Lessons from 30 Years of Large Scale Global Burden of Disease (GBD) Study

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GRAM Project, Institute for Health Metrics and Evaluation (US) & University of Oxford Big Data Institute (UK)

Adult Immunization Board (AIB) Technical Meeting, 20-21 April 2023 (University of Antwerp, Belgium)

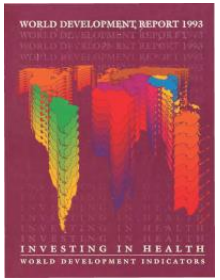
UNIVERSITY of WASHINGTON

Institute for Health Metrics and Evaluation

Historical timeline of the Global Burden of Disease (GBD)

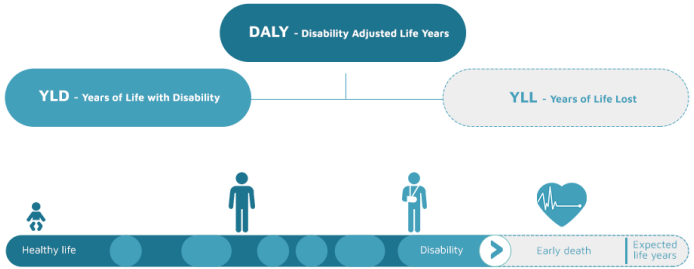
- **The first GBD study** began in 1991 and led to the first results being published in 1993 → 8 regions, 106 conditions and 10 risk factors, broken down into 5 age groups for the year 1990

- The GBD now provides estimates for each year from 1990 to the present for **371 diseases and injuries**, plus 3,499 clinical outcomes (sequelae) related to those diseases and injuries, for **204 countries and territories** and for subnational units in more than 20 countries



Core principles of the GBD

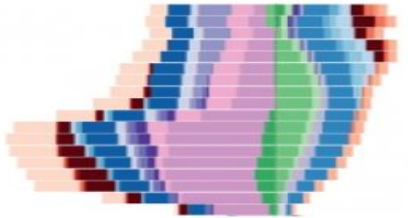
- **Best estimates** → for each quantity of interest for any location, irrespective of the data availability
- **Comprehensive accounting** → significant aid to establish priorities (diseases, injuries and risks)
- **Comparability of measurement** → measurement units meaning the same over time / place
- **Morbidity and disability** → disbaility-adjusted life years (DALYs) and healthy life expectancy (HLE)
- **Face validity** → verifying the ground truth of results and appraising internal consistency



- **Source:** Murray CJL. The Global Burden of Disease Study at 30 years. Nature Medicine. 2022; 28: 2019-2026. doi: 10.1038/s41591-022-01990-1

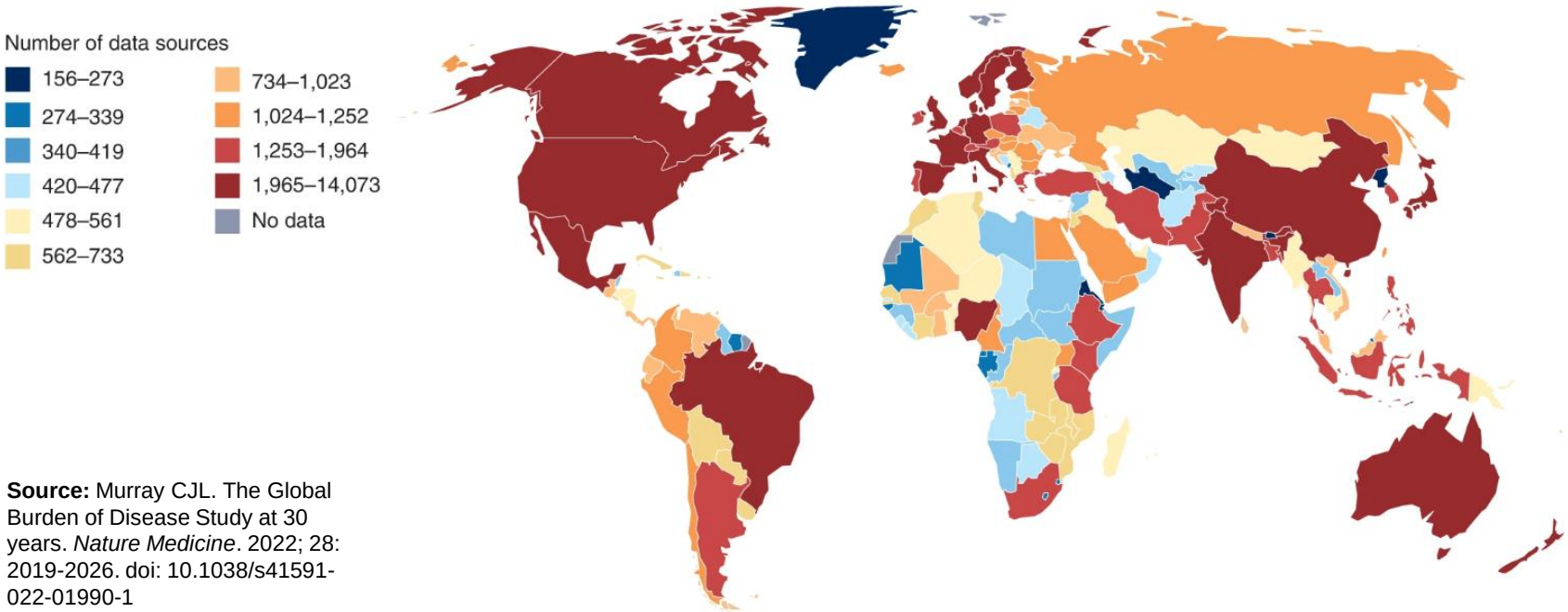
The dataverse – from data processing to evaluation

- Data processing, transparency and statistical analysis **does not equate** to simplicity
- The **star ratings** and the supporting detailed analysis of strengths and weaknesses of cause of death data are released along with the GBD results with each cycle of the GBD analysis
- Since GBD 2010 **many statistical tools** were developed to address main technical estimation challenges (e.g., CODEm that uses an ensemble model)
- **Cross-walking** → the statistical relationship among matched measurements using different case definitions, assays or instruments



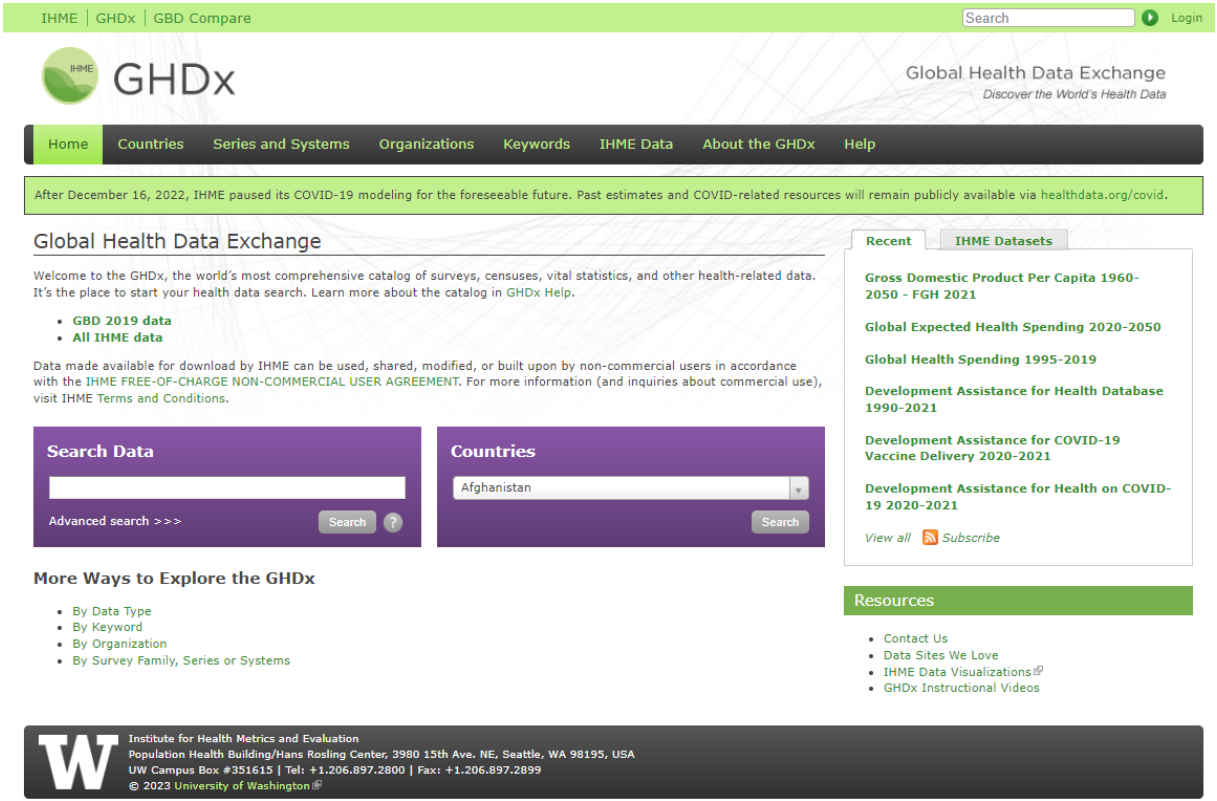
- **Source:** Murray CJL. The Global Burden of Disease Study at 30 years. Nature Medicine. 2022; 28: 2019-2026. doi: 10.1038/s41591-022-01990-1

