Joint Action
Antimicrobial Resistance and
Healthcare-Associated Infections

D9.3

Incorporating evidence into antibiotic prescribing guidelines

WP9 | Prioritizing and implementing research and innovation for public health needs

Leader acronym | INSERM, FHI

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List of abbreviations

AMR: AntiMicrobial Resistance

HCAI: HealthCare Associated Infection

MS: Member States

WP: WorkPackage

Summary

Every year over € 1 billion is invested in research related to antimicrobial resistance (AMR), including research for new technologies, improved stewardship and surveillance, and better understanding of select microbes. These investments are made not only in the pursuit of discovery and scientific knowledge but also to inform decision-making. Yet, translating scientific evidence into effective health policies is not an easy task.

To gain understanding on how European countries use scientific evidence to set their antibiotic guidelines and propose recommendations to improve the translation of evidence into policies, the EU-JAMRAI set out to interview human and animal policymakers in 10 European countries.

Nine of 10 European countries have antibiotic prescribing guidelines for human health. All nine countries use experts to establish and update the guidelines. Several interviewees were uncertain about how the experts used research evidence to update the guidelines. Three countries specifically mentioned that systematic reviews of evidence formed the basis for guideline updates. Nine of 10 countries also have species-specific, disease-specific antibiotic prescribing guidelines for veterinary health, also established and updated through expert opinion.

These results highlight that in Europe expert opinion is still the basis for antibiotic prescribing guidelines. However, research has revealed limitations with processes that rely solely on expert opinion. Experts may use non-systematic methods when they review research, potentially based upon bias.

Based on existing tools and finding from these interviews, the EU-JAMRAI proposes a framework to facilitate the translation of scientific evidence into health policies.

Introduction and objectives

WorkPackage (WP) "Research & Innovation" objectives.

The main objective of the WP "Research & Innovation" is to contribute to a coordinated European response against AMR by assisting MS in devising policies to prioritize, stimulate and utilize research and innovation related to AMR and HCAI.

This deliverable focuses on the third specific objective of the WP "Research and Innovation" whose overreaching goal is to ensure that scientific evidence on AMR inform policies.

The complicated translation of evidence into policies.

Every year over € 1 billion is invested in research related to antimicrobial resistance (AMR), including research for new technologies, improved stewardship and surveillance, and better understanding of select microbes.[1] These investments are made not only in the pursuit of discovery and scientific knowledge but also to inform decision-making. Coupled with significant investments in surveilling resistant pathogens of importance, this creates a dynamic pool of evidence to draw upon to inform policies and practices.

Yet, translating scientific evidence into effective health policies is not an easy task. Policy-makers and scientists speak different languages. Scientists are not trained to do politics and policymakers are not trained to judge the quality of scientific evidence. The result is an often inefficient process to translate evidence into policies.

The EU-JAMRAI setting out to understand how countries use evidence to set guidelines.

To gain understanding on how European countries use scientific evidence to set their antibiotic guidelines and propose recommendations to improve the translation of evidence into policies, the EU-JAMRAI set out to interview human and animal policymakers in several European countries.

Methodology

As a part of the EU Joint Action on AMR and Healthcare-Associated Infections (EU-JAMRAI), we wanted to better understand how countries utilize evidence to inform their policies and practices. We chose the **concrete case of antibiotic prescribing guidelines**, both for human and veterinary health. We performed **in-depth interviews** with **human health policymakers** in ten European countries: Belgium, Denmark, France, Germany, Luxembourg, the Netherlands, Norway, Romania, Spain, and Sweden. We also interviewed **policymakers from Ministries of Agriculture** in all countries except Romania. This qualitative data gives insights into how countries are utilizing evidence to inform antibiotic prescribing practices.

Figure 1: Countries interviewed

Results

How European countries set up their antibiotic prescribing guidelines?

Nine of 10 European countries have antibiotic prescribing guidelines for human health. Five of them have separate prescribing guidelines, one for community health and one for hospital care. All nine countries use experts to produce and update the guidelines. This may be through infectious disease societies, academic institutions, national agencies, or dedicated foundations. Several interviewees were uncertain about how the experts used research evidence to update the guidelines. Only three countries specifically mentioned that systematic reviews of evidence formed the basis for guideline updates. Interviewees mentioned that antibiotic guidelines often include only antibiotics available in the country. However, one country has rejected this approach. Instead, it has included the most scientifically, clinically appropriate antibiotic, regardless of its national availability. Alternative treatment options are always included in the guidelines when the recommended antibiotic is not available on a long-term basis.

