

**Received:** 11 January, 2022  
**Accepted:** 22 January, 2022  
**Published:** 24 January, 2022

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**Keywords:** Antimicrobials; Resistome; One health; Hygiene; Guidelines

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## Review Article

# Antimicrobial resistance: An unrelenting enemy

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## Abstract

Antimicrobial Resistance (AMR) poses an increasing threat to global public health and is projected to be one of the greatest challenges of healthcare in the future as the costs of healthcare, morbidity, and mortality will increase. AMR is likely to complicate many routine procedures such as elective surgery in the future. Together, healthcare professionals need to be aware of the significance antimicrobial resistance poses and make changes needed to mitigate the danger as a result of one of the most important developments in medicine.

## Key points

1. Resistance to antimicrobials (AMR) is increasing, posing a growing threat to public health, compromising the effectiveness of life-saving antimicrobials.
2. Increased and inappropriate exposure to antimicrobials increases the populations of resistant organisms.
3. Hygiene and adequate sanitation are important to limit environmental contamination with antimicrobials, resistant organisms, and mobile genetic elements that are identifiable in sewage.
4. Travel, including tourism, medical tourism, pilgrimages, refugee movements and other forms of human migration all promote AMR.
5. Medical practitioners should optimize hygiene in all patient interactions, diligently complying with local and national guidelines for antibiotic stewardship when prescribing antimicrobials.
6. Antimicrobial treatments are not always necessary or indicated in patients' care. This evidence is illustrated in the lack of indication of antimicrobials to treat acute bronchitis, Traveler's Diarrhea, upper respiratory tract infections, or otitis media in children.

## The extent of antimicrobial resistance

In the 2015 campaign from the World Health Organization (WHO) [1] and in the National Institute for Health and Care Excellence Sewage analysis in the UK [2], growing problems with the Antimicrobial Resistance (AMR) of many common pathogens were recognized in a large number of cities last year. These cities identified the largest frequencies of antimicrobial resistance genes, specifically in the countries

of Brazil, Vietnam, and India. This problem reflected the efficiency of sanitation. Other studies have identified shared plasmids and mobile genetic elements, including virulence factors, in hospital wastewater, also contributing to the rise in antimicrobial resistance [3,4].

Antimicrobial drugs currently have widespread use in human [5-8], veterinary and agricultural settings. Ease of access in over-the-counter prescriptions in some communities



allows for contamination of the environment with these chemicals, inherently contributing to the rise of populations of resistant organisms. Crucially, resistance generated in the community manifests in hospitals and there, sepsis and pneumonia with resistant organisms are the most frequent manifestation of the problem. However, infections following elective surgery are also found to be unresponsive to 'standard' or first-line antimicrobials, requiring expert opinions, and an increase in the number of antimicrobial strategies for optimal treatment [10-12].

The separation of community sources and complex hospital outcomes means management must span both parts in order to limit healthcare impacts. One individual doctor is unlikely to be able to see both sides of this problem.

Resistance is well documented in viral infections too [8,9]. Some infections with herpes viruses do not respond to acyclovir; human immunodeficiency virus may have resistance to protease or reverse transcriptase inhibitors, and pathogenic fungi including *Candida* and *Aspergillus* species have been found to have resistance to all of the major classes of antifungal agents.

### Microbial mechanisms of AMR

Resistance to antimicrobials is an ancient and inherent strategy for micro-organisms. Pathogens preserved from the pre-antibiotic era possess the genetic systems to develop resistance to many antimicrobials. This is not surprising given that many families of antimicrobials were derived from fungi and bacterial sources. The ability to develop resistance is particularly evident when bacteria form biofilms and when host responses to infections are compromised [13-15].

The use of antibiotic therapy to treat a specific infection, in the face of the complex ecology of massive human microbiomes in the gut and on the skin will predictably enhance resistance. This phenomenon has not been well researched. What is evident is that different species of microorganisms can exchange genes for resistance. Over 20,000 genes that confer microbial resistance have been identified. Gene exchange effectively increases the 'resistome' in a patient: the summation of resistance to an antimicrobial agent. Mechanisms of resistance to antimicrobials include limiting uptake of the drug; modifying a drug target; inactivating the drug; and developing active drug efflux. Horizontal gene transfer, through bacterial transduction, transformation, and conjugation attribute to the formation of antimicrobial-resistant prodigy. Conjugation is thought to be the greatest contributor to the spread of antimicrobial resistance [16-18].

