)
- Report the start and end of influenza season
- Warn early of pandemics
- Monitor health service capacity to cope with epidemic situation

SOME MEASURES OF INFECTIOUS DISEASE EPIDEMIOLOGY

Measures of infectious disease epidemiology

- Modes of transmission
- Temporal measures of infection dynamics
- Indicators of transmissibility
- Underdetection and how to assess it

Modes of transmission

Direct or person-to-person transmission: sneezing, coughing , vertical transmission (e.g. from mother to child), mucosa to mucosa (sexually transmitted), blood and transplants, skin to skin

Indirect transmission: e.g. by water, food and by objects

Complex transmission cycles: e.g. parasitic diseases

Please name some examples

Temporal measures in infection dynamics

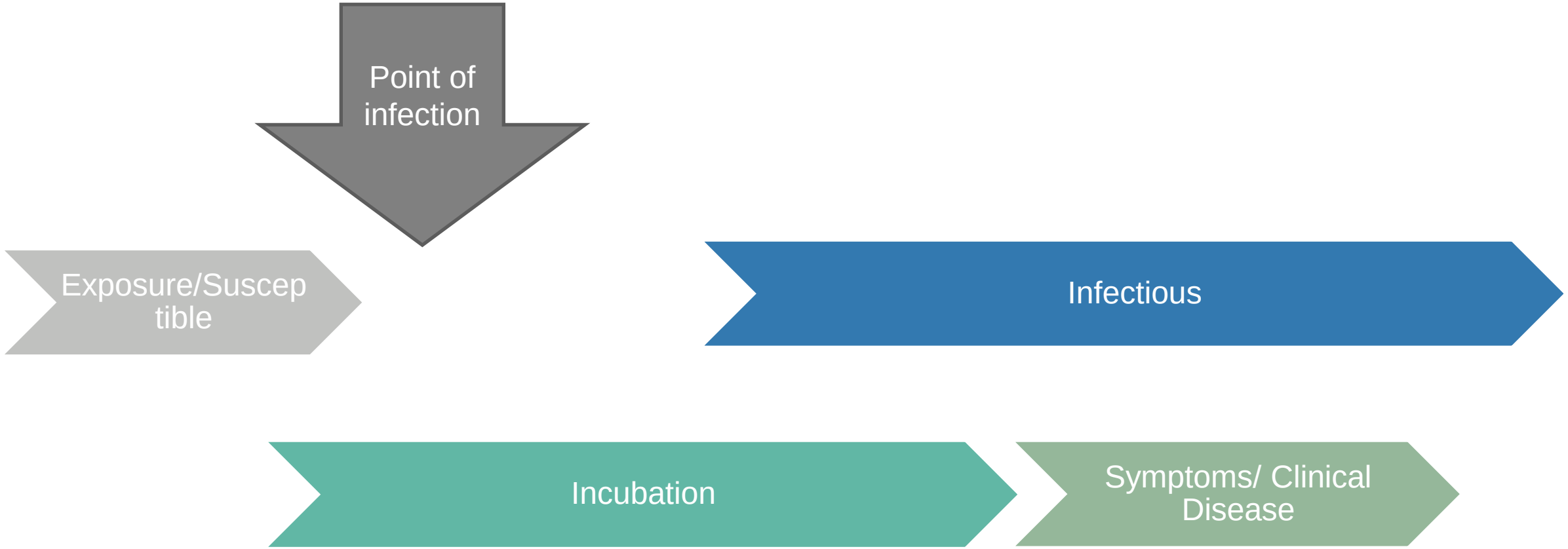
Exposure/Susceptible period

Point of infection

Incubation period

Infectious or communicable period

Temporal measures



Temporal measures

Exposure period: Time during which an individual is exposed and susceptible to an infection

Point of infection: when an exposed individual is initially infected

Incubation period: time from point of infection to onset of clinical illness

Infectious period: period during which a person can transmit the disease

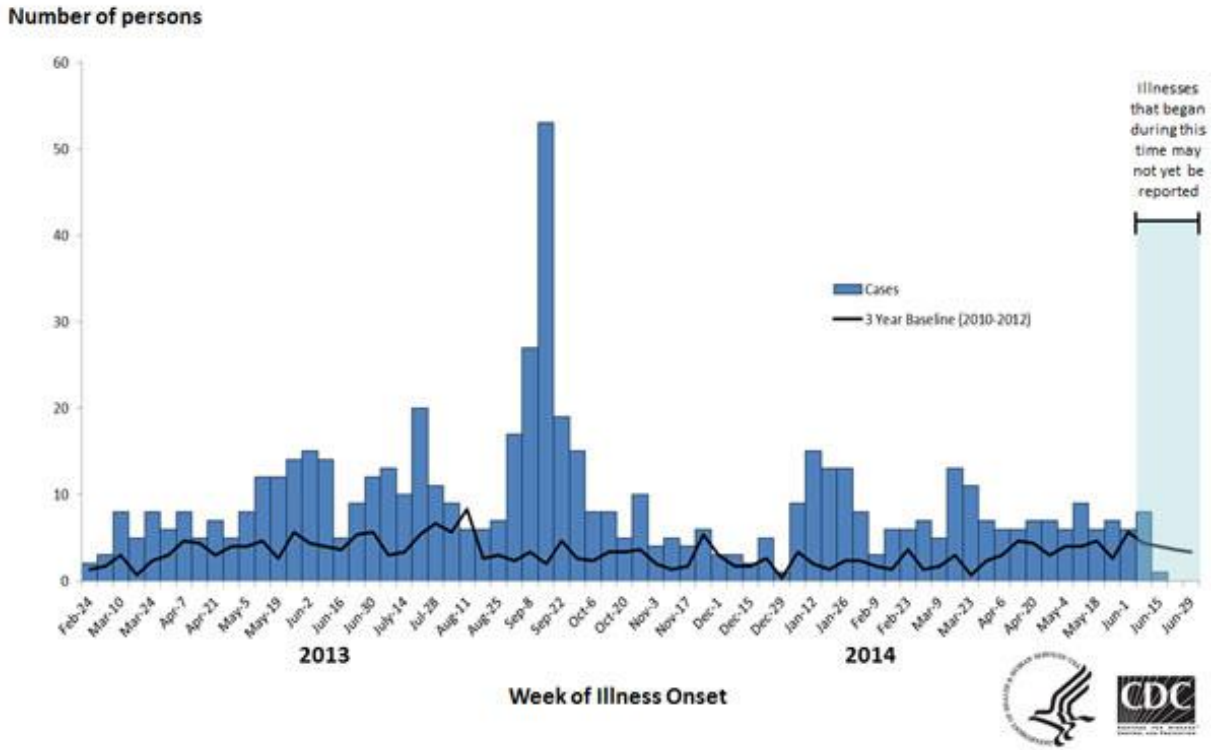
How is this for tuberculosis? How is it for the flu?

Epidemic curves

From epidemic curves you can deduce something about the disease causing the epidemic

Drawing an epidemic curve

- Select an appropriate interval
- Use squared paper and squares to represent cases



Use of epidemic curves

To determine the type of epidemic

To establish the difference between maximum and minimum incubation period

To determine the probable time of exposure , to determine the probable time and duration of exposure

To determine the incubation period when probable time of exposure is known

Secondary attack rate --- (not a rate!)

„Secondary attack rate“: proportion „attacked“ among (susceptible) individuals in contact with a primary case (eg in a household)

→not a rate!

Number of secondary cases / number of ***susceptible*** contacts of primary cases

What data do you need from public health authorities to under stand secondary attack rates?

UK: Secondary attack rates are available, linked to molecular surveillance (for SARS-CoV-2); not so in Germany

Variant/variant definition	Household/non-household exposure	Count of exposing cases	Count of contacts	Secondary attack rate (95% CI)
Delta	Household	60,364	147,057	10.7% (10.5%-10.8%)
Delta	Non-household	14,631	41,538	3.2% (3.1%-3.4%)
Omicron Confirmed	Household	107	227	21.6% (16.7%-27.4%)
Omicron Confirmed	Non-household	40	132	3.8% (1.6%-8.6%)

The basic reproduction number – R_0

- the average number of secondary cases that occur from a single index case in a susceptible population
    - If <1 outbreak will die out
    - If >1 outbreak will continue
- Varies from population to population

Examples of R_0

Disease	Mode of Transmission	R_0
Measles	Airborne	15
Rubella	Airborne	6
HIV	Sexual contact	3
SARS	Airborne	3
1918 infuenza	Airborne	1.5

Adapted from Rothman 2008

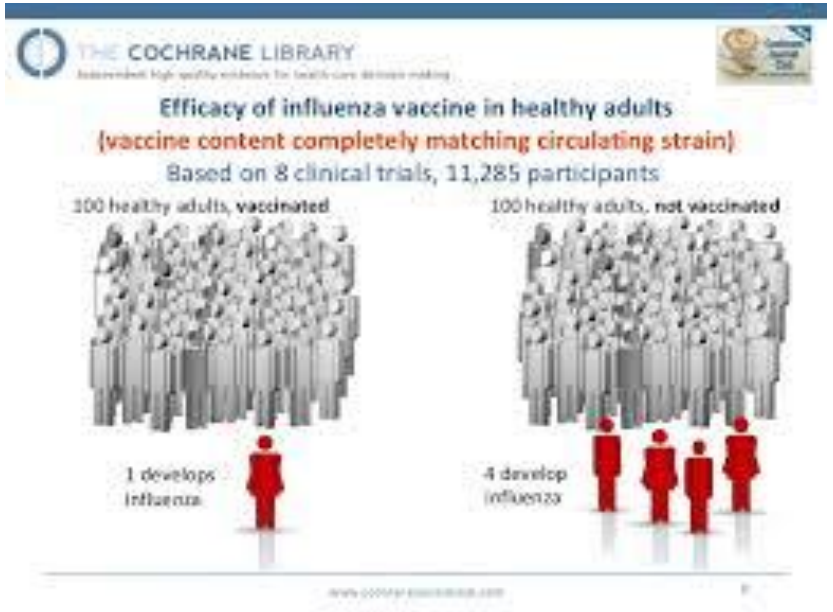
Vaccine efficacy

- Is the percent reduction in incidence (of the target disease) among vaccinated individuals which is attributable to vaccination

$$V_e = [(Incidence_{unvaccinated} – Incidence_{vaccinated}) / Incidence_{unvaccinated}] \times 100$$

$$V_e = (1 – RR_{v/u}) \times 100$$

Vaccine efficacy – how is it measured?



Disease	Vaccine efficacy
Influenza	20-70%
Measles	95%
Varicella	85-98%

Relation between R_0 , vaccine coverage and herd immunity

To have $R_t < 1$ without introducing quarantine or isolation measure:

What vaccine coverage hypothetically do we need to not have or end outbreaks/ to have herd immunity with a sterilizing vaccine?

-→ this is dependent on vaccine efficacy and R_0

Vaccine coverage > $(1-1/R_0)/ V_e$

Exercise: MMR or offices?

The MMR vaccine coverage in your region is 85%, which has increased by 20% compared to 5 years ago. At a local conference a regional director explains this very proudly and says that efforts to introduce more vaccination into the community can be suspended and the resulting funding should be used for much needed renovation of regional director offices. You understand that Vaccine efficacy for Measles,Rubella and Mumps is about 95%. Discuss.