Nine of 10 countries also have antibiotic prescribing guidelines for veterinary health, established and updated through expert opinion. Experts may include veterinarians, farmers, academics, feed industry, and pharmaceutical industry. The guidelines are generally based upon the guidance from the European Medicines Agency as well as national resistance patterns. Several interviewees pointed out that there is limited relevant research available, necessitating a focus on local experiences rather than evidence.

Generally, human and veterinary prescribing guidelines are infrequently updated, perhaps every five years. For human guidelines, this may make it difficult to include new antibiotics.

Conclusions

The challenges with relying solely on expert opinions.

Research has revealed limitations with processes that rely solely on expert opinion.[2] Experts may use non-systematic methods when reviewing research, potentially biased towards certain academic fields, journals, or research designs. Conducting a systematic review has several advantages over other methods of evidence collection, including reducing the risk of bias, ensuring a comprehensive research strategy, and ensuring transparent processes for critical appraisal[2].

Of course, the quality of a systematic review greatly depends on the quality of available evidence. In areas with little research available, like for veterinary antibiotic prescribing guidelines, a systematic review may not help to inform policymaking. On the contrary, in situations like creating antibiotic prescribing guidelines for human health, the amount of literature available may be overwhelming and hinder the process of evidence collection. Therefore, how evidence is used should be carefully weighed in order to provide the greatest impact with the resources available.

Opportunities to improve the use of evidence.

There are many resources available to assist in evidence-informed policymaking and practices. Based upon existing tools and learnings from interviews, the EU-JAMRAI summarizes standard processes to facilitate the translation of evidence into health policies.