### The challenge of unregulated antibiotics

Antimicrobials of several types have been employed in agriculture to prevent and control the disease [13-18]. At sub-therapeutic levels, antimicrobials may function as microbial growth promoters. In some situations, the efficacy of antimicrobials is unclear, for instance in the application of streptomycin and tetracyclines to treat oranges. In developing countries, these problems may be compounded. It has been

estimated that the majority of antibiotics imported into Kenya are for agricultural applications, and the majority of their use by small farmers is inappropriate.

### Spreading of AMR among microorganisms

Methicillin-Resistant *Staphylococcus Aureus* (MRSA) developed shortly after the widespread use of early penicillins. However, the development of increasing resistance of MRSA strains to other antibiotics vancomycin, linezolid, teicoplanin, and daptomycin have become challenging [14,15].

*Clostridiodes difficile*, formerly known as *Clostridium difficile*, is resistant to multiple antimicrobials and is found in hospitals and long-term care facilities. Attempts to decrease resistance have been initiated with recurrent testing of patients and proper isolation and cleaning protocols. *Clostridiodes difficile* resistance to aminoglycosides, lincomycin, tetracyclines, erythromycin, clindamycin, penicillins, cephalosporins, fluoroquinolones, rifamycins, fidaxomicin, tetracyclines, chloramphenicol, and metronidazole now leave vancomycin as the only potential treatment option.

*Mycobacterium Tuberculosis* (TB) is intrinsically resistant to many antibiotics as a result of the thick, waxy, hydrophobic envelope coating the cell, drug-degrading, and drug modifying enzymes. The mainstay treatment for TB, a combination of rifampicin, isoniazid, ethambutol, and pyrazinamide, is facing challenges with MDR as a result of acquired resistance to isoniazid and rifampicin. Additional TB treatment regimens using fluoroquinolones such as amikacin, kanamycin, and capreomycin have allowed for the development of XDR TB.

*Neisseria gonococcus*: Japan identified a gonococcus displaying high-level resistance to the antimicrobial ceftriaxone in 2011. Additionally, the United Kingdom and Australia, have both identified ceftriaxone and azithromycin resistant gonococcus cases in 2018.

Gram-negative organisms have increased resistance to the  $\beta$ -lactam antibiotics including penicillins and cephalosporins, by synthesizing extended-spectrum  $\beta$ -lactamases (ESBL).

### Antibiotic prescriptions that may not be needed

The CDC estimates approximately 30% of all antibiotics prescribed in outpatient clinics are unnecessary. The increased prescribing of antibiotics in diseases without need has resulted in increases in the prevalence of resistant organisms both within and outside of hospitals. Antimicrobial resistance is rising in pediatric populations in particular. This is thought to be the consequence of unnecessary prescriptions of antibiotics for fevers, viral upper respiratory tract infections, and for adolescents with acne. For example, clindamycin and methicillin resistance in *S. aureus* isolate from children increased from 9.3% to 16.7% between 2005-2014. A publication comparing the treatment of febrile children in emergency departments across Europe in 2019 identified a third of antimicrobial scripts as being inappropriate. Antimicrobial dosing in pediatric patients in the UK is guided by the pediatric British National Formulary (<https://bnfc.nice.org.uk>) which is kept up to date.



Increasing in penicillin resistance documented in *Streptococcus pneumoniae* dramatically decreased with the use of the pneumococcal vaccine.

Enterococcus resistance occurred as a result of the hardy nature of the bacterium which is able to withstand conventional cleaning and is able to survive several days on surfaces increasing the chance of transmissibility. Vancomycin-resistant enterococci are associated in children with prolonged antibiotic or healthcare exposure. Extended-spectrum  $\beta$ -lactamase-producing Enterobacteriaceae. The highest risk is associated with travel to the Indian subcontinent. Multi-drug-resistant enteric infections in travelers from *Salmonella spp.*, *Campylobacter spp.*, and *Shigella spp.* are increasing.

### Tackling AMR: Clinical strategies that Work and alternative treatments with antibiotics that can help treat AMR

Approaches to combat AMR require international, collaborative, and organized approaches that include the following elements:

