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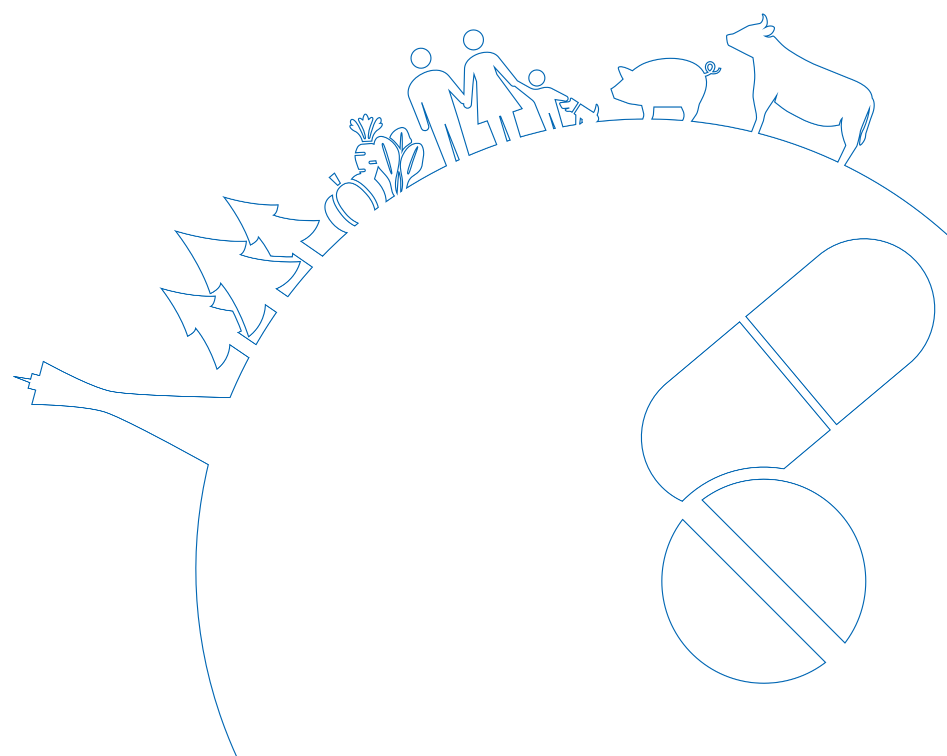
Proper Use of Antimicrobials

Antimicrobial Resistance (AMR)



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01

Context of the Fight against Antimicrobial Resistance (AMR)

■AMR, Global Social Issue [1-3]

Antimicrobials are one of the most essential drugs that prevent and treat infections and are widely used in modern medicine and healthcare. However, as the consumption of antimicrobials continues to increase, antimicrobial resistance (AMR) is also increasing. Consequently, the increase and spread of AMR have made it difficult to treat patients with infections using antimicrobial therapy and induce devastating social, and economic outcomes. In 2013, the number of deaths associated with AMR was reported to be approximately 700,000 globally, and the economic toll is expected to reach 10 million by 2050. Treatment of infections caused by antimicrobial-resistant pathogens requires long-term hospitalization and high-cost medications, which unavoidably imposes a significant economic burden. According to a joint estimate made by the US, the EU, and other countries with regard to the social and economic impact of AMR, it was found that if no measures are taken, quadrillion dollars of GDP will be lost by 2050 on a global scale. In Japan, the AMR Action Plan proposed by the Ministry of Health, Labor and Welfare has reported that the additional medical costs associated with methicillin-resistant *Staphylococcus aureus* (MRSA) infection for the Diagnosis Procedure Combination hospitals will reach ¥170 billion in total.

The COVID-19 pandemic has revealed the consequences of ineffective treatment of infections and of limited access by patients who require such treatment. AMR is also a threat to global public hygiene because if no countermeasures are taken, it would make infections difficult or impossible to treat. In addition, there is a “silent pandemic” of AMR, where asymptomatic carriers spread the virus without their knowledge. In response to these circumstances, the World Health Organization (WHO) and many other organizations consider AMR as a prominent social issue that needs to be globally addressed, and thus it is essential to provide educational activities on AMR such as promotion of the proper use of antimicrobials and prevention of infections. These efforts to address AMR will also help achieve sustainable development goals whose aim is to contribute to building a sustainable society.

