Global Research on AntiMicrobial resistance (GRAM) Project Overview

Background

Global Research on AntiMicrobial resistance (GRAM) is the flagship project of the Oxford GBD (Global Burden of Disease) Group, and aims to provide robust, comprehensive and timely evidence of the burden of antimicrobial resistance (AMR) globally, and in 195 countries and territories. The Oxford GBD Group is a partnership between the University of Oxford's Big Data Institute (BDI) and the Institute for Health Metrics and Evaluation (IHME) at the University of Washington. GRAM was launched with support from the UK Department of Health's Fleming Fund, the Wellcome Trust and the Bill and Melinda Gates Foundation. GRAM Project researchers and staff are listed at the end of this document.

The overall aim of the GRAM initiative is to strengthen the evidence base on the current global burden of AMR, and how, where and why it is changing. This will provide the essential health intelligence to help drive awareness of AMR, support better surveillance of AMR, and prompt policy action to control AMR, including facilitating antimicrobial stewardship.

Objectives

The GRAM project objectives are to:

1. Consolidate, review and analyse all available data and scientific information on AMR worldwide, drawing on the literature, country surveillance systems, vital statistics and other data systems on causes of death, clinical records, and data from antimicrobial sensitivity testing in order to generate comparable AMR burden estimates for all clinical syndromes and pathogen-drug combinations, from 1990 to the present, for the 195 countries and territories included in IHME's Global Burden of Disease study;
2. Produce granular geospatial maps of AMR burden as detailed as the data will allow to enable policymakers and researchers to tailor interventions to the local level; and
3. Promote the widespread dissemination of the results to the public, the development community, academics and policy makers via the use of tools and interactive data visualizations.

Our project initially focuses on 17 bacteria-antibacterial drug ("bug-drug") combinations, which include *Salmonella enterica* serovar Typhi and Paratyphi A, Non-Typhoidal Salmonella, *Shigella* species, *Mycobacterium tuberculosis* complex, *Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Klebsiella pneumoniae* complex and *Neisseria gonorrhoeae.* We plan to extend the study to all important pathogen-drug-clinical syndrome combinations in order to estimate the full burden of AMR globally.

International Collaboration

The GRAM project is a highly collaborative global project and we seek to work together with public health agencies, networks, research institutions, individual researchers, Ministries of Health, hospitals and others working in this area to determine the global burden of antimicrobial resistance using the best evidence available. Through our partnership with IHME, all collaborators are invited to join the official Global Burden of Diseases (GBD) collaborator network, a group of >3,500 researchers, clinicians, statisticians and other professionals in almost 150 countries. The role of a GBD Collaborator is to help identify all relevant science and data related to the disease, injury or risk factor of interest, review and provide timely feedback and suggestions related to interpretation of GBD results, data sources, and/or methodological approaches pertaining to their area of enrolled expertise. Collaborators are invited to co-author GBD publications, including those relating to AMR.

We would like to invite you to become part of this network to share expertise and data. The GBD estimates are updated annually and currently provide detailed estimates of premature death and disability from 359 diseases and injuries and 84 risk factors in 195 countries and territories, by age and sex, from 1990 to the present, allowing comparisons over time, across age groups, and among populations. The flexible design of the GBD allows for regular updates as new data and epidemiological research findings become available. In that way, the tools can be used at the global, national, and local levels to understand health trends over time. We plan the AMR work to be similarly collaborative under the umbrella of, and adhering to the same principles, expectations and privileges that govern the broader GBD collaboration. By joining the global network of GBD AMR collaborators you will have the opportunity to ensure that your data and scientific information is analysed in a comparable way to all other diseases and injuries and consolidated in a way that greatly increases their value for policy.

Data required

We aim to work in a collaborative way with investigators across the globe. We would like to work with you to include any retrospective data on AMR that you might have access to, including in your databases, to improve the scope and accuracy of the GBD estimates and thus make them more valuable for policy and global monitoring. In particular, we seek anonymised, non-identifiable, patient-level microbiology data linkable to clinical records and patient outcomes from 1990 onwards. We realise that microbiology data may not always be linked to patient diagnosis, demographics and/or outcomes, but we welcome a discussion with you about any data you believe might be appropriate to improve GBD estimates.