1. Develop public awareness of the challenges of AMR. Materials have been made available from the WHO (<https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance>) and the Global Alliance for Infections in Surgery (<https://infectionsinsurgery.org>). Travelers, in particular, need to be made aware of the risks of AMR; this should include details relating to travel-related diarrhea and safe sex practices.
2. Prevent the spread of infections with hygiene and sanitation. Managing sanitation alone may restrict the diversity of resistance genes and prolong the usefulness of antimicrobials. Isolation/containment and vaccination wherever possible of infectious disease will also limit AMR spread.
3. Deliver rapid diagnostic screening and surveillance of microorganisms to characterize them. together with their patterns of antimicrobial resistance wherever they are isolated. Microbiological expertise in the application of combination antibiotic treatments will augment efficient treatments.
4. Promote antibiotic stewardship among professionals to minimize prescription of unnecessary antimicrobials. National policies on health practice play a role as the first regulatory step. Regulate antimicrobial provision to limit environmental contamination, for instance across counter sales or use in veterinary and agricultural practices.
5. Financial and technical provision to develop and deliver new effective antimicrobial compounds and improved rapid diagnostic analyses.
6. Stressing the importance of properly fixed dosing, utilizing new biotechnology techniques, and continuing to fund research into new modalities can help create a more specified approach toward tackling bacterial infections.

### Antimicrobial stewardship by practitioners

The UK national strategy to tackle antibiotic resistance involves providing readily available guidelines, followed by repeated training by healthcare organizations to enhance professional behaviors (see the second reference). Training promotes hygiene, tackles the overuse of prescribed antibiotics, and improves adherence to evidence-based national guidelines. Continued training is required.

A number of antibiotic prescriptions are used for long-term prophylaxis; they may be life-long. For instance cotrimoxazole in HIV-positive patients or penicillin for those with sickle cell anemia. Studies suggest that within families and communities this low level, regular dosing does not increase microbial resistance within their families.

New antimicrobial strategies may involve the use of combination therapies, novel peptides, nano delivery systems.

### Pathogens and other forms of resistance: The greater resistome

Examination of combs and shaving machines in Ugandan salons identified *Staphylococci* that are resistant to disinfection with sodium hypochlorite (or bleach) preparations. This represents the challenge of the resistome. Microorganisms, parasites, or vectors all multiply faster than humans. They will therefore develop resistance to our various treatments, particularly chemical ones. This will include resistance to disinfectants and insecticides. We shall require all our wisdom to ensure effective therapies of infectious diseases in the future.

### Quiz

Below is a short quiz that is meant to provide a clinical vignette to help reinforce the information:

1. **A UK study suggested that there was a national increase in *C. difficile* infections, driven by the changes in the use and prescribing of fluoroquinolones. Which strategy is most likely to reduce this antibiotic resistance?**

1. Using narrow-spectrum antibiotics empirically as initial treatment
2. Switching from IV to oral antibiotics after 3 days of pyelonephritis with improvement.
3. Prescribing antibiotics only for serious infections
4. More liberal use of more potent antibiotics to decrease the load of resistant bacterial strains

#### Answer:

1. **Incorrect:** Although using narrow-spectrum antibiotics has been shown to decrease resistance, such empiric treatment could jeopardize the patient.
2. **Correct:** Antimicrobials converted from intravenous to oral administration as soon as is feasible and clinically indicated have had proven benefits to combating



resistance. This intervention has been shown to decrease costs, facilitate discharge, and reduce complications associated with intravenous access without compromising clinical outcomes

3. **Incorrect:** Using antibiotics sparingly will decrease resistance but not using them when clinically indicated, even in a mild infection, could cause deleterious effects on patients
4. **Incorrect:** Liberal use of more potent antibiotics will result in a broader spectrum of bacterial resistance.
2. **A 66-year-old female presents to an urgent care clinic after sustaining a fall; she lives in a nursing care home. She has a past medical history of hypertension, diabetes, dyslipidemia, and she has a chronic indwelling bladder catheter. As urine dipstick is positive for nitrates. What is the optimal next step in her management**

1. Initiate oral nitrofurantoin 500 mg three times a day, for 7 days
2. Initiate 80 mg/400mg Trimethoprim-sulfamethoxazole by mouth for 3 days
3. Supportive care but no further management necessary for her genitourinary tract
4. Collect urine for bacteriological culture

**Answer:**

1. **Incorrect:** Nitrofurantoin could cause complications such as diarrhea, interact with sugar measurements in diabetes or contribute to antimicrobial resistance.
  2. **Incorrect:** Antibiotic in this case as it will only contribute to increasing antibiotic resistance.
  3. **Correct:** Asymptomatic bacteriuria in those with indwelling catheters is common and should not be treated.
  4. **Incorrect:** A urine culture will not assist in the treatment in the case of an asymptomatic catheterized patient, as the result cannot be interpreted.
  3. **A 14-year-old female patient arrives at the emergency department with complaints of high fever, malaise, painful urination, and some flank pain. Microscopy and culture show white blood cells and E.coli in her urine. A diagnosis of pyelonephritis is made, and she is prescribed 500 mg Amoxicillin every 8 hours. She deteriorated rapidly and was admitted to the ICU. Which of the following statements is correct?**
1. Her deterioration could not have been prevented
  2. Increased antibiotic dose to 750 mg every 12 hours would have been effective
  3. Effective treatment required a prescription of fosfomycin,

a structural analog of phosphoenolpyruvate, to inhibit the early stages of bacterial cell wall synthesis.

