AMR CONTROL SUPPLEMENT

THE CHALLENGE FOR THE CANCER COMMUNITY

FOREWORD: ANIL D'CRUZ
PRESIDENT, UNION FOR INTERNATIONAL CANCER CONTROL

SUPPLEMENT EDITORS: SHALINI JAYASEKAR ZÜRN AND SONALI JOHNSON
UNION FOR INTERNATIONAL CANCER CONTROL

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GARDP

Life is precious.

Breast cancer is the most common type of cancer worldwide.

Over 2 million women are diagnosed with breast cancer each year. Common treatments include radiation and chemotherapy, which make patients especially vulnerable to bacterial infections.

These infections must be quickly treated with antibiotics, one of modern medicine's greatest successes.

But resistance to antibiotics is growing.

If we continue on the current path, it will become increasingly difficult to treat bacterial infections, especially in people with weakened immune systems.

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Professor Dame Sally Davies, UK Special Envoy on Antimicrobial Resistance

"Our world is facing an antimicrobial resistance (AMR) pandemic. Globally, almost 5 million deaths annually are associated with AMR. For health-care workers, for patients and their families, these data are real, lived, scary experiences – and a wake-up call that we are hurtling towards the undoing of modern medicine sooner than we predicted. AMR impacts all of us, and each of us can play a part in containing this insidious threat.

To save lives and livelihoods, we need to catalyze innovation for new and equitably accessible antimicrobial treatments. I am pleased that the G7 Finance and Health Ministers have committed to strengthening antibiotic innovation through piloting "pull incentives" that can grow the global marketplace for antibiotics, and level up access while avoiding excess use. The UK's new subscription model is now live, and the US PASTEUR Act is in Congress, and I call on all countries, and industry, to work together to value antimicrobials as critical infrastructure.

We need broad, integrated surveillance systems to help us anticipate outbreaks before it is too late to beat them back. Coordinated surveillance systems across communities, sectors and countries can enable targeted interventions against AMR. For politicians and policy-makers, accessible data provide an understanding and ownership of the challenge. On the ground, data empower health-care workers with the tools they need to drive solutions that work for the context they are facing.

We need to move forward together and take the public with us. From health-care workers and scientists singing about the discovery of penicillin and the toll of AMR in the musical production, *The Mould That Changed the World*, to cartoons depicting an apocalyptic world without antibiotics and to the Roll Back Antimicrobial Resistance Initiative running drama clubs in schools in Tanzania to educate children about AMR, I hope to see the arts harnessed to inspire communities to be activists and actors on AMR.

In 2024, there will be a High-Level Meeting on AMR at the United Nations General Assembly in New York. This will be a pivotal moment for global stakeholders to come together and reaffirm commitments on AMR, leveraging lessons from COVID-19 and from climate change, too. I urge everyone, everywhere, to help shape this meeting and the outcomes from it."

Dame Sally Davies was appointed as the UK Government's Special Envoy on AMR in 2019. She is also the 40th Master of Trinity College, Cambridge University. Dame Sally was the Chief Medical Officer for England and Senior Medical Adviser to the UK Government from 2011–2019. She has become a leading figure in global health, serving as a member of the World Health Organization (WHO) Executive Board 2014–2016 and as co-convener of the United Nations Inter-Agency Co-ordination Group (IACG) on Antimicrobial Resistance (AMR), which reported in 2019.

In the 2020 New Year Honours, Dame Sally became the second woman (and the first outside the British Royal family) to be appointed Dame Grand Cross of the Order of the Bath (GCB) for services to public health and research, having received her DBE in 2009.

Foreword

Anil D'Cruz, President, Union for International Cancer Control

The Union for International Cancer Control (UICC) and the UICC-led Task Force on Antimicrobial Resistance and Cancer Care are honoured to publish this *AMR Control Supplement* entitled *The Challenge for the Cancer Community*.

Antimicrobial resistance (AMR) or drug resistance is one of the most important global health issues today. The World Health Organization has identified AMR as a serious threat to global health, development and food security. Antimicrobial resistance can negatively affect cancer care outcomes and very often does. In fact, as many as one in five cancer patients undergoing treatment needs to be hospitalized due to infection, and antibiotics are the main line of defence for these patients. Unfortunately, drug-resistant pathogens are rapidly emerging, and our antimicrobials (including antibiotics) are simply not effective any more against these resistant organisms. The result is that treatments for infection are losing their effectiveness and the great advances made in treating cancer are currently being undermined.

