ODA Considerations for CARB-X Funded Projects

CARB-X[1] is a global non-profit funder of preclinical and early stage clinical research and development (R&D) targeting the most dangerous drug-resistant bacteria designated by the World Health Organization (WHO).[2] As of 2018, CARB-X receives funding from the UK Department of Health and Social Care (DHSC), through their Global AMR Innovation Fund (GAMRIF).[3] GAMRIF funds come from the UK's Official Development Assistance (ODA) budget which can be allocated by CARB-X to projects that are eligible for this type of funding.

ODA is government aid with a primary intention to: (A) promote the welfare and economic development of low- and middle-income countries (LMICs) on the OECD "Development Assistance Committee (DAC)" list[4] and (B) directly and primarily benefit people in LMICs. As such, ODA-eligible research:[5]

- Has to target problems directly and primarily relevant to LMICs;
- Should investigate a specific problem or seek a specific outcome which will impact LMICs in the immediate or longer-term;
- Demonstrate appropriate pathways to impact that ensure the LMICs benefit from the research; and
- While LMICs should be the primary beneficiaries, the research can also be relevant and have secondary benefits for other countries.

To be eligible for this funding, the product developer (PD) is responsible for preparing an ODA justification, which describes to CARB-X how their project is eligible. A template for this ODA Justification is provided as Annex 2 to this guidance note. CARB-X will review the ODA Justification submitted by PDs, giving feedback where appropriate, and will make decisions regarding ODA funding.

The purpose of this 'ODA Considerations' document is to provide additional understanding of the requirements for an impactful ODA Justification and to point to references and concepts (both in the body of the document but also Annex 1) that may be of use as the PD prepares the CARB-X application (project plan) and the ODA Justification document.

A. Promote the welfare and economic development of LMICs

The intention of CARB-X is to reduce the threat to human health from drug-resistant bacterial infections, which both the United Nations General Assembly[6] and the World Health Assembly[7] consider a threat to

[1] CARB-X, www.CARB-X.org.
[2] Tacconelli E, et al. Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antiobitics, 2017
[3] GAMRIF is part of the UK Government's Ross Fund
[4] DAC List of ODA Recipients: Effective for reporting on 2018, 2019 and 2020 flows
[5] Dr. Kate Hamer, Head of International, NERC. Official Development Assistance in the Research Context, slide 4 (undated) (available at https://nerc.ukri.org/research/partnerships/international/gcrf/news/workshop-outcomes/gcrf-workshop-kate-hamer/).
[6] Political Declaration of the high-level meeting of the General Assembly on antimicrobial resistance A/RES/71/3 (22 Sept. 2016).
[7] Global action plan on antimicrobial resistance WHA68.7 (26 May 2015).

global public health. The UN General Assembly particularly noted "that antimicrobial resistance challenges the sustainability and effectiveness of the public health response to these and other diseases as well as gains in health and development and the attainment of the 2030 Agenda."[8] Antimicrobial resistance "gravely challenge[s]" the many public health achievements brought about through social and economic development; hygiene, safe water and sanitation; disease prevention; nutrition and healthy food; and other health and development efforts.[9] Tackling antimicrobial resistance (AMR) will also support progress towards achievement of Sustainable Development Goal 3, with reductions in communicable diseases and improved access to medicines.[10]

The UN General Assembly specifically called for "sustained research and development" investments like those undertaken by CARB-X, which are aimed at "resolving the lack of investment in research and development, including through the provision of incentives to innovate and improve public health outcomes, particularly in the field of antibiotics[.]"[11] CARB-X supports "basic and applied innovative research and development," supporting "research and development on quality, safe, efficacious and affordable antimicrobial medicines, especially new antibiotics and alternative therapies, vaccines and diagnostics[.]"[12]

Similarly, the 2015 World Health Assembly highlighted "that hard-won gains in health and development, in particular those brought about through the health-related Millennium Development Goals, are put at risk by increasing resistance to antimicrobials" constituting a threat in high-, middle- and low-income countries.[13] Countries were required to develop National Action Plans on AMR in response; as of June 2019, 72 National Action Plans have been published on the WHO website.[14]