Total number of data sources for GBD 2021 by country

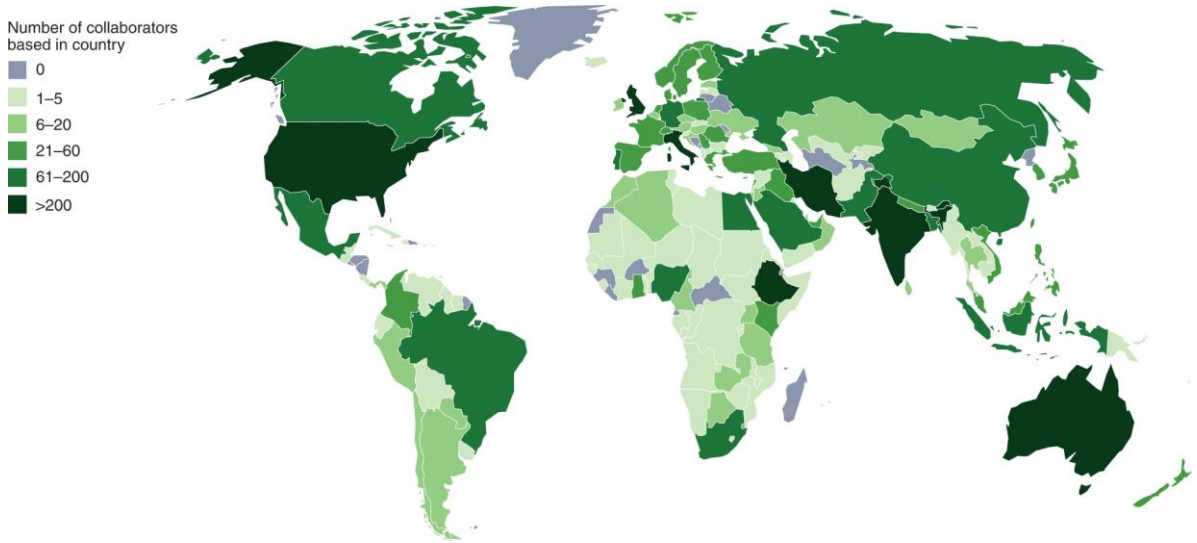


Source: Murray CJL. The Global Burden of Disease Study at 30 years. *Nature Medicine*. 2022; 28: 2019-2026. doi: 10.1038/s41591-022-01990-1

Publicly available data – Global Health Data Exchange



The pivotal role of collaborators and collaborator networks



ITALIAN GBD INITIATIVE

Publications
400+
since 2010

Data points generated
1 billion+
in 2022

Disease and injuries
350+
in 195 countries, 1990 - present

Contributors
7,000+
in over 156 countries and territories

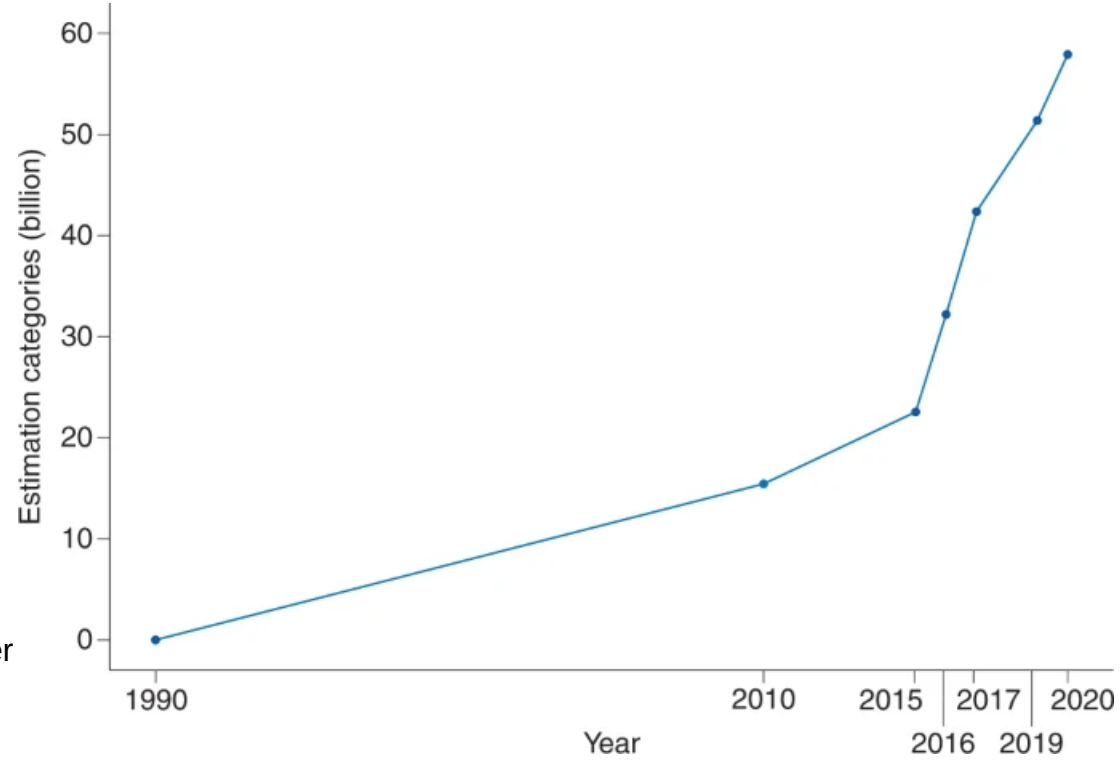
Strong local ownership of results and expertise: increased chances for positive change and policy formulation

Ten big lessons learned during 30 years of GBD

1. The importance of standardization
2. The value of data sources
3. The role of modelling
4. The importance of uncertainity
5. The value of transparency
6. The impact of interventions
7. The need for regional/country-level analyses
8. The strength of multidisciplinary collaboration
9. The role of advocacy
10. The need for continuous improvement

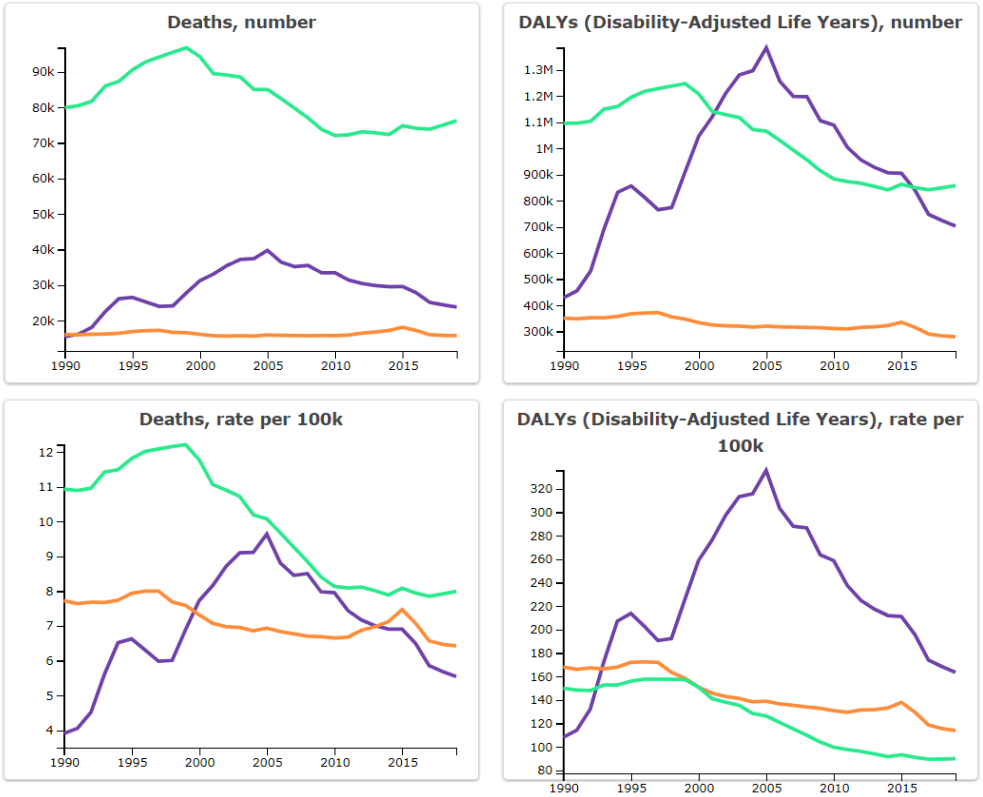
Continuous improvement: a glimpse into the GBD 2021

- **1,075** locations
- **376** causes
- **3,499** sequelae
- **88** risk factors
- **25** age groups
- **1990-2021** period



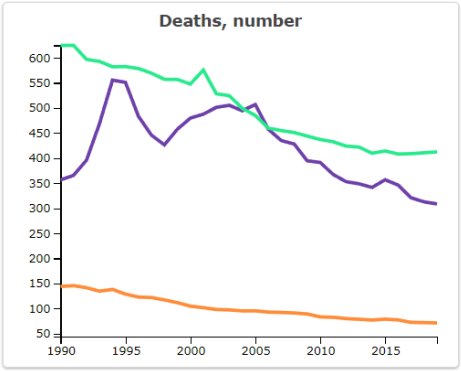
- **On the right:** Changes in the number of assessment categories

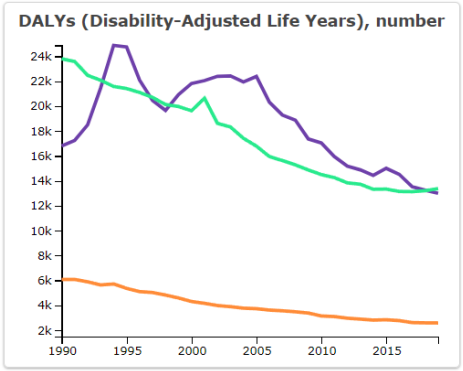
30 years of GBD and VPI in adults: *Streptococcus pneumoniae*

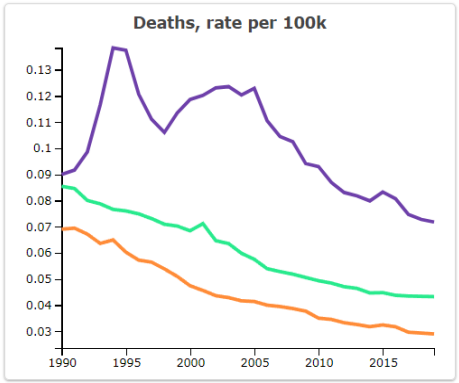


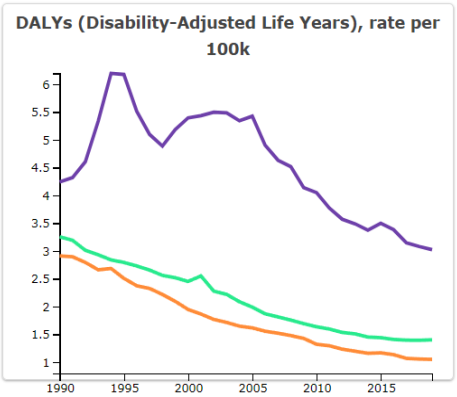
Source: Vos et al.; GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*. 2020; 396: 1204-1222. doi: 10.1016/S0140-6736(20)30925-9.