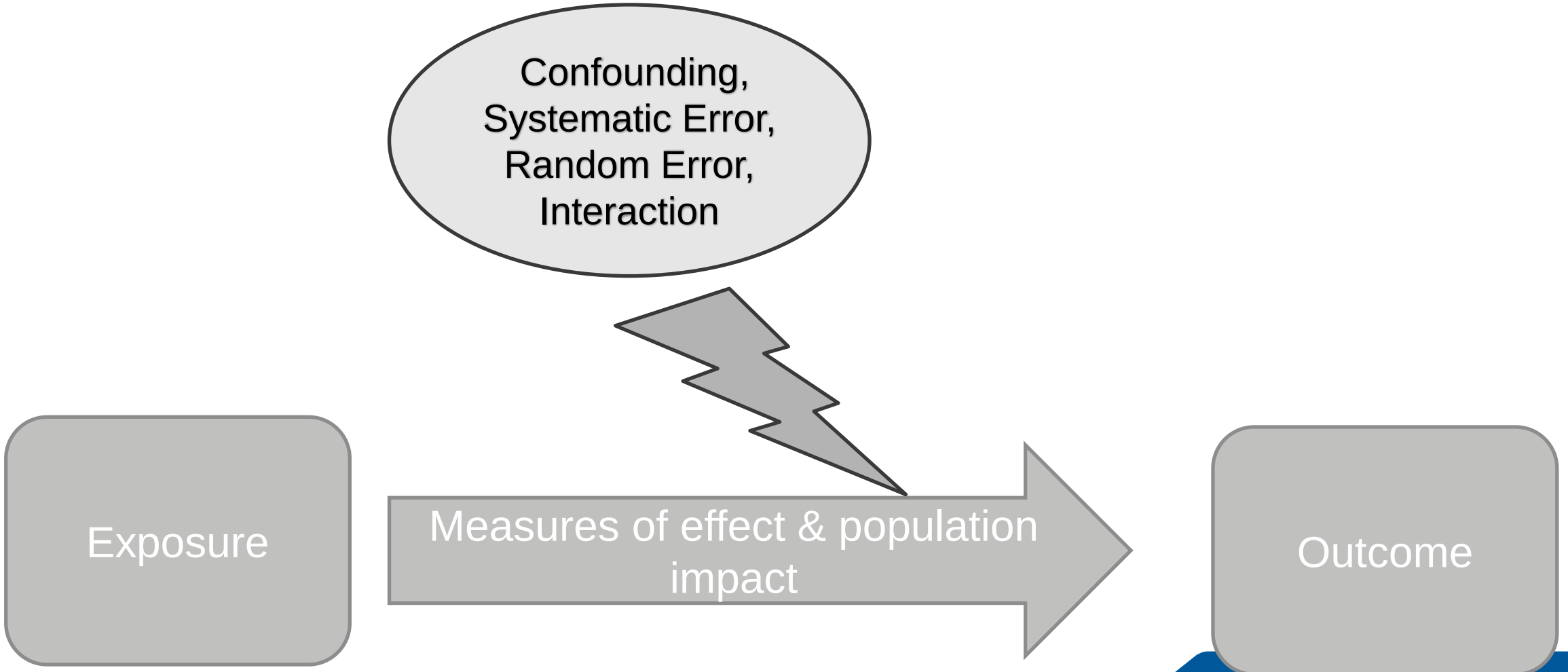
Disease	Mode of Transmission	R_0
Measles	Airborne	15
Rubella	Airborne	6
Mumps	Airborne	5

