

Global research agenda for antimicrobial resistance in human health

Policy brief

June 2023



Background

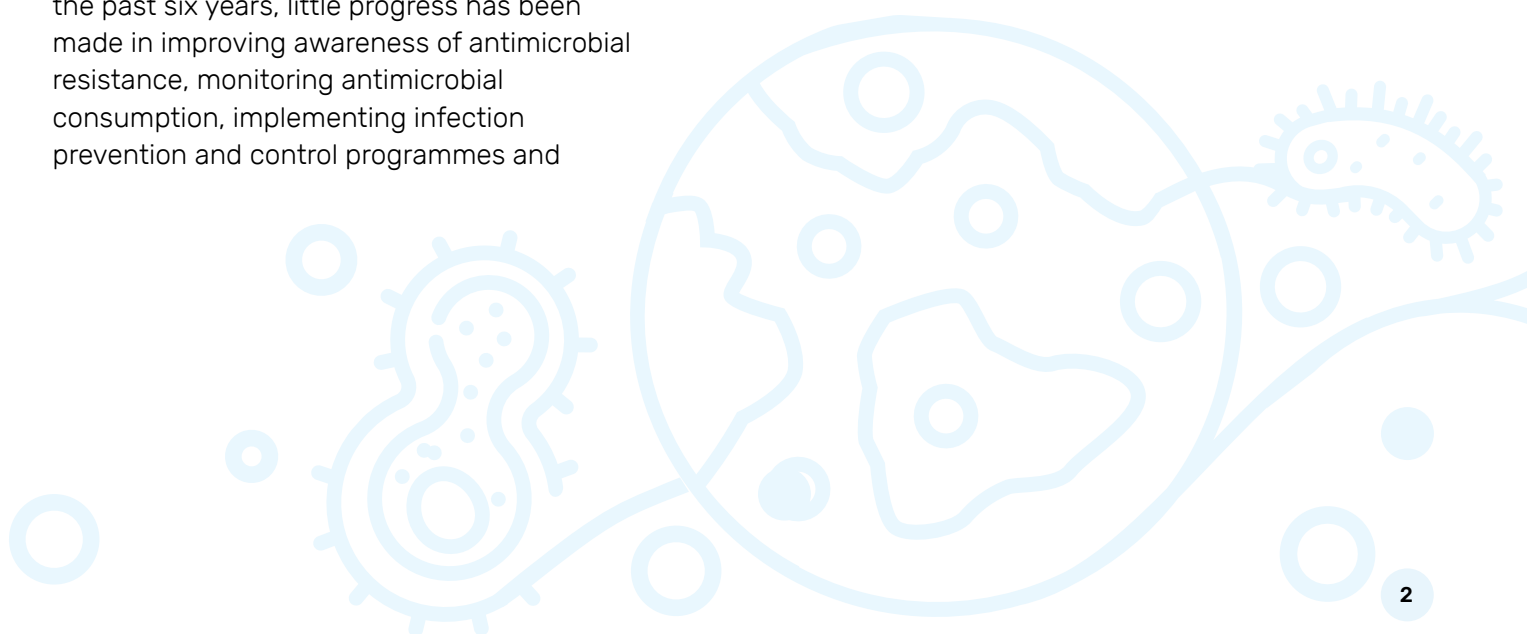
The global research agenda for antimicrobial resistance in human health prioritizes forty research topics for evidence generation to inform policy by 2030

Antimicrobial resistance poses a considerable threat to human health, with an estimated 4.95 million deaths associated with bacterial antimicrobial resistance in 2019.¹ Globally, there were an estimated 450 000 new cases of rifampicin- and multidrug-resistant tuberculosis in 2021.² Further, invasive fungal infections are increasing worldwide,³ and their management is challenged by antifungal resistance and difficulties in diagnosis. Low- and middle-income countries may be disproportionately affected, with higher mortality rates from infections with resistant organisms.¹

To mitigate the impact of antimicrobial resistance, in 2015, WHO launched a Global Action Plan on antimicrobial resistance, with the goal of mitigating the emergence and transmission of resistant infections.⁴ Although antimicrobial resistance is recognized as a global threat requiring urgent action, over the past six years, little progress has been made in improving awareness of antimicrobial resistance, monitoring antimicrobial consumption, implementing infection prevention and control programmes and

optimizing antimicrobial use in the human sector.⁵ Efforts to address the inequitable impact of antimicrobial resistance across populations have been limited, challenged by the lack of data, including data disaggregated by age, sex, socioeconomic status and other factors. Further, substantial knowledge gaps on antimicrobial resistance still exist and contribute to hampering an effective evidence-informed antimicrobial resistance response.