The situation will only get worse unless action is taken. As a head and neck surgical oncologist for 30 years, and President of UICC, I know the terrible impact that drug-resistant infections have on a patient's treatment journey. Along with treatment delays, longer stays in the intensive care unit and increased treatment costs, patients also face a fatal outcome if drug-resistant infections are not treated successfully. The global threat of AMR has evolved very rapidly due to a number of reasons, including a lack of awareness of the scale and potential impact of drug resistance, irrational prescriptions by prescribers, and a lack of access to treatments. Furthermore, low- and middle-income countries also face the highest burden of AMR due to limited access to the right treatments.

We can take steps to address AMR for better cancer care outcomes. This supplement will provide guidance for the cancer community on key topics that must be addressed and show the steps we can take to address this threat.

I am delighted to present this important publication, and thank the authors of the chapters and the UICC-led Task Force on Antimicrobial Resistance and Cancer Care for their commitment to this issue, for reviewing the articles, and also for contributing to this supplement. ■

Anil D'Cruz is the current Director of Oncology at Apollo Hospitals in India, ex-Director of the Tata Memorial Hospital, Mumbai, India, a researcher, administrator and crusader in the field of cancer control, as well as President of UICC for the 2020–2022 term.

The importance of addressing antimicrobial resistance for better cancer care outcomes


SHALINI JAYASEKAR ZÜRN


SONALI JOHNSON


CARY ADAMS

Shalini Jayasekar Zürn, Senior Advocacy Manager; **Sonali Johnson,** Head of Knowledge, Advocacy and Policy; and **Cary Adams,** Chief Executive Officer, Union for International Cancer Control

Antimicrobial resistance (AMR) is a rapidly growing global threat to health and wellbeing, and taking steps to address it in a collaborative, multisectoral way must be a priority action for governments. The World Health Organization has stated that AMR is one of the top 10 global public health emergencies we are currently facing *(1)*. By 2050, AMR could be the direct cause of death for an estimated 10 million people per year *(2)*. The economic loss caused by AMR will also be catastrophic, with over US$ 100 trillion in damage due to higher health-care costs affecting the global economy and world trade, as well as exerting a devastating impact on families and communities *(3)*. In addition to tackling AMR through policy and legislation, ways to tackle it effectively must happen every day in hospitals, in pharmacies and in our medicine cabinets *(4)*.

AMR occurs when microbes (such as bacteria, fungi, viruses and parasites) develop the capacity to continue to grow, even when exposed to medicines that are intended to destroy them or limit their growth (such as antibiotics, antifungals, antivirals, antimalarials and anthelmintics). The medicines then stop working effectively, and drug-resistant infections persist in the body, with the increased risk of these infections being spread to others *(5)*.

The misuse and overuse of antimicrobial medicines are key factors that have contributed to the increase in drug-resistant pathogens. In many places, antibiotics are overused and misused in people, livestock and agriculture and are often given without proper professional supervision. Examples of misuse include when people who have viral infections like a cold or flu take antibiotics, and when they are used as growth promoters for food-producing animals or used to prevent infections in healthy animals *(6)*.

An individual can pick up an infection from a health-care facility (these infections are called health-care-associated infections [HAIs] or from the community [community-acquired infections]). Health-care-associated infections can occur during surgery or from medical devices inserted into the body *(7)*. These infections can easily happen due to a contaminated surgical instrument or a catheter, which can facilitate pathogens to enter the bloodstream and cause an infection. On the other hand, community-acquired infections, which are infections acquired outside of a health-care facility, are also a cause for concern. This is because of unregulated access to medicines, bad prescribing practices and lack of knowledge on infection prevention and hygiene.

Increasingly, these infections are becoming more and more drug resistant. Antimicrobial resistance has an adverse effect on health outcomes, including longer stays in hospital, and increased mortality. The cancer community is particularly affected by this "silent pandemic". It is a silent pandemic because, unlike COVID-19, only a few understand the threat, but the impact of AMR is enormous. Antimicrobial resistance has a huge negative impact on treatment outcomes for people undergoing treatment for cancer. People with cancer are more susceptible to infections due to the underlying disease and a compromised immune system as a result of treatments for cancer like bone marrow transplants, radiotherapy and chemotherapy. In particular, a common side effect of treatment is neutropenia, which is the depletion of neutrophils (a type of white blood cell), which severely affects the ability of people living with cancer to fight bacterial and fungal infections *(8)*. As mentioned above, catheters and other medical devices used in treatment are additional factors that contribute to the increase in the risk of infection *(9)*. If these devices are contaminated, people living with cancer are at increased risk of developing bloodstream infections as they have to deal with repeated use of these devices.