Antimicrobial resistance also threatens economic prosperity. In 2016, the World Bank projected the economic effects of AMR. In its "optimistic" scenario, annual gross domestic product would fall by 1.1% and the GDP shortfall would exceed $1 trillion annually by 2030. The "high-impact" case was more than three times worse.[15] In both cases, the impact would disproportionately affect LMICs:

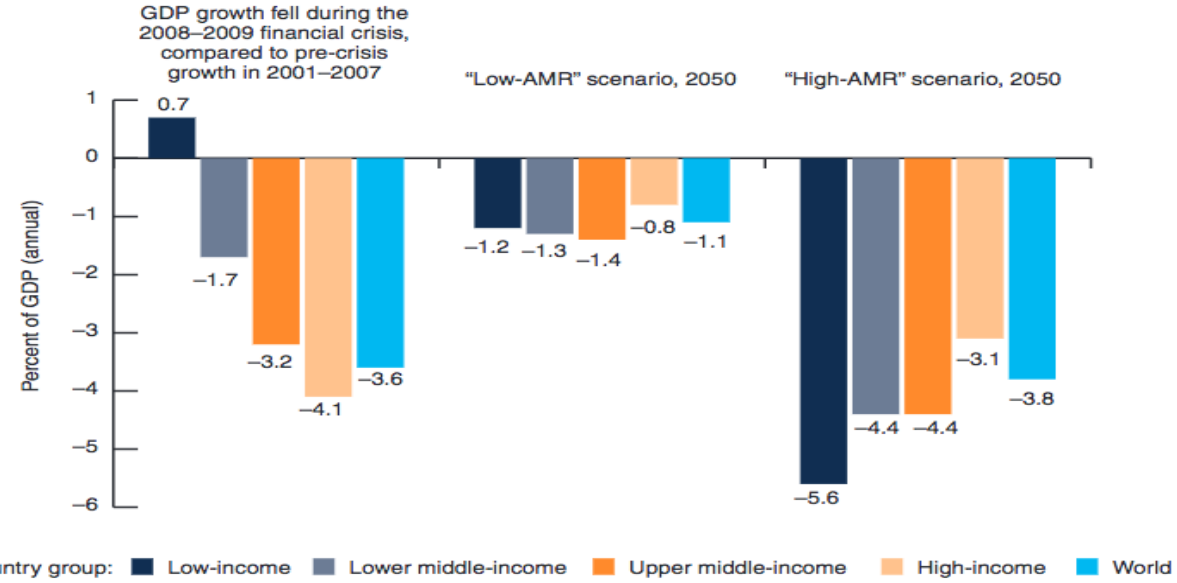
"Poorer Countries Will Suffer Most
Moreover, with AMR, low-income countries would experience larger drops in economic growth than wealthy countries, so economic inequality between countries would increase. The differential impacts on GDP result from higher infectious disease prevalence and greater dependence on labor incomes in countries with lower per capita incomes."[16]

A Figure from the World Bank report illustrates the magnitude of the risk and the disproportionate impact on poorer countries:[17]

[8] Political Declaration, at par. 2.
[9] Political Declaration, at par. 4.
[10] Sustainable Development Goal 3, https://sustainabledevelopment.un.org/sdg3.
[11] Political Declaration, at par. 9.
[12] Political Declaration, at par 10(b).
[13] Global action plan, at chapeau.
[14] WHO, Library of National Action Plans (visited 25 May 2018).
[15] World Bank, Drug-resistant infections: a threat to our economic future (Executive Summary, March 2017), at 6.
[16] Id.
[17] Id., at 7.

FIGURE ES2. Economic Costs of AMR May Be as Severe as During the Financial Crisis

AMR could reduce GDP substantially—but unlike in the recent financial crisis, the damage could last longer and affect low-income countries the most
(annual costs as % of GDP)



It should be noted that most of the published reports follow the more inclusive term "antimicrobial resistance" or "AMR," while the scope of CARB-X is more focused on drug-resistant bacterial infections. The WHO undertook an expert review of available evidence of the global burden of drug-resistant bacteria when it produced the Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics.[18] CARB-X uses this list to define scope for fundable projects.

