Review Article

A Systematic Review of Toxicity of Antibiotics Used in the Treatment of STIs with Special Emphasis on Web-based Toxicity Analyzing Software

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ABSTRACT

Aim/Background: For many years, toxicity tests have been conducted on animals. Long-term use of animal models for toxicity testing has its drawbacks, including time and effort, ethical considerations, and cost. As a result, various computational methods for estimating chemical toxicity and pharmacokinetic properties are thought to be necessary. This study aims to evaluate the toxicity of some commonly used antibiotics in the treatment of sexually transmitted infections, with a special emphasis on web-based toxicity analysis software and a systematic review. **Materials and Methods:** An extensive literature study was done to understand the toxicity of antibiotics. After that, *in silico* toxicity analysis was performed by STopTox, Lazar, SwissADME, and ProTox II software. **Results and Conclusion:** The results show that these softwares are helpful in the prediction or evaluation of the toxicity of antibiotic compounds. Hence, in this paper, the toxicity of antibiotics is reviewed with emphasis on *in silico* perspectives, particularly those used to treat bacterial sexually transmitted infections.

Keywords: Antibiotic toxicity, *In silico* toxicity, ProToxII, Sexually Transmitted Infection (STI), StopTox.

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INTRODUCTION

Sexually Transmitted Infections (STIs) are demarcated as "Infections that are spread primarily through person-to-person via sexual contact".[1] STIs are one of the world's most frequent infectious diseases. The Centers for Disease Control and Prevention (CDC) reported that "people aged 15 to 24 account for one-half of the 20 million new STIs identified each year in the United States." STIs continue to pose significant public health and socio-economic burden around the world, especially in the developing world.[2] Antimicrobials are easily accessible and may not be fully effective in many parts of the world, which leads to misuse. This may suppress an infection but not completely get rid of the infectious agent, allowing a population of resistant strains to develop. The high prevalence of antibiotic resistance, as well as the advent of new drug resistance, make STI treatment problematic. To improve our understanding of antimicrobial toxicity molecular pathways, we must closely monitor the antibiotic susceptibility of sexually transmitted pathogens. In addition to the current toxicity studies, *in silico* toxicology evaluations of antibiotics can be investigated to forecast toxicity, prioritize compounds, and decrease late-stage failures in drug creation. Various computational models are applied at several levels of biological complexity, including cells, micro-organisms, tissues, laboratory animals, and even humans and molecular targets.[3] Various *in silico* software programmes are available online, e.g., Swiss ADME (Absorption, Distribution, Metabolism, and

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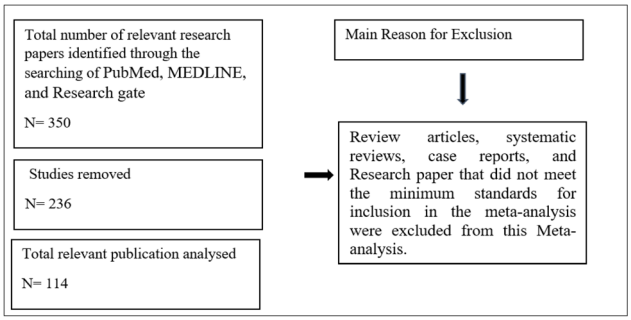
Elimination), ProToxII, Lazar, StopTox, etc., which are helpful in the prediction or evaluation of the toxicity of antibiotic compounds.[4] This work is meant to analyze the toxicity of ten antibiotics i.e., Amoxicillin, penicillin, ciprofloxacin, levofloxacin, moxifloxacin, erythromycin, clarithromycin, azithromycin, doxycycline, and minocycline via using four different software programmes i.e. StopTox, Lazar, Swiss ADME, and ProToxII. The current approaches may greatly contribute to understanding how antibiotics cause toxicity. Web-based analysis is time and money-saving. The review article contributes to a better understanding of the toxic effects of commonly used antibiotics in the treatment of sexually transmitted infections.

MATERIALS AND METHODS

Search Strategy

An extensive literature study was done to understand the toxicity of antibiotics used in the treatment of STIs. For this, a grey and published literature analysis using PubMed, MEDLINE, and Research gate searched to identify the toxicity of routinely used antibiotics in the treatment of STIs by using the keywords like "gonorrhoea" combined (using AND) with "gentamicin" OR "cefixime." A secondary search was performed via a review of references found from the initial search.

Data Extraction



Prediction of Toxicity Parameters

The PC Ideapad slim 3 Intel Core i3 and Windows 11 Pro 64-bit operating system were used in the present study. The software programmes used were ChemSketch (https://www.acdlabs.com/resources/freeware/chemsketch/index.php), STopTox (https://stoptox.mml.unc.edu/), Lazar (https://lazar.in-silico.ch/predict), SwissADME (http://www.swissadme.ch/index.php), and ProTox II (https://tox-new.charite.de/protox_II/).

RESULTS

In STopTox prediction, among the analyzed antibiotics, except minocycline, all depict Eye Irritation and Corrosion (EIC), whereas penicillin and erythromycin showed Skin Sensitization (SS) and clarithromycin and levofloxacin showed Acute Oral Toxicity (AOT) (Table 1). In the lazar toxicity prediction for the human Blood-Brain Barrier Penetration, penicillin, clarithromycin, minocycline, and doxycycline show the Blood-Brain Barrier Penetration (Table 1). Swiss ADME analysis predicts that three antibiotics (Penicillin, Moxifloxacin and Ciprofloxacin) show high GI absorption, whereas the remaining showed low GI absorption. Penicillin, Amoxicillin, and Levofloxacin are not P-Glycoprotein substrates; thus, these antibiotics do not adequately absorb, distribute, and eliminate. Moxifloxacin, Levofloxacin, and Clarithromycin are CYP450 inhibitors, and all antibiotics show negative Kp value means less skin permeation (Table 2). In Protox II Analysis, Immunotoxicity was depicted by all the analyzed antibiotics, whereas penicillin, doxycycline, minocycline, levofloxacin, moxifloxacin, and ciprofloxacin showed hepatoxicity. All analyzed antibiotics bind with aromatase, Estrogen Receptor Alpha (ER) and Estrogen Receptor Ligand Binding Domain (ER-LBD) (Table 3).