30 years of GBD and VPI in adults: meningococcal meningitis









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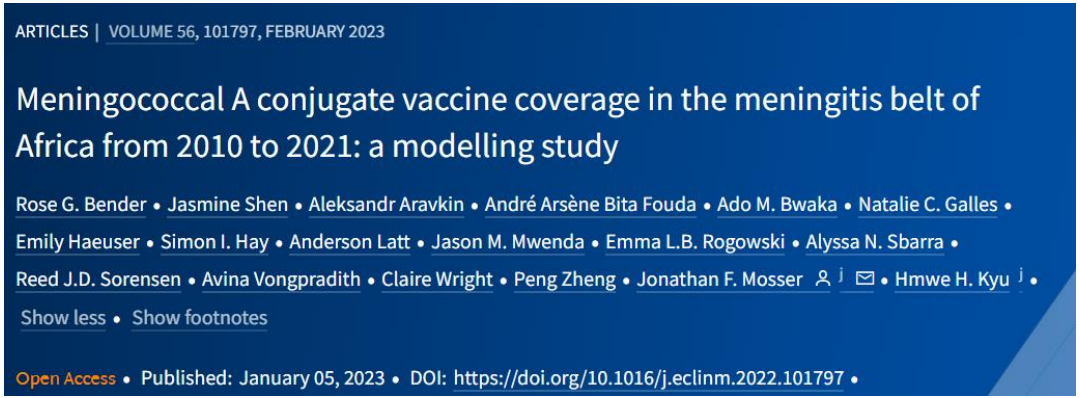
- Eastern Europe, Both sexes, 20+ years, Meningitis, etiology: Meningococcal meningitis
- Central Europe, Both sexes, 20+ years, Meningitis, etiology: Meningococcal meningitis
- Western Europe, Both sexes, 20+ years, Meningitis, etiology: Meningococcal meningitis

Meningococcal A conjugate vaccine coverage in high-risk area



ARTICLES | VOLUME 56, 101797, FEBRUARY 2023

Meningococcal A conjugate vaccine coverage in the meningitis belt of Africa from 2010 to 2021: a modelling study

Rose G. Bender • Jasmine Shen • Aleksandr Aravkin • André Arsène Bita Fouda • Ado M. Bwaka • Natalie C. Galles • Emily Haeuser • Simon I. Hay • Anderson Latt • Jason M. Mwenda • Emma L.B. Rogowski • Alyssa N. Sbarra • Reed J.D. Sorensen • Avina Vongpradith • Claire Wright • Peng Zheng • Jonathan F. Mosser [j] • Hmwe H. Kyu [j] •

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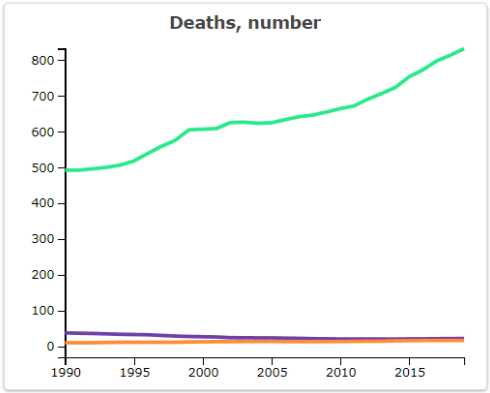
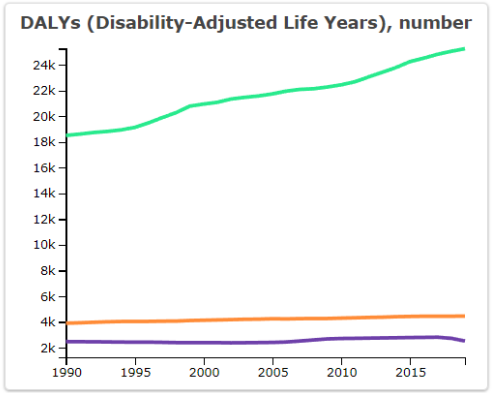
Open Access • Published: January 05, 2023 • DOI: https://doi.org/10.1016/j.eclinm.2022.101797 •

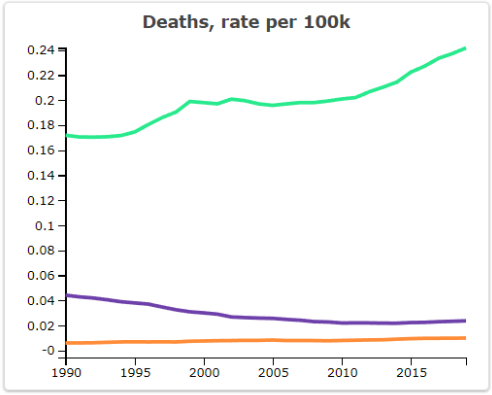
eClinicalMedicine
Part of THE LANCET *Discovery Science*

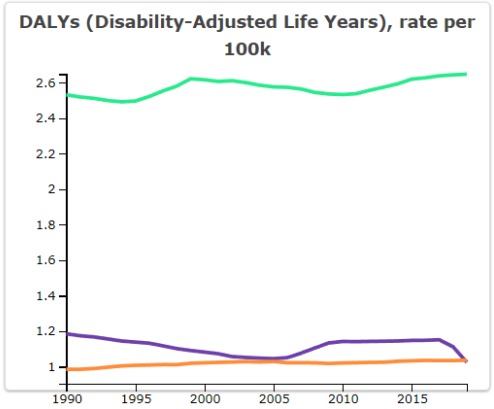
- **Lessons from Africa:** adolescents and those over 20 have lower vaccine uptake than young children
- **Limitation:** coverage was estimated at the national and high-risk area level only

30 years of GBD and VPI in adults: varicella and herpes zoster









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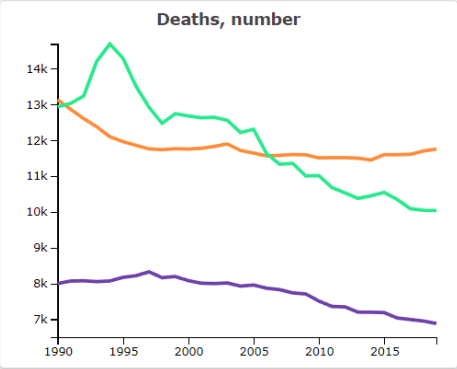
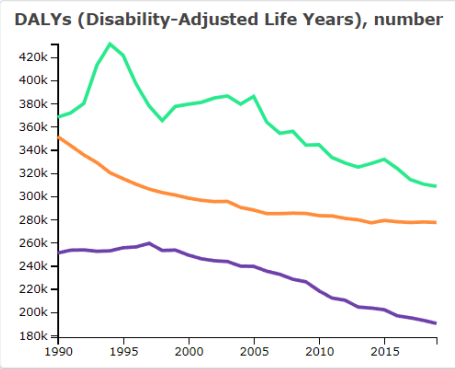
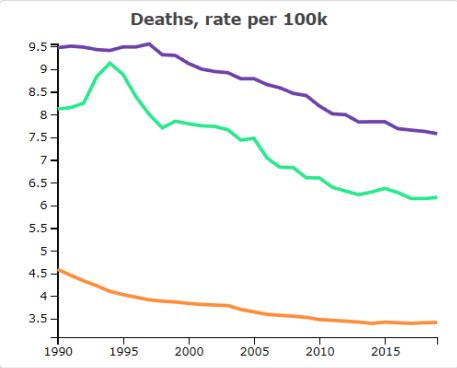
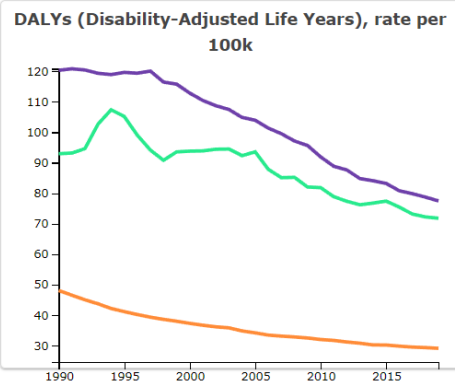
- Central Europe, Both sexes, 20+ years, Varicella and herpes zoster
- Eastern Europe, Both sexes, 20+ years, Varicella and herpes zoster
- Western Europe, Both sexes, 20+ years, Varicella and herpes zoster

30 years of GBD and VPI in adults: human papillomavirus









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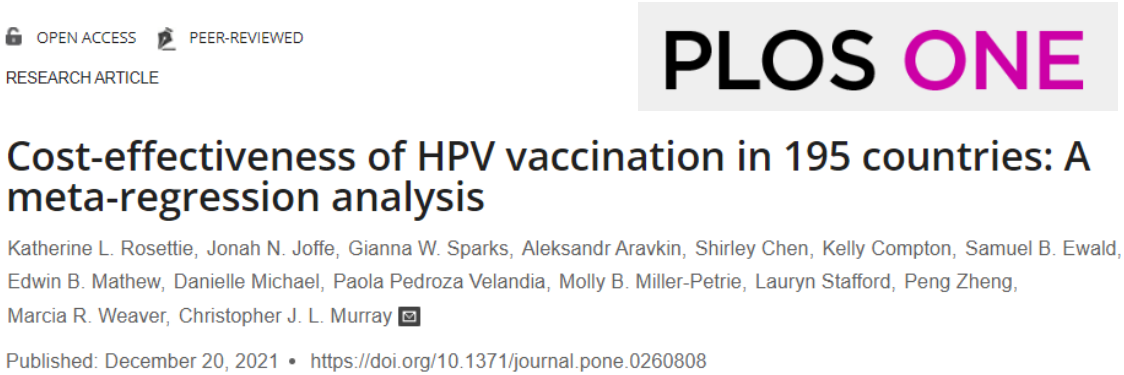
- Central Europe, Both sexes, 20+ years, Cervical cancer
- Western Europe, Both sexes, 20+ years, Cervical cancer
- Eastern Europe, Both sexes, 20+ years, Cervical cancer

Cost-effectiveness of HPV vaccination – informing future actions



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RESEARCH ARTICLE

PLOS ONE

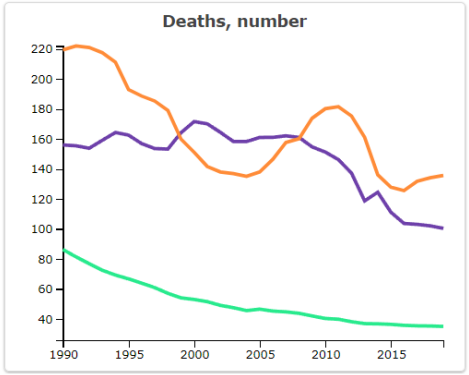
Cost-effectiveness of HPV vaccination in 195 countries: A meta-regression analysis