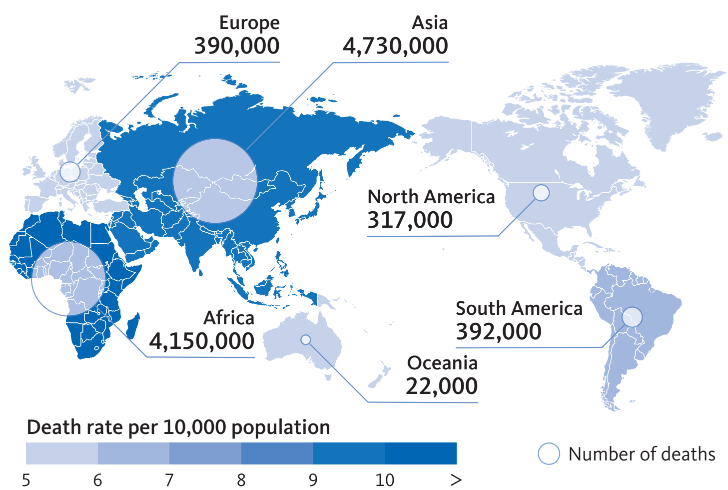
02

Global Status of AMR

AMR in Emerging Countries [4-5)]

In 2009, carbapenem-resistant Enterobacteriaceae (CRE) was identified in an Indian carrier living in Sweden, a finding that drew significant public attention. CRE is a family of bacteria that produce the novel carbapenemase New Delhi metallo-β-lactamase (NDM), which is considered to have been brought into Sweden from medical institutions in India via Indian patients. CRE infection widely spreads mainly among Commonwealth Nations, which were active in trading with India. CRE is now detected worldwide.

Currently, AMR is most serious in emerging countries in Asia, where this issue is expected to become even more significant in the near future because of further economic development, population increases, and increasing medical needs. The consumption of antimicrobials is rapidly increasing in emerging countries, including those in the Asian region. As has been pointed out, the increasing use of antimicrobials, in addition to other factors, is likely to contribute to the increase in AMR.



Expected number of deaths attributed to AMR by 2050 [6)]

AMR in Developed Countries [7)]

Among the developed countries, the UK started addressing AMR earlier than any other countries did. Since 1961, when MRSA infections became a concern, the UK has been implementing countermeasures over several decades that have facilitated the successful decrease of the resistance rate. In the USA, the Obama Administration released the National Action Plan to Combat Antibiotic-Resistant Bacteria, which promoted citizen education and proper use and development of antimicrobials. However, the Mediterranean countries in Europe are still lagging behind in addressing AMR issues and, thus, need to take prompt action.

In Japan, MRSA became a public health issue in the 1980s. In response, the country has implemented various measures against AMR. Thanks to the efforts made, drug resistance rates in hospitals have remained low. However, when it comes to social life settings, the rates of penicillin resistance in *Streptococcus pneumoniae*, macrolide resistance in hemolytic *Streptococcus*, and methicillin resistance in *Staphylococcus aureus* are substantially higher than other countries worldwide.

03

AMR in Society

Hospital-acquired Infections associated with AMR [8-10]

Outbreaks of antimicrobial-resistant bacterial infections sometimes occur in hospitals. Typical examples include MRSA, vancomycin-resistant *enterococci*, and *Clostridium difficile* colitis, which occur after taking antibiotics. The most common associated causes include hospitalization of patients with drug-resistant bacteria or microbes that acquire resistance to the administered antibiotics.

In Japan, hospital-acquired infections became a concern in the 1980s. Medical facilities have been required since 2006 to develop hospital-acquired infection control guidelines, set up a hospital-acquired infection control committee, and provide educational workshops on hospital-acquired infections. Currently, doctors and nurses specializing in infections and infection control are stationed regularly at hospitals to prevent hospital-acquired infections and promote the proper use of antimicrobials.

AMR as a Social Issue [11-17]

AMR issues are not limited to hospitals. At the 71st session of the United Nations General Assembly, the UN Secretary-General called for cooperation among the WHO, Food and Agriculture Organization of the United Nations (FAO), and World Organization for Animal Health (OIE) in combating AMR. Consequently, the Interagency Coordination Group on Antimicrobial Resistance (IACG) dedicated to AMR was established. IACG calls on its member states to develop and implement their national action plan based on a "One Health" approach, which recognizes that the health of people is closely connected to the health of animals and of our shared environment.

