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From antimicrobial resistance to disability: a One Health framework linking pandrug-resistant infections to amputation and irreversible functional decline

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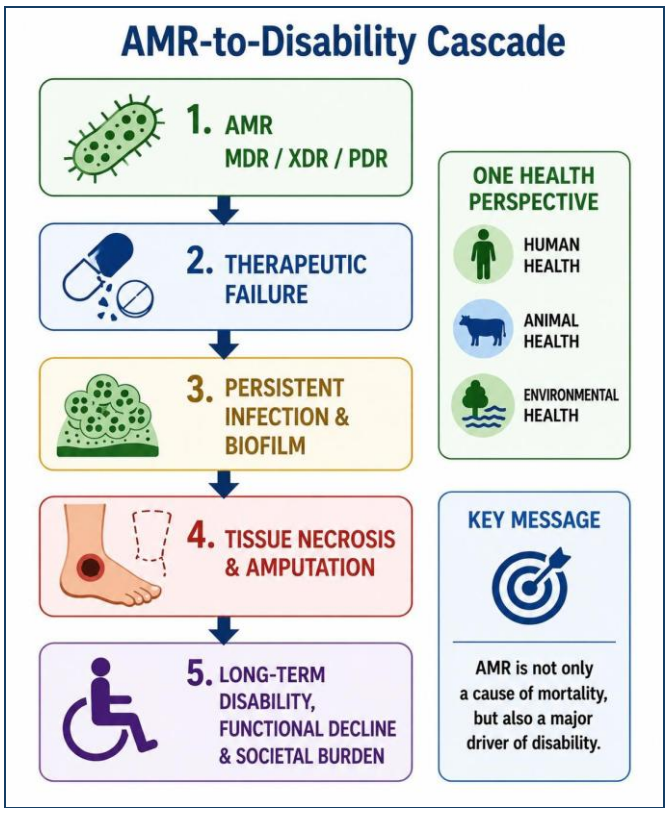
Abstract

Introduction: Antimicrobial resistance (AMR) has become one of the greatest challenges of the 21st century to global health. The impact of AMR is usually assessed in terms of morbidity, mortality, and cost of health care, but irreversible disability is significantly underrecognized. Multidrug-resistant (MDR) pathogens, extensively drug-resistant (XDR) and especially pandrug-resistant (PDR) pathogens often cause therapeutic failure, chronic infection, progressive destruction of tissue and permanent impairment in function. **Objective:** The objective of this review was to reframe AMR in a disability-focused and One Health perspective, by examining the link between resistant infections and amputation, long term functional decline, and disability. **Methods:** A narrative integrative review was performed with recent literature from clinical, microbiology, public health and One Health publications. The review is targeted at high-risk infections such as diabetic foot infections, infections associated with trauma, burn wounds, osteomyelitis and chronic soft tissue infections. **Results:** Available data has shown that there exists a link between resistant infections and delayed effective therapy, chronic infection with biofilm, necrosis of tissue, recurrence of surgical intervention and loss of the limb. PDR pathogens mark the ultimate point of therapeutic exhaustion of antimicrobial agents—often the last resort is surgical containment. The burden of disability due to AMR is especially high in LMICs due to delayed diagnosis, poor antimicrobial stewardship, limited access to newer antimicrobials, and lack of adequate rehabilitation services. **Conclusion:** AMR should no longer be considered solely a cause of death, but also as a leading cause of irreversible disability and long-term burden on society. The inclusion of disability prevention, functional preservation, rehabilitation and One Health in AMR frameworks is essential to future global strategies for health.

Keywords: Antimicrobial resistance. Pandrug-resistant bacteria. Disability. Amputation. One Health. Functional decline. Limb loss. Diabetic foot infection.

Graphical Abstract



Source: Own authorship.