Antimicrobials (especially antibiotics and antifungals) are a vital and indispensable part of cancer treatment. Drug-resistant infections can undermine all the progress made in cancer treatment. A 2019 survey of oncologists showed that more than four out of 10 oncologists were worried that chemotherapy would soon stop being viable *(10)*. Collective action must be taken immediately to address this threat for better cancer treatment outcomes.

In 2019, the Union for International Cancer Control (UICC) acknowledged the importance of addressing AMR for better

cancer care outcomes and made it a priority topic. The following year, UICC set up a task force of experts – from the infectious disease community and the cancer community. This UICC-led task force was established to guide UICC in highlighting current evidence on AMR, identify research gaps in knowledge of cancer and AMR, share best practices and engage the cancer community to collaborate and mobilize policy change, which includes addressing the threat of AMR for better cancer care outcomes. Since then, UICC, with guidance from the task force, has written extensively on the subject and held various events, including several virtual dialogues and an online purpose-built course on AMR to spread awareness and get the cancer community involved in solutions to the AMR crisis.

To sustain focus on the issue, promote greater dialogue and mobilize action on addressing AMR, the task force has collaborated with Global Health Dynamics, publisher of *AMR Control*, to create a special supplement emphasizing the impact of AMR on cancer care outcomes. Our aim is that this supplement will serve as a key reference for the cancer community and a resource to support advocacy efforts for policy change. This supplement is the first *AMR Control* supplement to focus on AMR and cancer in more depth and consider what this really means for the cancer community as a whole – administrators, health-care professionals, researchers, patients and communities. It also addresses how AMR is directly affecting cancer care and cancer patients, now and in the future.

The objective of the publication is to target policy-makers and other relevant stakeholders to come together and see AMR as an issue that concerns every country and all humanity, and to stress the need for collective and urgent action. As seen during the global COVID-19 pandemic, disease-causing pathogens are not confined to national borders.

Along with the key objective of raising awareness and sharing knowledge, the supplement also highlights what is currently being achieved and what practical solutions can be put in place. The articles, written by more than 50 experts, cover a wide range of topics which provide information on the negative impact that AMR has on cancer care outcomes and provide guidance on how the cancer community can counter the challenge of AMR.

We must continue to ensure that AMR is a priority on the global health agenda. It is encouraging that the first High-Level Meeting (HLM) on AMR took place in September 2016 at the General Assembly of the United Nations. Here, for the first time, governments committed to a coordinated approach to address the threat of AMR *(11)*. The next HLM on AMR, which is to be held in 2024 is an important opportunity for the cancer community to work side by side with other health communities to ensure that countries have national action plans on AMR in place with adequate funding, and that we continue to raise awareness and advocate for access to appropriate treatments and the implementation of infection prevention and control around the world. ■

Shalini Jayasekar Zürn is a Senior Advocacy Manager with the Union for International Cancer Control (UICC). She is a biologist by training and has extensive experience on the issues of access to quality-assured medicines. Shalini worked with the World Health Organization on their Model List of Essential Medicines as well as Médecins Sans Frontières's access campaign and other NGOs. She also has worked with the pharmaceutical industry.

Sonali Johnson is Head of Knowledge, Advocacy and Policy at the Union for International Cancer Control (UICC). Her main area of work is to ensure that cancer prevention, treatment, and care is positioned within the global health and development agenda. During her professional career, Sonali has worked on a range of public health issues including cancer control, gender and HIV/AIDS, reproductive and sexual health, gender based violence, knowledge translation, research ethics and health and human rights.

Dr Cary Adams has a BSc Hons in Economics, Computing and Statistics, a Masters degree (with Distinction) in Business Administration. He is a Harvard Business School Alumni, and has received two honorary doctorates for international relations and health. In 2009, Cary made a career change from international banking to become CEO of the Union for International Cancer Control (UICC), Geneva, Switzerland.

UICC, the task force, *AMR Control* and contributing authors hope the cancer community finds this supplement a useful resource and welcome feedback (please send comments to Shalini Jayasekar Zürn at Jayasekar-zurn@uicc.org).