In 2016, the Japanese Government announced the National Action Plan on Antimicrobial Resistance 2016–2020, which includes surveys on AMR not only in humans but also in animals, agriculture, food, and the environment, including the consumption of antimicrobials. There are overseas cases where the use of antimicrobials in the livestock industry has had a significant societal impact. In response, global efforts beyond the industry have been made with respect to combating AMR. It has also been reported that AMR is associated with water and other environmental pollution.

The concept of the One Health approach has spread worldwide. Through efforts to address AMR, we must be aware that the diverse living organisms on Earth are closely related with each other.

Delaying the Occurrence and Preventing the Spread of AMR [18]

The Japanese National Action Plan on Antimicrobial Resistance developed in 2016 outlines a total of six objectives: five from the global action plan on AMR, plus one more: international cooperation.

1	**Public awareness improvement and education**	Deepening knowledge and understanding of AMR and promoting education and training for specialists and other professionals.
2	**Trend surveillance and monitoring**	Continuously monitoring AMR and consumption of antimicrobials to correctly identify changes in AMR trends and signs of its spread.
3	**Infection prevention and control**	Properly preventing and controlling infection to prevent the spread of antimicrobial-resistant bacteria
4	**Proper use of antimicrobial medicines**	Promoting the proper use of antimicrobials in healthcare, livestock, fisheries, and other fields
5	**Research and development and drug discovery**	Promoting research on AMR and research and development processes to ensure measures for prevention, diagnosis, and treatment of antimicrobial-resistant organisms
6	**International cooperation**	Promoting the combat against AMR through cooperation in various fields from a global perspective

04

What We can Do to Prevent AMR

Understanding of and Compliance with Prescribed Antimicrobials [19)]

The mechanism of AMR is encoded in the bacterial genes, and a certain number of bacteria with AMR are present in our body. Human factors can sometimes cause rapid proliferation of these bacteria. One of the most influential factors is the use of antimicrobials. Under normal conditions, there are only a small number of antimicrobial-resistant bacteria. However, depending on antimicrobials, bacteria demonstrating resistance can grow unless they are completely eliminated.

How can we prevent such resistance? One of the most important things we can do is to comply with prescribed antimicrobials. Inappropriate use of antimicrobials can result in failing to eliminate bacteria, but it can also increase the risk of proliferating antimicrobial-resistant bacteria. Therefore, it is important to correctly understand and comply with the prescribed use of antimicrobials.

Do not Ask for Unnecessary Antimicrobials [20)]

One of the most common examples of unnecessary administration of antimicrobials involves the use of antimicrobials for the common cold, which is caused by a viral infection. Antimicrobials are effective against bacteria, which is not the cause of the common cold. However, there are still many patients who ask for an antimicrobial agent just in case. According to the Antimicrobial Awareness Survey Report 2019, antimicrobials are the third most frequently prescribed drugs for common cold, following antipyretics and antitussives. Requests for unnecessary antimicrobials are bound to result in excessive antimicrobial use and the consequent spreading of AMR.

Importance of Prevention through Handwashing, Vaccination, and Other Preventive Measures [21-22)]

In many cases, pathogens, such as bacteria and viruses that cause infections, first attach to our hands and then enter into the body through the mouth and/or nose to cause infection. In other words, hands are one of the important vehicles for pathogens. Therefore, we must prevent pathogens from invading the body through our hands. Hand washing is the most effective method to do so in our daily life. Washing our hands not only will prevent pathogens from entering the body but also will prevent infections from spreading to others around us.

Some infections can be prevented with vaccines. Vaccination enables us to acquire immunity against pathogens, thus protecting our bodies from infection. Even if infection occurs, symptoms can be mild. Infections that can be prevented with vaccination include *S. pneumoniae* infection, *Haemophilus influenzae* type b (Hib) infection, tetanus, pertussis, measles, and rubella.

Antimicrobials must be used in compliance with the physician's instructions.

A physician's prescription is required for antimicrobials. Antimicrobials must be used in compliance with the physician's instructions.

Do not save any antimicrobials for later use.

Do not give someone else your antimicrobials, and do not take antimicrobials prescribed for someone else.

If you have any questions, ask your physician.

Prevent infection.

