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

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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** → disability-adjusted life years (DALYs) and healthy life expectancy (HLE)
- **Face validity** → verifying the ground truth of results and appraising internal consistency

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

Total number of data sources for GBD 2021 by country

Publicly available data – Global Health Data Exchange
The pivotal role of collaborators and collaborator networks

Number of collaborators based in country
- 0
- 1-5
- 6-20
- 21-60
- 61-200
- >200

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 uncertainty
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*

30 years of GBD and VPI in adults: meningococcal meningitis

Meningococcal A conjugate vaccine coverage in high-risk area

- **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

30 years of GBD and VPI in adults: human papillomavirus

Cost-effectiveness of HPV vaccination – informing future actions

- 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

Progress towards SDG target for viral hepatitis B
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 **on a regional level and globally in 2019**

- Multiple sources of data (many data providers and the use of GBD Collaborator Network)
Data used for the estimation process

- Find the relative risk of death and relative length of stay
- Find the prevalence of resistance for each drug-bug combo
- Find the antibiotic use
- Find where infection plays a role (i.e. sepsis) to get a mortality envelope composed of infectious syndromes
- Find the case fatality ratio for each pathogen
- Find the pathogen distribution depending on the site/type of infection
- Literature studies
- Microbiology with outcome
- Hospital discharge
- Multiple cause of death data
- Linkage
- Single drug resistance profiles
- Antibiotic use
- Pharmaceutical sales
- 471 million individual records or isolates and 7585 study-location-years

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Find the antibiotic use
Two counterfactuals for estimating AMR Burden

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

\[
\text{Deaths due to Resistance}_{K\delta} = \sum_{J} \sum_{L} D_{J} \times S_{J} \times M_{LJ} \times P_{LK} \times \text{Mortality PAF}_{K\delta}
\]

\[
\text{Mortality PAF}_{K\delta} = \frac{R_{Kd}^\prime (RR_{Kd} - 1)}{1 + \sum_{\delta} R_{K\delta}^\prime (RR_{K\delta} - 1)}
\]

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

\[
\text{Deaths with Resistance}_{Kd} = \sum_{J} \sum_{L} D_{J} \times S_{J} \times M_{LJ} \times P_{LK} \times R_{Kd}
\]

\[
R_{Kd} = \frac{R_{Kd}^\prime RR_{Kd}}{(1 - R_{Kd}^\prime) + R_{Kd}^\prime RR_{Kd}}
\]
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 detailed 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!

AMR burden in the WHO European Region – country differences
AMR burden in the WHO European Region – country differences

B  Mortality associated with antimicrobial resistance
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)

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 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.
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.
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**.
• 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

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

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

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