Given these excerpts from the relevant UN institutions and the mission of CARB-X, it would seem reasonable that the majority of CARB-X funded projects within the technical funding scope specific to GAMRIF (see paragraph below) should be able to meet the broad "LMIC welfare and economic development" standard for ODA-eligibility in an ODA Justification. Applicants should include any additional information about the burden in LMICs of the specific drug-resistant bacteria targeted by the project, from the published literature. Currently, the Global Burden of Disease project is working on estimates for AMR, including for key drug-resistant bacteria.[19] Some additional sources of data are provided in Annex 1 to this note. Applicants should provide references/sources of data in the ODA Justification documents.

The technical funding scope specific to GAMRIF is as follows:

- The UK funding scope includes programs which can be designated as 'alternatives to traditional antibiotics.' Examples include:
    - Bacteriophage
    - Microbiome

[18] Tacconelli E, et al. Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics, 2017 (available at http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf).

[19] Hay S, et al. Measuring and mapping the global burden of antimicrobial resistance, BMC Medicine 2018 16:78.

  - Vaccines
  - Antibodies
  - Potentiators (including beta-lactamase inhibitors)
  - Anti-biofilm approaches
  - Anti-virulence approaches
  - Other approaches exemplified in the Lancet publication by Czaplewski et al[20] entitled Alternatives to antibiotics—a pipeline portfolio review (if they fall within the general CARB-X funding scope)
- Direct-acting small molecule and diagnostic programs are not included in the UK funding scope

B. Benefit directly and primarily people in LMICs

1. Direct benefit

"Direct" benefit for people in LMICs is clear: millions of people in LMICs are affected by drug-resistant infections, requiring the actions called for by the UN General Assembly, the World Health Assembly, and the relevant National Action Plans. The research and development projects supported by CARB-X should help LMICs to reduce the burden of drug-resistant disease and improve public health outcomes for their populations.

LMICs cannot benefit from the product if it is not available to them. CARB-X requires, as a contractual condition to receive funding, that each recipient commit to directly benefitting people in LMICs through a transparent Stewardship and Access Plan, supported by Wellcome Trust. Referencing this contractual commitment in an ODA Justification and how these access provisions would be addressed is one way to demonstrate the intention of enabling 'direct benefit' to LMICs but there may be additional avenues that the applicant intends to pursue either during the stages of development that CARB-X is funding, or in later stages post-CARB-X funding, which can be described e.g. a vaccine manufacturer might intend for their vaccine to become eligible for support from GAVI, meaning that the vaccine is prioritized for lower-cost distribution in LMICs.[21]