A priority research agenda for antimicrobial resistance is critical in guiding policy-makers, researchers, funders, implementing partners, industry and civil society in generating new evidence to inform antimicrobial resistance policies and interventions as part of collective efforts to address antimicrobial resistance.



What is the goal of this research agenda?

The goal of this research agenda is to identify and give priority to the research topics with the greatest impact on mitigating antimicrobial resistance in the human health sector, in accordance with objective 2 of the Global Action Plan (i.e. on strengthening the knowledge and evidence base through surveillance and research).⁴ The research agenda also aims to foster research by 2030 – in accordance with the Sustainable Development Goals timeline – and to catalyse scientific interest and investment among the scientific community and funders on the epidemiology and burden of resistant infections, strategies to prevent infections and the emergence of resistance, how to optimize and best deliver these in low- and middle-income countries, and optimized diagnostics and antimicrobial medicines. The current list of priority research topics should be further translated into tangible, concrete research proposals fundable by donors and implementable also in settings with limited resources.

What is the scope of this research agenda?

The research agenda is global in scope and focuses on antimicrobial resistance in the human health sector, especially infections caused by the WHO bacterial priority pathogens⁶ and WHO fungal priority pathogens with critical importance for antimicrobial resistance (such as *Candida auris*, *Aspergillus fumigatus* and *Cryptococcus neoformans*)⁷ and drug-resistant *Mycobacterium tuberculosis*.

How was this research agenda developed?

The research agenda was developed through an adapted Child Health and Nutrition Research Initiative method⁸ in close collaboration with a multidisciplinary expert group on antimicrobial resistance. In the preparatory phase, 2340 detailed knowledge gaps were identified through a systematic search of the peer-reviewed and grey literature, based on 3000 documents published in the past 10 years.⁹ These knowledge gaps were then mapped on an adapted Child Health and Nutrition Research Initiative knowledge matrix comprising four research domains (descriptive, delivery, development or discovery) and three themes in accordance with the people-centred framework for addressing antimicrobial resistance¹⁰ (antimicrobial resistance prevention, diagnosis, treatment and care), to ensure that different types of research and topics were captured.

Based on the technical input of a multidisciplinary group of external antimicrobial resistance experts and the WHO secretariat, the knowledge gaps were further consolidated into 175 research topics, by removing obsolete ones and including new relevant topics.

In the final phase, the external expert group was invited to score the 175 research topics according to five criteria: (1) filling critical knowledge gaps, (2) answerability and feasibility by 2030, (3) potential for translation into policy, (4) impact to mitigate antimicrobial resistance and (5) promoting health equity. Based on their experience and expertise, experts were asked to specify the income setting (high-income or low- or middle-income country or both) and population perspective (either adults, children or both) applied in the scoring. A research priority score was computed for each research topic based on the scores from 234 experts. The criteria scores for impact on antimicrobial resistance, filling critical knowledge gaps and translation into policy were weighted at 27% and health equity and answerability and feasibility by 2030 at 10%. The top 20% (35) global and low- and middle-income country research priorities were reviewed and deduplicated and some were combined into broader research topics, resulting in 33 research priorities for antimicrobial resistance in bacteria and fungi and seven research priorities relating to drug-resistant *Mycobacterium tuberculosis*.

Antimicrobial resistance research priorities



Prevention

- 1 Investigate the impact and contribution of community WASH and waste management interventions on the burden and drivers of antimicrobial resistance
- 2 Investigate implementation strategies and the impact of WASH-related interventions in health-care settings on the burden of health care-associated infections and antimicrobial medicine prescribing
- 3 Identify (cost-) effective, acceptable and feasible multimodal infection prevention and control strategies and the relative effect of their components on reducing health care-associated infections
- 4 Assess the impact of vaccines on colonization and infection by resistant pathogens, and on reducing the use of antimicrobial medicines, health-care encounters and health system costs



Diagnosis

- 5 Investigate and evaluate rapid point-of-care tests to discriminate bacterial versus non-bacterial infections
- 6 Investigate and evaluate rapid antimicrobial susceptibility testing methods from blood cultures
- 7 Investigate and evaluate diagnostic tests for detecting pathogens and antimicrobial susceptibility testing
- 8 Investigate and evaluate diagnostic tests for detecting fungal pathogens
- 9 Investigate the clinical and diagnostic value of phenotypic antifungal susceptibility testing
- 10 Investigate, assess and evaluate the implementation of novel rapid point-of-care assays and optimal testing approaches for (resistant) *Neisseria gonorrhoeae*