We have defined the list of variables which we believe would be of direct relevance for estimating the GBD from AMR in Appendix 1. However, we know that many collaborators will not be able to provide all, or even much, of this information. We have prioritized a critical subset of the data that is essential for deriving disease burden estimates, including microbiology results with patient demographic information, clinical diagnosis and causes of death (all conditions on the death certificate). Our analytical strategy is to use the de-identified patient-level data to model excess risks from AMR, by pathogen, by location, by time and by underlying cause of death in the GBD. At this stage, we wish to collect all microbiology data, not just for our target pathogens.

How will the data be analysed?

Briefly, the data analysis will consist of the following key components:

1) Quantification of the burden of disease, i.e., the number of deaths, disease incidence and prevalence, by age, sex, time and location, for each cause or clinical syndrome with pathogen involvement. This will generate the basic output of the GBD, namely disability-adjusted life years (DALYs) for all of the diseases and injuries where a pathogen is involved based on the ICD underlying causes, from which the fraction of DALYs attributable to AMR will be calculated;
2) Determine the prevalence of antibiotic drug resistance by pathogen by underlying cause of death, body sample source, whether the sample originates from the hospital or community, etc. Data that provide information on resistance testing may be used to inform models of the spatial-temporal variation in resistance patterns; and
3) Determine the excess risk of death or adverse outcome by pathogen and by drug resistance as compared to antimicrobial sensitive health outcomes. We anticipate that much of the linked data required to model excess risk is likely to be from middle- and high-income settings, but we highly value data from all countries. Variables that will be useful in building these models include: comorbidities, admission year, admission and discharge dates, length of

hospitalisation, Intensive Care Unit admission (ICU), previous surgical procedures or hospital acquired infections (HAI), treatment and time to bacteraemia.

Standard epidemiological population attributable fractions (PAFs) will be computed using this information (points 2 & 3) and applied to the GBD cause of death outcome list (see point 1).
The full list of requested variables can be found below in appendix 1. The most critical items for GBD modeling are highlighted in the table.
We also plan to use high quality datasets that link laboratory, clinical and vital registration together to examine the relationship between healthcare facility type (e.g. large urban tertiary referral centre versus small secondary care hospital serving a rural population) and patient complexity, frequency of blood cultures, rates of AMR and outcomes.

Data Management and Governance

As collaborators you will work directly with our researchers based at IHME and/or in Oxford. Provisions have been established for sharing with the research teams at IHME or Oxford via a secure server. All data will be shared under a collaboration and Data Use Agreement (DUA) signed by the University of Oxford or IHME as appropriate. Any data shared for these purposes will be held at both institutions in order to facilitate and accelerate data analysis for the burden of disease. Different levels of sharing data are envisaged. The preferred model, where possible, is to make the data as open as possible for researchers involved in the GBD AMR collaboration network to analyse the data bringing their particular expertise and established methodology based at IHME in public health and data analysis. If collaborators do not wish to have their data made more widely available for the purposes of the GBD AMR analysis, we are able to embargo your data so it is not available on the Global Health Data Exchange (GHDx) website (http://ghdx.healthdata.org) until you advise us otherwise. The governance of data in the IHME database is described fully in the GBD Protocol (http://www.healthdata.org/gbd/about/protocol).

Recognition of collaborators, authorship and further opportunities

The contribution of GRAM collaborators will be fully recognised and acknowledged according to the established principles contained in the GBD protocol (http://www.healthdata.org/gbd/about/protocol) which has been in use for many cycles of the GBD. In addition to an invitation to join the GBD collaborator network (http://www.healthdata.org/gbd/call-for-collaborators), collaboration offers opportunities to work with GRAM researchers to use the GBD outcome data to address questions of local interest within your network, to understand the numbers and work out and discuss with you how your data influences the global burden of disease for example, comparing the burden of AMR between regions.