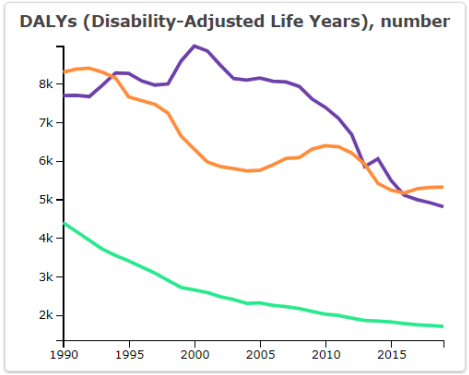
Katherine L. Rosettie, Jonah N. Joffe, Gianna W. Sparks, Aleksandr Aravkin, Shirley Chen, Kelly Compton, Samuel B. Ewald, Edwin B. Mathew, Danielle Michael, Paola Pedroza Velandia, Molly B. Miller-Petrie, Lauryn Stafford, Peng Zheng, Marcia R. Weaver, Christopher J. L. Murray

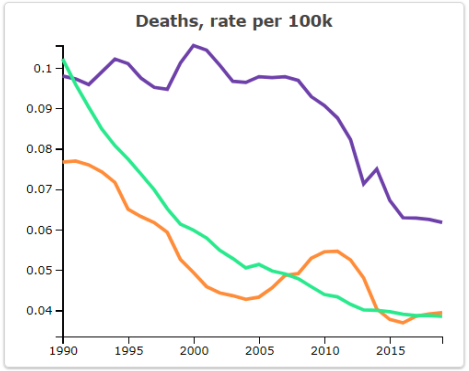
Published: December 20, 2021 • https://doi.org/10.1371/journal.pone.0260808

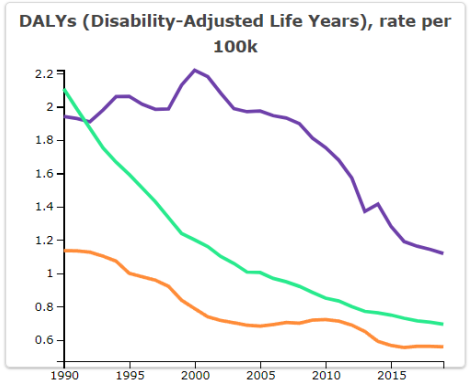
- **First meta-regression analysis of published CEAs –** uses the HPV vaccine as an example for transferring CEA results across settings
- The adjusted mean ICER for HPV vaccination was 2017 US $4,217 per DALY averted globally, and below US $800 per DALY averted for 64 countries
- Evidence for introducing and expanding HPV vaccination

30 years of GBD and VPI in adults: hepatitis B









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- Eastern Europe, Both sexes, 20+ years, Acute hepatitis B
- Western Europe, Both sexes, 20+ years, Acute hepatitis B
- Central Europe, Both sexes, 20+ years, Acute hepatitis B

Progress towards SDG target for viral hepatitis B

ARTICLES | VOLUME 7, ISSUE 9, P796-829, SEPTEMBER 2022

Global, regional, and national burden of hepatitis B, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019

GBD 2019 Hepatitis B Collaborators † • Show footnotes

Open Access • Published: June 20, 2022 • DOI: https://doi.org/10.1016/S2468-1253(22)00124-8 •

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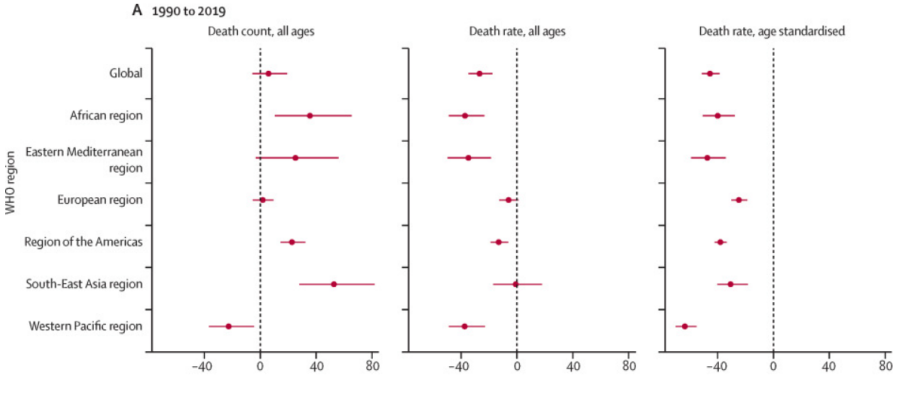
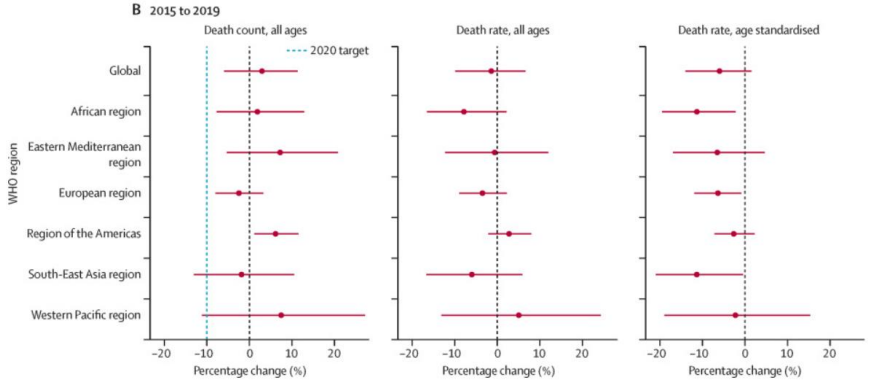
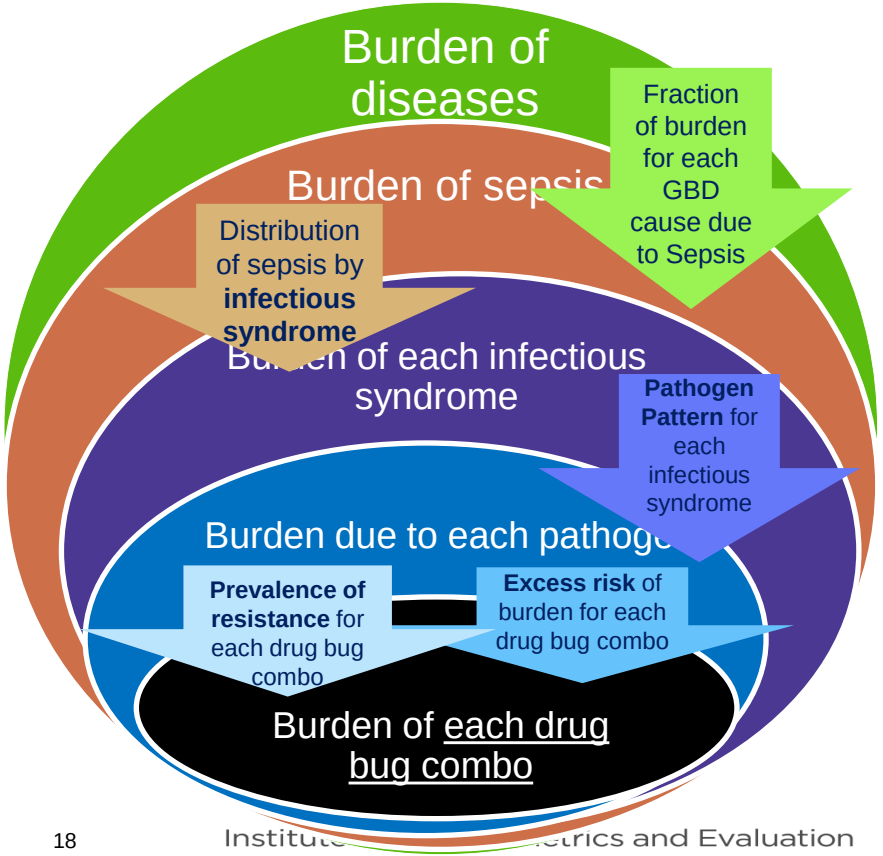