Vaccine coverage > $(1-1/R_0)/ V_e$

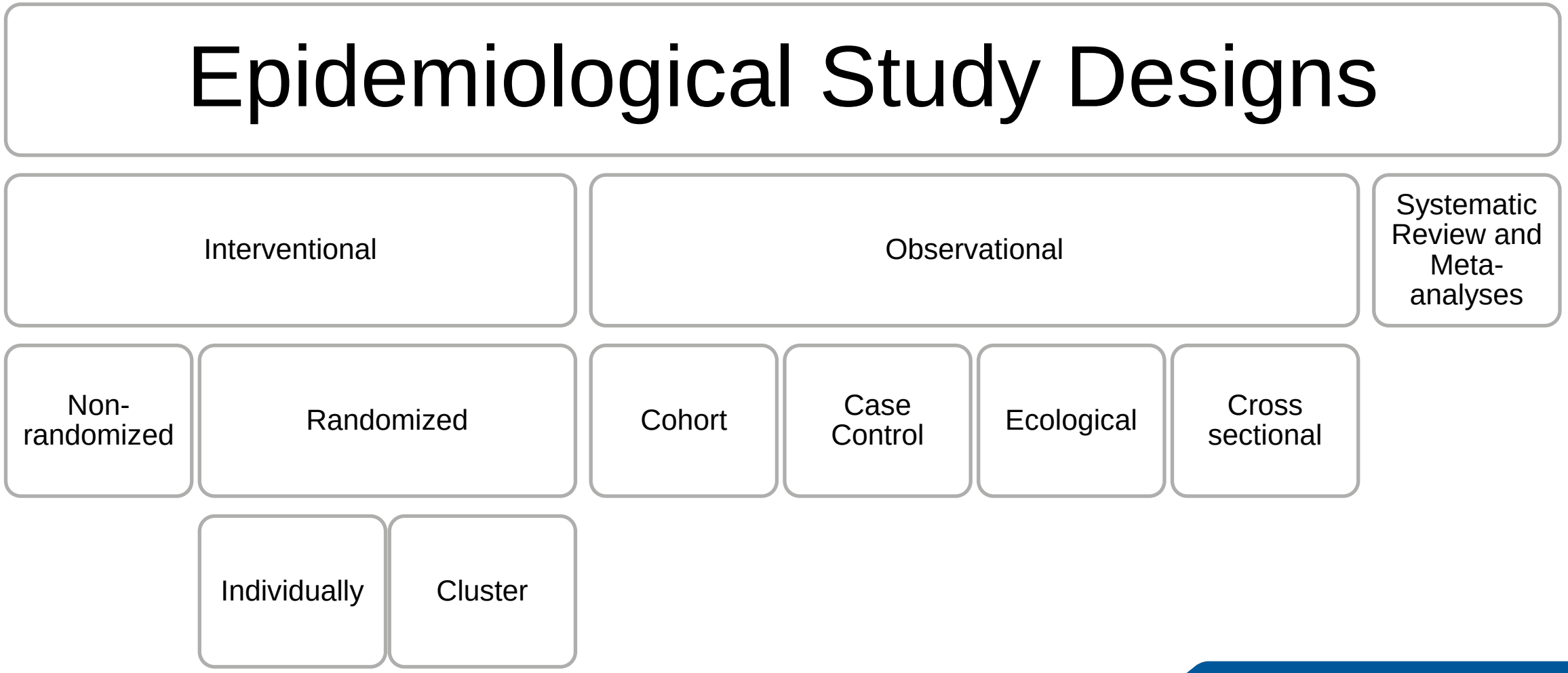
TYPICAL STUDY TYPES IN INFECTIOUS DISEASE EPIDEMIOLOGY

MAJOR EPIDEMIOLOGICAL STUDY DESIGNS

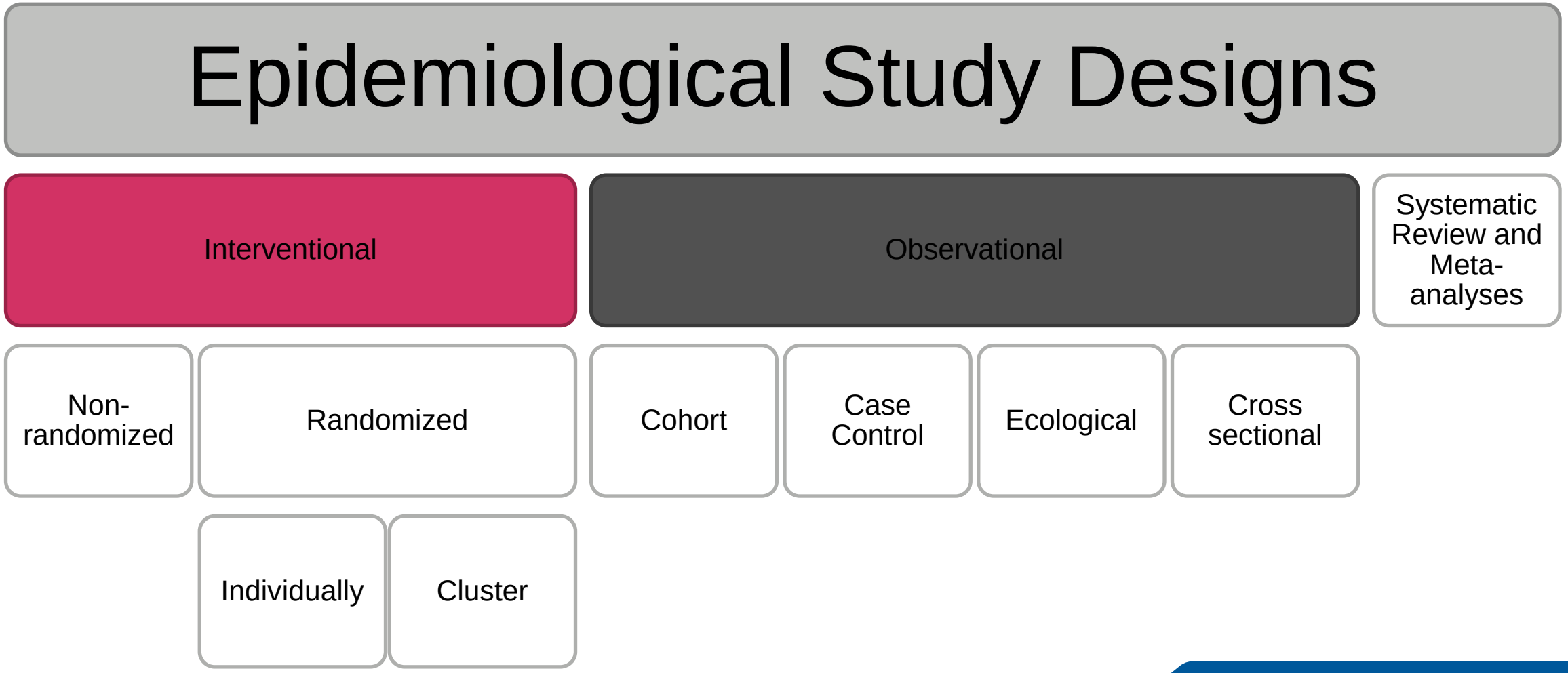
Epidemiological studies



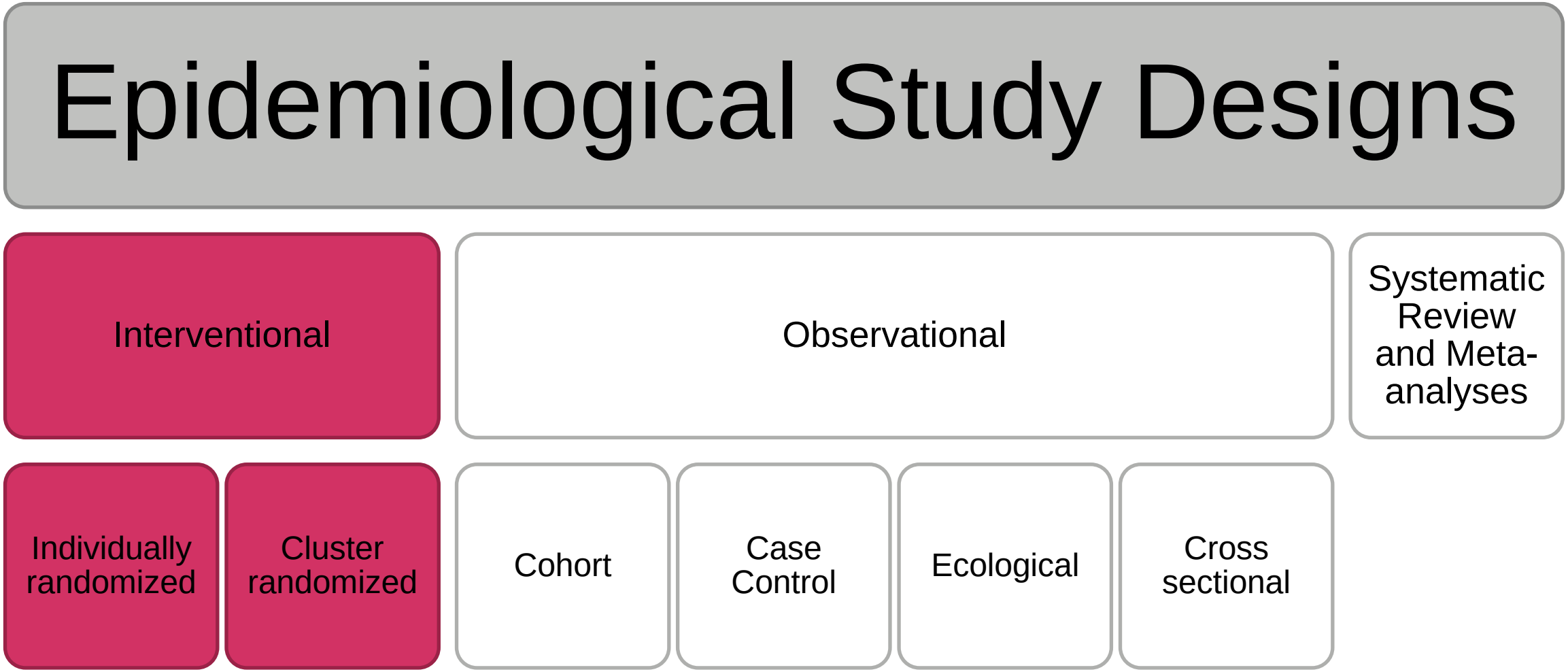
Study designs



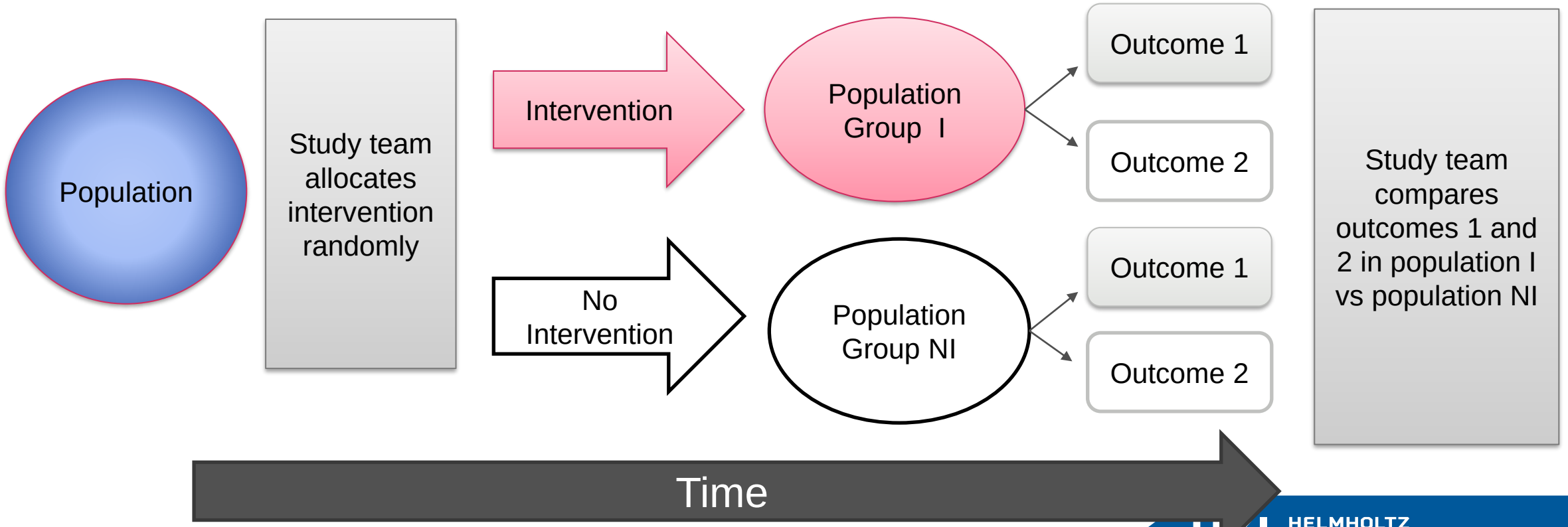
Study designs – intervention vs observation