4. A prescription of a broad-spectrum antibiotic with good tissue penetration and greater resistance to beta-lactamases would be effective.

**Answer:**

1. **Incorrect:** Amoxicillin has very poor efficacy against E.coli infections. A better choice of antibiotics should prevent deterioration and reduced the risk of this developing an antibiotic resistance E.coli
  2. **Incorrect:** Increasing the dose of an ineffective antibiotic is unlikely to prevent progression in bacterial pathology.
  3. **Incorrect:** Fosfomycin is used for treating uncomplicated UTIs and not pyelonephritis.
  4. **Correct:** The 3rd generation cephalosporin, ceftriaxone, is a parenteral, broad-spectrum beta-lactam and the preferred antibiotic for initial empiric therapy of pyelonephritis caused by most pathogens (e.g. E. coli, Proteus, Klebsiella).
  4. **A 13-year-old boy presents to the pediatrician after developing otitis media. Previous medical history showed he had a minor skin rash two years previously after being treated with penicillin for a UTI. The patient was given a dose of gentamicin and amoxicillin by his mother who had these medications in a cabinet. What would be a more logical treatment for this patient's problem?**
1. Prescribe a dose of 250 mg cefaclor PO q8hr
  2. Prescribe a dose of 250 mg ampicillin PO q8hr
  3. Continue with the patient's current regimen
  4. Obtain blood cultures before prescribing medication

**Answer:**

1. **Correct:** Cephalosporins are structurally different enough than penicillins to have only ~1-2% cross-reactivity with respect to allergies. This risk of cross-reactivity is acceptable when the patient has a history of a minor allergic-like reaction, but it is generally considered unacceptable if the patient has a history of an anaphylactic reaction to another beta-lactam antibiotic
2. **Incorrect:** Ampicillin is structurally very similar to amoxicillin, with the removal of a hydroxyl group. There is a safer therapeutic option with a <1% predicted incidence of cross-reactivity with amoxicillin.
3. **Incorrect:** This current regimen is potentially dangerous with respect to allergic reactions. Further, one of the main causes of increased antibiotic resistance is the unnecessary use of unrelated antibiotics.



4. **Incorrect:** Obtaining blood cultures is unlikely to improve treatment efficacy.

5. **You have recently been assigned to serve in hospitals out in the country, where a new initiative has recently been founded with the goal to discuss methods by which they can curb the antibiotic resistance that has been recently seen in cases among this community. If implemented which of the following strategies would have a meaningful impact on the outcome of this problem**

1. Restricting the use of antibiotics in meningitis patients until the obtainment of a positive CSF culture

2. Encourage the use of broad-spectrum antibiotics to stifle bacterial load

3. Encourage an across the board effort by inviting the farmers and veterinarian to the discussion

4. Improve diagnostic turnaround

**Answer:**

1. **Incorrect:** Although decreased antibiotics use, does lead to decrease resistance, in cases of serious suspected infections such as meningitis it would be unwise to delay treatment as it places the patient at a much higher risk of severe complications

2. **Incorrect:** Overuse of antibiotics can cause catastrophic results in the long run and worsen antibiotic resistance.

3. **Correct:** Responsible prescribing and use of antibiotics in pets and horses are especially important because of the close relationship they have with their owner. In a recent meta-analysis, there has been demonstrated an association between usage of antibiotics in livestock and antibiotic resistance in humans.

4. **Incorrect:** While improving the turnaround of diagnostic studies can assist, it will not address the problem facing the community mentioned in this question.

6. **A 67-year-old female presents to the hospital with shortness of breath and a cough. She describes the cough as a productive cough with green phlegm that has been progressively developing for the past 4 days and has not been allowing her to sleep properly. X-ray was completed and she is diagnosed with community-acquired pneumonia and is started on oral antibiotics for 5 days which is stopped after 3 days since it has fully resolved. She has a past medical history of chronic venous stasis, obesity, hypertension, dyslipidemia and was also treated 4 months ago for a urinary tract infection with nitrofurantoin. She is seen at the clinic 2 weeks later and mentions that she is feeling much better and has slept normally since treatment. What one of these would be the biggest modifiable risk factor for the development of antibiotic resistance in this patient?**

1. Use of antibiotics for urinary tract infection

2. Age > 65

3. Improper medication adherence

4. Immunosuppression

**Answer:**

1. **Incorrect:** The use of antibiotics within the past 90 days is associated with antibiotic-resistant organisms but because of the patient's use 4 months ago, this is unlikely to be a large contributing factor.

