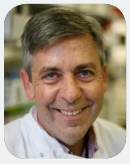
Being AWaRe of the risk of inappropriate antibiotic use in people living with cancer

Mike Sharland, Centre for Neonatal and Paediatric Infection, St George's University, London, UK; **Veronica Zanichelli,** Ottawa Hospital Research Institute, Ottawa, Ontario, Canada; **Bishal Gyawali,** Division of Cancer Care and Epidemiology, Queen's University Cancer Research Institute, Kingston, Canada; **Manju Sengar,** Department of Medical Oncology, Tata Memorial Centre, Affiliated to Homi Bhabha National Institute, Mumbai, India; **Bernadette Cappello,** Technical Officer, Essential Medicines, Access to Medicines and Health Products Division, World Health Organization, Geneva, Switzerland; **Lorenzo Moja,** Scientist, Essential Medicines, Access to Medicines and Health Products Division, World Health Organization, Geneva, Switzerland and **Benedikt Huttner,** Team Lead, Essential Medicines, Access to Medicines and Health Products Division, World Health Organization, Geneva, Switzerland

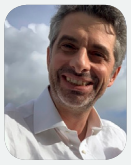

MIKE SHARLAND


VERONICA ZANICHELLI


BISHAL GYAWALI


MANJU SENGAR


BERNADETTE CAPPELLO


LORENZO MOJA


BENEDIKT HUTTNER

Antibiotics are essential medicines. Their inappropriate use can harm patients, particularly those with underlying diseases, such as cancer. In 2017, the World Health Organization (WHO) introduced the AWaRe classification of antibiotics into three groups: Access, Watch and Reserve. Broad-spectrum Watch antibiotics have a higher potential to select for antimicrobial resistance (AMR) than more narrow-spectrum Access antibiotics. Reserve antibiotics are last-resort options for the treatment of multidrug-resistant organisms. Watch antibiotics are overused worldwide, contributing to the global health threat of AMR, which disproportionally affects people living with cancer. Inappropriate use of antibiotics may also diminish the efficacy of certain cancer treatments and exposes patients to other adverse effects of antibiotics. Professionals providing care for patients living with cancer have a responsibility to promote the optimal use of antibiotics across the three AWaRe categories.

The success stories of modern oncology would not be possible without the major supportive care role of antibiotics. Many chemotherapeutic medicines are associated with neutropenia and mucositis, increasing a patient's susceptibility to life-threatening bacterial infections. Cancer care often requires the use of invasive medical devices from central intravenous lines to urinary catheters which further increase the risk of bacterial infections. Bone marrow transplant patients may spend prolonged periods in agranulocytosis and often require immunosuppressive treatments for graft versus host disease, further augmenting the risk of infections. Without antibiotics to effectively treat – and to a lesser degree prevent – bacterial infections, many patients would succumb to infectious complications rather than die of the cancer itself.

Unfortunately, the efficacy of antibiotics to act as a "substitute" for an impaired immune system can no longer be taken for granted. In 2019, there were an estimated 1.27 million deaths worldwide attributable to bacterial antimicrobial resistance (AMR), while many more had their health impacted by the adverse consequences of antibiotic resistance *(1)*. Because of the repeated and prolonged contact with the health-care environment and frequent antibiotic exposure, often with broad-spectrum antibiotics, people living with cancer are at higher risk of being colonized and infected by antibiotic-resistant bacteria than other populations. They also have a particularly high risk of experiencing negative outcomes, including death, when infections are caused by antibiotic-resistant bacteria *(2,3)*. The prevention and control of AMR, therefore, has a special urgency in oncology.

Many different factors contribute to the emergence and spread of AMR, but exposure to antibiotics has been consistently shown to increase the risk of being colonized or infected with antibiotic resistant bacteria *(4)*. Antibiotic

exposure also increases the probability of then transmitting these bacteria to other vulnerable patients *(5)*. Hospital oncology wards are particularly susceptible to outbreaks of antibiotic-resistant bacteria, such as vancomycin-resistant enterococci *(6)* or *Clostridoides difficile* infection (CDI), which can have severe consequences for patients and interfere with the safe and effective provision of health care *(7)*.