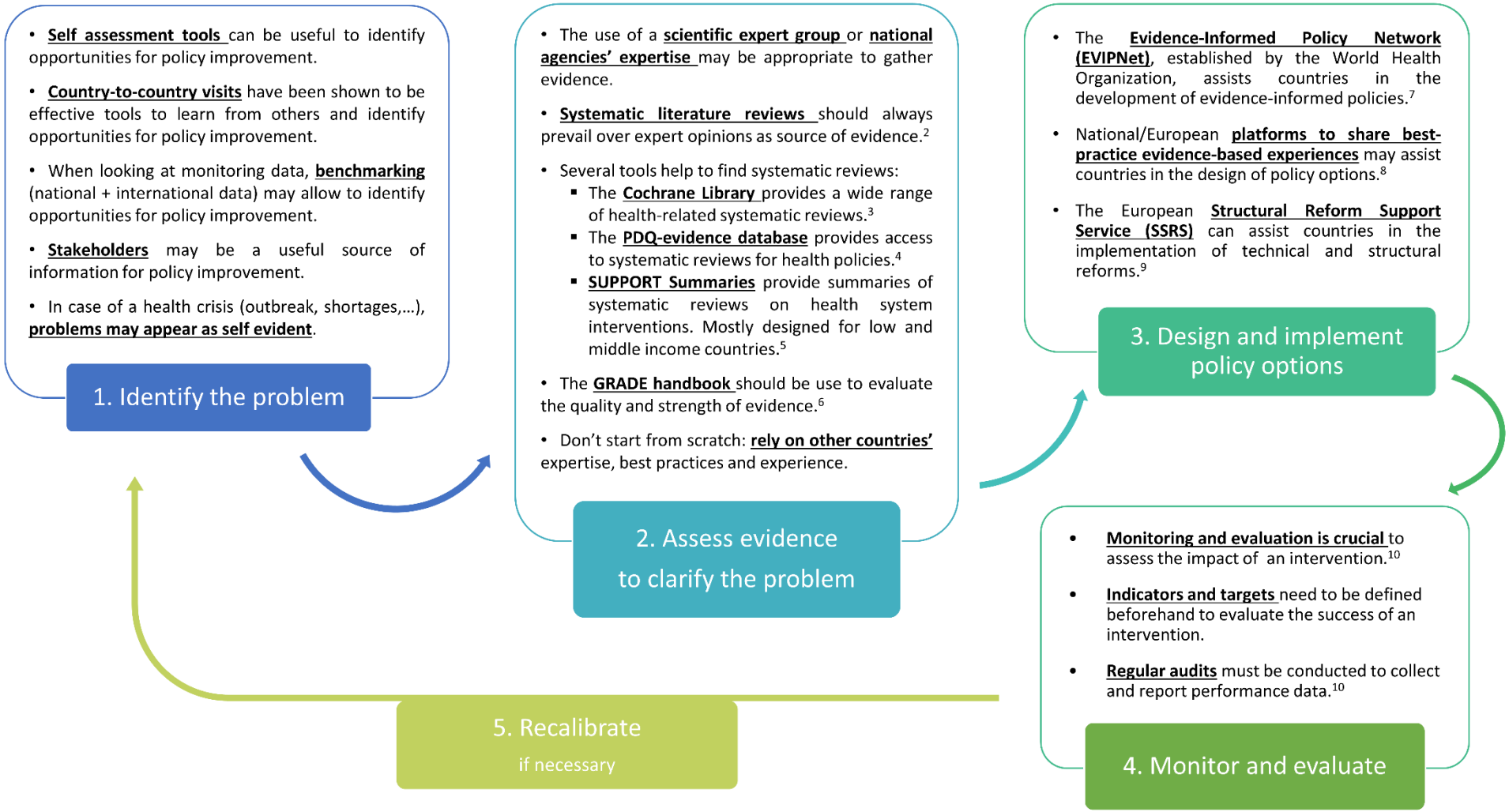

Figure 2: Opportunities for translating evidence into health policies.

These recommandations are based on EU-JAMRAI experiences, existing ressources, as well as literature (see References).

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Appendix 1

Example of evidence-informed hospital prescribing guidelines.

In Norway, the government has committed that the content of all guidelines shall be based on a systematic assessment of the current evidence. An evidence-informed approach means that all research, clinical experiences, and user experiences are systematically assessed against potential desired and undesirable consequences. Yet, when updating antibiotic hospital prescribing guidelines a pragmatic approach must be taken. The guidelines contain numerous recommendations, and it would not be practically possible within a reasonable time and budget to gather all research for every antibiotic/infection combination. Therefore, priorities had to be set in order to identify acceptable compromises.

As a starting point, it was decided that the Norwegian guidelines could be based upon the recommendations of high quality international guidelines, selected based upon the following criteria:

- Relevance: The guidelines must be relevant. Specifically, this means that the patient population, resistance conditions and available (registered) antibiotics correspond to Norwegian conditions.
- Evidence-based: Are the sources of the guideline recommendations comprehensive, of sufficient quality, and relevant? Is there a transparent methodology and process?
- Authorship: Are there recognized professional authorities, with sufficient insight into the problem and an overview of the subject area? Is there sufficient breadth in the composition? Do they represent the whole country or possibly multiple countries?

For each chapter, the team of experts reviewed the guidelines from other countries and used a standardized instrument to evaluate the quality and completeness of each recommendation. The team assessed the overall evidence base and transfer value to Norwegian conditions and prepared proposals for recommendations. When the literature did not provide clear answers, an assessment of Norwegian resistance conditions, Norwegian therapy tradition and expert assessments (the professional network) determined the recommendation. The rationale for every recommendation in the guidelines is clearly stated, including evidence base and assessment. Each recommendation is classified as strong or weak. A strong recommendation is suitable for most patients or one with a strong evidence base. Whereas a weak recommendation is given when different choices may be correct, depending on the patient and situation. The recommendations also balance considerations for the individual patient against the risk of increasing antibiotic resistance.

Appendix 2

Date and location of WP9 country visits.

Country visited	Date	Type of meeting
France	23-24 May 2019	Physical
Netherlands	25 June 2019	Physical
Norway	27-28-29 August 2019	Physical
Luxembourg	16-17 October 2019	Physical
Sweden	18-19-20 November 2019	Physical
Denmark	15-16 January 2020	Physical
Spain	29-30 January 2020	Physical
Belgium	11 February 2020	Physical
Romania	04 September 2020	Virtual
Germany	16 September 2020	Virtual

Appendix 3

WP9 country visits' interview guide.

Questions related to antibiotic prescribing guidelines are highlighted in yellow.

1. **Areas of greatest concern or vulnerability regarding research, innovation, and access.**
   - Briefly describe your country's biggest concerns regarding AMR & HCAI research, innovation, and access?
   - What are your greatest concerns or vulnerabilities regarding AMR and HCAI within animal and plant health?
   - What are your research priorities?
   - Do you feel like research priorities are being adequately funded and researched?

2. **Areas of greatest financial concern related to AMR and HCAI?**
   - Has your country assessed the cost of AMR?