Treatment and Care

- 11 Investigate antimicrobial stewardship interventions that are context specific, feasible, sustainable, effective and cost-effective in outpatient and inpatient settings
- 12 Identify feasible, effective and scalable pharmacist antimicrobial medicines dispensing practices and related regulatory frameworks to improve antimicrobial stewardship in the community, especially in low- and middle-income countries
- 13 Investigate criteria and strategies to optimize empirical antimicrobial therapy for main infectious syndromes, especially in settings with limited medicine availability, diagnostic capacity and access to health care services
- 14 Determine optimal methods, metrics and targets to monitor antimicrobial use and consumption
- 15 Determine the patterns and drivers of appropriate and inappropriate prescribing, use and consumption of antibiotics
- 16 Investigate approaches to effectively use antimicrobial consumption and antimicrobial resistance surveillance data to inform stewardship and guidelines
- 17 Investigate antibiotic treatment regimens for infections, especially for extended-spectrum beta-lactamase-producing and carbapenem-resistant Enterobacterales
- 18 Investigate antibiotic treatment regimens for infections by drug-resistant typhoid and non-typhoidal salmonellae
- 19 Investigate empirical antibiotic treatments for gram-negative bacteria causing bloodstream infections among neonates and young children in settings with high antimicrobial resistance prevalence
- 20 Investigate antifungal regimens for infections caused by WHO fungal priority pathogens with critical importance for antimicrobial resistance
- 21 Investigate regimens for urogenital and extragenital sexually transmitted infections in the context of increasing antimicrobial resistance levels

Cross-cutting



- 22 Investigate the epidemiology, mortality, morbidity and impact of infections by resistant WHO bacterial priority pathogens
- 23 Investigate the epidemiology, morbidity, mortality and impact of infections by resistant WHO fungal priority pathogens with critical importance for antimicrobial resistance
- 24 Investigate factors driving colonization and infection by resistant WHO bacterial priority and fungal pathogens
- 25 Identify optimal surveillance methods to generate accurate and reliable data on the epidemiology and burden of antimicrobial resistance
- 26 Assess the impact of mass administration of antimicrobial medicines on antimicrobial resistance
- 27 Evaluate how currently recommended syndromic sexually transmitted infection management and treatment of people with asymptomatic sexually transmitted infections affect antibiotic prescribing and antimicrobial resistance
- 28 Determine the most (cost-) effective behavioural change interventions to mitigate antimicrobial resistance emergence and spread
- 29 Evaluate the implementation of antimicrobial resistance-related policies and regulations and their effectiveness in mitigating antimicrobial resistance and improving health outcomes
- 30 Investigate implementation strategies for national policies, legislation and regulations to improve infection prevention, patient care and the use of antimicrobial medicines
- 31 Identify the most (cost-) effective interventions and an investment case to mitigate antimicrobial resistance globally and across countries
- 32 Investigate strategies to integrate antimicrobial resistance interventions into broader health, health financing, development and welfare structures and evaluate their impact
- 33 Investigate how regulatory frameworks, marketing incentives and financing models affect the sustainable development, availability, equitable access and use of new antimicrobial medicines

Antimicrobial-resistant bacterial and fungal infections

- 34 Investigate effective preventive TB vaccines that meet WHO preferred product characteristics criteria and demonstrate impact on prevention of infection, disease and recurrence
- 35 Investigate how the diagnostic performance of molecular assays can be improved to detect drug resistance among people with extrapulmonary and pulmonary TB
- 36 Determine optimal diagnostic and treatment delivery models to improve the access,

effectiveness, cost-effectiveness, feasibility and acceptability of drug-resistant TB treatment

- 37 Investigate better tolerated, optimally dosed, more effective and shorter combination regimens for treating all forms of drug-resistant TB
- 38 Determine the optimal, (cost-) effective, shortest duration and safest TB preventive treatment for the contacts of people with drug-resistant TB

Drug-resistant TB

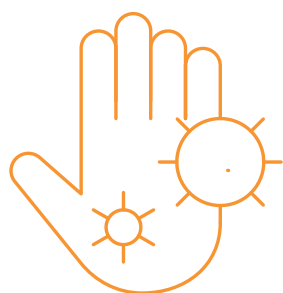


- 39 Investigate strategies for improving treatment outcomes among people with drug-resistant TB who have known risk factors and conditions and among populations experiencing vulnerability
- 40 Investigate the programmatic effectiveness, safety and tolerability of currently used WHO-recommended treatment regimens for drug-resistant TB

Note: Numbering does not imply order of priority.