Introduction

Antimicrobial resistance (AMR), or the resistance of microbes to antimicrobials, is now one of the world's most critical health, healthcare systems and sustainable development challenges **[1,2]**. The spread of resistant pathogens has developed at a fast pace and has rendered the contemporary antimicrobial therapy progressively ineffective, therefore greatly diminishing the capacity to handle grave bacterial infections **[1,3]**. Data from around the globe suggest that bacterial AMR contributed to millions of deaths globally in 2019, with an even greater burden in low- and middle-income countries (LMICs) because of diagnostic challenges and poor antimicrobial stewardship **[1,2]**.

The international discourse on AMR has traditionally been dominated by the issues of death, spread of AMR and its economic burden **[4]**. This, however, does not fully reflect the true impact of the resistant infections as a significant proportion of the survivors have long-term functional consequences **[5]**. Resistant infections often become more complex than just therapeutic failure and result in chronic destructive disease processes with constant inflammation, necrosis, osteomyelitis, organ damage, and loss of function of the limb or organ **[6]**.

AMR and disability are especially apparent in diabetic foot infections, burns, trauma-related wounds, chronic osteomyelitis and severe soft tissue infections **[7,8]**. Under these circumstances, the risk of each of these also rises significantly with delay in microbiological clearance and failure of antimicrobial treatment, and often leads to subsequent surgery, extended hospital stayed, and major amputation **[3,9,10]**. In such instances, the loss of a limb is not only a surgical consequence, but a life-changing event that is linked to permanent mobility impairment, chronic pain, psychological effects, diminished quality of life and socioeconomic instability **[4,5]**.

Pandrug-resistant (PDR) pathogens are the most advanced form of therapeutic exhaustion among antimicrobial-resistant phenotypes **[3]**. Since by definition PDR organisms are resistant to all currently available antimicrobial agents, there are no pharmacological options available for treatment **[3]**. As a result, more and more management tend to be focused on damage control, that is, performing aggressive debridement, resection and amputation to prevent the onset of sepsis and death **[3,7]**.

AMR is an ecosystemic problem from a One Health perspective where human and veterinary use of antibiotics, agricultural practices, food production systems and environmental reservoirs of antibiotic resistance genes are all part of the problem **[11-16]**. High use of antimicrobials in all these sectors creates a combined antimicrobial selection pressure, which will lead to the emergence and spread of MDR, XDR and PDR organisms **[1,3]**. In this highly integrated system, disability and amputation can be considered downstream components of the failure of antimicrobial therapy rather than as stand-alone clinical complications **[3,10]**.

There is growing recognition of AMR as a global threat, but the notion of disability remains insufficiently represented in policy literature, surveillance systems, and AMR monitoring frameworks. Current antimicrobial stewardship strategies primarily focus on reducing mortality, infection rates, and economic burden, whereas functional outcomes, rehabilitation needs, long-term disability prevention, and quality-of-life measures receive considerably less attention **[16–19]**. Additionally, although substantial microbiological and clinical research has been conducted, the conceptual links between antimicrobial resistance, amputation, irreversible disability, and One Health systems remain inadequately explored **[5,16,18]**. Consequently, the long-term consequences of resistant infections—including disability, functional decline, rehabilitation burden, and limb loss—remain understudied and are not sufficiently incorporated into existing AMR frameworks **[5,16,17]**. This knowledge gap highlights the need for a broader perspective in which disability is recognized as a major downstream consequence of antimicrobial resistance and therapeutic failure.

It was therefore the aim of this review to examine the relationship between antimicrobial resistance, disability, amputation, and long-term functional decline within a One Health framework. It also advocated a paradigm shift in the perception of AMR from being primarily a microbiological or mortality-related problem to being a multidimensional phenomenon associated with irreversible disability, functional decline, and long-term societal burden in interconnected One Health systems.

Disability Caused by Antimicrobial Resistance.

AMR is a multifaceted phenomenon, with both clinical, microbiological and systemic mechanisms contributing to the phenomenon **[2-15]**. The development of resistant infection to irreversible functional impairment is not a one-step process but occurs through a sequence of events of therapeutic failure, chronic infection, tissue destruction and late intervention **[5-18]**.