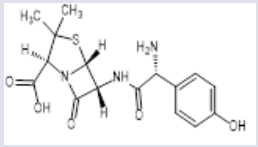
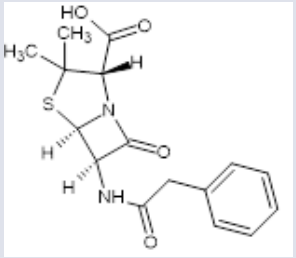
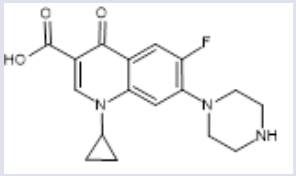
The results are helpful in the prediction or evaluation of the toxicity of antibiotic compounds.

DISCUSSION

Antimicrobial therapy is a critical component of bacterial STIs public health control. Various antibiotics are prescribed for different bacterial STIs. Based on the modes of action, we listed the ten most commonly used antibiotics. These ten antibiotics belong to four separate classes: beta-lactam (which inhibits the formation of cell walls), fluoroquinolones (which inhibit DNA gyrase), macrolides (which inhibits protein synthesis at the 50s subunit), and tetracycline (protein synthesis inhibitor at 30s subunit). Out of ten antibiotics used in this study, amoxicillin and penicillin are β-lactams, ciprofloxacin and levofloxacin are fluoroquinolones, erythromycin, clarithromycin, and azithromycin are macrolides, and doxycycline and minocycline are tetracyclines. Since antibiotics have a variety of modes of action, they can be effective against different bacteria. Using these in a diversified manner helped us choose the best effective medicine for STIs.

In 2010, India was the leading consumer of antibiotics, followed by China and the United States.[5] Antimicrobial side effects manifest themselves as unfavourable

Table 1: Analysis of antibiotics via STopTox 1.0 and lazar toxicity predictions software.

Sl. No.	Antibiotics	PubChem ID	Structure	STopTox 1.0 Prediction			lazar toxicity predictions
				Endpoint	Prediction	Confidence	
1.	Amoxicillin	33613		Acute Inhalation Toxicity	Non-Toxic	75.0%	Blood-Brain Barrier Penetration (Human) Type: Classification Prediction: non-penetrating Probability: non-penetrating: 0.26 penetrating: 0.26 Maximum Recommended Daily Dose (Human) Type: Regression Prediction: 0.0939 (mmol/kg-bw/day) 34.3 (mg/kg_bw/day) 95% Prediction interval: 0.0266 - 0.332 (mmol/kg-bw/day) 9.7 - 121.0 (mg/kg_bw/day)
				Acute Oral Toxicity	Non-Toxic	95.0%	
				Acute Dermal Toxicity	Non-Toxic	89.0%	
				Eye Irritation and Corrosion	Toxic	78.0%	
				Skin Sensitization	Non-Sensitizer	50%	
				Skin Irritation and Corrosion	Negative	70%	
2.	Penicillin	5904		Acute Inhalation Toxicity	Non-Toxic	69.0%	Blood-Brain Barrier Penetration (Human) Type: Classification Prediction: penetrating Probability: non-penetrating: 0.313 penetrating: 0.353 Maximum Recommended Daily Dose (Human) Type: Regression Prediction: 0.112 (mmol/kg-bw/day) 37.6 (mg/kg_bw/day) 95% Prediction interval: 0.0383 - 0.331 (mmol/kg-bw/day) 12.8 - 111.0 (mg/kg_bw/day)
				Acute Oral Toxicity	Non-Toxic	94.0%	
				Acute Dermal Toxicity	Non-Toxic	86.0%	
				Eye Irritation and Corrosion	Toxic	80.0%	
				Skin Sensitization	Sensitizer	70%	
				Skin Irritation and Corrosion	Negative	90%	
3.	Ciprofloxacin	2764		Acute Inhalation Toxicity	Non-Toxic	74.0%	Blood-Brain Barrier Penetration (Human) Measured activity: non-penetrating Prediction: non-penetrating Probability: non-penetrating: 0.739 penetrating: 0.0 Maximum Recommended Daily Dose (Human) Measured activity: 0.0401 (mmol/kg-bw/day) 13.3 (mg/kg_bw/day) Prediction: 0.0482 (mmol/kg-bw/day) 16.0 (mg/kg_bw/day) 95% Prediction interval: 0.00633 - 0.368 (mmol/kg-bw/day) 2.1 - 122.0 (mg/kg_bw/day)
				Acute Oral Toxicity	Non-Toxic	95.0%	
				Acute Dermal Toxicity	Non-Toxic	76.0%	
				Eye Irritation and Corrosion	Toxic	59.0%	
				Skin Sensitization	Non-Sensitizer	80%	
				Skin Irritation and Corrosion	Negative	80%	

continued...

Table 1: Cont'd.