Antimicrobial resistance research priorities

Forty research priorities in eleven AMR areas across five themes



Prevention

Water, sanitation and hygiene (WASH)

- 1 Investigate the impact, contribution, utility, effectiveness and cost-effectiveness of interventions to ensure safely managed water, sanitation and hygiene (including hand hygiene) and waste management practices in the community setting on reducing the burden and drivers of antimicrobial resistance, such as unnecessary antibiotic consumption for diarrhoeal diseases in low- and middle-income countries.
- 2 Investigate implementation strategies of WASH-related interventions in health-care settings (including ensuring access to safely managed water and sanitation, safe hand hygiene, safe management of waste and environmental cleaning), and assess their impact, acceptability, equity and cost-effectiveness on the burden and transmission of resistant health care-associated infections and antimicrobial medicine prescribing across socioeconomic settings.

Infection, prevention and control

- 3 Identify the most effective, cost-effective, acceptable and feasible multimodal infection and prevention control strategies (such as hand hygiene, contact precautions and patient isolation) and the relative effect of their components in reducing different types of health care-associated infections caused by multidrug-resistant pathogens across geographical and socioeconomic settings.

Immunization

- 4 Assess the impact of vaccines on preventing colonization and infection by resistant pathogens (whether specifically targeted by the vaccine or not) and on reducing the overall use of antimicrobial medicines, health-care encounters and health system costs among adults and children, and across socioeconomic settings.



Diagnosis

Diagnosis and diagnostics

- 5 Investigate and evaluate rapid point-of-care diagnostic tests (including biomarker-based tests) and diagnostic algorithms to discriminate between bacterial and viral infections and non-infectious syndromes that are feasible for use in limited-resource settings and among different subpopulations (including children and neonates).
- 6 Investigate and evaluate phenotypic and genotypic methods of rapid antimicrobial susceptibility testing and resistance detection directly from positive blood culture bottles, especially for use in low- and middle-income countries.
- 7 Investigate and evaluate diagnostic tests for isolating, identifying, antimicrobial susceptibility testing and/or detecting resistance of bacterial pathogens (including multiplex panel-based tests and tests using novel technologies) that are fast, (near) point of care, affordable, feasible for use in limited-resource settings and among different subpopulations and from a variety of specimen types.
- 8 Investigate and evaluate rapid, (near) point-of-care diagnostic tests (including antigen and multiplex panel-based tests) for detecting drug-resistant WHO fungal priority pathogens with critical importance for antimicrobial resistance (such as *Candida auris*, *Aspergillus fumigatus* and *Cryptococcus neoformans*) feasible for use in limited-resource settings and among different subpopulations.
- 9 Investigate and evaluate the clinical utility and diagnostic accuracy of phenotypic antifungal susceptibility testing (including determining minimal inhibitory concentration breakpoints and testing for in vitro and in vivo synergy between antifungal medicines) and their impact on clinical outcomes.
- 10 Investigate, assess the performance and evaluate the implementation of novel rapid point-of-care molecular and non-molecular assays and optimal testing and screening approaches (including self-testing) for *Neisseria gonorrhoeae* and antimicrobial resistance detection to reduce inappropriate antibiotic prescribing and emergence of antimicrobial resistance.



Treatment and care

Antimicrobial stewardship

- 11** Investigate antimicrobial stewardship interventions (such as implementing the WHO AWaRe antibiotic book,¹¹ guidelines, clinical algorithms, education and training, audit and feedback), alone or in combination, that are context specific, feasible, sustainable, effective and cost-effective to avoid antimicrobial misuse in outpatient and inpatient settings, especially where diagnostic capacity may be limited.
- 12** Identify feasible, effective and scalable pharmacist antimicrobial medicines dispensing practices in community pharmacies and related regulatory frameworks (such as incentives and disincentives) to improve antimicrobial stewardship in the community, especially in low- and middle-income countries.
- 13** Investigate criteria and strategies to optimize empirical antimicrobial therapy (such as antimicrobial spectrum, dose, timing of initiation, de-escalation, and stopping), weighting the benefits (e.g., improve outcomes, reduce cost) versus potential harms (e.g., clinical failure, infection relapse, resistance emergence, adverse events), for main community and health care-associated infectious syndromes in adults and children, especially in settings where medicine availability, diagnostic capacity and access to health care services may be limited.