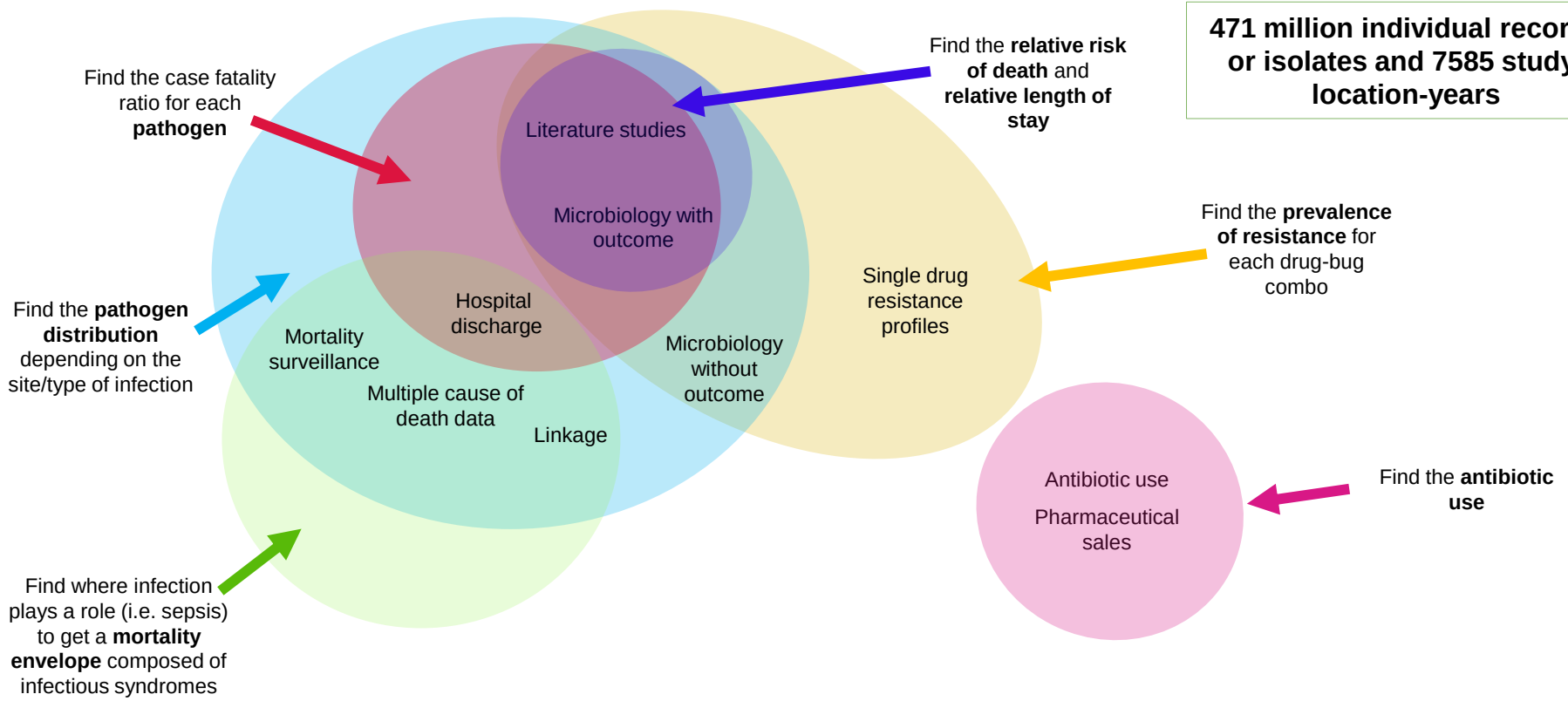
Building on GBD to estimate AMR burden

- The approach for estimating the burden of AMR that makes use of all available data and builds on death and incidence estimates for different underlying conditions from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019
- **Ten** estimation steps ➢ **five** broad modelling components ➢ **two** counterfactual scenarios
- Deaths and DALYs for <u>on a regional level and globally in 2019</u>
- Multiple sources of data (many data providers and the use of GBD Collaborator Network)



Data used for the estimation process

471 million individual records or isolates and 7585 study-location-years



Two counterfactuals for estimating AMR Burden

- **The burden attributable to bacterial AMR (based on the counterfactual of drug-sensitive infection)**

$$Deaths\ due\ to\ Resistance_{K\delta} = \sum_J \sum_L D_J \times S_J \times M_{LJ} \times P_{LK} \times Mortality\ PAF_{K\delta}$$

$$Mortality\ PAF_{K\delta} = \frac{R'_{K\delta}(RR_{Kd^*} - 1)}{1 + \sum_\delta R'_{K\delta}(RR_{Kd^*} - 1)}$$

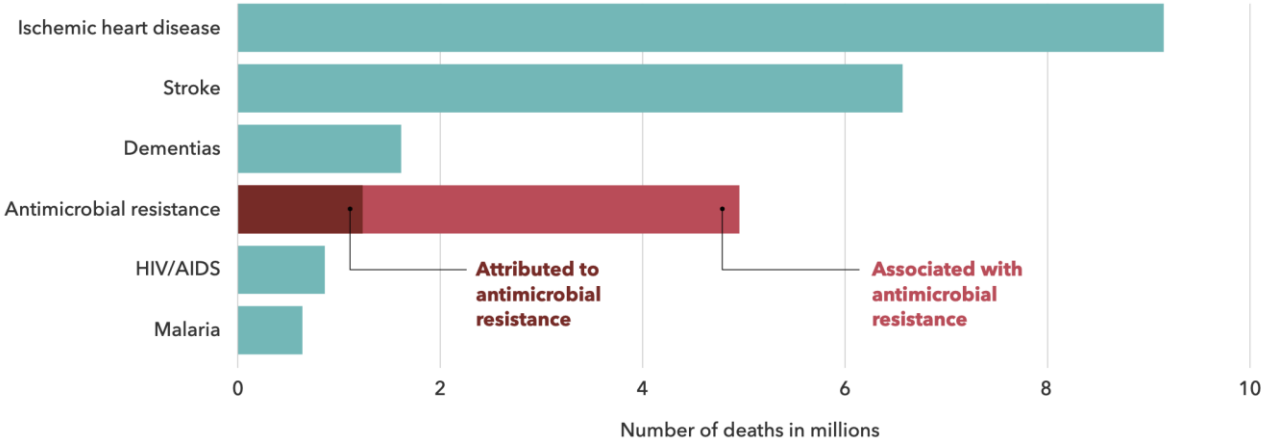
- **The burden associated with bacterial AMR (based on the counterfactual of no infection)**

$$Deaths\ with\ Resistance_{Kd} = \sum_J \sum_L D_J \times S_J \times M_{LJ} \times P_{LK} \times R_{Kd}$$

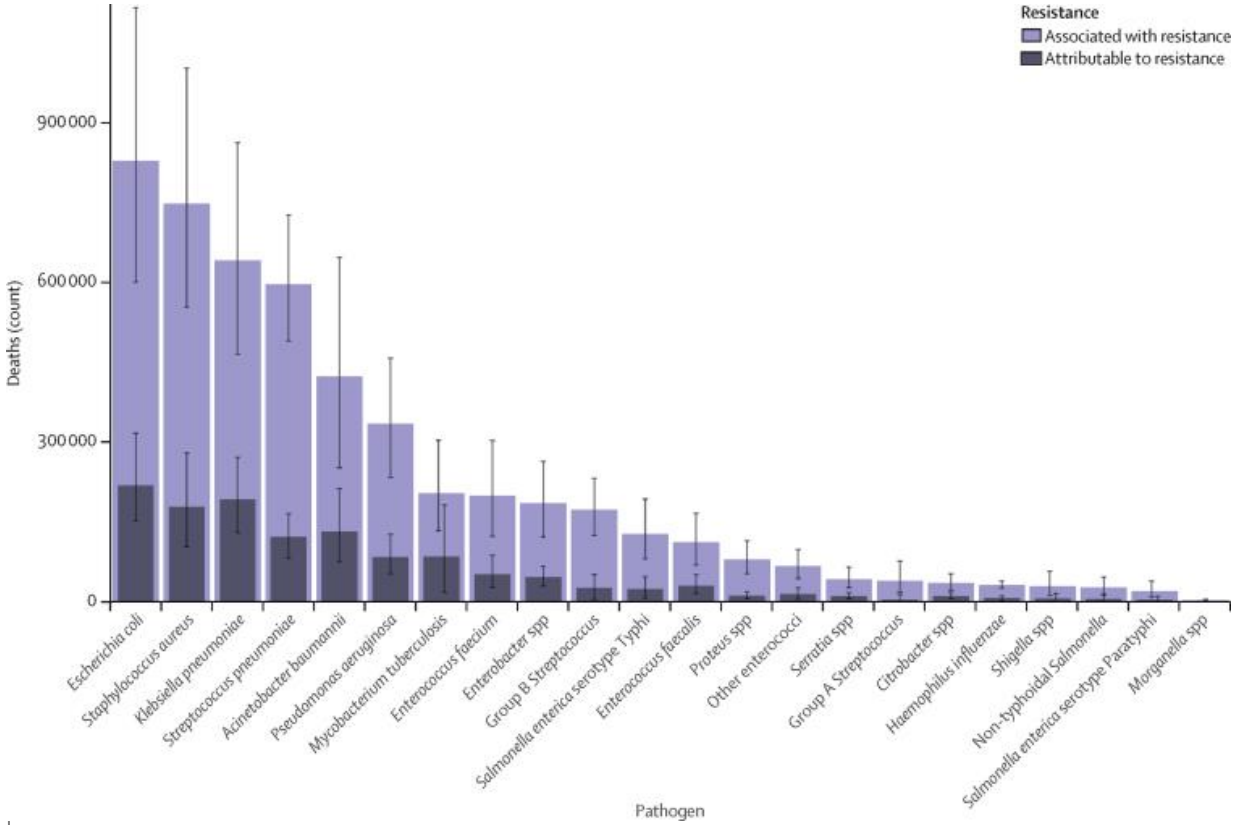
$$R_{Kd} = \frac{R'_{Kd} RR_{Kd}}{(1 - R'_{kd}) + R'_{Kd} RR_{Kd}}$$

Key findings on AMR burden on a global level

- **4.95 million (3.62-6.57) deaths** associated with bacterial AMR in 2019, including **1.27 million (95% UI 0.911-1.71) deaths** attributable to bacterial AMR.
- This makes bacterial AMR one of the leading causes of death



Key findings on a global level – different pathogens



AMR burden in the WHO European Region – Main findings

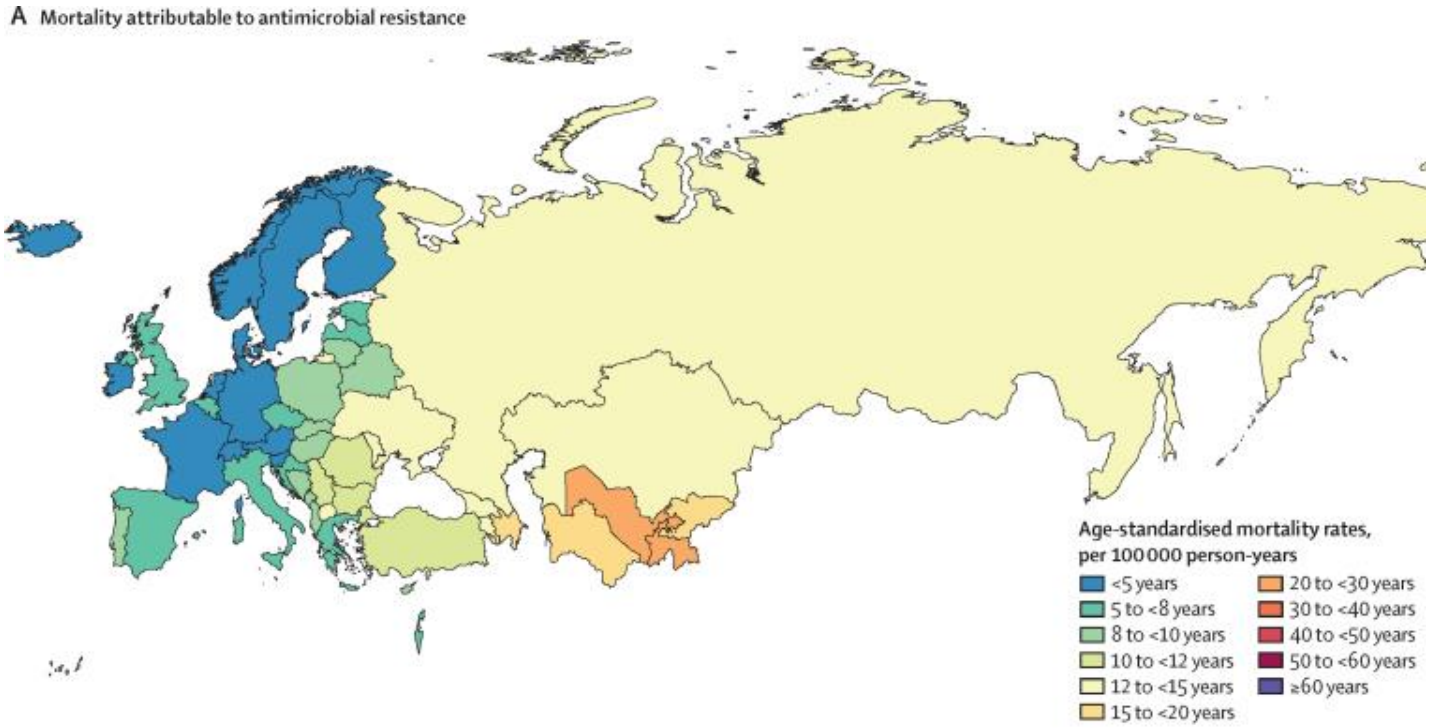
- The most detalied estimate of death and disability for the year **2019**
- **53** countries, **23** bacterial pathogens and **88** pathogen–drug combinations