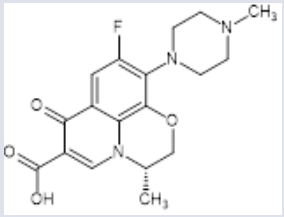
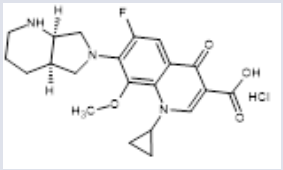
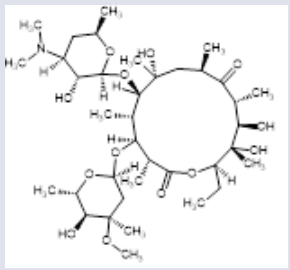
Sl. No.	Antibiotics	PubChem ID	Structure	STopTox 1.0 Prediction			Iazar toxicity predictions
				Endpoint	Prediction	Confidence	
4.	Levofloxacin	149096		Acute Inhalation Toxicity Acute Oral Toxicity Acute Dermal Toxicity Eye Irritation and Corrosion Skin Sensitization Skin Irritation and Corrosion	Non-Toxic Toxic Non-Toxic Toxic Non-Sensitizer Negative	76.0% 76.0% 74.0% 64.0% 80% 70%	Blood-Brain Barrier Penetration (Human) Measured activity: penetrating Prediction: non-penetrating Probability: penetrating: 0.163 non-penetrating: 0.423 Maximum Recommended Daily Dose (Human) Type: Regression Prediction: 0.0435 (mmol/kg-bw/day) 15.7 (mg/kg_bw/day) 95% Prediction interval: 0.0109 - 0.174 (mmol/kg-bw/day) 3.93 - 62.9 (mg/kg_bw/day)
5.	Moxifloxacin	71750825		Acute Inhalation Toxicity Acute Oral Toxicity Acute Dermal Toxicity Eye Irritation and Corrosion Skin Sensitization Skin Irritation and Corrosion	Non-Toxic Non-Toxic Non-Toxic Toxic Non-Sensitizer Negative	74.0% 64.0% 76.0% 70.0% 80% 80%	Blood-Brain Barrier Penetration (Human) Type: Classification Prediction: non-penetrating Probability: penetrating: 0.0798 non-penetrating: 0.337 Maximum Recommended Daily Dose (Human) Type: Regression Prediction: 0.0329 (mmol/kg-bw/day) 14.4 (mg/kg_bw/day) 95% Prediction interval: 0.00975 - 0.111 (mmol/kg-bw/day) 4.27 - 48.6 (mg/kg_bw/day)
6.	Erythromycin	12560		Acute Inhalation Toxicity Acute Oral Toxicity Acute Dermal Toxicity Eye Irritation and Corrosion Skin Sensitization Skin Irritation and Corrosion	Non-Toxic Non-Toxic Non-Toxic Toxic Non-Sensitizer Negative	62% 92.0% 66.0% 65.0% 60% 60%	Blood-Brain Barrier Penetration (Human) Type: Classification Prediction: non-penetrating Probability: non-penetrating: 0.733 penetrating: 0.0 Maximum Recommended Daily Dose (Human) Type: Regression Prediction: 0.0566 (mmol/kg-bw/day) 41.5 (mg/kg_bw/day) 95% Prediction interval: 0.00826 - 0.388 (mmol/kg-bw/day) 6.06 - 284.0 (mg/kg_bw/day)

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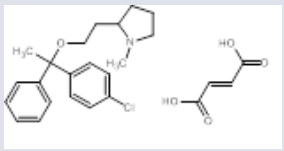
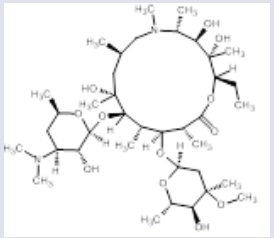
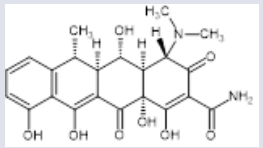
Table 1: Cont'd.

Sl. No.	Antibiotics	PubChem ID	Structure	STopTox 1.0 Prediction			lazar toxicity predictions
				Endpoint	Prediction	Confidence	
7.	Clarithromycin	9868848		Acute Inhalation Toxicity	Non-Toxic	54.0%	**Blood-Brain Barrier Penetration (Human)** Type: Classification Prediction: penetrating Probability: penetrating: 0.192 non-penetrating: 0.0494
				Acute Oral Toxicity	Toxic	58.0%	
				Acute Dermal Toxicity	Non-Toxic	77.0%	
				Eye Irritation and Corrosion	Toxic	53.0%	**Maximum Recommended Daily Dose (Human)** Type: Regression Prediction: 0.0041 (mmol/kg-bw/day) 1.89 (mg/kg_bw/day) **95% Prediction interval:** 0.000113 - 0.149 (mmol/kg-bw/day) 0.052 - 68.3 (mg/kg_bw/day)
				Skin Sensitization	Non-Sensitizer	60%	
				Skin Irritation and Corrosion	Negative	70%	
8.	Azithromycin	447043		Acute Inhalation Toxicity	Non-Toxic	60.0%	Blood-Brain Barrier Penetration (Human) Type: Classification Prediction: non-penetrating Probability: non-penetrating: 1.0 penetrating: 0.0 Maximum Recommended Daily Dose (Human) Type: Regression Prediction: 0.0575 (mmol/kg-bw/day) 43.0 (mg/kg_bw/day) 95% Prediction interval: 0.0136 - 0.243 (mmol/kg-bw/day) 10.2 - 182.0 (mg/kg_bw/day)
				Acute Oral Toxicity	Non-Toxic	85.0%	
				Acute Dermal Toxicity	Non-Toxic	69.0%	
				Eye Irritation and Corrosion	Toxic	73.0%	
				Skin Sensitization	Sensitizer	60%	
				Skin Irritation and Corrosion	Negative	70%	
9.	Doxycycline	54671203		Acute Inhalation Toxicity	Non-Toxic	70.0%	Blood-Brain Barrier Penetration (Human) Prediction: penetrating Probability: non-penetrating: 0.256 penetrating: 0.744 Maximum Recommended Daily Dose (Human) Type: Regression Prediction: 0.0452 (mmol/kg-bw/day) 20.1 (mg/kg_bw/day) 95% Prediction interval: 0.00854 - 0.239 (mmol/kg-bw/day) 3.8 - 106.0 (mg/kg_bw/day)
				Acute Oral Toxicity	Non-Toxic	89.0%	
				Acute Dermal Toxicity	Non-Toxic	74.0%	
				Eye Irritation and Corrosion	Toxic	55.0%	
				Skin Sensitization	Non-Sensitizer	70%	
				Skin Irritation and Corrosion	Negative	70%	

continued...

Table 1: Cont'd.

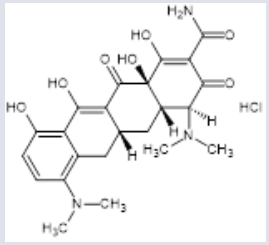
Sl. No.	Antibiotics	PubChem ID	Structure	STopTox 1.0 Prediction			lazar toxicity predictions
				Endpoint	Prediction	Confidence	
10.	Minocycline	54685925		Acute Inhalation Toxicity	Non-Toxic	70.0%	Blood-Brain Barrier Penetration (Human) Type: Classification Prediction: penetrating Probability: non-penetrating: 0.277 penetrating: 0.69 Maximum Recommended Daily Dose (Human) Type: Regression Prediction: 0.0535 (mmol/kg-bw/day) 26.4 (mg/kg_bw/day) 95% Prediction interval: 0.0209 - 0.137 (mmol/kg-bw/day) 10.3 - 67.6 (mg/kg_bw/day)
				Acute Oral Toxicity	Non-Toxic	58.0%	
				Acute Dermal Toxicity	Non-Toxic	71.0%	
				Eye Irritation and Corrosion	Toxic	59.0%	
				Skin Sensitization	Non-Sensitizer	60%	
				Skin Irritation and Corrosion	Negative	70%	

Table 2: Pharmacokinetics property analysis using Swiss ADME.