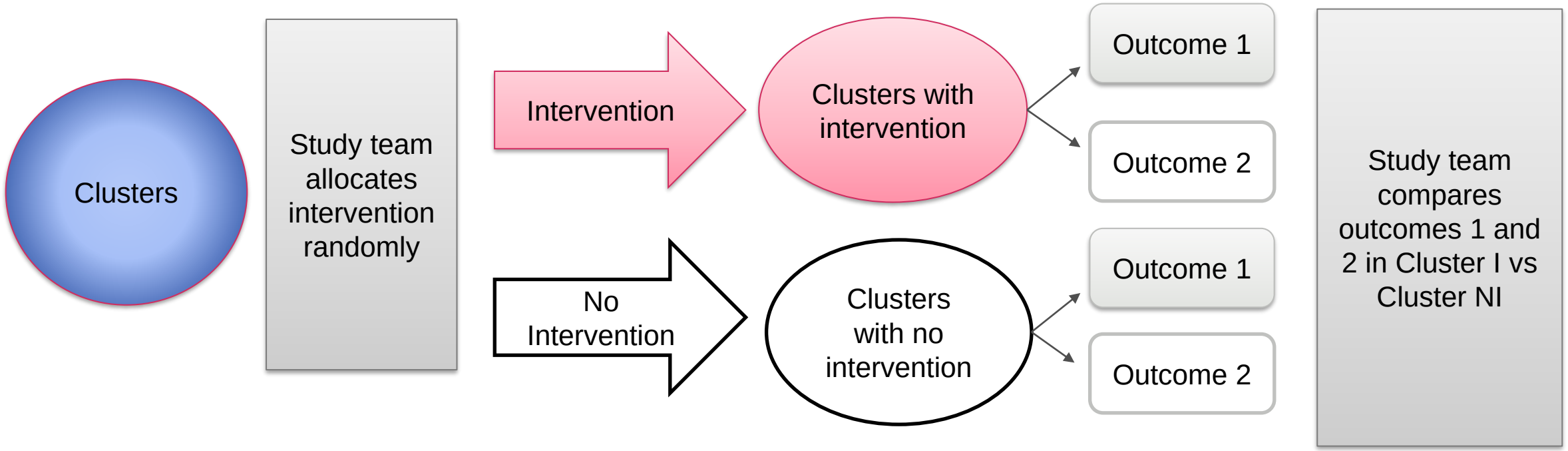
Study designs – interventional studies



Interventional studies – Randomized controlled trial

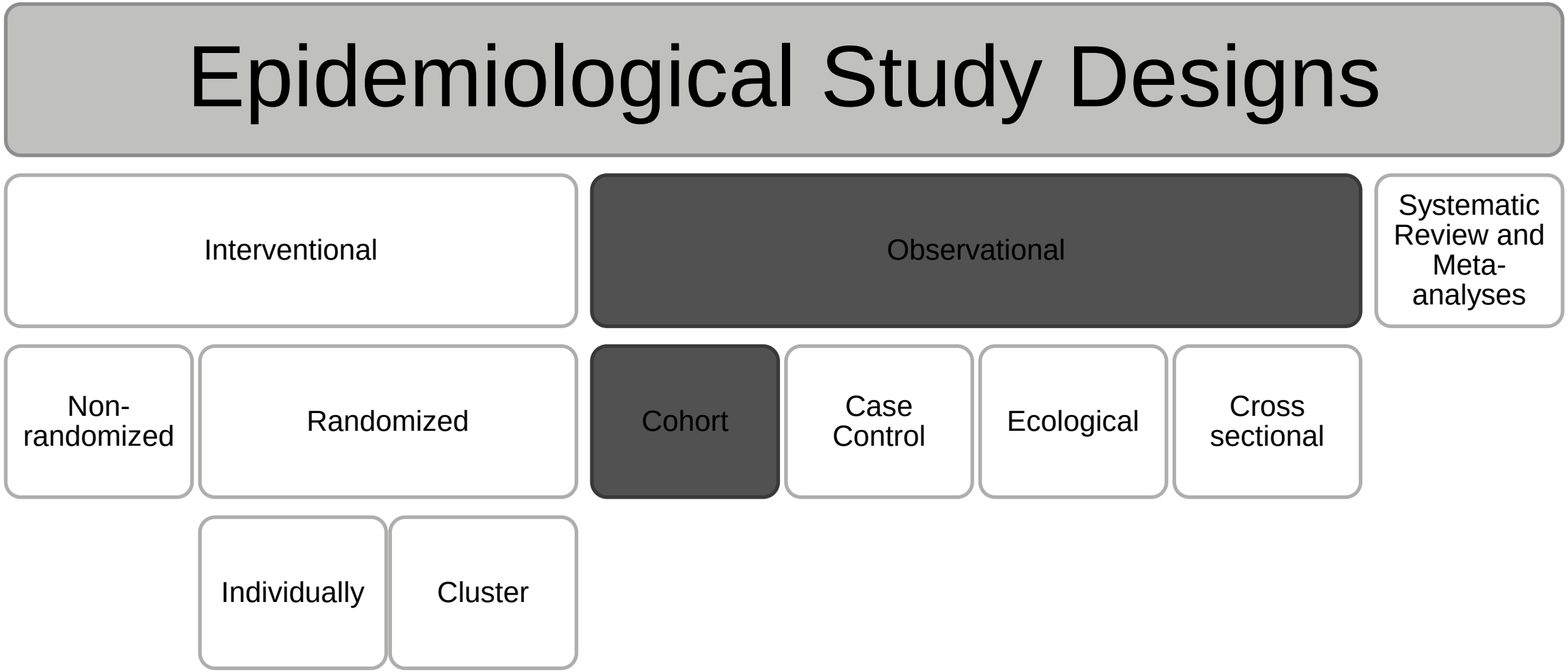


Interventional studies – Cluster randomized trial

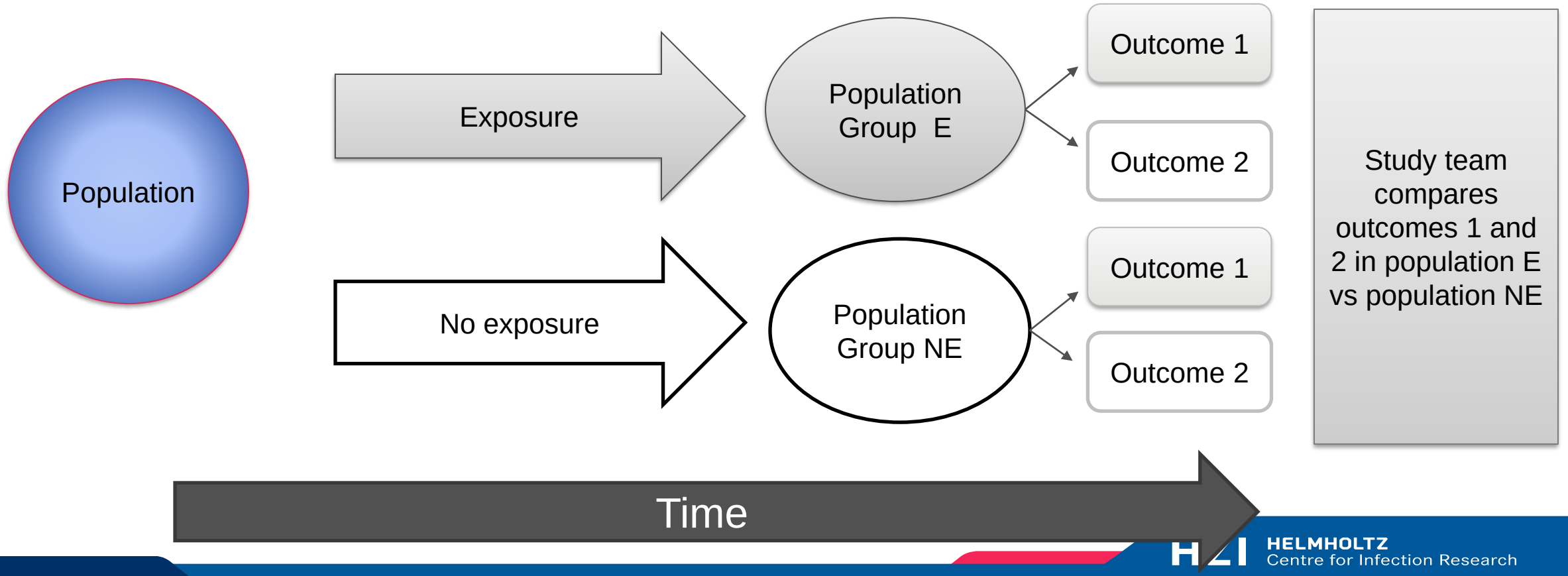


OBSERVATIONAL DESIGNS

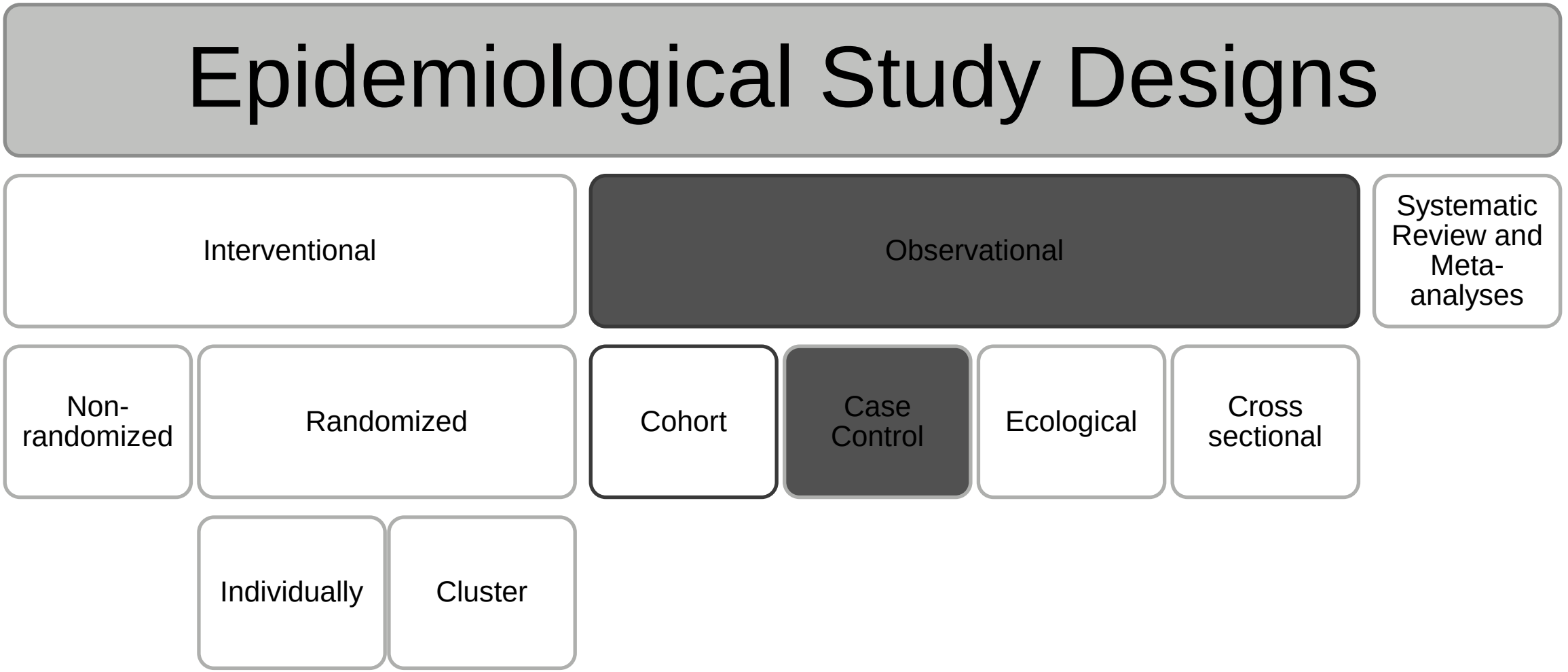
Study designs – cohort study



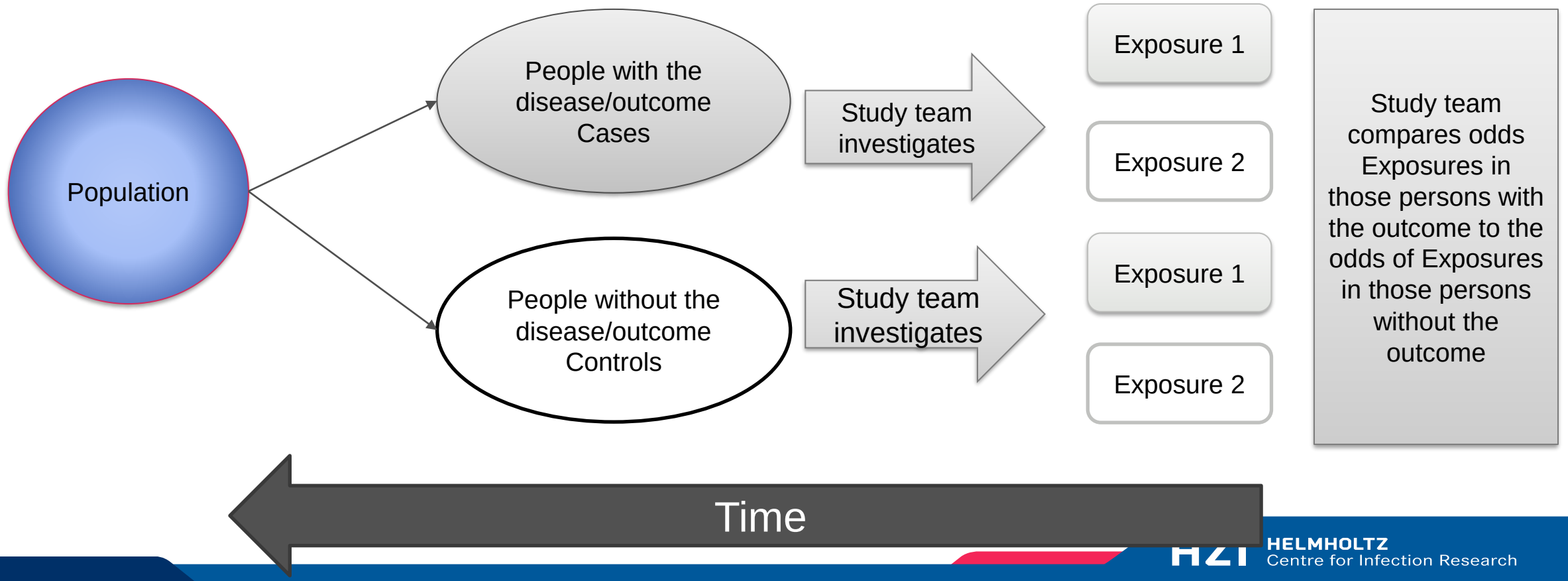
Cohort study



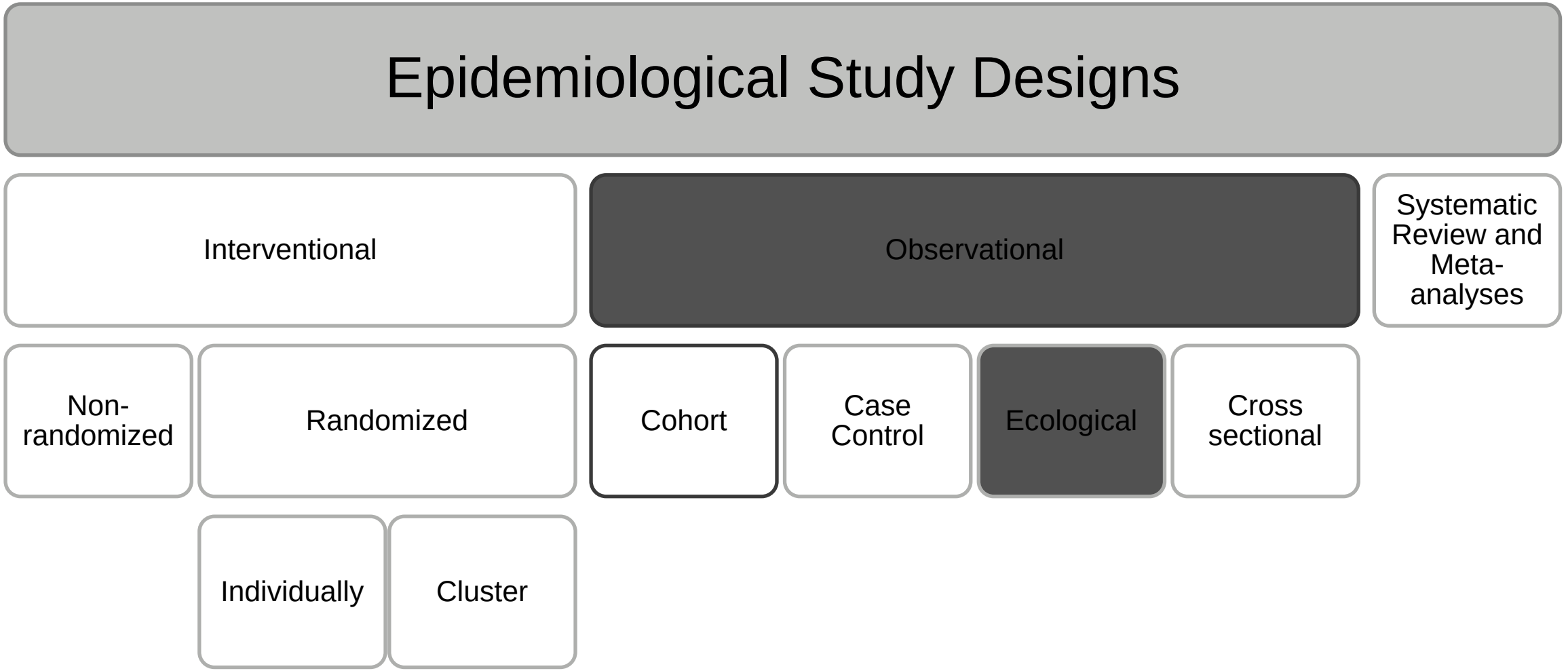
Study designs



Case (Patient)-control study



Study designs - ecological studies

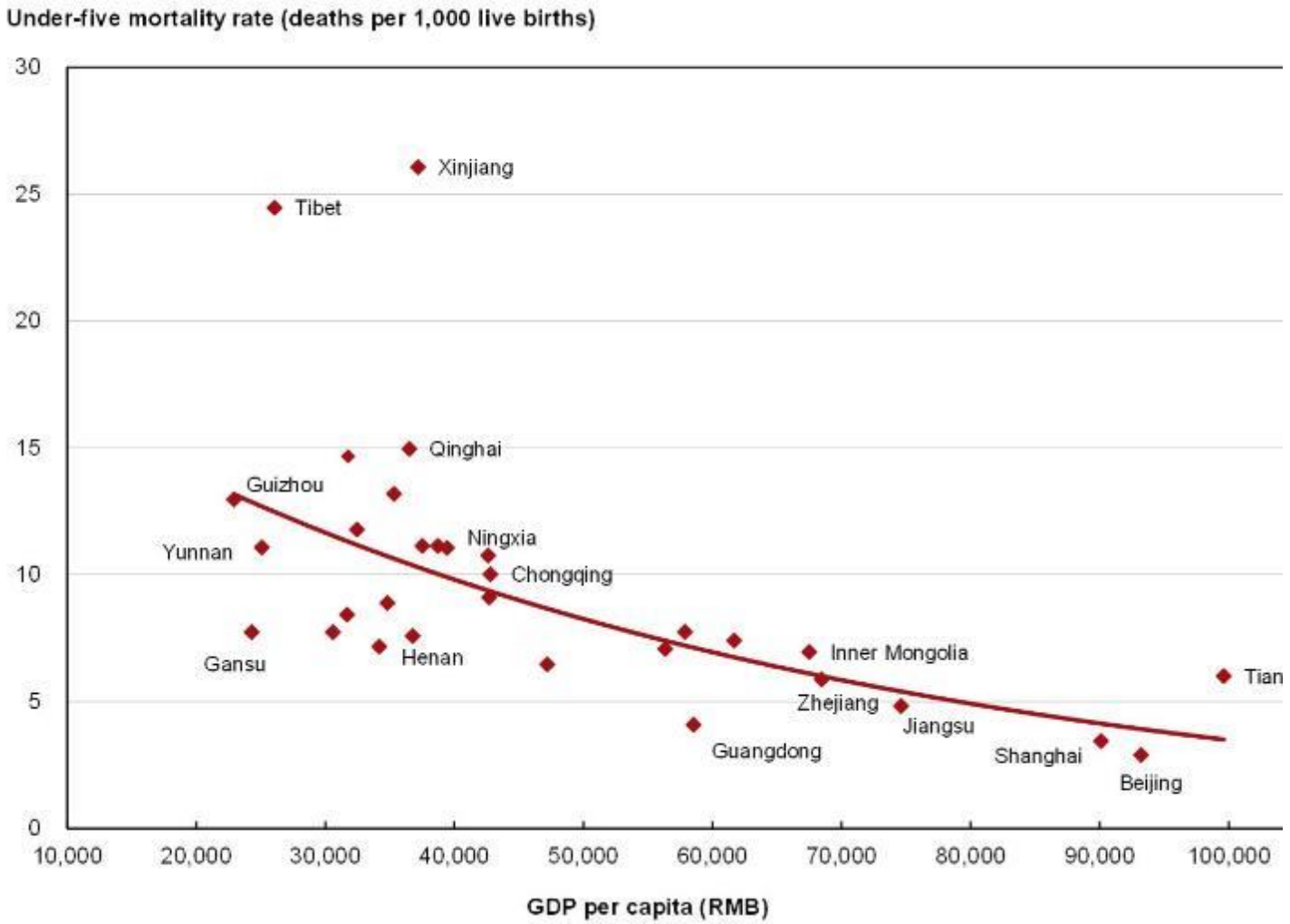