05

AMR and Testing

Testing to Prevent AMR [23)]

Antimicrobials are used to treat and prevent infections in various settings. There are cases of inappropriate prescriptions, such as unnecessary antimicrobial prescriptions and prescriptions of antimicrobials that are ineffective against bacteria responsible for the infection. According to a report released in 2019, 43% of antimicrobial use in the US was inappropriate. Since then, more efforts have been sought to ensure the proper use of antimicrobials.

Screening tests are necessary to ensure proper antimicrobial use. Identification of the bacterial type that causes the infection in patients and determination of the presence or absence of AMR enable physicians to select an effective antimicrobial agent for the patient. In the case of a viral infection, antimicrobials are not effective. Therefore, it is necessary to determine whether a virus causes the patient's symptoms or not. However, obtaining the results from these tests can sometimes be very time-consuming. It is generally impossible to obtain timely detailed information of the bacteria responsible for the infection for prescribing antimicrobials. Therefore, rapid screening tests for infection are sought in healthcare settings.

Urinary Tract Infection and Testing [24)]

Urinary tract infection (UTI) is one of the common infections that we encounter in our daily life. As *Escherichia coli* and *Enterococcus*, which are responsible for UTI, have acquired resistance to more antimicrobials, it has become important to address AMR in both diagnosis and treatment. Typical antimicrobial-resistant bacteria include quinolone-resistant *E. coli* and extended-spectrum beta-lactamase (ESBL)-producing *E. coli*. In recent years, multidrug-resistant *Pseudomonas aeruginosa* and CRE have increasingly emerged, which has now become a significant concern.

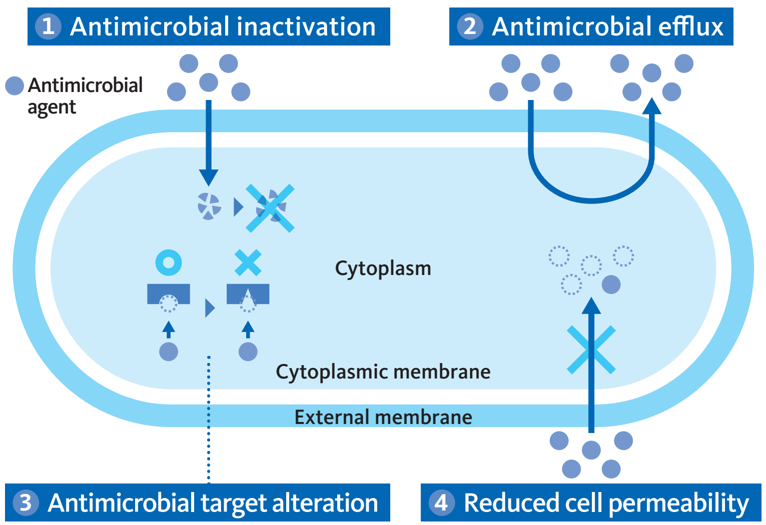
UTIs are diagnosed based on the respective symptoms and urine examination findings. Urinalysis plays a significantly important role as a guideline for the subsequent diagnosis. Different urinalysis techniques are used on a case-by-case basis, such as quantitative culture testing, dipstick testing, microscopy using centrifuged urine, and the flow cytometry method.

06

Relationship between Antimicrobials and AMR Occurrence

AMR Mechanisms [25-26)]

It was not until antimicrobials became available that antimicrobial-resistant bacteria emerged. A certain number of such bacteria have long been present in nature, and some were discovered from the permafrost in the North Pole. Particularly since the 1940s when antimicrobials were first introduced, AMR bacteria have emerged one after another, and the increase in AMR has become a great concern. It has been suggested that the use of antimicrobials has significantly contributed to this increase. Possible reasons for the development of their resistance include genetic mutations and remnants of bacteria with AMR.
When exposed to antimicrobials, bacteria start to develop resistance using various methods to adopt for their survival. There are four main mechanisms by which bacteria become resistant: 1) inactivation of the antimicrobial drug via degradation, 2) efflux of antimicrobials from the cell, 3) alterations of the properties of antimicrobial targets, and 4) reduced permeability by changing membranes to make it difficult for antimicrobials to enter into the cell. Biofilm formation to protect themselves from antimicrobials is another mechanism.



07

Common Examples of AMR that you should know

In addition to bacteria, AMR in viruses and parasites has become a great concern in many countries worldwide.