Sl.No.	Name of antibiotics	GI absorption	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log K_p (skin permeation)
1.	Penicillin CID2349	High	No	No	No	No	No	No	No	-7.04 cm/s
2.	Amoxicillin CID33613	Low	No	No	No	No	No	No	No	-9.94 cm/s
3.	Azithromycin CID447043	Low	No	Yes	No	No	No	No	No	-8.01 cm/s
4.	Erythromycin CID 12560	Low	No	Yes	No	No	No	No	No	-8.60 cm/s
5.	Clarithromycin CID 84029	Low	No	Yes	No	No	No	No	Yes	-8.62 cm/s
6.	Doxycycline CID 54671203	Low	No	Yes	No	No	No	No	No	-8.63 cm/s
7.	Minocycline CID54675783	Low	No	Yes	No	No	No	No	No	-8.16 cm/s
8.	Levofloxacin CID3033924	Low	No	No	No	No	Yes	No	No	-11.49 cm/s
9.	Moxifloxacin CID 152946	High	No	Yes	No	No	No	Yes	No	-8.32 cm/s
10.	Ciprofloxacin CID 2764	High	No	Yes	No	No	No	No	No	-9.09 cm/s

Table 3: Antibiotics with their targets for toxicity.

Sl. No.	Antibiotics Name	Classification	Target	Prediction	Probability
1.	Penicillin CID 2349	Organ toxicity	Hepatotoxicity	Active	0.69
		Toxicity end points	Immunotoxicity	Active	0.96
		Tox21-Nuclear receptor signaling pathways	Aromatase	Active	1.0
		Tox21-Nuclear receptor signaling pathways	ER	Active	0.99
		Tox21-Nuclear receptor signaling pathways	ER-LBD	Active	1.0
2.	Amoxicillin CID 33613	Toxicity end points	Immunotoxicity	Active	0.96
		Tox21-Nuclear Receptor signaling pathways	Aromatase	Active	1.0
		Tox21-Nuclear receptor signalling pathways	ER	Active	0.99
		Tox21-Nuclear receptor signalling pathways	ER- LBD	Active	1.0
3.	Azithromycin CID 447043	Toxicity endpoints	Immunotoxicity	Active	0.96
		Tox21-Nuclear receptor signaling Pathways	Aromatase	Active	1.0
		Tox21-Nuclear receptor signaling pathways	ER	Active	0.99
		Tox21-Nuclear receptor signalling pathways	ER- LBD	Active	1.0
4.	Erythromycin CID 12560	Toxicity end points	Immunotoxicity	Active	0.96
		Tox21-Nuclear receptor signaling Pathways	Aromatase	Active	1.0
		Tox21-Nuclear receptor signaling pathways	ER	Active	0.99
		Tox21-Nuclear receptor signaling pathways	ER-LBD	Active	1.0
5.	Clarithromycin CID 84029	Toxicity end points	Immunotoxicity	Active	0.96
		Tox21-Nuclear receptor signaling pathways	Aromatase	Active	1.0
		Tox21-Nuclear receptor signaling Pathways	ER	Active	0.99
		Tox21-Nuclear receptor signaling pathways	ER-LBD	Active	1.0
6.	Doxycycline CID 54671203	Toxicity end points	Hepatotoxicity	Active	0.69
		Toxicity end points	Immunotoxicity	Active	0.96
		Tox21-Nuclear receptor signaling pathways	Aromatase	Active	1.0
		Tox21-Nuclear receptor signaling pathways	ER	Active	0.99
		Tox21-Nuclear receptor signaling pathways	ER-LBD	Active	1.0
7.	Minocycline CID 54675783	Organ toxicity	Hepatotoxicity	Active	0.69
		Toxicity end points	Immunotoxicity	Active	0.96
		Tox21 Nuclear receptor signaling Pathways	Aromatase	Active	1.0
		Tox21-Nuclear receptor signaling pathways	ER	Active	0.99
		Tox21-Nuclear receptor signaling pathway	ER-LBD	Active	1.0
8.	Levofloxacin CID 3033924	Organ toxicity	Hepatotoxicity	Active	0.69
		Toxicity end points	Immunotoxicity	Active	0.96
		Tox21-Nuclear receptor signaling pathways	Aromatase	Active	1.0
		Tox21-Nuclear receptor signaling pathways	ER	Active	0.99
		Tox21-Nuclear receptor signaling pathways	ER-LBD	Active	1.0
9.	Moxifloxacin CID 152946	Organ toxicity	Hepatotoxicity	Active	0.69
		Toxicity end points	Immunotoxicity	Active	0.96
		Tox21-Nuclear receptor signaling Pathways	Aromatase	Active	1.0
		Tox21-Nuclear receptor signaling pathways	ER	Active	0.99
		Tox21-Nuclear receptor signaling pathways	ER-LBD	Active	1.0
10.	Ciprofloxacin CID 2764	Organ toxicity	Hepatotoxicity	Active	0.69
		Toxicity end points	Immunotoxicity	Active	0.96
		Tox21-Nuclear receptor signaling pathways	Aromatase	Active	1.0
		Tox21-Nuclear receptor signaling Pathways	ER	Active	0.99
		Tox21-Nuclear receptor signaling pathways	ER-LBD	Active	1.0

medication reactions affecting one or more organ systems. Fever, rash, diarrhoea, and nephrotoxicity are the most common antibiotic side effects. Even though most antibiotics are safe due to their widespread use, some antimicrobials have the potential to cause life-threatening side effects.