2. **Incorrect:** Age is a non-modifiable risk factor for antibiotic resistance.

3. **Correct:** Poor adherence to antibiotics along with premature termination of antibiotics have been shown to drastically increase antibiotic resistance in the general population.

4. **Incorrect:** Although immunosuppression is a risk factor for antibiotic-resistant infection this patient's past medical history does not show signs or symptoms of immunosuppression.

7. **An 11-year-old boy is brought to the emergency department by his mother: he is febrile, tachycardic, tachypneic, and hypotensive, his blood cultures come back positive for a Methicillin-resistant Staphylococcus aureus (MRSA). The microbiologist recommends three different types of antibiotics that inhibit bacterial protein synthesis. Which combination of drugs should be used in this patient?**

1. Daptomycin, Polymyxins, Sulfonamides

2. Metronidazole, Mupirocin, Isoniazid

3. Clindamycin, Macrolides, Streptogramins

4. Aminoglycosides, Tetracyclines & Penicillin

**Answer:**

1. **Incorrect:** These drugs have different mechanisms of action, including the bacterial cell membrane (daptomycin & polymyxins) and folic acid synthesis (sulfonamides).

2. **Incorrect:** These drugs have different mechanisms of action including causing DNA strand breaks (metronidazole), tRNA synthetase (mupirocin), and biosynthesis of mycolic acids (isoniazid).

3. **Correct:** All three of these drugs target bacterial protein synthesis.

4. **Incorrect:** Aminoglycosides and tetracyclines inhibit the 30S ribosomal subunit at different locations while penicillin affects the cell wall.



8. A 7-year-old girl is brought into the clinic complaining of ear tugging; her outer ear is erythematous and swollen. Blood cultures are positive for *Pseudomonas* with extended-spectrum beta-lactamase activity (ESBL positive). Which type of antibiotic is most effective in treating most infections caused by this type of bacteria?

What is the most likely cause of these findings?

1. Monobactams
2. Carbapenems
3. Piperacillin and tazobactam
4. Narrow spectrum Penicillin

**Answer:**

1. **Incorrect:** ESBLs will inactivate monobactams
2. **Correct:** Drugs from this class such as imipenem, meropenem, doripenem, and ertapenem currently produce the best outcomes in terms of bacteriologic clearance. Carbapenems are one of the last lines against bacteria resistant to multiple antibiotics
3. **Incorrect:** A combination of extended penicillin plus a beta-lactamases inhibitor (e.g. piperacillin + tazobactam) has been used to treat ESBL infections, but the outcomes are not as favorable as when using another drug option listed
4. **Incorrect:** ESBLs will inactivate all narrow-spectrum penicillin.
9. **The 4-year-old child is brought by his mother to the hospital, he has been irritable and drowsy with poor appetite and trouble sleeping. He had developed chills and became febrile with tachypnea. His fever has been gradually rising over the past few days, spiking suddenly to 40.6°C. His mother tells you that they have recently returned from a trip to see their extended family back in India. The family was not compliant with the medication prophylaxis that had been provided to them. Based on your knowledge of the most likely diagnosis, how would you handle the treatment of this child**

1. A dose of 10 mg base/kg of chloroquine
2. A 2.4 mg/kg/dose IV Artesunate
3. A dose of 200 mg IV of Doxycycline
4. A dose of 8 mg/kg/ day PO Q6 of Halofantrine.

**Answer:**

1. **Incorrect:** This patient has been most likely exposed to an area of chloroquine-resistant malaria.
2. **Correct:** This patient comes from an area known to have chloroquine-resistant Malaria species, therefore a dose

of Artemisinin would be recommended, further this drug and its derivatives are safe and well-tolerated by young children, further per the WHO, due to the clinical condition of children with malaria can deteriorate rapidly, there should be a low threshold for the use of parenteral treatment. Recent data support the use of intravenous artesunate in preference to artemether or quinine for the treatment of severe malaria in children.

3. **Incorrect:** A dose of Doxycycline can be used as an additional therapy for chloroquine-resistant Malaria alongside a dose of quinine/quinidine, but it is not indicated as a monotherapy.
4. **Incorrect:** While this regimen may be used to treat chloroquine-resistant malaria, it is not recognized as a first-line treatment in children.

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