Classical ecological study: GDP and under five mortality rate in China

Geographical grouping of populations

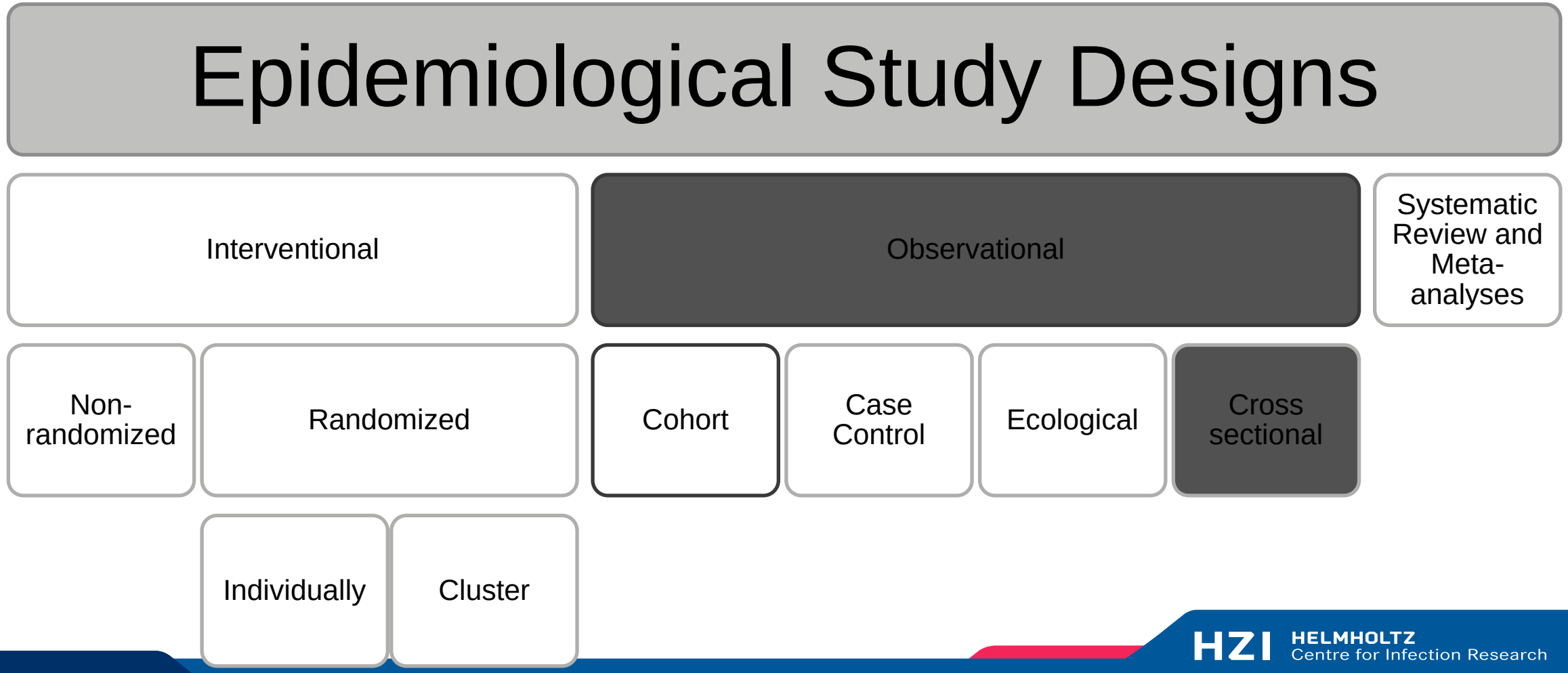
A regression method to show an association

Population estimates for both exposure and outcome



Source: Unicef

Study designs – cross sectional, the most simplest study design of all!

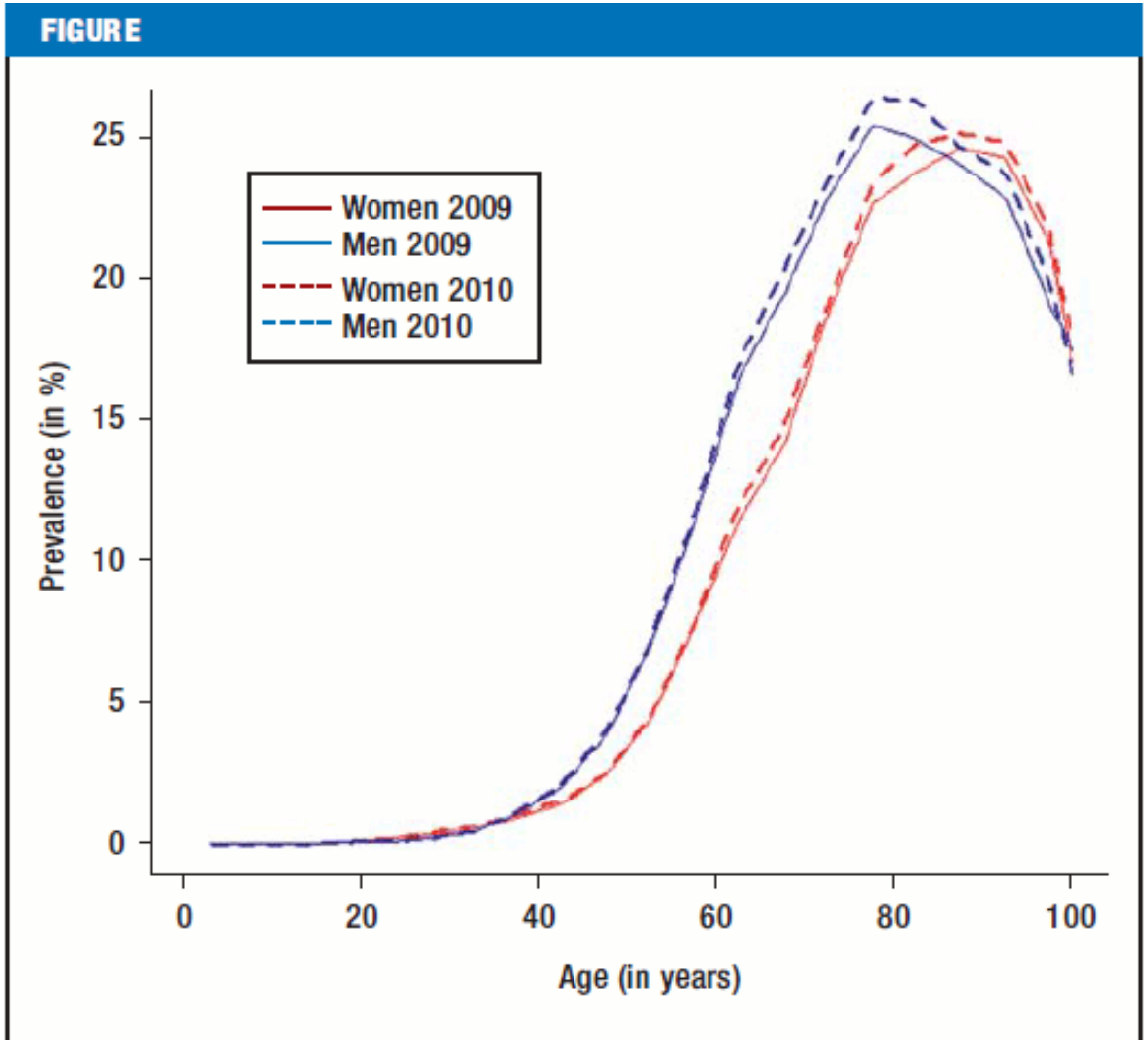


Classical cross sectional study

Prevalence estimates

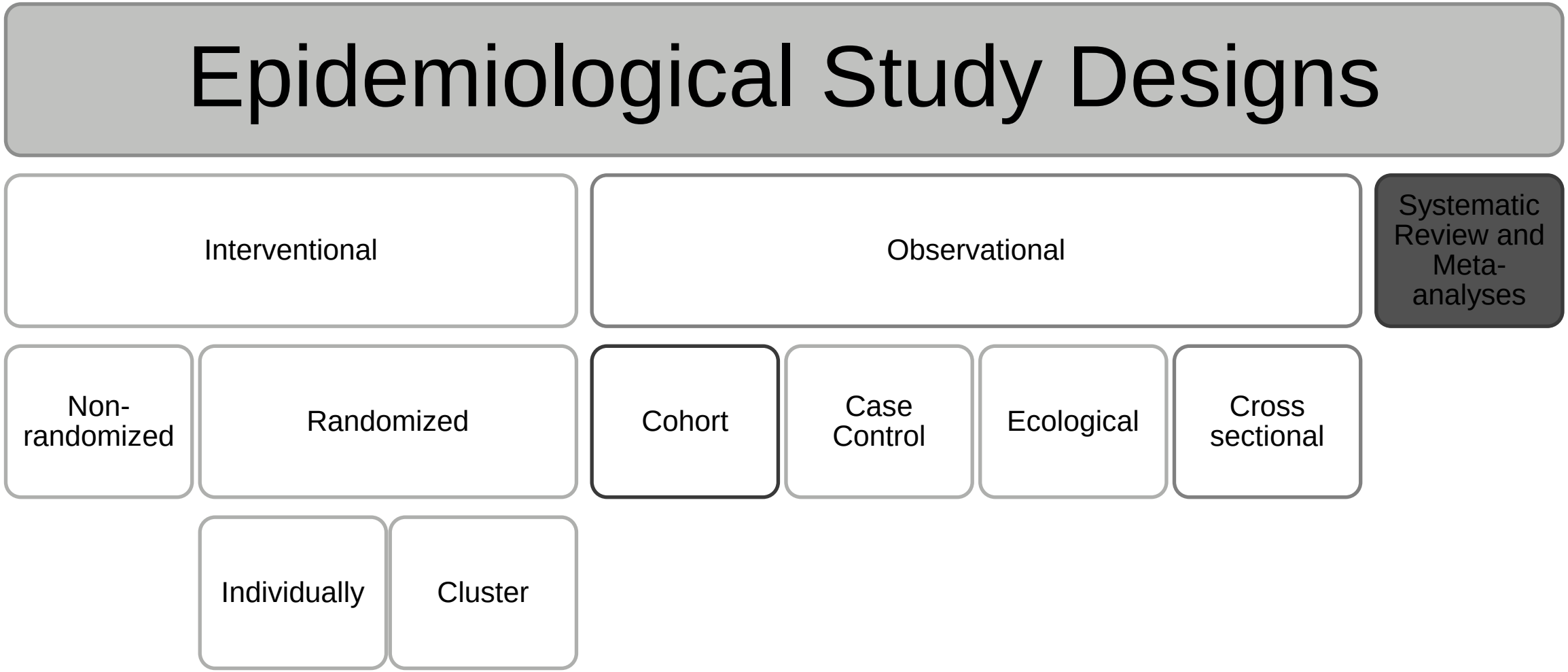
Analytical cohort study as the association of age and diabetes prevalence is looked at