In humans, antibiotic residues can cause "allergies, immunopathological effects, carcinogenicity, mutagenicity, nephropathy, hepatotoxicity, reproductive problems, bone marrow toxicity, and even anaphylactic".[6]

Antibiotics have yet to be studied in terms of their long-term toxic effects on human health. Antibiotics that are β-lactams are less harmful. They were, however, found to be responsible for most antimicrobial-related allergic responses in people.[7] Nausea, diarrhoea, stomach discomfort, and headaches are some of the most common yet minor and predictable side effects of β-lactams. Oral formulations are thought to have a higher incidence of them.[8] The major antibiotics of this class are penicillin and cephalosporins. Despite rising antimicrobial resistance, penicillin remains an important component of current antibiotic therapy.[9] Many patients experience penicillin allergy symptoms, but a small percentage of a patient report intermediate allergy testing based on clinical history or high-risk symptoms.[10] Various antibiotic-induced liver impairments were observed following β-lactam administration, ranging from minor elevations in liver enzymes to acute hepatitis and cholestatic jaundice.[8] When penicillin is given in high quantities to human patients, a cephalopathic personality may emerge. This includes hyperreflexia, hallucinations, and myoclonic twitches, which can lead to focal seizures, generalized convulsions, and in rare cases, coma.[11] Gastrointestinal side effects including nausea, loss of appetite, cramping, vomiting, flatulence, reduced salivation, and oral candidiasis. Aplastic anaemia, haemolytic anaemia, haemorrhage, toxic nephropathy, hepatic impairment, agranulocytosis, and pancytopenia are only a few of the disorders that have been noted. Seizures have been linked to a number of cephalosporins, especially in individuals with renal impairment whose dosage was not accustomed to renal characteristics.[12]

Fluoroquinolones have been shown to induce acute renal failure when consumed in high doses; however, it is now documented that fluoroquinolones at therapeutic doses can also result in renal impairment.[13] The use of fluoroquinolones is linked to a significant increase in the risk of arrhythmia and cardiovascular disease mortality.[14] Ciprofloxacin side effects might be gastrointestinal or neurological. The latter can result in seizures, hallucinations, migraines, and dizziness. Patients with weak renal function are more likely to have adverse effects since the medication is mostly removed through the kidneys; hence drug doses should be adjusted as required.[15] The nephrotoxicity of ciprofloxacin is usually underrated. Acute tubular necrosis is a common side effect of ciprofloxacin overdose. The improvement in renal function is seen after discontinuing the offending medication supports. Ciprofloxacin-induced acute renal failure has also been reported.[16]

Lipsky and Baker in 1999, reported cases of acute renal failure related to fluoroquinolones in people over the age of 50. A hypersensitive response or a direct toxic effect of fluoroquinolones were considered potential causes of renal failure. The incidence of higher blood creatinine levels associated with ciprofloxacin, norfloxacin, ofloxacin, or pefloxacin medication was estimated to be between 0.2 and 1.3 percent.[17] The risk of 'silent' acute renal failure has also been observed.[18-20] has documented the adverse effects of fluroquinolones, such as dizziness, restlessness, sleeplessness, tremors, hallucination, depression, anxiety, and convulsions. The new quinolone derivatives, also known as gyrase inhibitors (levofloxacin, sparfloxacin, grepafloxacin, trovafloxacin, gatifloxacin, and moxifloxacin), are notable for their capacity to produce adverse effects on the central nervous system, such as headache, dizziness, and sleeplessness. Renal insufficiency, underlying CNS illness, and higher medication CNS penetration are all risk factors for neurotoxicity. Acute delirium caused by levofloxacin medication is an extremely unusual event that is suspected to be more common in elderly people.[21] The usage of various fluoroquinolones, has resulted in varying degrees of hepatotoxicity. Hepatotoxicity should be considered as a potential side effect of fluoroquinolones by prescribers. Furthermore, patients should be warned about the potential signs and symptoms of hepatotoxicity, such as nausea, vomiting, stomach discomfort, rash, anorexia, jaundice, or dark urine.[22]

Because of safety concerns, fluoroquinolone antibiotics have recently received increased national attention. The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have identified three fluoroquinolones, ciprofloxacin, levofloxacin, and moxifloxacin, as being Strongly linked to neuropsychiatric toxicity, can cause long-term impairment, aortic dissections/aneurysms, and suicide.[23] Further research is needed to determine the true pathophysiology of levofloxacin-induced hepatotoxicity.[24] The clinical efficacy of levofloxacin, as well as the relative scarcity of

major adverse effects, have contributed to its extensive use.[25]

Macrolides are widely used to treat upper respiratory infections and have been associated with ototoxicity through cochlear damage. This may result in balance dysfunction as well as hearing loss. Early detection is essential to reduce the chance of long-term vestibulocochlear system impairment in the future.[26,27] Azithromycin is still used to treat cervicitis and other STIs. Azithromycin disrupted the equilibrium of hepatocyte growth and apoptosis, causing foetal liver developmental toxicity.[28] The long-term use of azithromycin increases the risk of cardiovascular and sudden cardiac death, despite the fact that the underlying mechanisms remain unclear.[29] The French Society of Dermatology reported in 2016 that azithromycin is only effective at large dosages (2g), which produces major stomach difficulties. As a result, this antibiotic has no place in this indication at the moment, especially given the rapid emergence of resistance.[30] Ruptured tendons, peripheral neuropathy, CNS difficulties, chest pain, and heart problems are some of the more serious toxicity consequences, but they are extremely rare. Neither ciprofloxacin nor azithromycin is mutagenic or carcinogenic to humans.[31] Chronic azithromycin exposure raises cardiac Na^+ current to enhance intracellular Na+ loading, suggesting a potential molecular basis for the unique proarrhythmia reported with this macrolide antibiotic.[29]

Tetracyclines have been linked to cranial nerve damage as well as neuromuscular obstruction.[27,31] Furthermore, certain occurrences of benign intracranial hypertension have been linked to a neurotoxic event caused by tetracycline.[27,32] Major antibiotics in this class are Doxycycline and Minocycline. Doxycycline has been linked to photosensitivity, redness, and erythroderma. The most common dermatological side effect of doxycycline is photosensitivity.[33] Based on the ongoing issues of bacterial resistance and antibiotic toxicity, practitioners should try to achieve the greatest serum concentrations that may be safely achieved while ensuring that these toxicity thresholds are not exceeded by using TDM (Therapeutic Drug Monitoring) early during antibiotic treatment.