Methicillin-resistant *Staphylococcus aureus* (MRSA) [27-29)]

The consumption of penicillin G increased greatly in the 1940s due to the mass production of natural penicillin. Penicillin was effective against *S. aureus*, but gradually bacteria developed resistance against this drug. This is because the increased use of penicillin G enabled *S. aureus* to start producing penicillinase, an enzyme that is resistant to penicillin. Methicillin was the next antimicrobial agent developed. Soon after its launch in around 1960, MRSA was detected and globally spread. Since the 1970s, it has been a grave healthcare concern.
MRSA is one of the infections with high mortality rates. These bacteria enter the bloodstream and cause infections in multiple organs. Symptoms can sometimes become severe. In Japan, the general public became aware of MRSAs in the late 1980s when these bacteria were isolated in hospitals. Currently, community-acquired MRSA cases are also reported. MRSA is sometimes categorized into two groups: hospital-acquired MRSA and community-acquired MRSA, which demonstrate slight differences in their characteristics.

Penicillin-resistant *Streptococcus pneumoniae* (PRSP) [30)]

PRSP are resistant to penicillin, a drug that is effective against both *S. pneumoniae* and *Streptococcus pyogenes*. PRSP drew significant attention for the first time in 1967 when clinicians in Australia detected the presence of *S. pneumoniae* that displayed low susceptibility to penicillin. These bacteria, which are natural habitats of the oral cavity, do not cause any symptoms in most cases in healthy people. However, in patients with laryngitis or tonsillitis, PRSP proliferates at the inflammatory sites, causing symptoms of infection such as fever and pain.
PRSP also cause purulent meningitis in infants and otitis media and pneumonia in children. To prevent these infections, the polyvalent pneumococcal vaccine is approved for use in children. In recent years, the incidence of PRSP in adults has been reduced as an indirect effect of the high vaccine coverage.

Extended-spectrum β-lactamase (ESBL)-producing bacteria [31]

There are certain bacteria that produce a class of enzymes called beta-lactamases, which degrade beta-lactam antimicrobials, such as penicillin, cephem, and carbapenem, and, thus, are resistant to them. Beta-lactamases are divided into several types, according to which antimicrobials they degrade. Those that have become able of degrading many antimicrobials through genetic mutations are called ESBL. ESBL-producing bacteria were discovered in the 1980s in Europe. ESBL-producing bacteria are frequently associated with outbreaks of hospital-acquired infections because they are harbored in the intestinal tract. They cause various infections, including sepsis, meningitis, pneumonia, wound infection, and UTI.
Carbapenem antibiotics have been used to treat ESBL-producing bacteria. It has recently been suggested that penicillin-based compounds and cephamycin antibiotics may also be effective.

Multidrug-resistant *Pseudomonas aeruginosa* (MDRP) [32]

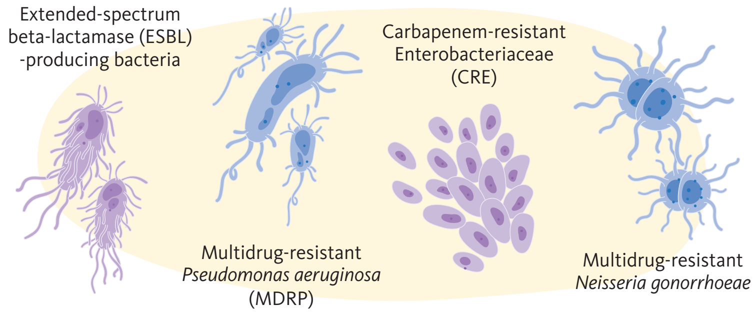
MDRP was first reported in the 1970s in scientific publications. Currently, *P. aeruginosa* is resistant to the following three antimicrobial classes that are collectively known as MDRP: fluoroquinolones, carbapenems, and aminoglycosides.
While *P. aeruginosa*, whose pathogenicity is weak, is less likely to cause infection in healthy individuals, it may cause severe infection in individuals with immunodeficiencies and malnutrition. Due to its multidrug resistance, there are only a limited number of antimicrobials that are suitable for the subsequent treatment. Therefore, MDRP is regarded as one of the bacteria that are difficult to treat.