In MDR, XDR and PDR infections, inability to rapidly clear the microbiological load (and

inflammation) allows bacteria to continue growing, inflammatory damage to continue and progressive structural damage **[19-21]**. Chronicity is often exacerbated by virulence factors of resistant pathogens such as the ability to form biofilms, evade host immune responses, produce toxins and increase tissue invasiveness **[5,6]**.

Chronic wounds and osteomyelitis are important applications of the importance of biofilms. Bacteria in the biofilm communities are significantly more resistant to antimicrobial agents as well as host immune defenses. This chronic microbial environment leads to chronic inflammation, delayed wound healing, vascular compromise and gradual, progressive tissue necrosis **[5,6]**.

Delays in the health care system are a strong predictor for the path to disability. Poor outcomes are due to delayed delivery of effective therapy, absence of rapid diagnostics, inappropriate empirical therapy, poor surgical care and limited access to advanced antimicrobial agents **[2]**.

Importantly, disability associated with AMR is not only the loss of a limb, but includes disability related to the infection and disability associated with the recovery process. Survivors frequently experience: **[4,5]**.

- Permanent mobility impairment
- Chronic pain syndromes
- Reduced functional independence
- Psychological trauma and depression
- Recurrent hospitalization
- Decreased productivity and job loss
- Social and economic instability

This wider view shows that the burden of disability due to AMR is not only a by-product of infection, but also constitutes a significant burden of AMR on a global scale.

Clinical Pathways that connect with Resistant Infection and Irreversible Functional Loss.

Diabetic Foot Infections

Diabetic foot infections are one of the most obvious clinical models that can be associated with AMR and disability **[8]**. Often these infections are polymicrobial and show an increasing association with resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), MDR *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and resistant Enterobacterales **[19,21]**.

When there is antimicrobial resistance, it adds a significant challenge to diabetic foot management, as it will slow down the control of the infection, with possible tissue necrosis, osteomyelitis, systemic dissemination and major amputation. All of these repeated debridement procedures, long-term antibiotic use, vascular loss, and healing problems, together, lead to an inevitable decline in function **[4,5]**.

Burn Wound Infections

Burn units are one of the most high-risk settings related to MDR and PDR infections, due to the high level of antibiotic exposure, the length of hospital stay, the high amounts of invasive procedures as well as the breakdown of the skin barrier **[7,13]**. Resistant Gram-negative pathogens often cause burn wound infections that evolve into chronic destructive infections, which are defined by persistent inflammation, formation of biofilms, and a delay in epithelialization and the presence of significant tissue loss. In late disease, extensive surgery is required, and in some cases the affected limb should be amputated to stop the general deterioration **[5-7]**.

Trauma-Associated Resistant Infections

The combination of trauma and wounds, particularly in situations where conflict is ongoing, leads to favorable conditions for the formation of resistant infections **[9]**. High rate of MDR Gram-negative infection is due to contaminated injuries, delay in medical care, poor infection control and lack of access to advanced antimicrobials **[2,3]**. Resistant infections are common in trauma patients, and these infections may recur and lead to amputation or loss of a limb especially in the setting of scarcity of reconstructive and rehabilitation facilities **[4,5]**.

Osteomyelitis and Chronic Biofilm Infection

Osteomyelitis is a serious infection that can develop when bacteria invade the bone **[6]**. Another pathway to disability is osteomyelitis as a result of resistant pathogens. Biofilm-mediated persistence within the bone tissue significantly limits antimicrobial penetration and eradication **[6]**. Long hospitalizations, multiple surgeries, loss of mobility, bone deformity and chronic pain are common outcomes of chronic osteomyelitis. Amputation might be the only therapeutic option in severe cases **[8]**.

Conceptual Model: AMR-to-Disability Cascade

This pathway to resistant infection and permanent disability can be thought of as a series of steps:

Infection → MDR/XDR/PDR → Therapeutic Failure → Persistent Infection and Biofilm Formation → Tissue Necrosis → Surgical Escalation → Amputation → Long-Term Disability (Figure 1) **[6,21]**.

