

OHEJP PhD PROJECT OUTCOMES

LIN-RES

Investigation of the molecular basis, origin, transferability and risk factors associated with linezolid-resistance emergence in Gram-positive bacteria of human and animal origin



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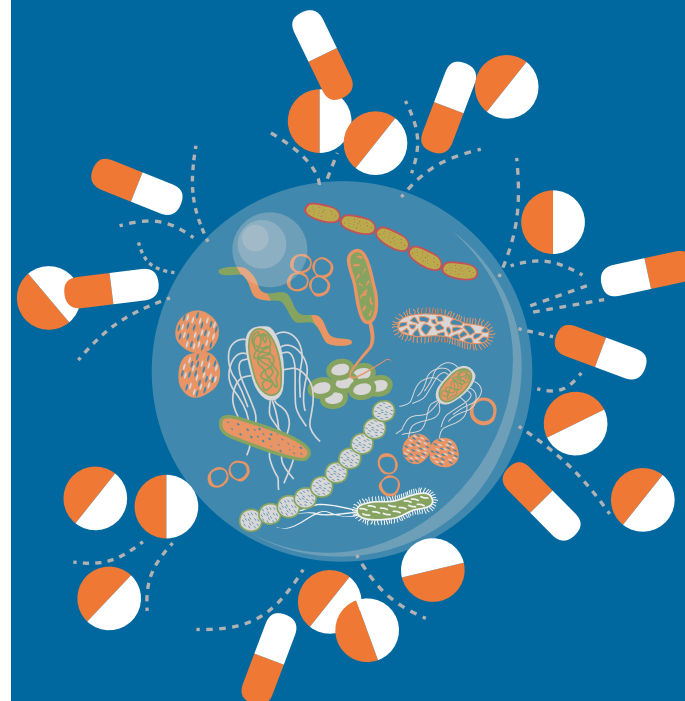
WHAT IS ANTIMICROBIAL RESISTANCE? HOW CAN THE MONITORING AND DETECTION OF ANTIMICROBIAL RESISTANCE BE IMPROVED USING A ONE HEALTH APPROACH?

Antimicrobial resistance (AMR) occurs when microorganisms (e.g., bacteria, fungi, parasites, etc.) evolve a natural level of resistance to a drug that is often accelerated through the overuse or misuse of antimicrobials in human and veterinary medicine. Resistance means that it becomes more difficult to find efficient treatments for a growing number of infections, increasing the risk of disease spread, serious illness, and co-morbidities if not addressed ([O'Neill, 2016](#); [WHO, 2021](#)). Factors that accelerate resistance development include poor infectious disease prevention and control measures in the health and agricultural sectors, lack of personal hygiene and medicines, and the use of heavy metals and biocides ([WHO, 2021](#); [McEwen & Collignon, 2018](#); [Holmes et al., 2016](#)).

AMR is a global One Health problem, which has been recognised by the World Health Organisation (WHO) as 'one of the most urgent health threats of our time' ([WHO, 2021](#)). Globally, 1.27 million deaths have been directly attributed to antibiotic-resistant bacteria in 2019 ([Murray et al., 2022](#)); which has a significant economic impact on European health care systems, costing an estimated €1.5 billion each year ([EU, 2021](#)). The issue is projected to rise, causing 10 million deaths annually and costing an estimated \$100 trillion globally by 2050 if not addressed ([O'Neill, 2016](#)).