3. **National processes to determine national research priorities.**
   - What national processes do you use to determine your research priorities? (including priority technologies, infection prevention and control (IPC) knowledge gaps, and behavioral change interventions)

4. **Incentives.**
   - Incentives for new antibiotics and other treatments
     - Access - What steps are your country pursuing (if any) to secure access to new antibiotics (or other treatments)? Are you concerned that your country will not have access to the newest antibiotics developed by small companies?
     - Pull - What focus does your country have on pull incentives? What are the biggest barriers to implementation?

- Pooled funds - Would your country be willing to pool funds with other European countries? If so, which facilities are considered the strongest candidates for a pooled fund? (European Investment Bank?)
- Selecting products worthy of a reward - Does your country feel that the priority pathogens identified by WHO are aligned with your unmet public health need?
- Higher unit prices – Is your country open to assessing the societal value of a new antibiotic as a part of the health technology process in order to award a higher unit prices?
- Pilots – Sweden and the UK are moving forward on pull incentive pilots.
    - How open is your country to attempting to pilot new incentives within well-defined parameters and financing constraints? For example, an innovative new antibiotic for WHO critical pathogen.
    - Or would your country prefer a European-based pilot? If so, how many other countries would need to commit?
    - What are the barriers and influencing factors?
    - What might be the first steps towards a pilot?

- Incentives/measures to maintain access to older antibiotics
    - Are you experiencing shortages of antibiotics?
    - Is your country pursuing measures to secure availability of older antibiotics?
    - Which older antibiotics are you most concerned about? Do you have a list of critical antibiotics?
    - Is your country attempting to grow its consumption of older antibiotics through expanded susceptibility testing?
    - Is there a willingness to pay higher unit prices for older antibiotics? Or what other incentives might your country be interested in? Netflix models?
    - Piloting

        - How open is your country to attempting to pilot new incentives within well-defined parameters and financing constraints?
        - Or would your country prefer a European-based pilot? If so, how many other countries would need to commit?
        - What are the barriers and influencing factors?
        - What might be the first steps towards a pilot?
    - Are you experiencing shortages of veterinary antibiotics and/or vaccines?
    - Are there any incentives or regulations in place to support veterinary vaccinations?
    - Might your country be open to attempting to pilot new incentives for veterinary vaccines within well-defined parameters and financing constraints? What are the barriers and influencing factors?

- Incentives/measures to support IPC
    - OECD has demonstrated that significant cost savings can be achieved by improving IPC measures. Do you feel that this is relevant for your country?
    - If so, these often require upfront financing to achieve the savings. Are there mechanisms in your country to finance these efforts?
    - Could economic incentives be useful for infection prevention and control? For example, upfront financing in line with expected outcomes, followed by sharing of cost savings between the healthcare institution and government?

5. Financing national positions and ambitions.

- Are there national mechanisms to assist companies to bring products to market or support small businesses? Could these mechanisms be used to finance potential pilots for new or old antibiotics?
- Are there other mechanisms that may be potentially used to finance pilot for new or old antibiotics?
- Does your country work with the European Investment Bank regarding financing for health research?

- Has your country considered carving out the antibiotic reimbursement from the DRG?
- What are your thoughts about placing a fee onto EMA registrations of all other medicines with the exception of anti-infectives in order to finance antibacterial innovation?
- Is there any consideration of lessening regulatory requirements for SMEs, for example, local office for pharmacovigilance?

6. Guidelines.

- Do you have national stewardship or IPC guidelines?
- In animals and/or plants too?

7. National processes to update clinical guidelines, IPC routines, and other AMR and HCAI-related policies and practices.

- What processes and procedures do you have to update the above? How often? How do you incorporate new evidence?
- Are there any barriers to gathering the evidence and updating the policies/guidelines?

Appendix 4

WP9 policybrief on evidence based policies.

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Every year, more than €1 billion is invested worldwide in research related to antimicrobial resistance (AMR), including research for new technologies, improved stewardship and surveillance, and better understanding of microbes and their transmission.[1] These investments are made not only in the pursuit of discovery and scientific knowledge but also to inform decision-making for the benefit of patients, animals and the environment. Coupled with efforts to monitor highly resistant pathogens, this creates a dynamic pool of evidence to draw upon to inform policies and practices.