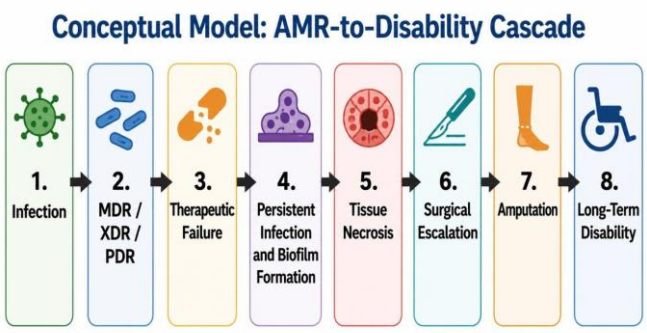


Figure 1. One Health–AMR–Disability Cascade **[6,21]**.

The emergence and spread of MDR, XDR and PDR pathogens is a result of antimicrobial selective pressure from antimicrobial use in human medicine, veterinary medicine, agriculture and environmental reservoirs **[15,16]**. These resistant organisms cause therapeutic failure, chronic biofilm-associated infection, tissue necrosis, surgical escalation and ultimately result in irreversible disability and limb loss as mentioned in Figure 1 **[5,6]**. This framework helps to demonstrate how disability is a downstream, predictable and expected outcome of uncontrolled antimicrobial resistance and repeated therapeutic failure, and not just an isolated clinical outcome (Table 1) **[15]**.

Table 1. Major Clinical Pathways Linking Antimicrobial Resistance to Disability.

Clinical Condition	Common Resistant Pathogens	Major Clinical Complications	Potential Disability Outcomes
Diabetic foot infections	MRSA, MDR *Acinetobacter baumannii*, resistant Enterobacterales	Osteomyelitis, tissue necrosis, chronic ulceration	Lower-limb amputation, impaired mobility
Burn wound infections	PDR *Pseudomonas aeruginosa*, MDR *A. baumannii*	Persistent wound infection, biofilm formation, sepsis	Functional impairment, limb loss
Trauma-associated infections	MDR Gram-negative bacteria	Repeated surgical debridement, chronic infection	Permanent disability, reduced functional independence
Chronic osteomyelitis	XDR Enterobacterales, resistant *Staphylococcus aureus*	Bone destruction, chronic inflammation	Skeletal deformity, chronic pain, mobility limitation
Healthcare-associated wound infections	MDR/XDR hospital pathogens	Delayed healing, recurrent infection	Long-term disability, prolonged rehabilitation

Source: **[15]**.

All of these pathways collectively illustrate that antimicrobial resistance is not just a cause of infection-related mortality, but also of a progressive functional decline, rehabilitation burden and irreversible disability **[4,5]**.

Pandrug Resistant Infections: The Point of Therapeutic Collapse

PDR infections are the ultimate stage of antimicrobial therapeutic failure **[3,21]**. Clinicians have no effective pharmacological treatment and management approaches at this level focus on surgery to contain the disease **[18]**. In high-risk hospital environments, like intensive care units, surgical wards and burn units, PDR pathogens are particularly prevalent **[3,7]**. These settings impose significant antimicrobial selection pressures because of repeated use of broad-spectrum antibiotics, immunocompromised patients, prolonged hospital stays, and the use of invasive procedures **[13,20]**. *Acinetobacter baumannii* has become one of the most clinically devastating PDR pathogens due to its unique environmental persistence, biofilm-forming capacity and ability to acquire resistance determinants **[3]**.

In the absence of adequate antimicrobial treatment, the course of the infection is harder to manage **[18]**. Continued bacterial growth results in progressive necrosis, systemic inflammation, risk of sepsis, and repeated surgical failure **[5,6]**. Amputation often is the last surgical procedure that can prevent the spread of infection and death **[5]**. Collectively, PDR infections serve as a clinical threshold on the AMR-disability continuum: Treatable Infection - Limited Treatment Options - Therapeutic Exhaustion - Surgical Damage Control - Amputation - Irreversible Disability **[3,18]**.