Sample size aims to assess a certain proportion with certain magin of errors



Dtsch Arztebl Int 2016; 113(11): 177-82; DOI: 10.3238/arztebl.2016.0177

Study designs – cross sectional



Systematic reviews and meta-analyses

Systematic reviews

protocol following PRISMA and using PICOs or similar

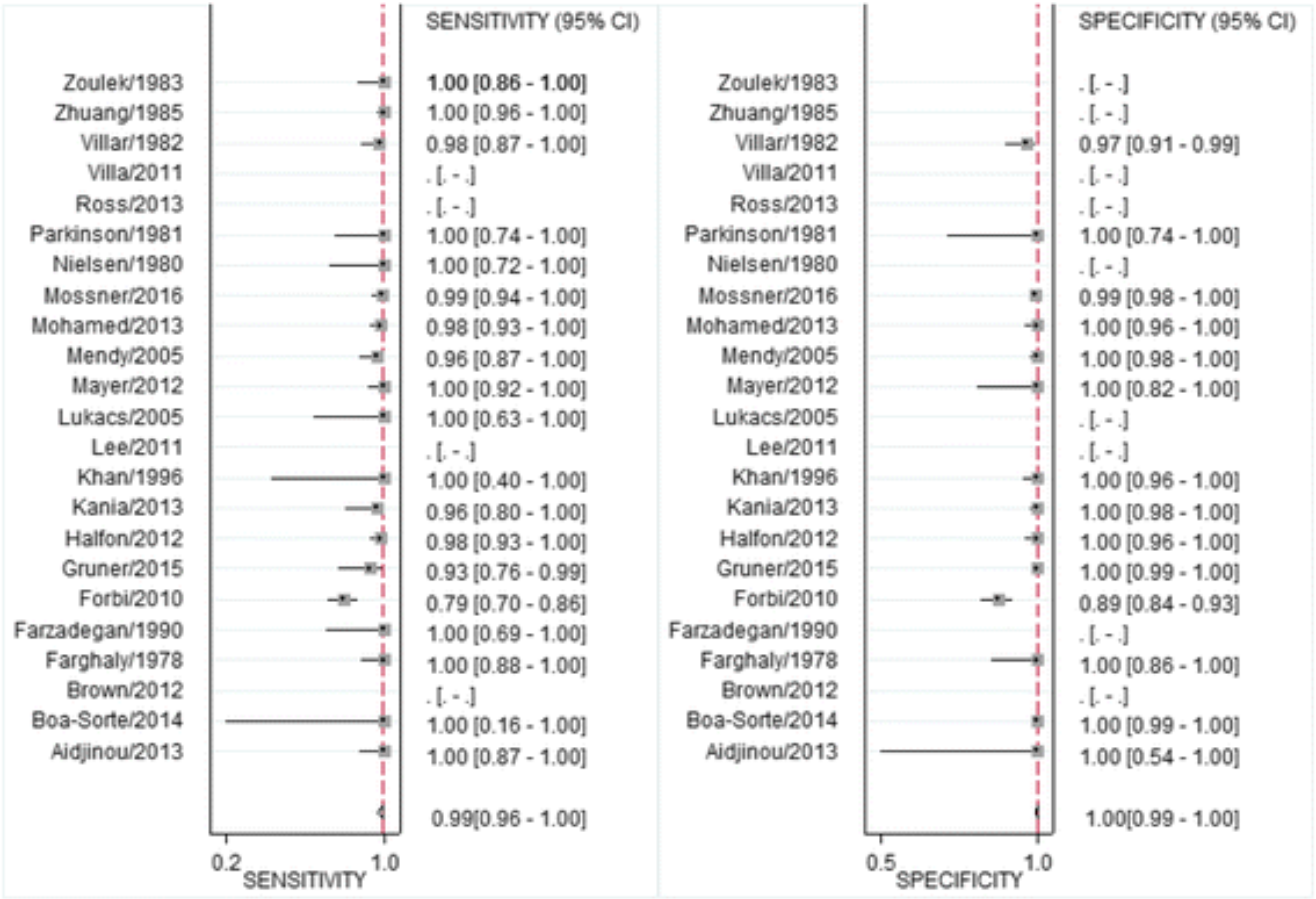
systematic search

data extraction

analysis in duplicate

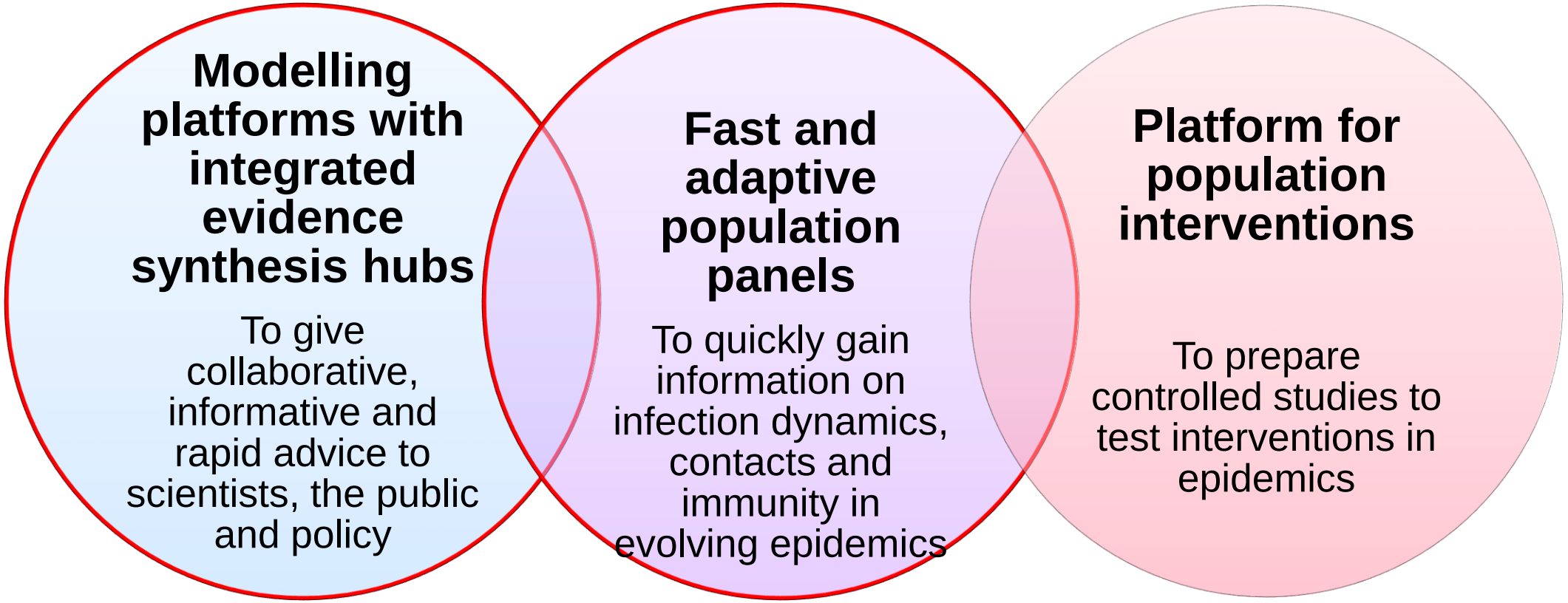
Meta-analyses

Is the analysis when we get pooled results from several studies or datasets



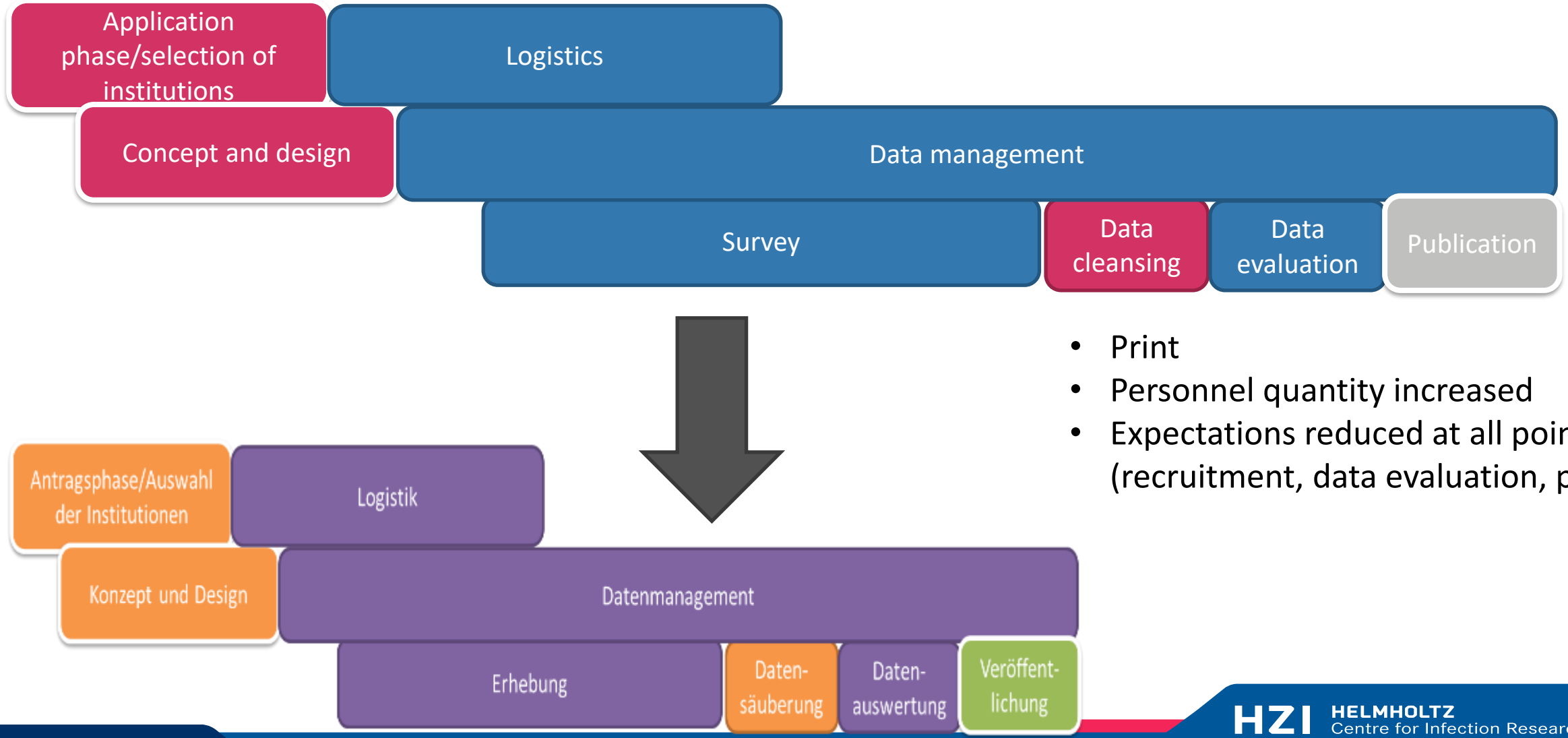
INFECTIOUS DISEASE EPIDEMIOLOGY INFRASTRUCTURES NEEDED

Research infrastructures in infectious disease epidemiology needed for the next pandemic



Beermann et al, Dt. Ärzteblatt

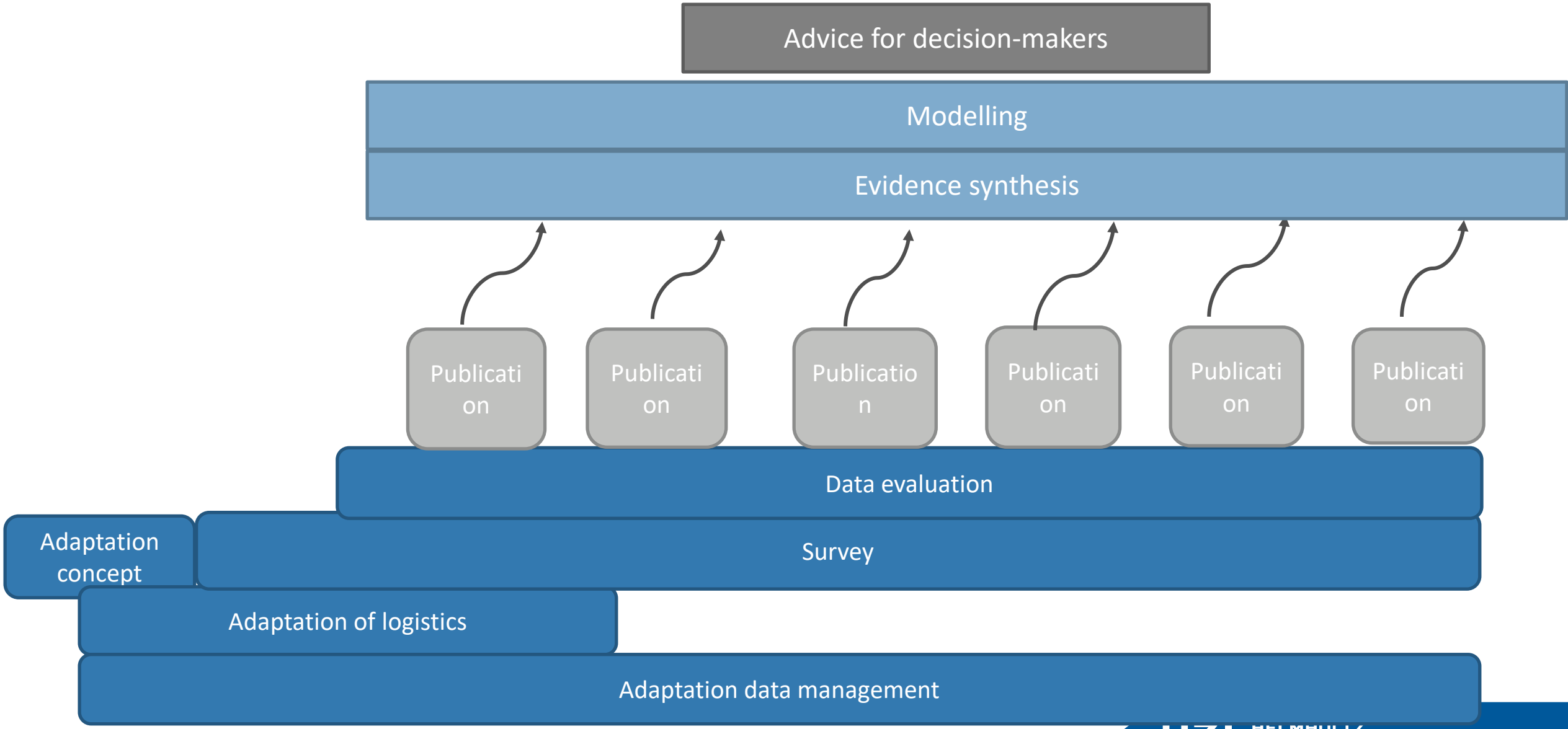
Population-based survey of infection frequency and dynamics
How it was during the pandemic