Web-based toxicity analyzing software

SToptox analysis

SToptox is defined as "comprehensive collection of computational models that can be used to predict the toxicity hazard of small organic molecules as an alternative to *in vivo* 6-pack tests". The models were developed and validated in accordance with standard practices for QSAR (quantitative structure-activity relationship) modelling. The SToptox site may be used as a regulator to find potential toxicants or non-toxicants in relevant chemical libraries.[34]

Lazar toxicity predictions

A modular system called lazar (lazy structure-activity relationships) was developed for predictive toxicology. Lazar develops local QSAR models for each component to be forecasted in toxicity risk evaluation.[35] The Blood-Brain Barrier Penetration signifies the key element of the efficient administration of drugs to the CNS. If the target location is inside the CNS, it is essential to have good access via the Blood-Brain Barrier; otherwise, it might be toxic.[36]

Swiss ADME

Swiss ADME is a web application that provides "free access to a collection of quick but reliable predictive models for physicochemical properties, pharmacokinetics, drug-likeness, and medicinal chemistry friendliness, including effective in-house techniques like the BOILED-Egg, iLOGP, and Bioavailability Radar".[37] During *in silico* study of antibiotics used in STIs using Swiss ADME out of ten antibiotics penicillin, moxifloxacin, and ciprofloxacin showed high gastrointestinal absorption. If there is low GI absorption, the plasma drug concentration falls below the MIC for a particular organism. In this case, therapeutic failure may occur.[38]

Swiss ADME is an efflux transporter that regulates drug absorption, distribution, and elimination. Thus, the main role of P-glycoprotein (P-GP) is to minimize the systemic exposure of its substrates.[39] There are three antibiotics which are not the substrate of P-glycoprotein. These are Penicillin, Amoxicillin and Levofloxacin. Role of P-glycoprotein on absorption, distribution, and excretion; thus, these antibiotics do not adequately absorb, distribute and eliminate.

Cytochrome P450 (CYP) helps in metabolism; thus, antibiotics should not have to be an inhibitor of CYP450 family members, but Levofloxacin is an inhibitor of CYP19, Moxifloxacin of CYP2D6 and Clarithromycin of CYP3A4. This cause problem in the metabolism of various xenobiotics.

The health risks associated with skin exposure to hazardous compounds have conventionally been assessed by measuring the chemical's skin penetration coefficient (Kp) in the stratum corneum of human skin, this work characterized the molecular level physicochemical parameters involved in chemical transdermal transport and created a QSAR for Kp prediction. Kp was linearly

related to molecular size and lipophilicity. The lower the log Kp (in cm/s), the less permeative the molecule is to the skin. The more negative the log Kp, the less skin permeant is the molecule.[40]

Protox II Analysis

Based on a total of 33 models for the prediction of various toxicity endpoints, such as "acute toxicity, hepatotoxicity, cytotoxicity, carcinogenicity, mutagenicity, immunotoxicity, adverse outcomes (Tox21) pathways, and toxicity targets", ProTox-II uses molecular similarity, fragment propensities, most frequent features, and (fragment similarity-based CLUSTER cross-validation) machine learning. The predictive models are based on data from both *in vivo* cases and *in vitro* assays, such as the Tox21 assay, the Ames bacterial mutation assay, the hepG2 cytotoxicity assay, and the immunotoxicity assay (e.g., carcinogenicity, hepatotoxicity). Thus, ProTox-II methods probably support risk assessments for monitoring decisions, including the ability to develop original hypotheses and gain an understanding of the mechanisms of toxicity.[41]

There is very little information available on the genotoxicity of the antibiotics used in this study. Amoxicillin most likely does not have genotoxic effects on humans, according to *in vivo* research of plasma and an *in vitro* analysis of peripheral blood cells conducted by Istifli and Topaktaş in 2010.[42] Although some studies provide evidence of genotoxicity. Minocycline disturbs the physiology of glial-like cells at a dose of 10 g/mL, according to Puty *et al*. analysis of cytotoxic and genotoxic characteristics in 2020.[43] Similarly, Kayraldz and Durmuş reported in 2017 that Levofloxacin is not cytotoxic in human peripheral lymphocytes but may be genotoxic.[44]

The management of STIs is becoming a serious therapeutic concern because of the fast development of antibiotic-resistant bacteria. Antibiotic resistance develops naturally, but overuse of antibiotics accelerates the process. Many factors contribute to antibiotic resistance, including inappropriate prescribing, suboptimal dosing, drug overuse, and low-quality antibiotics.[45] To prevent and control the spread of antibiotic resistance, policymakers can ensure that a robust national action plan to tackle antibiotic resistance is in place. This involves improving antibiotic-resistant pathogen surveillance, developing policy programmes, implementing infection prevention and control measures, and encouraging the proper use as well as disposal of quality pharmaceuticals. And also, should make information available on the impact of antibiotic resistance.[46]

One of the reasons behind the toxicity of Antibiotics could be the intake of inappropriate drugs without a proper prescription from the doctor. Regularly ingesting unnecessary drugs in excessive doses initially causes resistance and eventually severe toxicity. The other reasons for toxicity may be due to disease progression, as tribal people believe in practising witchcraft and superstitions, ultimately worsening their conditions and visiting hospitals and seeking treatment at a later stage of infection. Failure of treatment at the budding stage may require multiple antibiotics, which leads to toxicity.

CONCLUSION

Nowadays, *in silico* approaches can offer significant advantages for both monitoring demands and necessities for risk assessments, as well as for the pharmacological sector to examine the safety profile of frequently used antibiotics. Animal models have long been used for toxicity assessment, but they are limited by time, ethical concerns, and economic constraints. As a result, various computational approaches for analyzing chemical toxicity and pharmacokinetic properties are thought to be essential. *In silico* toxicology, evaluation may balance current toxicity testing to predict toxicity, choose compounds, coordinate toxicity tests, and reduce late-stage failures in drug design. Various computational models are applied at several levels of biological complexity, including cells, micro-organisms, tissues, laboratory animals, and even humans and molecular targets. Various *in silico* software's are available online, which is helpful in the prediction or evaluation of toxicity online. Along with that, Advances in high-throughput Whole-Genome Sequencing (WGS) provide valuable tools for improving diagnosis, treatment, and management capacities, eventually aiding in the global control of antibiotic-resistant STIs.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

CDC: Centre for Disease Control and Prevention; **ER:** Estrogen Receptor Alpha; **ER-LBD:** Estrogen ReceptorLigand Binding Domain; **QSAR:** Quantitative Structure-Activity Relationship; **STIs:** Sexually Transmitted Infections; **TDM:** Therapeutic Drug Monitoring; **WGS:** Whole-genome sequencing.