References

1. World Health Organization (WHO). Antimicrobial resistance – key facts.2017. Accessed 1 September 2022 (Antimicrobial resistance (who.int)
2. World Health Organization (WHO). New report calls for urgent action to avert antimicrobial resistance crisis. 23 April 2019. Accessed 15 August 2022. New report calls for urgent action to avert antimicrobial resistance crisis (who.int)
3. The World Bank. By 2050, drug-resistant infections could cause global economic damage on par with 2008 financial crisis. 20 September 2016. Accessed 1 July 2022. By 2050, drug-resistant infections could cause global economic damage on par with 2008 financial crisis (worldbank.org)
4. Dame Sally Davies. Dame Sally Davies: Antimicrobial resistance is the silent pandemic growing in the shadows. inews. 27 May 2021. Accessed 15 August 2022. Dame Sally Davies: Antimicrobial resistance is the silent pandemic growing in the shadows (inews.co.uk)
5. Union For International Cancer Control (UICC). Antimicrobial resistance and its impact on cancer care. 10 May 2022. Accessed 22 August 2022. Antimicrobial resistance (AMR) and its impact on cancer care (uicc.org)
6. World Health Organization (WHO). Antimicrobial resistance – key facts.2017. Accessed 1 September 2022 (Antimicrobial resistance (who.int)
7. Centers for Disease Control and Prevention (CDC). Where Resistance Spreads: Healthcare Facilities. 9 November 2021. Cdc.gov. Accessed 5 September 2022. Where Resistance Spreads: Healthcare Facilities | CDC
8. Yehoda M Martei and Shalini J Zurn. Addressing antimicrobial resistance for better care in cancer patients. Revive (GARDP). 24 September 2021. Accessed 20 July 2022. Addressing antimicrobial resistance for better care in cancer patients – by Yehoda M. Martei and Shalini J. Zürn – REVIVE (gardp.org)
9. Rolston KV. Infections in Cancer Patients with Solid Tumors: A Review. Infectious Diseases Therapy. 2017; 6(1):69-83.
10. Longitude Prize. Effectiveness of cancer treatments threatened by rising antibiotic resistance. February 2020. Accessed 2 September 2022. Longitude Prize
11. Press Release: High-Level Meeting on Antimicrobial Resistance | General Assembly of the United Nations

Ulrika Årehed Kågström, Secretary General, Swedish Cancer Society

"Over the last decades, there has been substantial progress in cancer care, with key advances across the core pillars of surgery, radiotherapy and medicines. However, the significant and growing threat of drug-resistant bacteria can undermine all these efforts.

Today, it is estimated that at least one in five cancer patients need antibiotics during their treatment. The consequences for cancer treatment when antibiotics are no longer effective against resistant bacteria are serious because people living with cancer rely on antibiotics for the prevention and treatment of infections. Whether it is for surgery, chemotherapy or stem cell transplants, the availability of antibiotics is crucial for cancer care outcomes. Today, the threat of antibiotic resistance is a major issue that needs to be urgently addressed to ensure cancer control.

Antibiotic resistance spreads across borders, and efforts to address it must therefore be conducted both nationally and globally. The Swedish Cancer Society is actively engaged in the important activity of spreading awareness at the national level as well as advocating for the threat of antimicrobial resistance (AMR) to be put high on the international political agenda.

Ensuring access to effective antibiotics largely depends on global efforts in slowing down the development of resistant bacteria and developing new antibiotics. Therefore, we must strengthen an already huge international commitment regarding antibiotic resistance, and ensure everyone's right to effective antibiotics by working in parallel in three areas:

- Advocacy – Ensuring that the issue of addressing AMR for better cancer care outcomes is high on the global health agenda.
- Engagement of the health workforce – Health-care personnel are leaders in addressing this issue and have an active role in drawing attention to AMR, ensuring the appropriate use of medicines and strong infection control practice in medical settings, as well as providing key input to national policy on AMR.
- Ensuring access to treatment – Prioritizing access to and rational use of antimicrobials and ensuring access to diagnostics."

Ulrika Årehed Kågström is Secretary-General of the Swedish Cancer Society and has successfully led the organization since 2016. It is now the largest fundraising organization in Sweden.

She is also an active leader in the Nordic Cancer Union and a board member of the Union for International Cancer Control (UICC), where she serves as treasurer as well as an initiator and active member of various UICC task forces and committees.