- A total of **541 000 deaths** (95% UI 370 000–763 000) **associated with** bacterial resistance and **133 000 deaths** (95% UI 90 100–188 000) **attributable to** bacterial resistance
- Most pervasive syndrome: **bloodstream infections** (195 000 fatal outcomes)

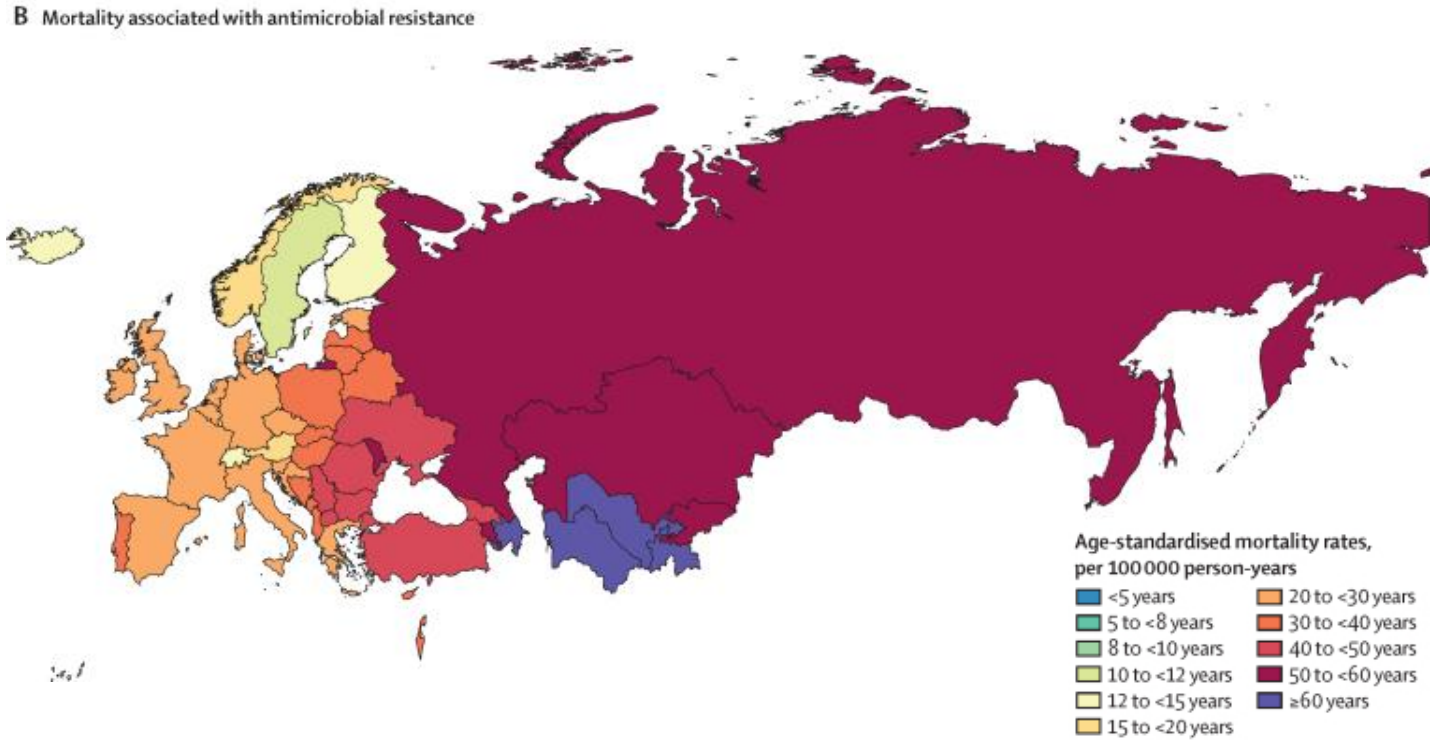
- Notable differences among different countries!

- **Source:** Meštrović T, Robles Aguilar G, Swetschinski LR, Ikuta KS, Gray A, Weaver ND i sur. The burden of bacterial antimicrobial resistance in the WHO European region in 2019: a cross-country systematic analysis. *The Lancet Public Health*. 2022; 7: e897-e913.

AMR burden in the WHO European Region – country differences

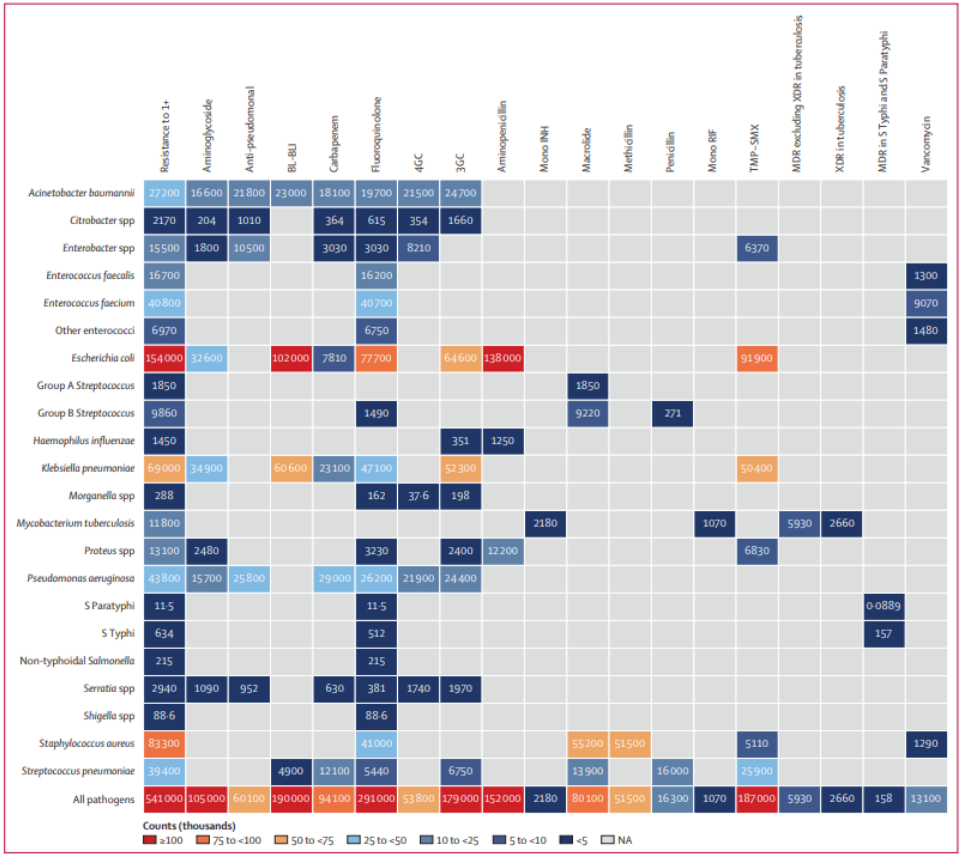


AMR burden in the WHO European Region – country differences



AMR burden in the WHO European Region by pathogen

- **Most common pathogens:** *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*
- **The highest burden of vaccine-preventable bacterial infection (deaths associated with AMR):** *Streptococcus pneumoniae* (39 000)



- **Source:** Meštrović T, Robles Aguilar G, Swetschinski LR, Ikuta KS, Gray A, Weaver ND i sur. The burden of bacterial antimicrobial resistance in the WHO European region in 2019: a cross-country systematic analysis. *The Lancet Public Health*. 2022; 7: e897-e913.