2. Primary benefit to LMICs

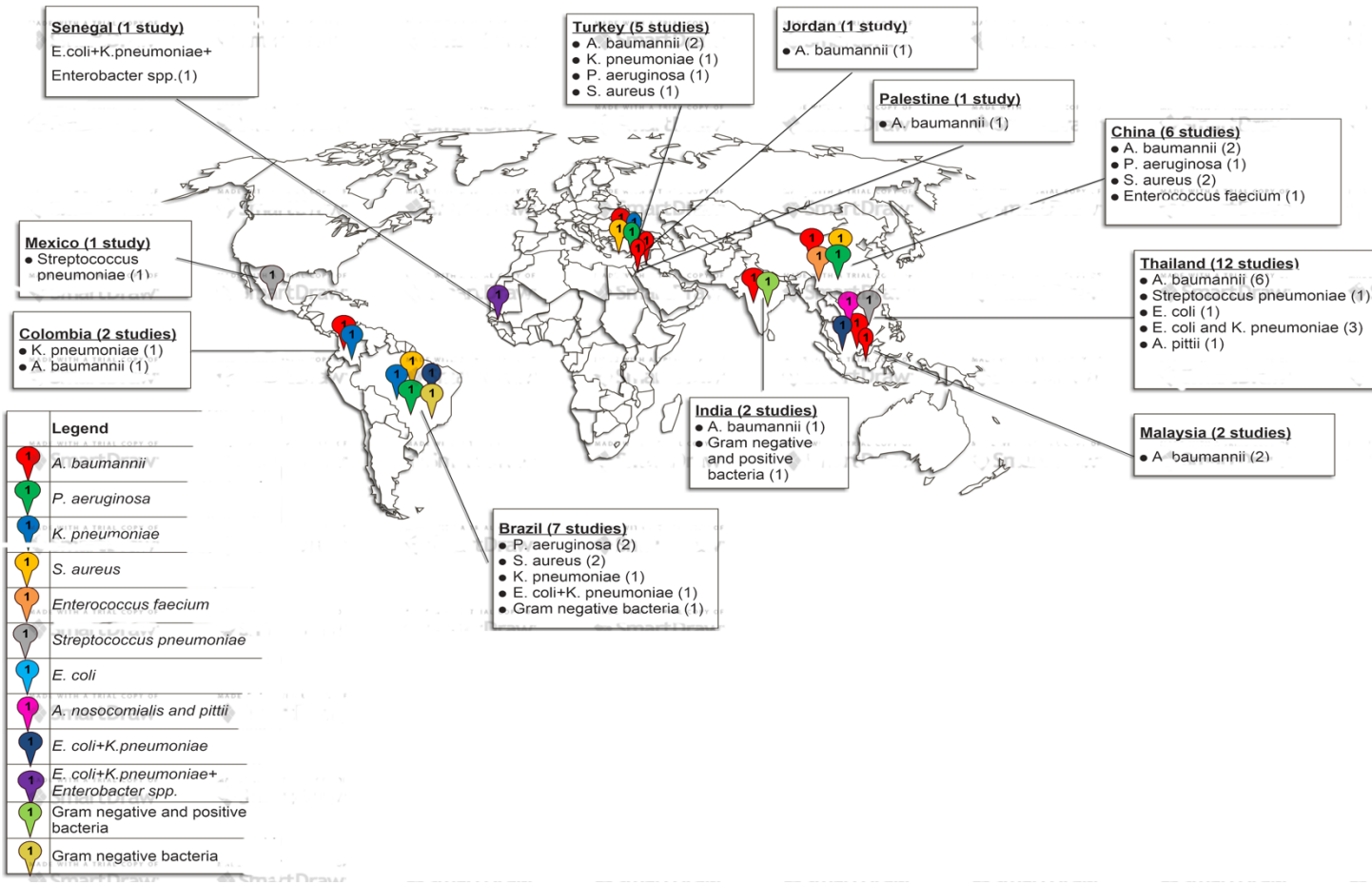
"Primary" benefit for people in LMICs must be fundamental in the design and impact of the project and as an explicit objective of the project.[22] This can be supported on several levels.

First, CARB-X applicants should use data to show relevance for the proposed actions against one or more relevant bacterial species that are prevalent in LMICs, based on the available databases and literature (listing the references in the ODA Justification). To be considered relevant, the bacterial

[20] Czaplewski et al, Lancet Infect Dis 2016; 16: 239–51. https://doi.org/10.1016/S1473-3099(15)00466-1
[21] Gavi, the vaccine alliance www.gavi.org/.
[22] OECD (Development Assistance Committee). Converged Statistical Reporting Directives for the Creditor Reporting System (CRS) and the Annual DAC Questionnaire, par. 184 (8 Apr 2016) (available at https://www.oecd.org/dac/financing-sustainable-development/development-finance-standards/DCDDAC(2016)3FINAL.pdf).

species MUST be listed on the WHO Global Priority List[23] or the 2013 CDC Priority List[24] however please note that the GAMRIF funding scope does not include *C. difficile* as this is still largely considered a high-income country issue. While the surveillance data is not perfect, and is being improved by the WHO GLASS initiative and the Surveillance and Epidemiology of Drug-Resistant Infections Consortium (SEDRIC) program coordinated by the Wellcome Trust, the best available data can demonstrate that the primary population benefiting from investment in R&D for drug-resistant bacterial infections will be in LMICs.[25]

For example, a systematic review and meta-analysis of the clinical and economic impact of antibiotic resistance in LMICs over the period 2000-2016 showed that drug-resistant infections, specifically those caused by the ESKAPE pathogens were associated with a high mortality risk and increased economic costs.[26] The Figure below provides insight into this study.