Antimicrobial use and consumption

- 14** Determine optimal (feasible, accurate and cost-effective) methods and metrics to monitor antimicrobial use and consumption in the community and health-care settings and appropriate targets to monitor progress in reducing inappropriate antimicrobial use and consumption.
- 15** Determine the levels, patterns, trends and drivers of appropriate and inappropriate prescribing, use and consumption of access, watch and reserve (AWaRe) antibiotics¹¹ across countries and community and health-care settings, with data disaggregated by sex, age, socioeconomic status and subpopulations, including those experiencing vulnerability and with comorbidities (such as people living with HIV, people with TB and people with malaria).
- 16** Investigate optimal approaches to effectively use facility- and/or national-level antimicrobial consumption and antimicrobial resistance surveillance data to inform antimicrobial stewardship programmes and treatment guidelines.

Antimicrobial medicines

- 17 Investigate efficacious and safe antibiotic treatment regimens based on old and new agents and combinations for infections, especially for extended-spectrum beta-lactamase-producing and/or carbapenem-resistant Enterobacterales, with minimum selection and transmission risk for antimicrobial resistance, especially among children and other subpopulations experiencing vulnerability.
- 18 Investigate efficacious and safe antibiotic treatment regimens for infections by drug-resistant typhoid and non-typhoidal salmonellae (including for pathogens resistant to cephalosporins and fluoroquinolones) across socioeconomic settings.
- 19 Investigate efficacious and safe empirical antibiotic treatment (drug choice, drug combination, route, dose and duration) for gram-negative bacteria causing bloodstream infections or sepsis among neonates and young children, especially in settings with high antimicrobial resistance prevalence, limited diagnostic capacity, and antimicrobial medicine availability.
- 20 Investigate antifungal regimens optimized for efficacy, cost, safety and duration for the treatment of infections caused by WHO fungal priority pathogens with critical importance for antimicrobial resistance (such as *Candida auris*, *Aspergillus fumigatus* and *Cryptococcus neoformans*) in settings with increasing or high prevalence of antifungal resistance.
- 21 Investigate efficacious and safe regimens based on new or existing antimicrobial medicines for urogenital and extragenital sexually transmitted infections (such as resistant *Neisseria gonorrhoeae* and resistant *Mycoplasma genitalium*) in the context of increasing antimicrobial resistance levels, including in populations experiencing vulnerability (such as people living with HIV, pregnant women and adolescents).



Cross-cutting

Antimicrobial resistance epidemiology, burden and drivers

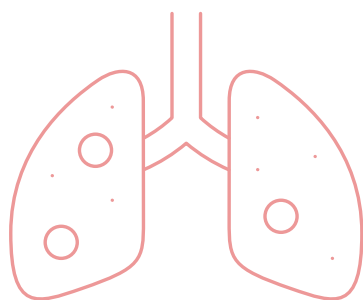
- 22** Investigate the prevalence, incidence, mortality, morbidity and socioeconomic impact of community acquired infections (respiratory tract infections, urinary tract infections and bloodstream infections) and health care-associated infections (bloodstream infections, urinary tract infections, surgical site infections and respiratory tract infections) by resistant WHO bacterial priority pathogens, with data disaggregated by sex, age, socioeconomic status and subpopulations (e.g. populations experiencing vulnerability or with comorbidities such as people living with HIV, people with TB and people with malaria) and across socioeconomic settings, especially in low- and middle-income countries.
- 23** Investigate the prevalence, incidence, morbidity, mortality and socioeconomic impact, and identify and quantify the routes and dynamic of infections by resistant WHO fungal priority pathogens with critical importance for antimicrobial resistance (such as *Candida auris*, *Aspergillus fumigatus* and *Cryptococcus neoformans*) across geographical and socioeconomic settings and in populations experiencing vulnerability.
- 24** Investigate the association, contribution and impact of structural and health system factors (such as hospital microbiome, sanitation infrastructure, waste management, health expenditure, governance, distribution of resources, population displacement, conflict and disruptions in the care continuum) on colonization (selection, persistence and spread or loss of bacterial populations) and infection by WHO bacterial and fungal priority pathogens in various subpopulations, including those experiencing vulnerability (such as migrants and refugees) and people with comorbidities, across various socioeconomic settings.
- 25** Identify optimal (efficient, effective and cost-effective) surveillance methods to generate accurate and reliable data on the epidemiology and burden of antimicrobial resistance among WHO bacterial and fungal priority pathogens (including determining the genotypic predictors of resistance), in community and health-care settings and disaggregated by sex, age and subpopulations that are relevant and actionable at the local and national levels, especially in low- and middle-income countries.
- 26** Assess the short- and long-term impact on antimicrobial resistance of the programmatic use of antimicrobial medicines in mass administration, focusing on subpopulations experiencing vulnerability in low-income settings.
- 27** Evaluate the public health benefits, cost, impact on unnecessary or inappropriate antibiotic prescribing and potential antimicrobial resistance consequences of currently recommended syndromic sexually transmitted infection management and treatment of people with asymptomatic sexually transmitted infections (including *Neisseria gonorrhoeae*) in settings with variable diagnostic capacity.