The GRAM project researchers

The strategic lead for the Oxford BDI-IHME GBD partnership, including the GRAM project, is Prof. Alan Lopez, who co-authored the seminal Global Burden of Disease Study in 1996 with IHME Director Prof. Christopher Murray. Prof. Murray serves as Scientific Lead, along with Prof. Simon Hay of IHME and Dr. Christiane Dolecek of the University of Oxford. Within Oxford, the BDI team is supervised by Senior Research Manager/Group Leader Dr. Catrin Moore, with Dr. Dolecek and Prof. Susanna Dunachie providing expertise from the Centre for Tropical Medicine and Global Health. Prof. Andy Stergachis and Prof. Mohsen Naghavi are senior investigators based at the University of Washington or IHME. Learn more about our research and the staff working on the project here: https://www.bdi.ox.ac.uk/oxfordgbdgroup/about.

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Appendix 1 Data sought for GRAM project

The critical variables which we are prioritizing have been highlighted in the table below:

Microbiology related	*Microbiology Laboratory related*	*Healthcare facility-related*	*Patient-related (where available)*
1.Clinical specimen type (e.g. blood culture, urine)	**5.Method used for bacterial isolation and identification**	**10. Type of healthcare facility:** **primary - direct from community** **secondary hospital - referrals from community** **tertiary - larger hospital - referrals smaller hospitals**	**21. Patient unique identifier (only linkable to other personally identifiable data by the source laboratory)**
2.Date of specimen collection	**6.Method used for antibiotic susceptibility**	**11. Number of inpatient beds per hospital**	**22. Admission date**
3.Species identified	**7.Laboratory standard followed (CLSI, EUCAST etc), year of guideline**	**12. Aggregated antibiotic usage data**	**23. Admission ward type/unit where sample was collected (if available) e.g. medical/surgical/ITU/maternity/out-patient**
4.Antibiotic susceptibility – Minimum inhibitory concentration (MIC) results where available: disc concentrations, zone sizes or interpretation (Resistant/Intermediate/Sensitive)	**8.External Quality Assessment scheme used by laboratory (NEQAS etc)**	**13. The names of antibiotics available/prescribed in the hospital**	**24. Admission diagnosis (ICD code preferred)**
	9.Accreditation of microbiology laboratory (e.g. ISO)	**14. Name of healthcare facility**	25. **Date of discharge if applicable**
		15. Geographical location of healthcare facility – address and GPS if available	26. **Community acquired or Hospital associated? Include definition**
		16. Number of blood culture bottles received per year	27. **Date of birth (or age on date of specimen collection, in years for adults, months for children <5 years of age, days if <one month)**
		17. Funding source for patient care (e.g. government, private or NGO)	28. **Gender**
		18. Catchment population of healthcare facility	29. **Clinical syndrome at time of specimen collection e.g. meningitis, diarrhoea, UTI**
		19. Catchment population of laboratory (if different from healthcare facility)	30. **Diagnosis/diagnoses at discharge (ICD code preferred)**

		20. Any guidelines used at the hospital for antibiotic prescribing	31. **Patient outcome: status at discharge if admitted – alive, dead, moribund**
			32. **ICD code (s) for immediate, intermediate and underlying cause of death, if applicable**
			33. Date of death, if applicable
			34. Patient home address to level which is sharable (e.g. district/village)
			35. Antibiotics prescribed to the patient while in hospital
			36. Co-morbidities (e.g. diabetes, cardiovascular disease, renal disease, cancer, chronic lung disease, alcohol excess, HIV, hepatitis, cystic fibrosis, prosthetic material, malnutrition)
			37. Severity of illness measure (such as Acute Physiology and Chronic Health Evaluation – APACHE II, Apgar score, others if available)
			38. Mortality status at 28 days: alive or dead
			39. Previous/current surgical status (e.g. operations)
			40. Additional/recurrent admissions (including site, unit, date, diagnosis and outcomes)
			41. Additional/recurrent isolates/infections (including site, unit, date, diagnosis and outcomes)
			42. Weight and height where available
			43. For neonates (1 month or less) – prematurity (birth at <37 weeks gestation)
			44. For neonates (1 month or less) - birthweight
			45. Patient code for socio-economic status (e.g. deprivation index score) if available, with explanation for codes
			46. Patient level of education
			47. Patient ethnicity
			48. Antibiotics received prior to culture, if available