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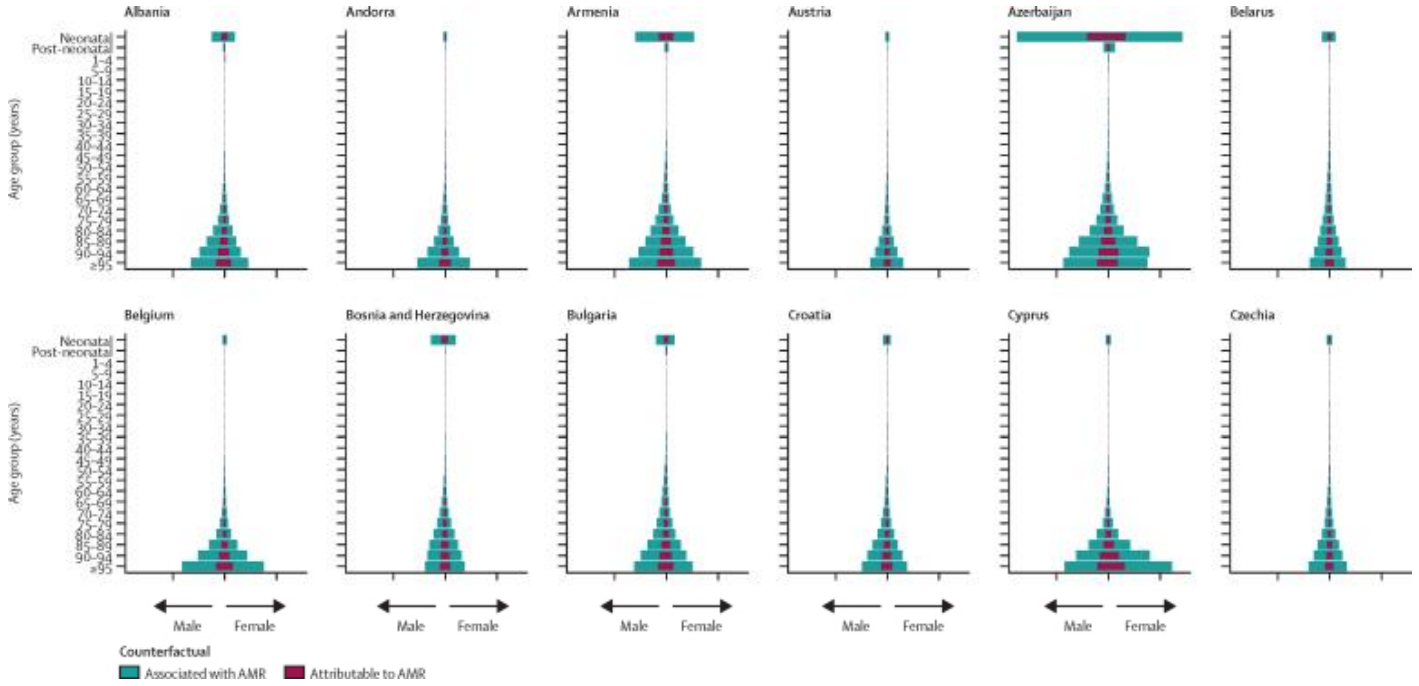
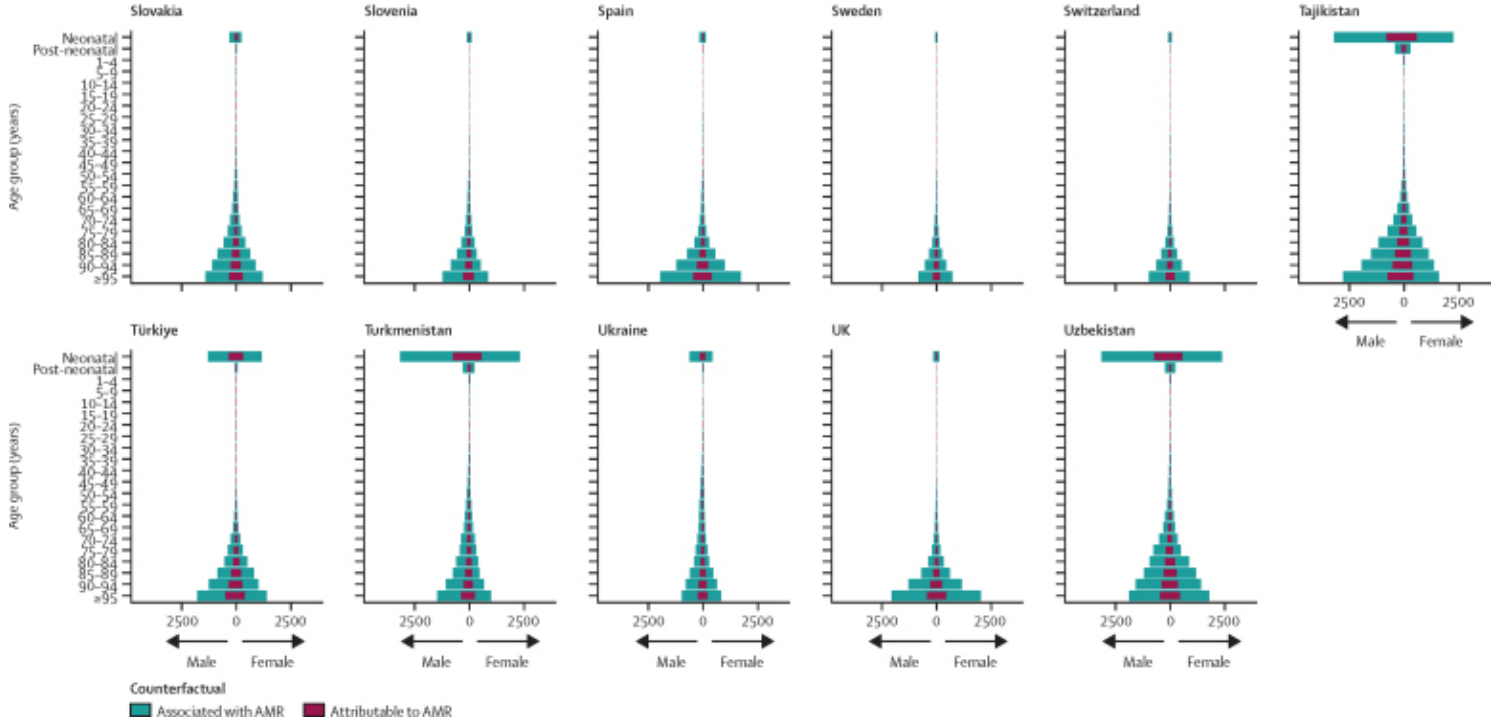
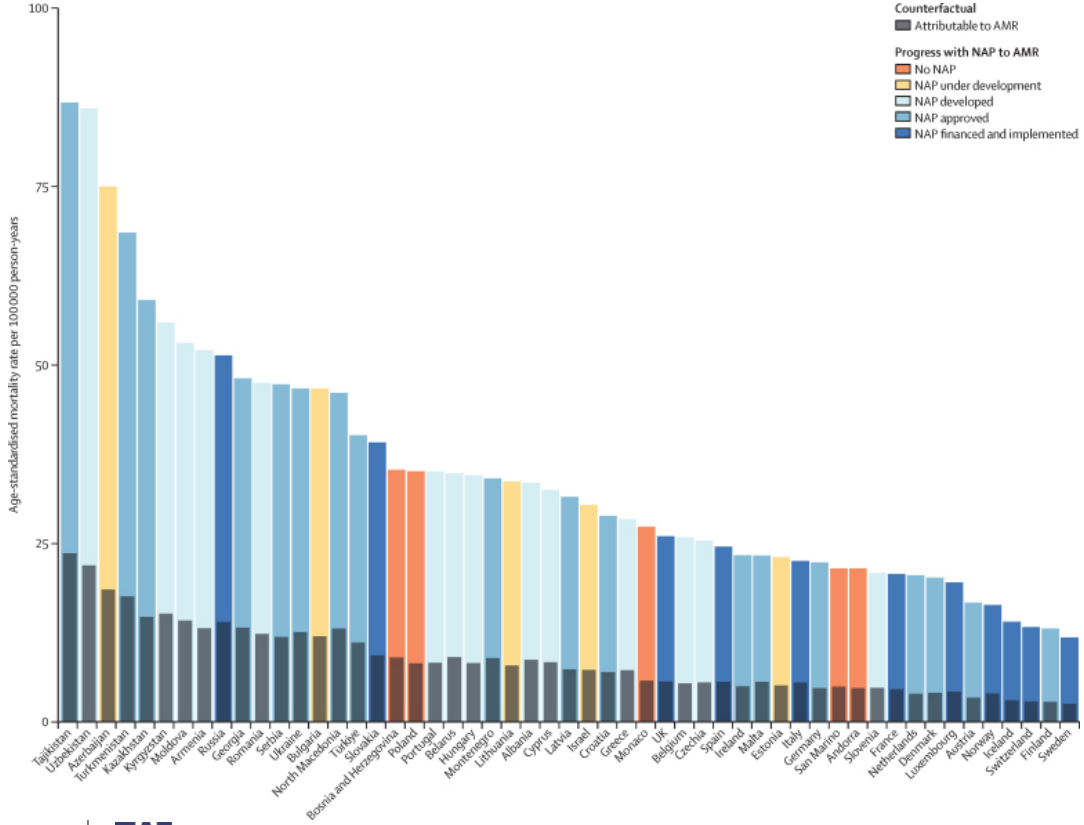
AMR burden in the WHO European Region – age stratification



AMR burden in the WHO European Region – age stratification



AMR burden in the WHO European Region – relationship with NAPs



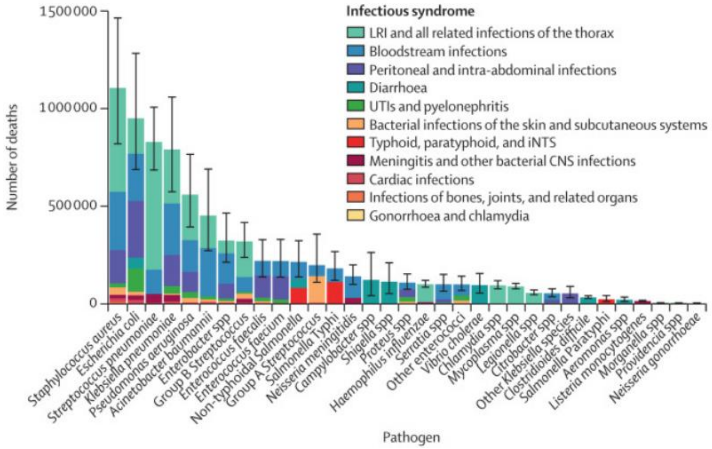
Methodological comparisons with a recent ECDC report

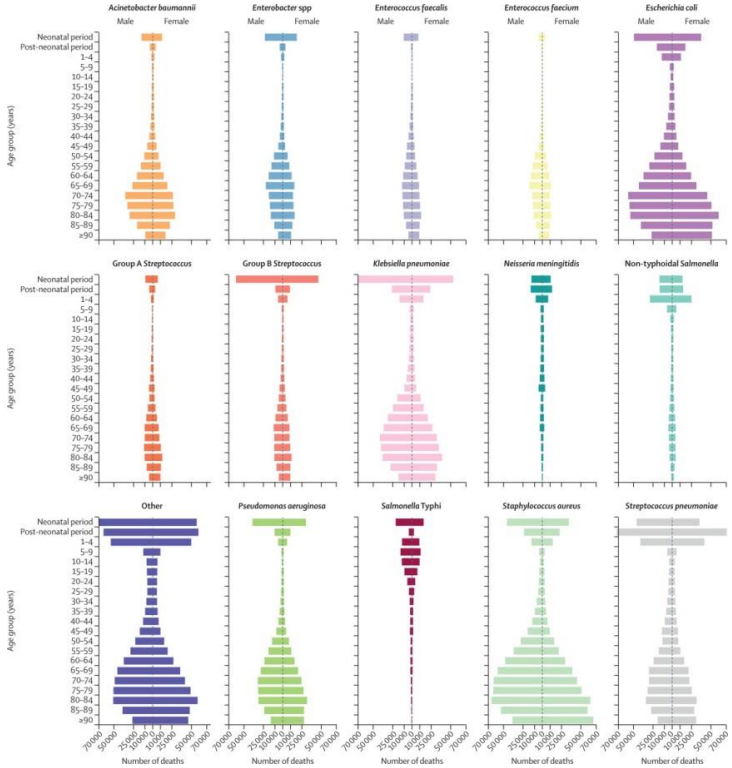
- ECDC report (2022) provides estimates were on the EU-level for 12 pathogen-drug combinations in 2019; GRAM AMR WHO Europe paper (2022) produces estimates for 9 of these 12 combinations