As a part of the EU Joint Action on AMR and Healthcare-Associated Infections (EU-JAMRAI), we wanted to understand how countries use evidence to inform their policies and practices. We chose the concrete case of antibiotic prescribing guidelines, both for human and veterinary health. We performed in-depth interviews with human health policymakers in ten countries: Belgium, Denmark, France, Germany, Luxembourg, the Netherlands, Norway, Romania, Spain, and Sweden. We interviewed policymakers from Ministries of Agriculture in all countries except Romania. This qualitative data gives insights into how countries are using evidence to inform antibiotic prescribing practices.

IN GENERAL, EXPERT OPINION IS THE BASIS FOR ANTIBIOTIC PRESCRIBING GUIDELINES

Nine of 10 European countries have antibiotic prescribing guidelines for human health. Five of them have separate prescribing guidelines, one for community health and one for hospital care. All nine countries use experts to produce and update the guidelines. This may be through infectious disease societies, academic institutions, national agencies, or dedicated foundations. Several interviewees were uncertain about how the experts used research evidence to update the guidelines. Only three countries specifically mentioned that systematic reviews of evidence formed the basis for guideline updates. Interviewees mentioned that antibiotic guidelines often include only antibiotics available in the country. However, one country has rejected this approach. Instead, it has included the most scientifically, clinically appropriate antibiotic, regardless of its

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national availability. Alternative treatment options are always included in the guidelines when the recommended antibiotic is not available on a long-term basis.

Nine of 10 countries also have antibiotic prescribing guidelines for veterinary health, established and updated through expert opinion. Experts may include veterinarians, farmers, academics, feed industry, and pharmaceutical industry. The guidelines are generally based upon the guidance from the European Medicines Agency as well as national resistance patterns. Several interviewees pointed out that there is limited relevant research available, necessitating a focus on local experiences rather than evidence.

Generally, human and veterinary prescribing guidelines are infrequently updated, perhaps every five years. For human guidelines, this may make it difficult to include new antibiotics.

THERE ARE CHALLENGES WITH RELYING SOLELY ON EXPERT OPINION

Research has revealed limitations with processes that rely solely on expert opinion.[2] Experts may use non-systematic methods when reviewing research, potentially biased towards certain academic fields, journals, or research designs. Conducting a systematic review has several advantages over other methods of evidence collection, including reducing the risk of bias, ensuring a comprehensive research strategy, and ensuring transparent processes for critical appraisal[2].

Of course, the quality of a systematic review greatly depends on the quality of available evidence. In areas with little research available, like for veterinary antibiotic prescribing guidelines, a systematic review may not help to inform policymaking. On the contrary, in situations like creating antibiotic prescribing guidelines for human health, the amount of literature available may be overwhelming and hinder the process of evidence collection. Therefore, how evidence is used should be carefully weighed in order to provide the greatest impact with the resources available.

OPPORTUNITIES TO IMPROVE THE USE OF EVIDENCE IN POLICYMAKING

There are many resources available to assist in evidence-informed policymaking and practices. Based upon existing tools and learnings from interviews, the EU-JAMRAI summarizes standard processes to facilitate the translation of evidence into health policies.

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1. IDENTIFY THE PROBLEM

- **Self assessment tools** can be useful to identify opportunities for policy improvement.
- **Country-to-country visits** have been shown to be effective tools to learn from others and identify opportunities for policy improvement.
- When looking at monitoring data, **benchmarking** (national + international data) may allow to identify opportunities for policy improvement.
- **Stakeholders** may be a useful source of information for policy improvement.
- In case of a health crisis (outbreak, shortages,...), **problems may appear as self evident.**

2. ASSESS EVIDENCE TO CLARIFY THE PROBLEM

- The use of a **scientific expert group or national agencies' expertise** may be appropriate to gather evidence.
- **Systematic literature reviews** should always prevail over expert opinions as source of evidence.[2]
- Several tools help to find systematic reviews:
  - The **Cochrane Library** provides a wide range of health-related systematic reviews.[3]
  - The **PDQ-evidence database** provides access to systematic reviews for health policies.[4]
  - **SUPPORT Summaries** provide summaries of systematic reviews on health system interventions. Mostly designed for low and middle income countries.[5]
- The **GRADE handbook** should be use to evaluate the quality and strength of evidence.[6]
- Don't start from scratch: **rely on other countries'** expertise, best practices and experience.