SUMMARY

Humans and microbes have coexisted since the beginning of civilization. Excess of anything is not tolerated by nature, and antibiotics are now so widely used that they are starting to exhibit adverse effects. Excess accumulation of antibiotics enhances toxicity. Antibiotic toxicity must be properly characterized and understood in order to protect human healthcare delivery systems. *In silico* toxicity analysis approaches may greatly contribute to understanding how antibiotic causes toxicity. This approach may be time and money-saving.

REFERENCES

1. WHO. Guidelines for the management of sexually transmitted infections. Geneva, Switzerland; 2004.
2. Caruso G, Giammanco A, Virruso R, Fasciana T. Current and future trends in the laboratory diagnosis of sexually transmitted infections. Int J Environ Res Public Health. 2021;18(3):1-17. doi: 10.3390/ijerph18031038, PMID 33503917.
3. Han Y, Zhang J, Hu C. A systematic toxicity evaluation of cephalosporins via transcriptomics in zebrafish and *in silico* ADMET studies. Food Chem Toxicol. 2018;116(B):264-71. doi: 10.1016/j.fct.2018.04.046, PMID 29689360.
4. Pinzi L, Rastelli G. Molecular docking: shifting paradigms in drug discovery. Int J Mol Sci. 2019;20:4331. doi: 10.3390/ijms20184331, PMID 31487867.
5. van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, *et al*. Global antibiotic consumption 2000 to 2010: An analysis of national pharmaceutical sales data. Lancet Infect Dis. 2014;14(8):742-50. doi: 10.1016/S1473-3099(14)70780-7, PMID 25022435.
6. Nisha AR. Antibiotic residues—A global health hazard. Vet World. 2008;2(2):375-7. doi: 10.5455/vetworld.2008.375-377.
7. Davies J. Origins and evolution of antibiotic resistance. Microbiologia. 1996;12(1):9-16. PMID: 9019139.
8. Vardakas KZ, Kalimeris GD, Triarides NA, Falagas ME. An update on adverse drug reactions related to β-lactam antibiotics. Expert Opin Drug Saf. 2018;17(5):499-508. doi: 10.1080/14740338.2018.1462334, PMID 29633867.
9. Eyler RF, Shvets K. Clinical pharmacology of antibiotics. Clin J Am Soc Nephrol. 2019;14(7):1080-90. doi: 10.2215/CJN.08140718, PMID 30862698.
10. Zembles T, Mitchell M, Alqurashi W, Castells M, Phillips EJ, Vyles D. Skin testing for penicillin allergy: A review of the literature. Curr Allergy Asthma Rep. 2021;21(3):21. doi: 10.1007/s11882-021-00997-x, PMID 33738621.
11. Nicholls PJ. Neurotoxicity of penicillin. J Antimicrob Chemother. 1980;6(2):161-5. doi: 10.1093/jac/6.2.161, PMID 7380762.
12. Chugh K, Agrawal S. Cefpodoxime: Pharmacokinetics and therapeutic uses. Indian J Pediatr. 2003;70(3):227-31. doi: 10.1007/BF02725589, PMID 12785294.
13. Hootkins R, Fenves AZ, Stephens MK. Acute renal failure secondary to oral ciprofloxacin therapy: A presentation of three cases and a review of the literature. Clin Nephrol. 1989;32(2):75-8. PMID 2670382.
14. Gorelik E, Masarwa R, Perlman A, Rotshild V, Muszkat M, Matok I. Systematic review, meta-analysis, and network meta-analysis of the cardiovascular safety of macrolides. Antimicrob Agents Chemother. 2018;62(6):e00438-18. doi: 10.1128/AAC.00438-18, PMID 29610207, PMCID PMC5971614.
15. Lee CH, Cheung RT, Chan TM. Ciprofloxacin-induced oral facial dyskinesia in a patient with normal liver and renal function. Hosp Med. 2000;61(2):142-3. doi: 10.12968/hosp.2000.61.2.2404, PMID 10748799.
16. Hajji M, Jebali H, Mrad A, Blel Y, Brahmi N, Kheder R, *et al*. Nephrotoxicity of Ciprofloxacin: Five Cases and a Review of the Literature. Drug Saf Case Rep. 2018;5(1):17. doi: 10.1007/s40800-018-0073-4. PMID: 29671145; PMCID: PMC5906393.
17. Lipsky BA, Baker CA. Fluoroquinolone toxicity profiles: a review focusing on newer agents. Clin Infect Dis. 1999;28(2):352-64. doi: 10.1086/515104, PMID 10064255.
18. Lomaestro BM. Fluoroquinolone-induced renal failure. Drug Saf. 2000;22(6):479-85. doi: 10.2165/00002018-200022060-00006, PMID 10877041.
19. Akahane K, Kato M, Takayama S. Involvement of inhibitory and excitatory neurotransmitters in levofloxacin-and ciprofloxacin-induced convulsions in mice. Antimicrob Agents Chemother. 1993;37(9):1764-70. doi: 10.1128/AAC.37.9.1764, PMID 7902066.
20. De Sarro A, De Sarro G. Adverse reactions to fluoroquinolones. An overview on mechanistic aspects. Curr Med Chem. 2001;8(4):371-84. doi: 10.2174/0929867013373435, PMID 11172695.
21. Kiangkitiwan B, Doppalapudi A, Fonder M, Solberg K, Bohner B. Levofloxacin-induced delirium with psychotic features. Gen Hosp Psychiatry. 2008;30(4):381-3. doi: 10.1016/j.genhosppsych.2007.11.003, PMID 18585545.
22. Coleman CI, v Spencer JV, Chung JO, Reddy P. Possible gatifloxacin-induced fulminant hepatic failure. Ann Pharmacother. 2002;36(7-8):1162-7. doi: 10.1345/aph.1A414, PMID 12086547.
23. Bennett AC, Bennett CL, Witherspoon BJ, Knopf KB. An evaluation of reports of ciprofloxacin, levofloxacin, and moxifloxacin-association neuropsychiatric toxicities, long-term disability, and aortic aneurysms/dissections disseminated by the Food and Drug Administration and the European Medicines Agency. Expert Opin Drug Saf. 2019;18(11):1055-63. doi: 10.1080/14740338.2019.1665022, PMID 31500468.
24. Schloss M, Becak D, Tosto ST, Velayati A. A Case of Levofloxacin-Induced Hepatotoxicity. Am J Case Rep. 2018;19:272-6. doi: 10.12659/ajcr.907440. PMID: 29523775; PMCID: PMC5859667.
25. Famularo G, de Simone C. Nephrotoxicity and purpura associated with levofloxacin. Ann Pharmacother. 2002;36(9):1380-2. doi: 10.1345/aph.1A474, PMID 12196055.
26. Principi N, Esposito S. Comparative tolerability of erythromycin and newer macrolide antibacterials in paediatric patients. Drug Saf. 1999;20(1):25-41. doi: 10.2165/00002018-199920010-00004, PMID 9935275.
27. Grill MF, Maganti RK. Neurotoxic effects associated with antibiotic use: Management considerations. Br J Clin Pharmacol. 2011;72(3):381-93. doi: 10.1111/j.1365-2125.2011.03991.x, PMID 21501212.
28. Liu K, Wang G, Li L, Chen G, Gong X, Zhang Q, *et al*. GR-C/EBPα-IGF1 axis mediated azithromycin-induced liver developmental toxicity in fetal mice. Biochem Pharmacol. 2020;180:114130. doi: 10.1016/j.bcp.2020.114130. Epub 2020 Jun 29. PMID: 32615080.
29. Yang Z, Prinsen JK, Bersell KR, Shen W, Yermalitskaya L, Sidorova T, *et al*. Azithromycin Causes a Novel Proarrhythmic Syndrome. Circ Arrhythm Electrophysiol. 2017;10(4):e003560. doi: 10.1161/CIRCEP.115.003560. PMID: 28408648; PMCID: PMC5396181.
30. Peyriere H, Makinson A, Marchandin H, Reynes J. Doxycycline in the management of sexually transmitted infections. J Antimicrob Chemother. 2018;73(3):553-63. doi: 10.1093/jac/dkx420, PMID 29182717.
31. Sidhu H, O'Connor G, McAvoy D. Risk assessment of biosolids-borne ciprofloxacin and azithromycin. Sci Total Environ. 2019;651(2):3151-60. doi: 10.1016/j.scitotenv.2018.10.194, PMID 30463165.
32. Thomas RJ. Neurotoxicity of antibacterial therapy. South Med J. 1994;87(9):869-74. doi: 10.1097/00007611-199409000-00001, PMID 8091248.
33. Kesler A, Goldhammer Y, Hadayer A, Pianka P. The outcome of pseudotumor cerebri induced by tetracycline therapy. Acta Neurol Scand. 2004;110(6):408-11. doi: 10.1111/j.1600-0404.2004.00327.x, PMID 15527455.