Carbapenem-resistant Enterobacteriaceae (CRE) [33]

CRE is resistant to carbapenems, which are broad-spectrum beta-lactam antibiotics and used to treat Gram-negative bacterial infections. Enterobacteriaceae are bacteria that ferment glucose in the gut to produce energy. Common CRE include *E. coli*, *Klebsiella*, and *Proteus*. The first reports of CRE were published around 2000. Some CRE bacteria are resistant to all antibiotics. This type of bacteria is regarded as one of the most difficult bacteria to treat.
In Japan, some CRE outbreaks have occurred in hospitals. It is now required to report cases of CRE infections to the government.

Multidrug-resistant *Neisseria gonorrhoeae* [34-36]

N. gonorrhoeae is a bacterium that causes a sexually transmitted disease. It is transmitted from person to person mainly through sexual contact. While the number of patients with *N. gonorrhoeae* has been decreasing since its peak in 2002–2003, the decreasing trend has stagnated in recent years, thus posing a serious public health concern. Certain strains of *N. gonorrhoeae* bacteria have been reported to demonstrate resistance against all antibiotics used to treat sexually transmitted diseases. Therefore, treatment can be significantly challenging. The US Center for Disease Control and Prevention (CDC) lists multidrug-resistant *N. gonorrhoeae* as one of the most urgent antibiotic-resistant threats.



Drug Resistance in Malaria and Insecticide Resistance [37-39]

In 2019, there was an estimated 229 million cases of malaria worldwide caused by *Plasmodium*-infected mosquitoes, and the estimated number of malaria deaths was 409,000. While various efforts for the eradication of malaria are being made worldwide, malaria vector mosquitoes resistant to insecticides and protozoa resistant to antimalarial drugs have become great threats to these efforts. Measures to address protozoa are being implemented mainly in the Mekong region in Southeast Asia. In addition, in Africa where 90% of the worldwide reported patients with malaria reside, efforts to raise awareness regarding the importance of drug resistance have been conducted. It has been emphasized that it is necessary to improve the quality of these efforts to address drug resistance to minimize the resultant risks. In particular, correct diagnosis is considered important for the appropriate drug prescription and use.

Drug-resistant Viruses [40-43]

As viruses and bacteria are different organisms, antimicrobials used to treat bacterial infections are not effective against viral infections. Therefore, antiviral agents are being developed. Viruses make a large number of copies of their genes in the host cell to proliferate. While an antiviral agent fully exerts its effect, viral proliferation is suppressed. However, insufficient antiviral treatment due to failure of taking the prescribed medication or dose, or as a result of other reasons, the risk of developing resistance to the prescribed antiviral increases. This is because viruses are prone to making copy mistakes (mutations) in the proliferation process.

Commonly known examples of antiviral resistance include resistance to anti-HIV drugs and anti-influenza drugs. In 2008, an influenza virus that was resistant to antiviral drugs was first reported in Norway and subsequently spread globally. It is suggested that because HIV tends to develop resistance through mutations, a combination of multiple drugs can be effective for HIV treatment.

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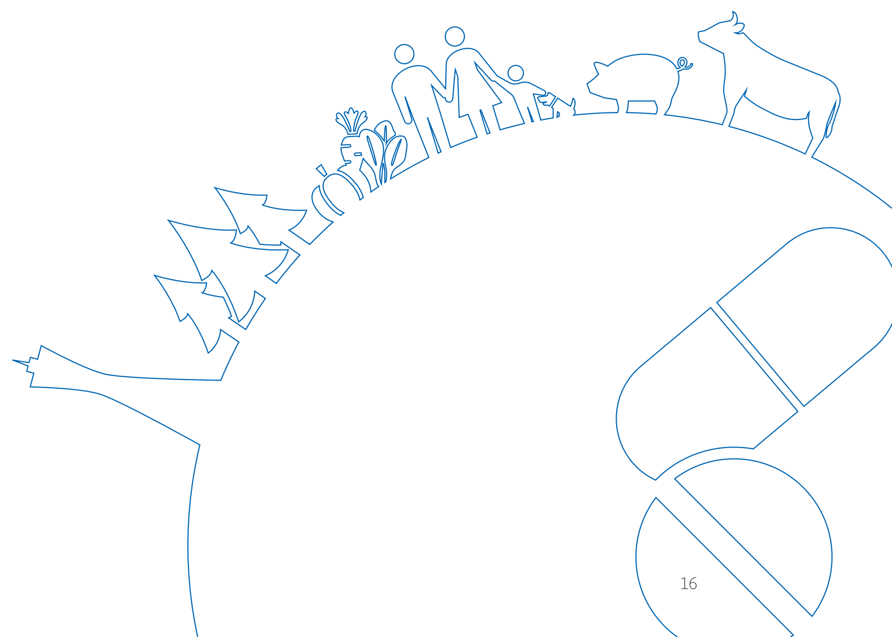