Bacteria	Antibiotic resistance*
Acinetobacter species	Carbapenem-resistant
	Aminoglycoside and fluoroquinolone-resistant (excluding isolates also resistant to carbapenems)
Enterococcus faecalis and *E. faecium*	Vancomycin-resistant
Escherichia coli	Carbapenem-resistant
	Third-generation cephalosporin-resistant (excluding isolates also resistant to carbapenems)
Klebsiella pneumoniae	Carbapenem-resistant
	Third-generation cephalosporin-resistant (excluding isolates also resistant to carbapenems)
Pseudomonas aeruginosa	Carbapenem-resistant
	Resistant to three or more antibiotic groups (piperacillin-tazobactam, ceftazidime, fluoroquinolones, aminoglycosides; excluding isolates also resistant to carbapenems)
Staphylococcus aureus	Meticillin-resistant
Streptococcus pneumoniae	Penicillin-non-wild-type**
	Penicillin-non-wild-type and macrolide-resistant (excluding isolates being only penicillin-non-wild-type)

Estimating the burden by pathogen: extending the AMR analysis

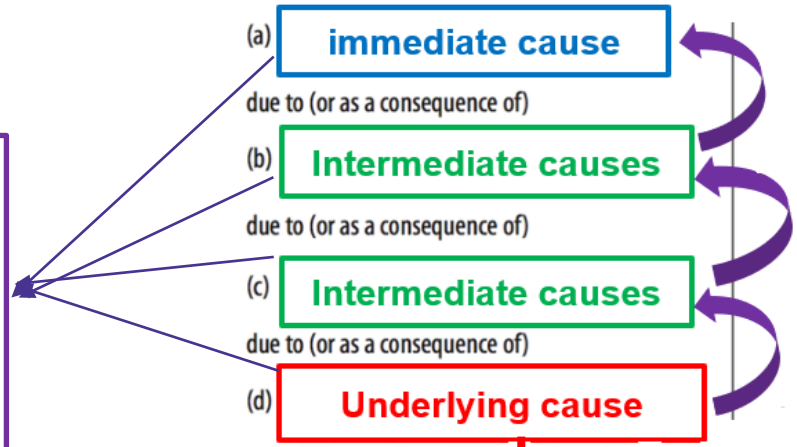
- Analytical framework developed for AMR was **extended to estimate the burden of 33 bacterial agents** (excluding TB from AMR work) – whether from resistant or susceptible organisms and published in November 2022



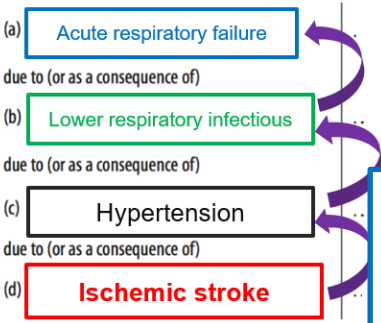


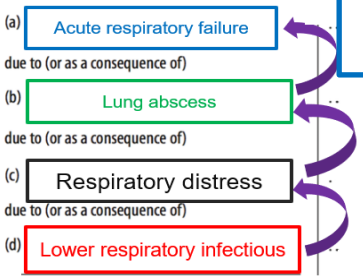
Estimating the burden by pathogen: combining GBD and AMR

In AMR we included death when infection happened in any part of chain of death



In GBD we just include death based on underlying cause





In AMR we calculated 2 deaths related to LRI / in GBD we calculated one death due to LRI

Estimating the burden by pathogen: combining GBD and AMR

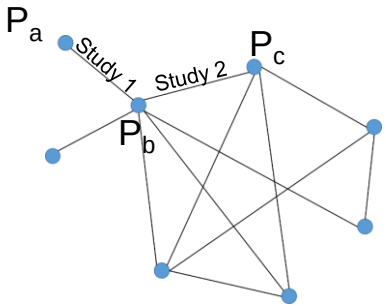
- Both the burden of AMR work and the bacterial pathogen work used a **pathway to death framework:** events are included in the analysis if a bacterial pathogen was on the pathway to death
- GBD analyses by pathogen are based on the **ICD construct of underlying cause of death**: the event initiating the series of events leading to death
- Incomplete and heterogeneous data means that quantifying the burden of AMR requires **harmonizing multiple types of data sources**

Pathogen Distribution: Network Analysis Framework

- Data about pathogen distribution can be **very partial**
- Estimating the probability of pathogen; as each study has a different set of pathogens and, therefore, a different denominator, this is not observed directly
- Instead, we observe the **log ratios of proportions** between two pathogens

$$\log\left(\frac{P_a}{P_b}\right) = \log\left(\frac{\frac{cases\ of\ pathogen\ a}{total\ of\ all\ pathogens}}{\frac{cases\ of\ pathogen\ b}{total\ of\ all\ pathogens}}\right) = \log\left(\frac{cases\ of\ pathogen\ a}{cases\ of\ pathogen\ b}\right)$$

- Can use these pairwise comparisons to deduce overall relationship between all pathogens in network



Intuitively *(contrived example):*
Study 1 – *S. pneumoniae* : *A. baumannii* = 3:1
Study 2 – *A. baumannii* : *Legionella* spp. = 4:1
Can infer that *S. pneumoniae* : *Legionella* = 12:1

Combining two approaches for pathogen analysis

1) Pathway to death, underlying cause and attributable cause views are **different** – to expand to a full analysis of pathogen burden we need to understand when these three views differ substantially
2) **Pathway to death analysis** counts every death where a pathogen played a role on the pathway to death – in ICD terms, these would include deaths where the pathogen is listed on Part 1 of the WHO death certificate (immediate or intermediate causes)
3) **Underlying cause** counts every death where the pathogen was the initiating event leading to death – how many more deaths would be counted using a pathway to death framework from multiple cause of death data.
4) **Attributable cause** compares the deaths (and other events) that occurred minus the deaths (events) that would have occurred in the absence of the pathogen

Attributable burden by pathogen

1) To estimate **attributable burden by pathogen**, we need to **estimate the change in YLLs and YLDs** in the counterfactual state without the pathogen. This requires knowledge of two things:

   - What would be the lifespan of an individual with a given cause with and without the pathogen e.g. the lung cancer patient with *Streptococcus pneumoniae* LRI would have lived how long without the *Streptococcus pneumoniae* infection?
   - In some cases, depending on individual history/comorbidities, some individuals may be more prone to certain types of infections. Adjusting for this propensity to get infected would require individual cohort data to figure out the relative risk of death with and without an infection for different groups of people.

Limitations of the approach

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THE LANCET

Global burden of antimicrobial resistance: essential pieces of a global puzzle

Mohsen Naghavi ✉ • Christopher J L Murray • Kevin S Ikuta • Tomislav Mestrovic • Lucien Swetschinski • Benn Sartorius

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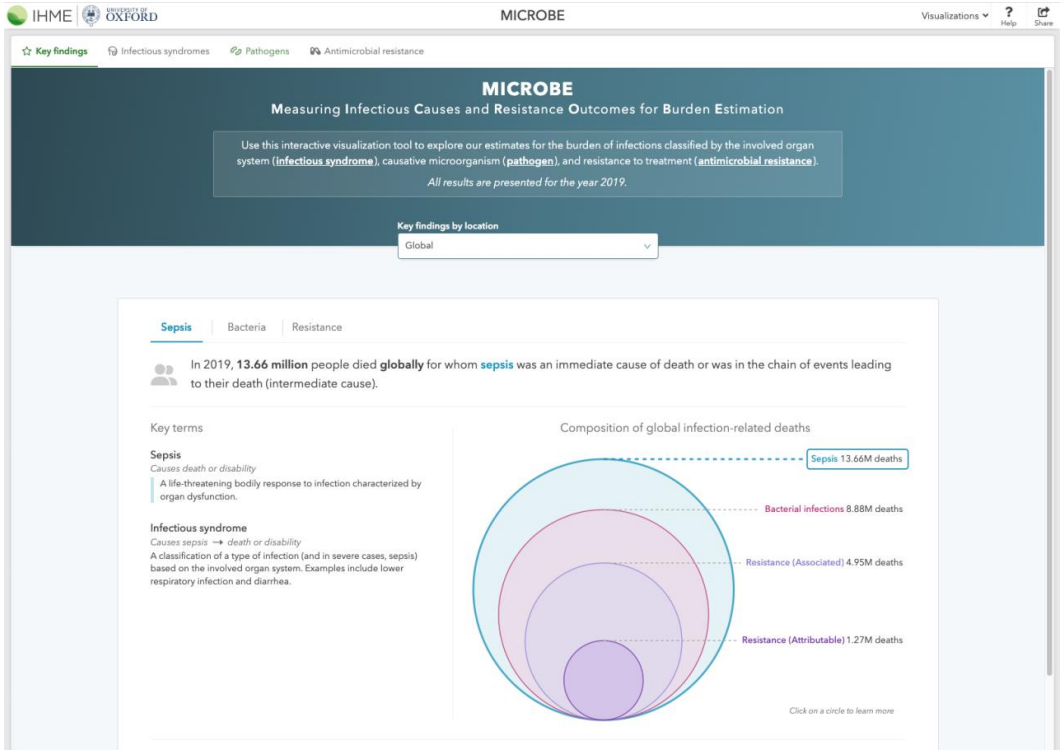
- **Scarcity of data** linking laboratory results to outcomes such as death / **varying quality** of data
- Polymicrobial category can lead to an underestimation of the specified microorganisms
- Possible risks of misclassification and selection bias in some instances
- **Heterogeneity** in the interpretation guidelines used for antimicrobial susceptibility testing

MICROBE visualization tool – *https://vizhub.healthdata.org/microbe/*



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Thank you for your attention!