Antimicrobial resistance awareness and education

- 28 Determine the most (cost-) effective behavioural change interventions to mitigate antimicrobial resistance emergence and spread by targeting and engaging the general public, young people, mass media, health-care providers and policy-makers across socioeconomic settings.

Policies and regulations related to antimicrobial resistance

- 29 Evaluate the implementation of antimicrobial resistance-related policies and regulations at the national level and their effectiveness in mitigating antimicrobial resistance and improving health outcomes in the community and health-care settings across socioeconomic contexts.
- 30 Investigate strategies for the sustainable and (cost-) effective implementation of national policies, legislation and regulations (including sustainable financing and optimal governance structures) to improve infection prevention and patient care practices and the use of antimicrobial medicines in the community and health-care settings, across socioeconomic contexts.
- 31 Identify the most (cost-) effective interventions to mitigate antimicrobial resistance in the human health sector, globally and within countries or regions, and determine the rationale, costs, benefits, feasibility, sustainability and potential returns on investment to achieve the greatest benefit.
- 32 Investigate strategies to integrate antimicrobial resistance interventions into broader health, health financing, development, welfare structures and national policies, and evaluate their impact on mitigating antimicrobial resistance, enhancing health system efficiency, reducing people's out-of-pocket expenses and improving equitable access to and use of diagnostics and antimicrobial medicines.
- 33 Investigate how existing regulatory frameworks, marketing incentives (or their absence) and sustainable financing models affect the development and availability of new antimicrobial medicines and identify effective strategies to adapt these approaches to low-income settings to improve availability for adults and children.



Drug-resistant TB

Prevention

- 34 Investigate effective preventive TB vaccines that meet WHO preferred product characteristics criteria and demonstrate impact on preventing infection, disease, and recurrence (relapse or reinfection) and thereby preventing or reducing the incidence of drug-resistant TB.

Diagnosis

- 35 Investigate how the diagnostic performance of molecular assays can be improved to detect drug resistance among people with extrapulmonary and pulmonary TB, from non-respiratory specimens, including among children and adolescents.
- 36 Determine optimal diagnostic and treatment delivery models to improve the access, effectiveness, cost-effectiveness, feasibility and acceptability of drug-resistant TB testing and treatment across settings and subpopulations (such as people living with HIV, children and adolescents, and prisoners) and evaluate their impact on reducing drug-resistant TB at the population level.

Treatment and care

- 37 Investigate better tolerated, optimally dosed, more effective and shorter combination regimens, using a stratified risk approach, for treating all forms of drug-resistant TB, including in populations experiencing vulnerability (such as children, pregnant and breastfeeding women, and people living with HIV).
- 38 Determine the optimal, (cost-) effective, shortest duration and safest TB preventive treatment for the contacts of people with drug-resistant TB, especially among people at high-risk of TB infection and disease, as identified in WHO guidance, and eligible populations experiencing vulnerability (such as children, adolescents, people living with HIV and pregnant women).
- 39 Investigate strategies for improving treatment outcomes among people with drug-resistant TB who have known risk factors and co-occurring conditions (such as HIV, undernutrition, diabetes mellitus, tobacco use, alcohol and other substance use, and mental health disorders), and populations experiencing vulnerability (such as pregnant and breastfeeding women, children, adolescents and prisoners) in various geographical and socioeconomic settings.
- 40 Investigate the programmatic effectiveness, safety and tolerability of currently used WHO-recommended treatment regimens for drug-resistant TB (including combinations with bedaquiline, delamanid and/or pretomanid) on patient outcomes and drug-resistant TB emergence across populations and settings and identify the drivers of treatment failure.

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