Given the risk of AMR, oncology patients are often treated empirically with broad-spectrum antibiotics including antibiotics active against multidrug-resistant organisms, potentially exacerbating AMR further. This situation is further exacerbated in settings where microbiologic diagnostics capacity is insufficient.

In recent years, there has been growing recognition that interventions to promote the appropriate use of antibiotics (also called "antibiotic stewardship") for patients living with cancer are important to prevent harm to both patients and hospitals *(8)*. Increasing evidence suggests that gut microbiota play a crucial role in the effectiveness of novel cancer treatments such as immune checkpoint inhibitors (ICIs) *(9)*. While some bacterial species significantly enhance the anticancer effect of ICIs, antibiotic-mediated alterations of the microbiome may be associated with a reduced clinical response to ICIs *(10)*. In addition, some studies also suggest that antibiotic treatment may be associated with poorer outcomes in people receiving platinum-based chemotherapy for certain cancers *(11)*. Thus, there are many good reasons beyond AMR to use antibiotics appropriately in cancer patients and avoid an unnecessary and prolonged use of antibiotics, as well as limiting the use of antibiotics (or combinations of antibiotics) with an unnecessarily broad spectrum. The importance of antibiotic stewardship is, however, not specific to cancer care and it can ultimately only be successful if its principles are applied by health-care professionals throughout the entire health-care system.

In May 2015, the World Health Assembly adopted a global action plan on AMR *(12)*, and all antibiotics on the WHO Model List of Essential Medicines (EML) were reviewed, defining first- and second-choice options for 34 infections in primary health care and in hospitals (including infections affecting cancer patients such as febrile neutropenia and sepsis). In the context of the global action plan, the AWaRe (**A**ccess, **W**atch, **Re**serve) classification of antibiotics was introduced in 2017 as a stewardship tool to classify antibiotics according to their potential for resistance *(13)*:

- **Access** antibiotics have a narrow spectrum of activity, lower cost, a good safety profile and generally low resistance potential. They are recommended as empiric first- or second-choice treatment options for common infections. Examples of Access antibiotics include penicillin, amoxicillin and gentamicin.
- **Watch** antibiotics are broader-spectrum antibiotics, generally with higher cost and toxicity, and are recommended only as first-choice options for patients with more severe clinical presentations or for infections where the causative pathogens are more likely to be resistant to Access antibiotics (e.g., upper urinary tract infections). Examples of Watch antibiotics include ciprofloxacin, ceftriaxone and azithromycin.
- **Reserve** antibiotics are last-choice antibiotics used to treat infections caused by multidrug-resistant (MDR) bacteria. Examples of Reserve antibiotics include ceftazidime and avibactam, colistin and linezolid.

Analyses of global antibiotic use data have shown that there is important overuse of Watch antibiotics in many countries, with an overall increasing trend *(14)*. Therefore, WHO has established a global target: for at least 60% of all country-level antibiotic use (comprised mostly of community use) to be antibiotics from the Access category. This is a realistically achievable target given that the large majority of infections encountered in primary health care can either be treated symptomatically without antibiotics or with Access antibiotics if treatment is indicated *(14)*. In order to help countries reach the 60% target, WHO has developed the AWaRe Antibiotic Book which not only provides guidance on what antibiotics to use (favouring Access over Watch antibiotics whenever possible), but also how to use them (e.g., dose and duration for both adults and children), taking into account antibiotic stewardship principles.