34. Borba JVB, Alves VM, Braga RC, Korn DR, Overdahl K, Silva AC, *et al*. STopTox: An *in-silico* alternative to animal testing for acute systemic and topical toxicity. Environ Health Perspect. 2022;130(2):1-12. doi: 10.1289/EHP9341.
35. Maunz A, Gütlein M, Rautenberg M, Vorgrimmler D, Gebele D, Helma C. Lazar: a modular predictive toxicology framework. Front Pharmacol. 2013;4:38. doi: 10.3389/fphar.2013.00038. PMID: 23761761; PMCID: PMC3669891.
36. Mangas-Sanjuan V, González-Alvarez M, Gonzalez-Alvarez I, Bermejo M. Drug penetration across the blood–brain barrier: An overview. Ther Deliv. 2010;1(4):535-62. doi: 10.4155/tde.10.37, PMID 22833966.
37. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep. 2017;7:42717. doi: 10.1038/srep42717. PMID: 28256516; PMCID: PMC5335600.
38. Parsons RL. Drug absorption in gastrointestinal disease with particular reference to malabsorption syndromes. Clin Pharmacokinet. 1977;2(1):45-60. doi: 10.2165/00003088-197702010-00004, PMID 322910.
39. Elmeliegy M, Vourvahis M, Guo C, Wang DD. Effect of P-glycoprotein (P-gp) inducers on exposure of P-gp substrates: review of clinical drug–drug interaction studies. Clin Pharmacokinet. 2020;59(6):699-714. doi: 10.1007/s40262-020-00867-1, PMID 32052379.
40. Chang YC, Chen CP, Chen CC. Predicting skin permeability of chemical substances using a quantitative structure-activity relationship. Procedia Eng. 2012;45:875-9. doi: 10.1016/j.proeng.2012.08.252.
41. Banerjee P, Eckert AO, Schrey AK, Preissner R. ProTox-II: A webserver for the prediction of toxicity of chemicals. Nucleic Acids Res. 2018;46(W1):W257-63. doi: 10.1093/nar/gky318, PMID 29718510.
42. Istifli ES, Topaktaş M. Cytogenetic genotoxicity of amoxicillin. Environ Mol Mutagen. 2010;51(3):222-8. doi: 10.1002/em.20531. PMID: 19790260.
43. Puty B, Nogueira ICDC, Nogueira LS, Vasconcelos CP, Araújo TMC, Bittencourt LO, Ferreira RO, Oliveira EHC, Leal WG, Lima RR. Genotoxic effect of non-lethal concentrations of minocycline in human glial cell culture. Biomed Pharmacother. 2020;128:110285. doi: 10.1016/j.biopha.2020.110285. Epub 2020 May 30. PMID: 32485569.
44. Kayraldız A, Durmuş ZY. Evaluation of genotoxic effects of levofloxacin in human peripheral lymphocytes. IJAR. 2017;7(4). https://www.researchgate.net/publication/318225692.
45. Mohammed Ali H. *In-silico* investigation of a novel inhibitors against the antibiotic-resistant Neisseria gonorrhoeae bacteria. Saudi J Biol Sci. 2022 Oct;29(10):103424. doi: 10.1016/j.sjbs.2022.103424. Epub 2022 Aug 22. PMID: 36091725; PMCID: PMC9460163.
46. WHO. Antibiotic resistance. 31 July 2020. https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance.

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