3. DESIGN AND IMPLEMENT POLICY OPTIONS

- The **Evidence-Informed Policy Network (EVIPNet)**, established by the World Health Organization, assists countries in the development of evidence-informed policies.[7]
- National/European **platforms to share best-practice evidence-based experiences** may assist countries in the design of policy options.[8]
- The European **Structural Reform Support Service (SSRS)** can assist countries in the implementation of technical and structural reforms.[9]

4. MONITOR AND EVALUATE

- **Monitoring and evaluation is crucial** to assess the impact of an intervention.10
- **Indicators and targets** need to be defined beforehand to evaluate the success of an intervention.
- **Regular audits** must be conducted to collect and report performance data.10

5. RECALIBRATE
If necessary

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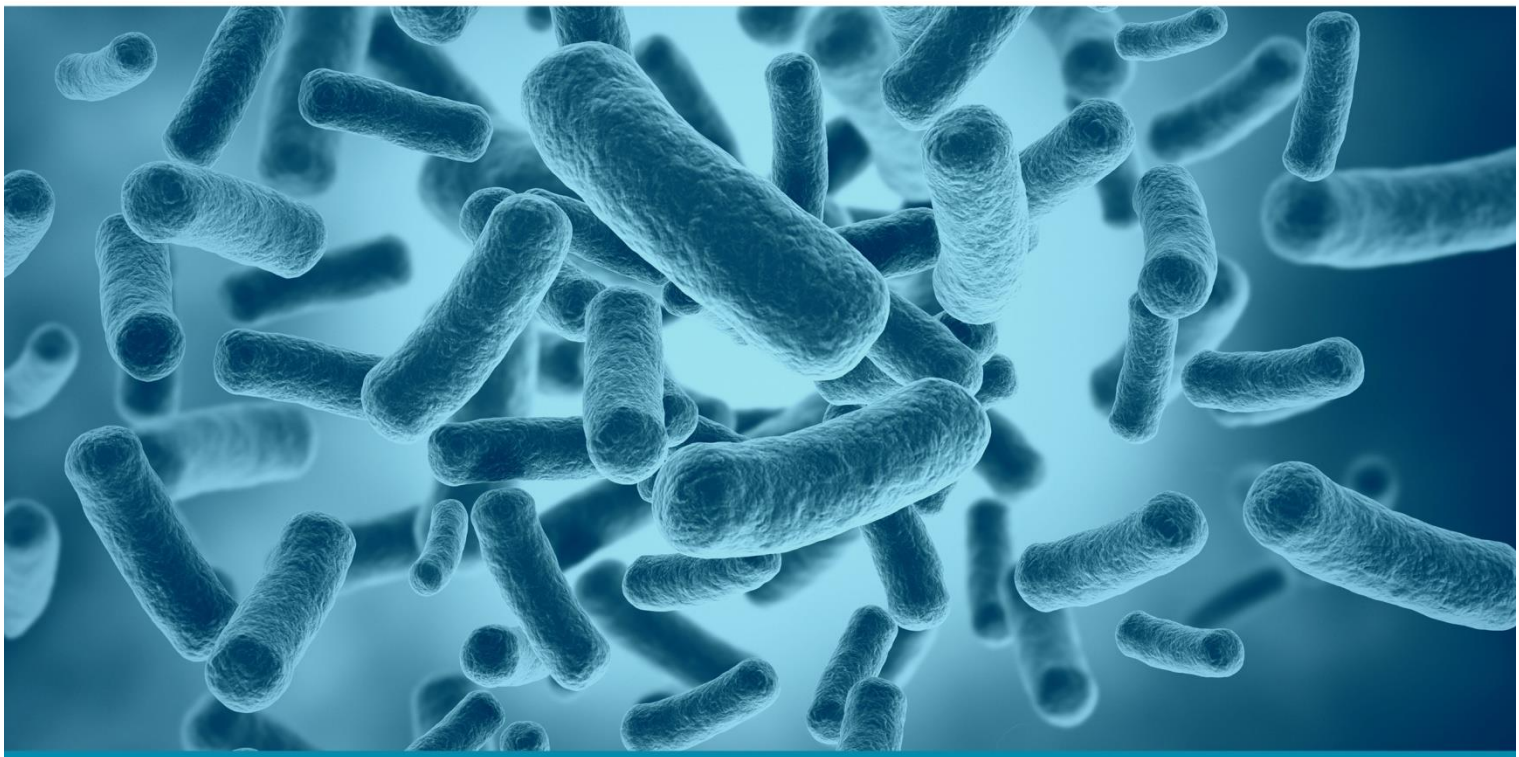

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