References

1) [Activity Report] Policy Brief on the Current Status of and Measures against Antimicrobial Resistance (AMR) in Japan and Abroad (November 20, 2020) https://hgpi.org/research/amr-16.html (Refer to 2021-05-26)
2) Ensuring sustainable access to effective antibiotics for EVERYONE-EVERYWHERE. https://www.reactgroup.org/wp-content/uploads/2021/03/ReAct-Report-Ensuring-sustainable-access-to-effective-antibiotics-for-everyone-everywhere-How-to-address-the-global-crisis-in-antibiotic-Research-and-Development-March-2021.pdf, (Refer to 2021-05-26)
3) Antimicrobial resistance. http://www.emro.who.int/health-topics/drug-resistance/regional-situation.html, (Refer to 2021-05-26)
4) Current Status and Impact of Carbapenem-resistant Enterobacteriaceae in India, Nepal and other Countries http://medical.radionikkei.jp/kansenshotoday_pdf/kansenshotoday-160330.pdf, (Refer to 2021-05-26)
5) Gu Y, Ohmagari N. Overseas Current Status of Drug Resistance and Use of Antimicrobials. Journal of Japanese Society of Chemotherapy. 2019;67 (1): 13-22.
6) Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. https://amr-review.org/sites/default/files/AMR Review Paper - Tackling a crisis for the health and wealth of nations_1.pdf, (Refer to 2021-05-26)
7) Ohmagari N. Action Plan on Antimicrobial Resistance (AMR) 2016-2020. Journal of the Japanese Society of Internal Medicine. 2017 Oct 10;106 (10): 2259-64.
8) Nagao M. Measures against Hospital-acquired Infection and antimicrobial Stewardship Program. Journal of the Japanese Society of Internal Medicine. 2019 Sep 10;108 (9): 1815-19.
9) Kobayashi H. Current Status of Methicillin-Resistant *Staphylococcus Aureus* (MRSA). Antiseptics and Disinfectants for Infection Control. 2006;13:71-3.
10) Guide to Proper Use of Antimicrobial Drugs, 1st edition. https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000166612.pdf, (Refer to 2021-05-26)
11) Antimicrobial resistance: a global threat. https://www.unep.org/explore-topics/chemicals-waste/what-we-do/emerging-issues/antimicrobial-resistance-global-threat, (Refer to 2021-05-26)
12) van Loo I, Huijsdens X, et al. Emergence of methicillin-resistant Staphylococcus aureus of animal origin in humans. Emerg Infect Dis. 2007 Dec;13(12):1834-9.
13) Lazarus B, Paterson DL, et al. Do human extraintestinal Escherichia coli infections resistant to expanded-spectrum cephalosporins originate from food-producing animals? A systematic review. Clin Infect Dis. 2015 Feb 1;60(3):439-52.
14) Liu YY, Wang Y, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. Lancet Infect Dis. 2016 Feb;16(2):161-8.
15) Urase T, Sato T. Quantitative Monitoring of Resistance in Escherichia coli to Clinically Important Antimicrobials in an Urban Watershed. Journal of Water and Environment Technology. 2016;14 (5):341-9.
16) Komori K. Suzuki Y. Survey on the Presence of Drugs in River Basins. EICA. 2013;17(4):41-4.
17) Initiatives for Addressing Antimicrobial Resistance in the Environment: Current Situation and Challenges. https://amr.ncgm.go.jp/pdf/20200128AMRenvironmentJP.pdf, (Refer to 2021-05-26)
18) Action Plan. http://amr.ncgm.go.jp/general/1-4.html, (Refer to 2021-05-26)
19) Antimicrobials are not effective: Antimicrobial Resistance (AMR) is Spreading! What Can Each of Us Do? https://www.gov-online.go.jp/useful/article/201611/2.html, (Refer to 2021-05-26)
20) Antimicrobial Awareness Survey Report 2019 http://amr.ncgm.go.jp/pdf/20190927_report_press.pdf, (Refer to 2021-05-26)
21) Essential Measures to Prevent Infection https://amr.ncgm.go.jp/general/1-6-3.html, (Refer to 2021-05-26)