It is important that WHO's overarching antibiotic stewardship approach is applied to cancer care. People living with cancer suffer from many of the same common infections as the general population and unless patients are severely immunocompromised, these can be managed similarly. Viral respiratory tract infections are frequently treated unnecessarily with antibiotics, exposing patients to unnecessary risks without the accompanying benefits *(15)*. The *AWaRe Antibiotic Book* clearly indicates when a "No antibiotic care" approach is possible and provides guidance on diagnosis, likely pathogens and symptomatic treatment options. It is evident that in cancer patients, treatment decisions will need to be individualized taking into account the degree of immunosuppression, colonization with MDR organisms and recent antibiotic treatment. The guidance provided in the *AWaRe Antibiotic Book* can help prescribers avoid unnecessary antibiotic use in general – and Watch antibiotic use in particular – in people living with cancer.

The *AWaRe Antibiotic Book* also provides guidance on Reserve antibiotics. Currently, eight Reserve antibiotics are considered essential medicines and included on the 2021 WHO Model

List of Essential Medicines *(16)*. Given that most of them need to be given intravenously, their use is mostly restricted to the health-care facility setting. These are "last-resort" options for the treatment of infections caused by the critical- and high-priority pathogens according to the WHO 2017 priority pathogens list *(17)*, notably carbapenem-resistant Gram-negative bacteria. Carbapenem-resistant Enterobacterales pose a particular challenge to delivering safe health care to people with cancer because of their increasing global spread and the limited treatment options available *(18,19)*. In addition to ensuring appropriate use of Reserve antibiotics, effective infection control measures are the key to preventing these pathogens from spreading in cancer wards and clinics *(20)*.

Reserve antibiotics must be used judiciously, with unnecessary and inappropriate use kept as low as possible since we cannot expect many new antibiotics with new mechanisms of action to become available in the coming years. On the other hand, essential Reserve antibiotics must be accessible globally for patients who need them, especially in low- and middle-income countries, and cancer patients are likely to represent an important proportion of these patients. Unfortunately, the optimal use of Reserve antibiotics is hampered by the fact that existing evidence to guide use is mostly based on studies with low internal and external validity *(21)*. While fully acknowledging the limitations of the available evidence, the *AWaRe Antibiotic Book* provides guidance on how the essential Reserve antibiotics should be used, including criteria when empiric use – i.e., before identification of the responsible pathogen – may be justified. Surveillance of the use of Reserve antibiotics should be part of any antibiotic stewardship programme *(22)*.

Countries and regions are encouraged to use the *AWaRe Antibiotic Book* as model for the development or adaptation of local and national guidelines. Providing optimal care for patients with cancer requires a careful balance between access to essential antibiotics to treat life-threatening infections, including Reserve antibiotics, and avoiding the inappropriate use of these invaluable medicines. Practical examples of antibiotic conservation in oncology include taking a careful risk based-approach to the use of antibiotic prophylaxis during episodes of neutropenia; using short durations of treatment for febrile neutropenia where appropriate, following evidence-based empiric guidelines; preferential use of narrow-spectrum antibiotics when sensitivity patterns allow; rapid step-down from intravenous to oral treatment whenever possible, discharge from hospital at the earliest appropriate opportunity and the continuous avoidance where possible of multiple, prolonged, broad-spectrum antibiotic treatment. The AWaRe classification and the *AWaRe Antibiotic Book* aim to contribute to achieving the critical goal of maintaining the availability of optimal antibiotic treatment options for current and future cancer patients globally. ■

Professor Mike Sharland is a globally leading expert in antimicrobial prescribing, resistance and health-care-associated infection in children. He is the lead clinical advisor for the neonatal and paediatric programme of the Global Antibiotic Research and Development Partnership (GARDP) and Vice-Chair and AMR lead of the Penta Foundation, a global Paediatric Infectious Diseases research network.

He has Chaired the Department of Health's National Expert Advisory Committee of Antimicrobial Prescribing, Resistance and Healthcare Associated Infection (APRHAI) from 2011 to 2018. He has also been an adviser to the World Health Organization for many years, which includes being a member of the Expert Committee on the Selection and Use of Essential Medicines and the Chair of the Antibiotic Working Group of the EML/EMLc, which developed the Access/Watch/Reserve (AWaRe) grouping of antibiotics.