- Print
- Personnel quantity increased
- Expectations reduced at all points (recruitment, data evaluation, publicati

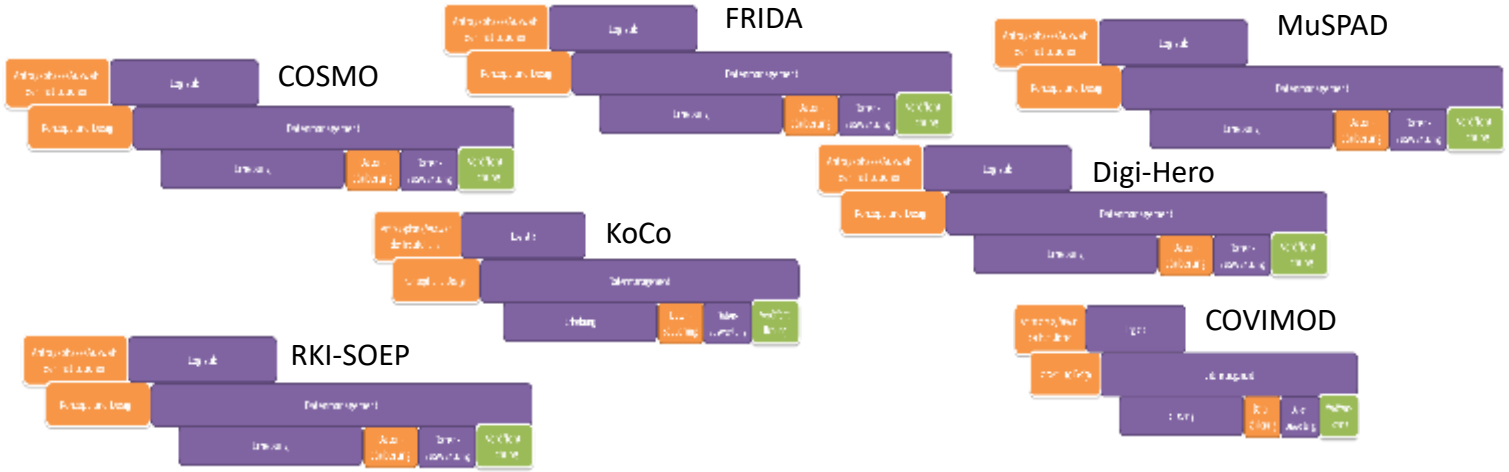
Population-based survey of infection frequency and dynamics

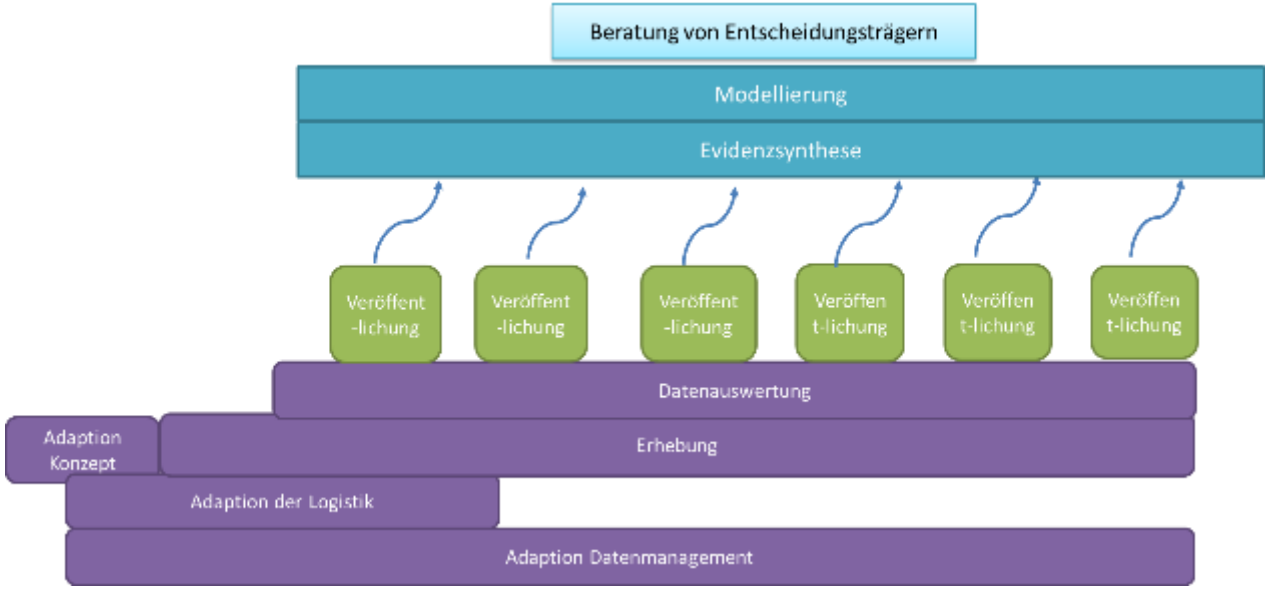
The vision for the future



Population-based survey of infection frequency and dynamics

How we get there





PREPARED, IMMUNEBRIDGE (NUM), OPTIMagent, RESPINOW

- Joint planning and concept, e.g. also within NUM-PREPARED
- Adaptation possible for different pathogens, regions, population groups
- Regular use within the respiratory infection seasons
- Clear link to evidence synthesis, modelling and decision makers

Building MuSPAD into a fast adaptive population panel


Manuela Harries


Julia Ortmann


Christina Suckel


Max Hassenstein

02/20 – 08/21

Built up as a mainly **cross-sectional seroprevalence survey with > 33.000 participants with 8 locations across Germany**

05/22 ethical approval

changing MuSPAD into a longitudinal, fast, adaptive population panel

06-07/2022

Resampled 3000 participants from 3 locations in June/July 2022 with a preparation time of 2 months:

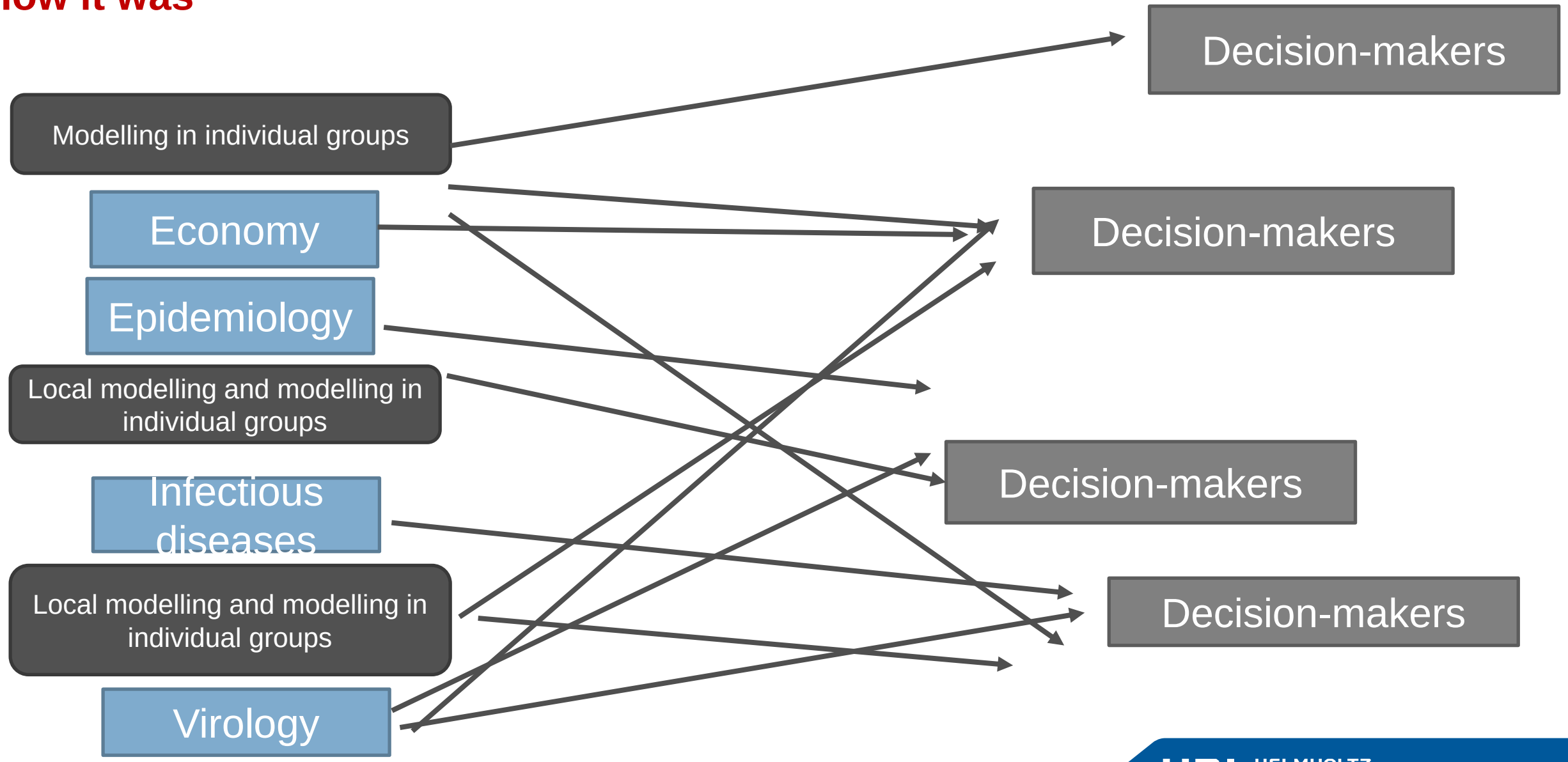
RESPINOW: influenza, RSV and pneumococcal dynamics