22) Learn about AMR; Think about Drug Resistance http://amr.ncgm.go.jp/pdf/ig-1.pdf, (Refer to 2021-05-26)
23) Ray MJ, Tallman GB, et al. Antibiotic prescribing without documented indication in ambulatory care clinics: national cross-sectional study. BMJ. 2019 Dec 11;367.
24) Shigemura K. Arakawa S. Fujisawa M. Antimicrobial Treatment for Urinary Tract Infections with Drug Resistance Taken Into Account. Journal of Japanese Society of Chemotherapy. 2015 Sep;63(5): 462-8.
25) Ozawa M. Current Situation associated with Veterinary Antimicrobial Substances (4) Drug Resistance Mechanisms. Journal of Japan Veterinary Medical Association. 2016;69:713-7.
26) Smart Use of Antimicrobials to Ensure Cures for Bacterial Infections https://amr.ncgm.go.jp/general/, (Refer to 2021-05-26)
27) Abraham EP, Chain E. An enzyme from bacteria able to destroy penicillin. Nature. 1940;146:837.
28) Cafferkey MT, Hone R, et al. Methicillin-resistant Staphylococcus aureus in Dublin 1971-84. Lancet. 1985 Sep 28;326(8457):705-8.
29) Paulsen J, Solligard E, et al. The Impact of Infectious Disease Specialist Consultation for Staphylococcus aureus Bloodstream Infections: A Systematic Review. Open Forum Infect Dis. 2016 Apr;3(2): ofw048.
30) Whitney CG, Farley MM, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med. 2003 May 1;348(18):1737-46.
31) Seo YB, Lee J, et al. Randomized controlled trial of piperacillin-tazobactam, cefepime and ertapenem for the treatment of urinary tract infection caused by extended-spectrum beta-lactamase-producing Escherichia coli. BMC Infect Dis. 2017 Jun 7;17(1):404.
32) Suzuki S, Miyoshi Y, Nakaya R. R plasmids among Gram-negative bacteria with multiple drug resistance isolated in a general hospital, Microbiol. Immunol. 1978;22(5):235-47.
33) Yigit H, Queenan AM, et al. Novel carbapenem-hydrolyzing beta-lactamase, KPC-1, from a carbapenem-resistant strain of Klebsiella pneumoniae. Antimicrob Agents Chemother. 2001 Apr;45(4):1151-61.
34) Current Status of Gonococcal and Chlamydial Infections and Associated Issues http://medical.radionikkei.jp/kansenshotoday_pdf/kansenshotoday-150304.pdf, (Refer to 2021-05-26)
35) Drug-resistant Neisseria Gonorrhoeae, the Most Imminent Threat https://medical.nikkeibp.co.jp/leaf/mem/pub/report/t278/201610/548625.html, (Refer to 2021-05-26)
36) Gonorrhoea https://seibyou.net/qa_gonorrhea, (Refer to 2021-05-26)
37) World malaria report 2018. https://www.who.int/publications/i/item/9789241565653, (Refer to 2021-05-26)
38) Report on antimalarial drug efficacy, resistance and response: 10 years of surveillance (2010-2019). https://www.who.int/publications/i/item/9789240012813, (Refer to 2021-05-26)
39) AMR week: Antimalaria drug resistance not alarming but growing fast, says WHO report. https://www.downtoearth.org.in/news/health/amr-week-antimalaria-drug-resistance-not-alarming-but-growing-fast-says-who-report-74328, (Refer to 2021-05-26)
40) Drug Resistance-associated Issues [Current Status of Treatment and Associated Issues] https://www.hiv-resistance.jp/knowledge01.htm, (Refer to 2021-05-26)
41) Resistance of Influenza Virus to Anti-influenza Virus Agents https://www.city. yokohama.lg.jp/kurashi/kenko-iryo/eiken/kansen-center/shikkan/a/influresistance1.html, (Refer to 2021-05-26)
42) Drug-resistant Viruses https://influ-info.jp/faq/faq4.html#q02, (Refer to 2021-05-26)
43) Resistance against Anti-influenza Virus Agents and Measures against the Resistance https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou01/kouen-kensyuukai/pdf/h28/kouen-kensyuukai_04.pdf, (Refer to 2021-05-26)