This model highlights that high virulence of the micro-organisms alone is not enough to cause severe disability in AMR, but there is an additional component of cumulative therapeutic failure **[6,21,22]**.

Therapeutic Failure to Amputation: Clinical Decision-Making in the Age of PDR

The transition from therapeutic failure to amputation is one of the most severe implications of resistant infection **[3,5]**. Severe infections are traditionally treated with antimicrobial treatment plus conservative surgery **[8]**.The situation in PDR infection, however, is somewhat different because there is no effective antimicrobial agent; treatment goals, therefore, must be altered **[3,18]**. The focus of care has moved from eradication of the microbes to:

- Infection containment
- Prevention of sepsis
- Preservation of survival
- Damage-control surgery

The road to surgery may take several steps:

- Initial debridement
- Repeated debridement
- Local tissue resection
- Major amputation

In resistant infections this progression is accelerated, due to the inability to reliably control microbiological growth **[6,23]**. The risk of amputation in AMR-associated infection is significantly greater by several factors: **[6-8]**.

- Failure to commence effective treatment promptly
- Infection with biofilm-forming pathogens
- Osteomyelitis
- Diabetes and vascular insufficiency
- Prolonged hospitalization
- Prior broad-spectrum antibiotic exposure has been reported to increase the risk of CPE
- Inadequate infection control

While amputation can save a life, it also has a life-altering impact on disability. Common outcomes of survivors include decreased mobility, chronic pain, psychological distress, dependence, and significant socioeconomic consequences **[4,5]**. In the severe AMR setting, amputation should thus not only be viewed as a surgical complication, but as the end point of cumulative therapeutic and systemic failures **[15,16]**. AMR Associated Disability is included as a Global Burden of Disease.

Disability-Adjusted Life Years (DALYs)

Traditionally the global burden of AMR has been estimated by mortality data **[1]**. However, this approach substantially underestimates the long-term consequences experienced by survivors **[5]**. A more complete measure is disability-adjusted life years (DALYs) which combines both years of life lost and years lived with disability**[1]**. Resistant infections not only cause death, but also cause long-term functional disability, chronic morbidity and decreased quality of life **[4,5]**.

Disproportionate Burden in LMICs

The highest burden of AMR-associated disability in LMICs is due to: **[2,24]**.

- Limited microbiological diagnostics
- Delayed treatment
- Weak antimicrobial stewardship
- Poor infection prevention and control practices
- Inadequate rehabilitation systems
- Limited access to advanced therapeutics

Patients often have advanced infections by the time they present, and limb salvage is not possible **[5,6]**.

Conflict and Trauma Settings

AMR-related disability burden is especially high in conflict-affected areas where trauma-associated infections often include resistant Gram-negative pathogens **[3,24]**. Prevalence of repeated surgeries, chronic infection, delayed reconstruction, and amputation is disproportionately affecting young and economically productive populations **[4,5]**.

Economic and Rehabilitation Burden

The impact of AMR-related disability is not limited to acute medical care, and involves: **[4,5]**.

- Prosthetic costs
- Long-term rehabilitation
- Chronic wound management
- Loss of productivity
- Family caregiving burden
- Mental health consequences
- Long-term healthcare expenditure

Rehabilitation services are also not available in many resource-limited settings, exacerbating long-term disability outcomes **[15]**.

One Health and System-Level Perspectives

Disability due to AMR cannot be viewed **solely** within the hospital setting. Instead, it represents a consequence of multiple shortcomings in human health systems, agriculture, veterinary medicine, environmental management and public health policy **[15,16]**. The overuse and misuse of antimicrobials in humans, livestock and agriculture contribute to increasing antimicrobial pressure within interconnected ecological reservoirs **[25]**. Transfer of resistance genes to environmental microbial isolates, together with environmental contamination by resistant organisms, further facilitates pathogen dissemination **[25,26]**. Within this One Health context, disability and amputation are downstream consequences of systemic antimicrobial imbalance as mention in figure 2 **[15]**. Hospitals act as ecological amplifiers of resistance through: **[3,16]**.