[23] World Health Organization, Global Priority List of Antibiotic-Resistant Bacteria To Guide Research, Discovery, and Development of New Antibiotics (2017).

[24] US Centers for Disease Control and Prevention, Antibiotic Resistance Threats in the Unites States, 2013.

[25] Tacconelli E, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis 2018;317-27; WHO, Global Antimicrobial Surveillance System Report (2018); Theuretzbacher U. Global antimicrobial resistance in Gram-negative pathogens and clinical need. Curr Ops Microbiol 2017;39:106-112.

[26] Founou RC, Founou LL, Essack SY. Clinical and economic impact of antibiotic resistance in developing countries: A systematic review and meta-analysis. PLoS ONE 2017 12(12): e0189621. https://doi.org/10.1371/journal.pone.0189621

Second, drug resistance is undermining the effectiveness of a several antibiotics on the WHO Model List of Essential Medicines.[25, 27] In the 2017 list, essential antibiotics are for the first time classified into three groups: access, watch, and reserve. This classification was developed in response to the crisis of antibiotic resistance. A CARB-X applicant might intend for their product to eventually added to future editions of that list. For alternatives to antibiotics, for which no such list is directly applicable, CARB-X applicants should describe how the project intends to protect or replace a threatened antibiotic on the WHO Essential Medicines List or the WHO Essential Medicines List for Children.

Third, CARB-X awards may be made to companies or research teams that have substantial presence in LMICs, for example through their headquarters, their research facilities, contract research organizations or other development partners, and this could be primarily benefitting LMICs at an economic level, or through ensuring the proposed product are based on contextually-specific data. Additionally, some applicants may be engaged in the training of, or collaborations with scientists and other professionals in LMICs, building research capacity, generating an evidence base on the nature, extent and potential sequalae of AMR and anti-microbial usage and sharing knowledge.

Fourth, some CARB-X projects may include additional development requirements that are uniquely relevant to LMICs, including shelf stability, route of administration, cost of goods sold (to promote access), testing and efficacy against clinical strains more prevalent in LMICs, and other work to develop the product so it is more useful in LMICs. We note that CARB-X funding comes during an early stage of development, beginning for therapeutics at hit-to-lead and ending with Phase I Single (SAD) and Multiple Ascending Dose (MAD) studies in humans. Some of the types of work described in this paragraph may normally occur in later development phases, after CARB-X funding is completed. Applicants should consider whether it is of benefit and feasible to carry-out some of this work earlier and incorporate some of this work in the plan presented to CARB-X for funding and this should be specifically mentioned in the ODA Justification. At a minimum the applicant should confirm their intent to do such work downstream of CARB-X and describe those plans in a reasonable level of detail. As part of their contractual commitments to Stewardship and Access, all product developers will work with CARB-X during these later stages to support achievement of these goals, and earlier considerations on how to promote Access and Stewardship in LMICs is beneficial.

Fifth, the CARB-X applicant may have other unique characteristics that demonstrate primary benefit to LMICs, and can make the case for primary benefit to LMICs in other ways.

[27] World Health Organization, WHO Model List of Essential Medicines (20th ed., March 2017). The WHO also published the WHO Model List of Essential Medicines for Children (6th ed., March 2017).

3. Secondary intention or benefit

As stated at the start of this document, the proposal submitted to CARB-X in consideration of ODA funding must be stated to have a primary intention to (A) promote the welfare and economic development of low- and middle-income countries on the OECD "Development Assistance Committee" list ("LMICs"); and (B) benefit directly and primarily people in LMICs.