AMR bacteria can be transmitted between animals and humans, including between other bacterial species either through the environment or the farm-to-fork pathway ([Woolhouse and Ward, 2013](#); [WHO, 2021](#)); therefore, only a One Health approach can tackle this issue. Linezolid resistance first emerged in 2008 in the United States of America, before being more widely detected throughout the American and European continents ([Flamm et al., 2012](#)). Linezolid belongs to the family oxazolidinones, and are the final line of antibiotics in the fight against human infections caused by multi-resistant Gram-positive bacteria such as *Streptococci*, *Staphylococci*, and *Enterococci*. One of the resistance genes encoding linezolid resistance is the chloramphenicol-florfenicol resistance gene (*cfr*) ([Wali et al., 2022](#)). The gene *cfr* emerged in European livestock first in coagulase-negative *Staphylococci* spp. and very recently in Methicillin-Resistant *Staphylococcus aureus* (LA-MRSA) strains isolated from healthy pigs, despite linezolid not being licensed for food-producing animals ([Mittal et al., 2019](#)). The LIN-RES PhD project investigated the presence of linezolid resistance in Gram-positive bacteria through a One Health approach, in Belgium.

The One Health EJP used its unique position to facilitate a collaborative approach between institutes to deliver important multisectoral research and achieve optimal health and well-being outcomes for humans, animals, and the environment. The One Health EJP brought together 43 acclaimed European scientific institutes and the Med-Vet-Net Association working together on 47 research projects to address potential and existing risks that originate at the animal-human- environment interface.





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WHAT IS THE LIN-RES PhD PROJECT?

The [LIN-RES](#) PhD project drew mainly on samples collected from the Federal Agency for the Safety of the Food Chain – Belgian Antimicrobial Resistance Official Monitoring programme and produced outputs that:

- Suggest a new surveillance methodology to specifically monitor resistance to linezolid.
- Make publicly available the results, including genomic data, to compare with future monitoring/ research in this field.
- Make available a collection of linezolid resistance strains gathered through the project to help other member states launch a similar monitoring.
- Raise awareness of the human and animal sector on the linezolid-resistance issue.

Fully aligned with the One Health concept, the LIN-RES PhD project may ultimately provide insight into the challenges and opportunities in monitoring linezolid resistance; having already been disseminated key results with Belgian institutions ([FASFC](#), [FAMHP](#), [AMCRA](#)) and European institutions, including the [EU Reference Laboratories – Antimicrobial Resistance](#) (EURL-AR), the [European Food Safety Authority](#), and the European Commission. Promoting EURL-AR to work with Sciensano to assess the interest and feasibility of conducting linezolid selective monitoring across Europe.





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The LIN-RES PhD project produced an in-depth peer-reviewed publication, [demonstrating a large diversity of linezolid-resistant](#) (LZD-R) isolates circulating in the agricultural sector in faeces from veal calves, pigs, breeding hens, broilers, and laying hens, and in nasal swabs samples from pigs collected in 2019 in Belgium. The results have evidenced that 25.7% of nasal swabs from pigs and 16.4% of faeces from veal calves carrying LZD-R bacteria; further evidencing no clear correlation between phylogenies and AMR genotypes, suggesting that these genomic features are easily transferable. These results highlight a reservoir of LZD-R bacteria in Belgium, posing a risk to human health; suggesting the importance placed on the antibiotics that could cross-select this resistance (i.e., phenicol's) should be reassessed.

In conclusion, LIN-RES provided insight into LZD-R bacterial populations in Europe, highlighting the need for an integrated One Health approach.





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[1] Timmermans, M., Bogaerts, B., Vanneste, K., De Keersmaecker, S. C., Rossens, N. H. C., Kowalewicz, C., Simon, G., Argudin, M. A., Deplano, A., Hallin, M., Wattiau, P., Fretin, D., Denis, O., Boland, C. (2021). Large diversity of linezolid-resistant isolates discovered in food-producing animals through linezolid selective monitoring in Belgium in 2019. *Journal of Antimicrobial Therapy*. 77 (1). DOI: <https://doi.org/10.1093/jac/dkab376>



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Each of the One Health EJP PhD projects brought together a supervision team from our unique Europewide network of institutes with the wide-ranging expertise to achieve using a cohesive One Health approach.

The One Health EJP LIN-RES PhD project worked collaboratively to achieve its aims and to produce impactful outcomes regarding the operationalisation of the One Health approach.

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