- Selection pressure caused by intensive antibiotic use
- Cross-transmission between patients
- Invasive procedures
- Prolonged hospitalization
- Weak infection prevention and control systems

Current AMR policies still place strong emphasis on reducing mortality and antimicrobial stewardship, while insufficiently addressing: **[4,5]**.

- Functional preservation
- Limb-salvage strategies
- Rehabilitation systems
- Long-term disability prevention

- Quality-of-life outcomes

AMR also overlaps with several Sustainable Development Goals (SDGs), particularly: **[4,16]**.

- SDG 3: Good Health and Well-being
- SDG 6: Clean Water and Sanitation
- SDG 10: Reduced Inequalities
- SDG 12: Responsible Consumption and Production

This highlights the importance of incorporating disability into AMR frameworks and future global health policies (Figure 2).

Source: Adapted from references [3,4,5,15,16,25,26].

Figure 2. One Health Pathways Linking Antimicrobial Resistance to Disability.

Artificial Intelligence and Future Directions

Due to the increasing complexity of AMR, there is an urgent need to shift from reactive therapeutic approaches toward predictive and preventive strategies **[27,29]**. Artificial Intelligence (AI) and machine-learning–based technologies provide valuable opportunities for the early identification of high-risk patients before the development of irreversible functional damage **[27-30]**.

AI-driven systems can integrate: **[26,28]**.

- Microbiological resistance profiles
- Clinical severity indicators
- Comorbidity data
- Treatment history
- Wound characteristics
- Systemic inflammatory biomarkers

These multidimensional predictive models may be utilized to estimate: **[27,29]**.

- Amputation risk
- Therapeutic failure
- Sepsis progression
- Long-term disability outcomes

Explainable AI approaches, such as SHAP analysis, may further improve transparency by identifying the clinical variables most strongly associated with severe outcomes, thereby enhancing clinical interpretability and trust **[27]**. Future AMR frameworks should therefore incorporate: **[27,28]**.

- Rapid diagnostic technologies
- Predictive analytics
- Early limb-preservation strategies
- Integrated rehabilitation pathways
- One Health surveillance systems

Ultimately, the future of AMR management should focus not only on survival, but also on preserving function, mobility, dignity and quality of life **[27,28]**.

Limitations

There are several limitations to this review. Firstly, it is a narrative review rather than a quantitative meta-analysis. Second, there is still relatively limited evidence directly linking antimicrobial resistance (AMR) to disability outcomes, compared to the extensive literature addressing mortality, infection incidence, and economic burden. Third, there is substantial heterogeneity among studies regarding patient populations, resistant pathogens, clinical settings, and disability assessment methods, making direct comparisons challenging. Fourth, much of the available evidence originates from high-income settings, whereas data from low- and middle-income countries, where the burden of AMR-associated disability may be greater, remain underrepresented. Finally, disability is not routinely incorporated as an outcome measure in AMR surveillance systems, limiting the availability of robust long-term data on functional decline and rehabilitation outcomes.

Conclusion

Antimicrobial resistance (AMR), particularly pandrug-resistant infections (PDRIs), represents one of the most significant yet underrecognized causes of permanent disability worldwide. The transition from resistant infection to functional decline is a multidimensional process involving therapeutic failure, chronic biofilm-associated infection, tissue destruction, repeated surgical interventions and, ultimately, limb loss. This review emphasizes the need to reconsider AMR as a multidimensional global threat extending far

beyond mortality alone. Within the One Health framework, AMR-associated disability should be recognized as a downstream consequence of failures in antimicrobial stewardship, infection prevention, environmental control and healthcare system resilience. Future AMR strategies should therefore evolve beyond merely improving survival and instead prioritize:

- Functional preservation
- Disability prevention
- Limb-salvage approaches
- Rehabilitation integration
- Predictive and preventive medicine

Finally, the success of AMR management should not be evaluated solely by survival rates, but also by the preservation of mobility, independence, dignity and overall quality of life.

CRediT

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No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate[@].

Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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