It is, however, understood and accepted that the majority of the proposals submitted to CARB-X will have other secondary intentions or benefits for, for example, in high-income countries. The key consideration is that the benefit to LMICs is the primary intention.[28] Indeed, it is recognized that in many examples, the product may need to be registered in a high-income country prior to being approved by regulatory bodies for sale or import in some LMICs. It is also understood that commercialization in high-income countries may provide sufficient volumes of product to enable lower costs of goods to be achievable.

C. Pathway to impact

The pathways to impact must be realistic and appropriate to the particular LMICs for which the ODA Justification is based on. Clear and tangible plans or intentions need to be described which support either the economic or welfare benefit to the countries and these should be well documented in ODA Justification and in the project plan and budget proposal submitted to CARB-X. Examples are: 'collaborate with Hospital X in country Y to access clinical isolates for pathogen Z on the WHO PPL list to evaluate our product's effectiveness using in vitro MIC (minimal inhibitory concentrations) and in vivo efficacy models'; 'contract with manufacturer X to evaluate cost of good efficiencies'; 'contract with CRO XX in country YY that has research capacity and expertise to ….'. For intended downstream pathways to impact, these should be tangible and clear with timeframes and potential deliverables.

* * *

In conclusion, to be considered for ODA funding from GAMRIF through CARB-X, an applicant must submit a CARB-X ODA justification. A Justification form has been prepared for this purpose, which is given as Annex 2 to this note. Applicants may use, as appropriate, the guidelines above to support their ODA justification, which should set out their primary intention to promote the welfare and economic development of LMICs, and articulate how their project will benefit directly and primarily the health of people in LMICs. Further resources are listed in Annex 1.

[28] Dr. Kate Hamer, Head of International, NERC. Official Development Assistance in the Research Context, slide 4 (undated) (available at https://nerc.ukri.org/research/partnerships/international/gcrf/news/workshop-outcomes/gcrf-workshop-kate-hamer/).

Annex 1: Information sources to support CARB-X ODA justification

Antibiotic resistance data sources

Global Antibiotic Resistance Partnership (GARP) data and reports https://cddep.org/partners/global-antibiotic-resistance-partnership, particularly their resistance map https://resistancemap.cddep.org

Global Antimicrobial Resistance Surveillance System (GLASS) Report: Early implementation 2016-17, which includes some LMIC country profiles with 2016 resistance data for key bacteria http://apps.who.int/iris/bitstream/handle/10665/259744/9789241513449-eng.pdf?sequence=1 and supplementary country data https://www.who.int/glass/resources/publications/early-implementation-report-supplementary-materials/en/

National Action Plans on antimicrobial resistance https://www.who.int/antimicrobial-resistance/national-action-plans/en/

Gates Foundation Project: Antibiotic Resistance Situation Analysis and Needs Assessment (ARSANA) in Uganda and Zambia http://emerald.tufts.edu/med/apua/research/gates.shtml

Conducting health research in LMICs

The Global Health Network https://tghn.org includes a wealth of resources and good practice materials as well as online fora related to global health research

CARB-X applicants without existing LMIC research partnerships may find it helpful to look at the websites of relevant LMIC research institutions. Some examples are:

- Kenya Medical Research Institute (KEMRI) www.kemri.org
- The Noguchi Memorial Institute for Medical Research, University of Ghana www.noguchimedres.org
- The South Africa Medical Research Council www.mrc.ac.za
- An extramural research institute of the South Africa MRC focused on AMR specifically https://lunginstitute.co.za/camra/ and its clinical trials unit https://lunginstitute.co.za/commercial-clinical-trials-unit/
- The UK MRC research unit in The Gambia (provides clinical trial and other research services) www.mrc.gm
- The Centre for Infectious Disease Research in Zambia www.cidrz.org
- Relevant WHO Collaborating Centers on AMR based in LMICs:
    - Antimicrobial Resistance Laboratory, Centre for Opportunistic, Tropical and Hospital Infections (CHARM), National Institute for Communicable Diseases, South Africa
    - Clinical Epidemiology Unit, Department of Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
- RESAOLAB https://www.fondation-merieux.org/en/projects/resaolab
- African Association for Research and Control of Antimicrobial Resistance http://africaamr.org