POXIMUN : Immunity after smallpox vaccination and monkeypox exposure

NUM IMMUNEBRIDGE: SARS-CoV-2 immunity

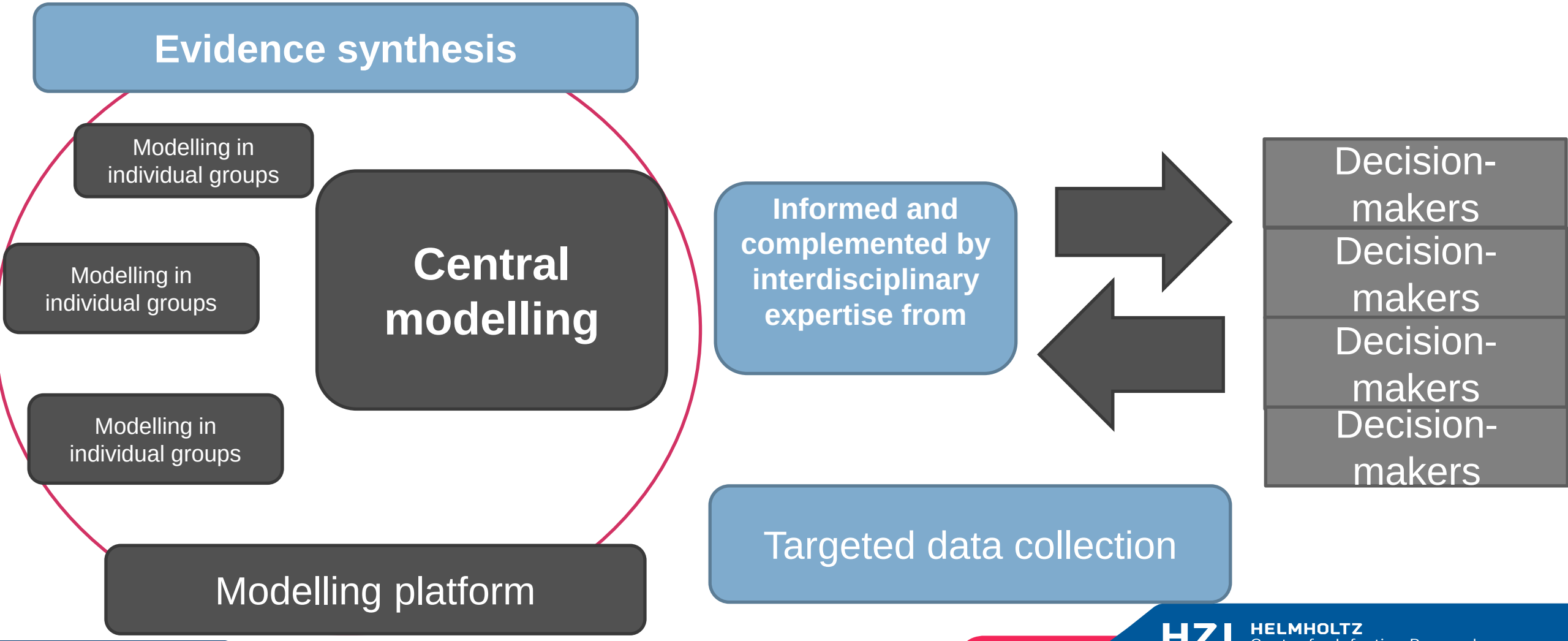
Modelling and advising decision-makers

How it was



Modelling and advising decision-makers

What it would ideally be like



Koordinierungsstelle für die neuen Modellierungsplattformen in Deutschland (BMBF)

Research Consortia with coordinators (1-3 Mio Euro/ 5-10 groups per consortium)

OptimAgent
Rafael Mikolajczyk,
Alex Kuhlmann, André Karch

RESPINOW
Berit Lange

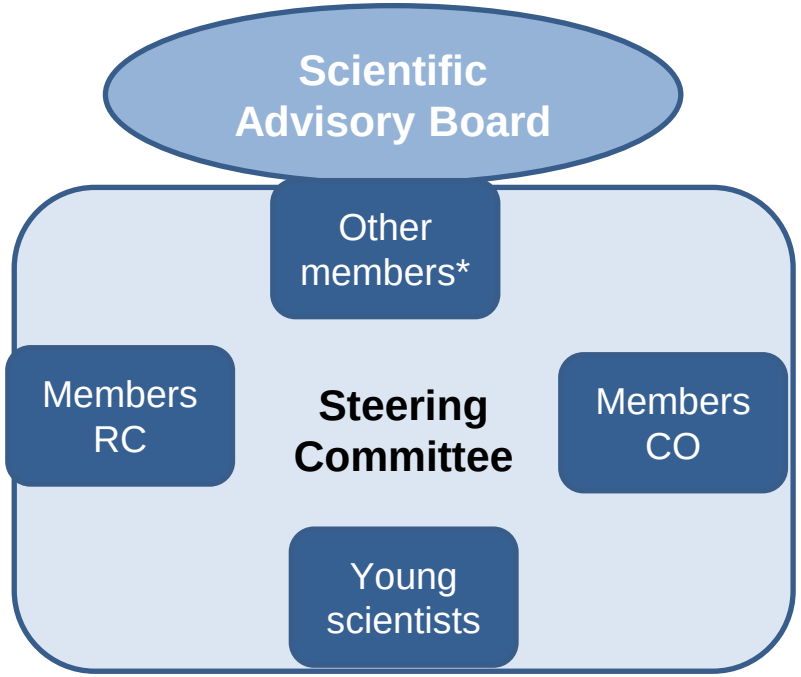
infoXpand
Viola Priesemann

PROGNOSIS
Marcus Scholz

INSIDe
Jan Hasenauer

MODUS
Kai Nagel

SEMSAI
Ingo Timm



Coordination Office
Alexander Kuhlmann & Stefan Scholz

*public health services, RKI, etc

Linking population panels and central modelling structures in NUM-IMMUNEBRIDGE



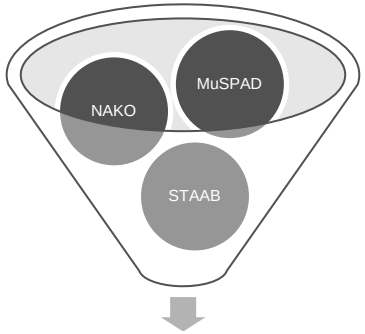

Manuela Harries Max Hassenstein Veronika Jäger, WWU André Karch, WWU

& IMMUNEBRIDGE analysis and cohort team

Invitation of cohorts 04/22

Development minimal data set 05/22

Sampling in cohorts 06-07/22

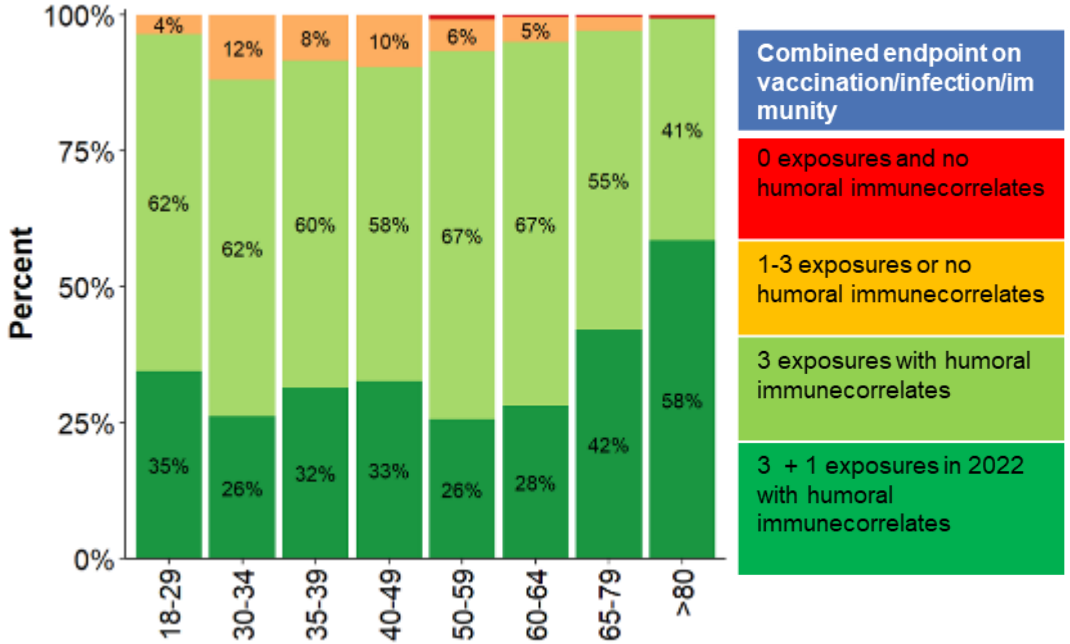


LEOSS COVIM sero-survey serohub HZI HELMHOLTZ Centre for Infection Research

First data cut in 25.07.22

Presentation of data to modelling consortia on 04.08.22

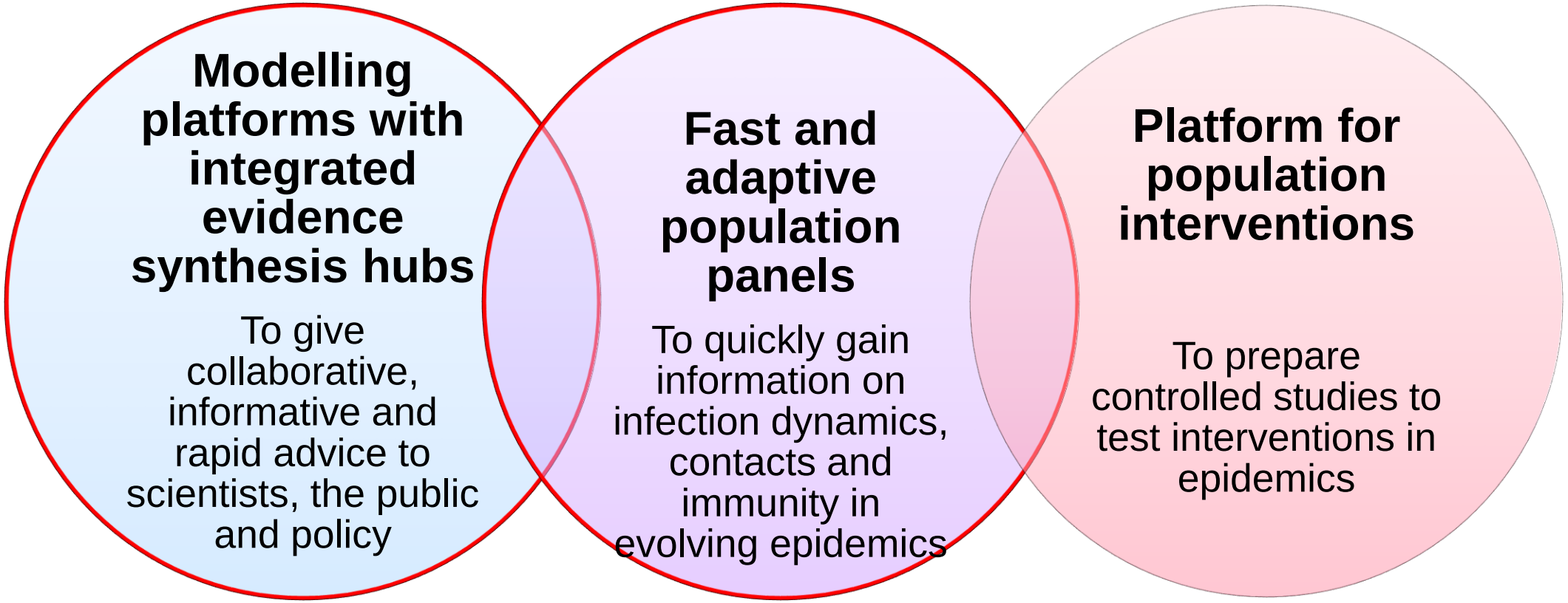
Model-usable dataset for modelling consortia on 08.08.22



Lange et al, doi: 10.5281/zenodo.6968574
Harries, Jäger, Rodiah et al, in preparation

6037 participants in 6 cohorts (MuSPAD, NAKO, STAAB, Dresden) with sampling in June/July 2022

Research infrastructures in infectious disease epidemiology needed for the next pandemic



Beermann et al, Dt. Ärzteblatt 2022

Summary

- After COVID, tuberculosis is the infectious disease that kills most people globally, even though it is well treatable

- Flu surveillance systems in Europe are in principal designed to give information both for seasonal epidemics and early warning for pandemics

- In new infectious diseases you are particularly interested in the infectious period, incubation period, secondary attack rates, underdetection of notified cases or infection fatality rates

- You need to be able to find or set up appropriate epidemioogical studies and ideally be able to link to surveillance data

- Infrastructures now being built in Germany: Modelling platforms, rapid and adaptive population panels as well as infrastructures linking the two

Over to you

finding out about an infectious disease

1. Designing a systematic review on the infectious period for monkeypox

2. Designing a population study on immunity against monkeypox by smallpox vaccination

3. Designing a study on secondary attack rates of monkeypox cases in kindergarten together with public health agencies in Germany