Professor Sharland's principal research interest is optimizing the best use of antimicrobials in children. He has a long-standing interest in developing the evidence base for the use of all paediatric antimicrobials and has developed a clear research strategy using both cohort studies and clinical trials to improve the evidence base for antimicrobial prescribing. He leads a wide number of clinical projects in the globally with active EDCTP, EU H2020, GARDP, NIHR, MRC, and Wellcome Trust funding.

Veronica Zanichelli is an infectious diseases physician who trained at Padua University, Italy. Since 2014, she has been working as research fellow and research assistant in different institutions in Switzerland. including the Geneva University Hospitals, in Canada at the Jewish General Hospital in Montreal and Ottawa Hospital Research Institute, focusing her work and research on AMR and health-care-associated infections. Since 2019, she has been working remotely as a consultant for World Health Organization in the Access to Medicines and Health Products Division).

Bishal Gyawali, MD, PhD is a medical oncologist and an Associate Professor in Oncology and Public Health Sciences at Queen's University, Kingston, Canada. His areas of research include cancer policy and global oncology. He is an advocate of the "cancer groundshot", a phrase he coined to imply that investment should be made on known high-value interventions in cancer care that are easy to implement globally and are affordable. He has written or co-written more than 140 peer-reviewed articles.

Professor Manju Sengar, MD (Medicine), DM (Medical Oncology) is Professor, Adult Hematolymphoid Disease Management Group, Medical Oncology, at the Tata Memorial Hospital, Mumbai, India. Dr Sengar completed her training in internal medicine and medical

oncology from the All India Institute of Medical Sciences, New Delhi, india. She completed her post graduate diploma in clinical trials at the London School of Hygiene & Tropical Medicine (external programme). She is a faculty member for the CReDO (international collaboration for research methods development in oncology) workshop. She is a recipient of American Society of Hematology visitor training programme fellowship at Duke University, Durham, USA. She is a core group member of National Cancer Grid, India. She is a founder member of Hematology Cancer Consortium. Her main areas of clinical research are non-Hodgkin lymphomas, lymphomas in HIV/AIDS and acute lymphoblastic leukaemia.

Bernadette Cappello is a technical officer in the Essential Medicines Team at the World Health Organization (WHO) in Geneva, Switzerland. She is a pharmacist with a Master's in Public Health and has expertise in medicines evaluation and health technology assessment in national and international settings. Prior to joining WHO, she was Director of the Pharmaceutical Benefits Advisory Committee Secretariat in the Australian Government's Department of Health.

Lorenzo Moja is a scientist in the Secretariat of the Expert Committee on Selection and Use of Essential Medicines at the World Health Organization in Geneva, Switzerland. His work focuses on the comparative effectiveness of new and existing pharmaceuticals, health policy evaluation, and pharma regulation.

Benedikt Huttner is the Secretary of the Expert Committee on the Selection and Use of Essential Medicines and team lead Essential Medicines at the World Health Organization (WHO), a position he has held since March 2021. He obtained his medical degree in Munich, Germany, in 2001 and then moved to Switzerland. After training in internal medicine in Bellinzona (2002–2004) he specialized in infectious diseases in Zurich (2004–2006). Between 2006 and 2021 he worked at the Geneva University Hospitals, first in the Infection Control Department and then in the Division of Infectious Diseases (since 2014) as an attending physician. Between 2010 and 2012, he completed a research fellowship in Salt Lake City, USA, where he obtained a master's degree in clinical research. In 2020, he became Assistant Professor at the Faculty of Medicine at the University of Geneva with his research focusing on appropriate use of antimicrobials and other medicines and the control of multidrug-resistant bacteria. Before joining WHO as staff member he worked as part-time consultant with the EML team since 2017,

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