Clinical trials in LMICs

Global Health Trials platform https://globalhealthtrials.tghn.org

The European & Developing Countries Clinical Trials Partnership (EDCTP) http://www.edctp.org and related Knowledge Hub https://edctpknowledgehub.tghn.org

Pharma and vaccine company access issues

AMR Industry Alliance https://www.amrindustryalliance.org and its 2018 Progress Report https://www.amrindustryalliance.org/progress-report/

AMR Benchmark report 2018 https://amrbenchmark.org/wp-content/uploads/2018/04/Antimicrobial-Resistance-Benchmark-2018.pdf

Access to Medicines Index 2018 https://accesstomedicinefoundation.org/media/uploads/downloads/5c0e475363842_Access-to-Medicine-Index-2018.pdf

Access to Vaccines Index 2017 https://accesstovaccinesindex.org/media/atvi/2017-Access-to-Vaccines-Index.pdf

CARB-X applicants may find it helpful to look at the websites of global health initiatives that support LMIC access to pharmaceuticals, vaccines and other health technologies. Some examples are:

- Gavi, the vaccine alliance www.gavi.org
- The Global Fund to fight AIDS, TB and Malaria www.theglobalfund.org
- One World Health www.oneworldhealth.com
- UNITAID https://unitaid.org

Annex 2: CARB-X ODA Justification Form

To be eligible for Official Development Assistance (ODA) funding, CARB-X projects must be primarily and directly relevant to public health needs and development goals in the low- and middle-income countries on the OECD-DAC list. This form gives you an opportunity to set out how your research will have a positive impact on the economic development and welfare of people in these countries.

Please refer to ODA Considerations for CARB-X Funded Projects to assist you.

Basic project data (please complete)**:**

Applicant name (organization):

Project name:

Target technology or product(s):

Target pathogen(s):

ODA Justification (please complete, adding as much data and information as you need to each box, in order to support your case)**:**

1. ***Please explain how your research is DIRECTLY relevant to the burden of disease, and specifically the burden of anti-microbial resistance, in countries on the OECD-DAC list.*** *(You should cite evidence such as data and reports from the World Health Organization and/or US Centers for Disease Control, surveillance data from sources such as the Global Antimicrobial Resistance Surveillance System (GLASS), in-country policy documents, monographs and situational analyses used to inform National Action Plans, conference presentations available as references and research results documented in published journals.)*
2. ***Please explain how your project will be of PRIMARY benefit to low- and middle-income countries (LMICs) on the*** *OECD-DAC list. (Refer to section B2 of ODA Considerations for CARB-X Funded Projects. You may want to consider alleviating the drug-resistant communicable disease burden, accessibility (e.g., ease of administration and use) and affordability (e.g., cost of goods). Please note: while LMICs should be the primary beneficiaries, the research can also be relevant and have secondary benefits for other countries).*

3. ***Will you be engaging any research institutions in countries on the OECD-DAC list in your project?*** *(For example, by partnering with them to collect isolates, gather data or conduct trials.) If so, will your project include any support to those institutions to build their research capacity?*
4. ***Does your project intend to create wider socio-economic benefits for countries on the OECD-DAC list****, for example through the transfer of technology, sharing of knowledge, or out-licensing of intellectual property for further product development or manufacture?*
5. ***Please describe your pathway to impact in LMICs on the OECD-DAC list****. What are the key steps to achieving the objectives (specify the outputs and outcomes) outlined above, and over what timescale? When and how would funding from CARB-X support this pathway to impact?*
6. ***Please identify the specific activities in your CARB-X project plan that will enable you to achieve your objectives.*** *Activities must be articulated in the project plan and include timescales and costs.*