The Challenge of AMR

Interview: Malin Grape

***AMR Control* interviews Malin Grape, the newly appointed and first Swedish Ambassador for Antimicrobial Resistance**

The new AMR Ambassador, Malin Grape, is currently head of the Public Health Agency of Sweden's Unit for Antibiotics and Infection Control and has long worked on these issues, both nationally and internationally. She was responsible for the Public Health Agency's work to build and develop the WHO's Global Antimicrobial Resistance and Use Surveillance System (GLASS) and also worked on the European Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (JAMRAI) project.

AMR Control: Please tell us how you became involved in antimicrobial resistance (AMR)?

Malin Grape: My first encounter with AMR was when I did my Master's thesis and was invited to the clinical microbiology laboratory at Karolinska University Hospital to start up a study on molecular resistance mechanisms in urinary tract infections. The complexity of the issue sparked my interest; the span from molecular microbiology to policy, behavioural science and health economy intrigued me. Though my experience in public health has broadened, this interdisciplinarity is what still keeps my curiosity and engagement in the topic.

AMR Control: Can you explain the reasons that led the Swedish Government to establish this important position of AMR Ambassador? What is the nature of the role and how will your ambassadorship fit into the existing network of organizations involved in AMR?

Malin Grape: AMR has been a priority for the Swedish health professional community and the Government for many years. In 1986, we banned the use of antibiotics for growth promotion in animals, the first Swedish national strategic stewardship programme, Strama, started in 1995 and our first cross-sectorial national action plan on AMR was published in 2000. Hence, it is only natural that new steps continue to be taken; my country has high ambitions and a long-standing commitment to the fight against AMR. What I particularly appreciate with the appointment of this role is the focus on how we may contribute more in the international arena. The aim is to strengthen the Swedish AMR work internationally, both in regarding bilateral exchange and support, with multilateral organizations and the United Nations and within the European Union.

AMR Control: What will be your first steps in the role?

Malin Grape: The first months have been a lot about re-connecting and establishing my network in the area in the wake of the pandemic. Most of us working with AMR have been busy with hands-on pandemic management and it has been a real pleasure to again meet colleagues from around the world and talk about AMR and what lessons can be brought from COVID-19 to tackle AMR. Furthermore, I have "jumpstarted" our preparations for the Swedish EU presidency in 2023, during which AMR will be a priority topic.

AMR Control: This edition of AMR Control has a special focus on the cancer community and AMR. Do you have any specific thoughts on how this community can help with the challenge of AMR?

Malin Grape: AMR is relevant for so many more areas than most people currently recognize. Even in Sweden, where work to counteract AMR gets quite a lot of attention, it is not by default on the radar of many oncologists as an issue that urgently concerns them. The cancer community is an important and vocal group that can contribute by showing how AMR is relevant to us all and support the increase in awareness that is necessary to achieve sufficient action.

AMR Control: Some have called AMR the "silent" or "quiet" pandemic. Do you think the COVID-19 pandemic has helped or hindered progress on tackling AMR?

Malin Grape: Of course, during the most intense period of COVID-19 not much attention could be given to AMR, being a much more slowly developing pandemic. In that sense, as for many other areas, it has been two years lost and a boost in the momentum of our work is now critical. On the other hand, I think that the general awareness and understanding of communicable diseases and their prevention has increased immensely in the public and this is an opportunity we must use. Hand hygiene and infection control have never been the hottest topics, but they will probably never be hotter than now. I regard this awareness as a window of opportunity, which, if used wisely, may contribute

to more resilient health systems with a stronger focus on prevention. Hospitals will always be the most important risk environments for the spread of resistant microorganisms, with susceptible patients and lots of antimicrobials being used giving the resistant microbes a clear competitive advantage. This is a chance to maintain and strengthen the IPC (infection prevention and control) programmes that might not come back in the near future. It is also important to understand that the responsible use of antimicrobials will never in itself be enough to curb the negative development of AMR.

Also, the very necessary and life-saving use of antimicrobials drives resistance and we need to become better at preventing the spread, both of resistant microorganisms and the infections that require antimicrobial treatment.

AMR Control: In what ways do you see AMR as a global health security threat?

Malin Grape: We haven't yet seen the full consequences of AMR for public health, but the current context of cancer illustrates very well how it may have devastating effects on both modern advanced medicine and public health development in low- and middle-income countries. With its One Health characteristics and ability to effectively spread around the globe it is also an obvious part of pandemic threats and should be included in systems strengthening aiming at pandemic prevention, preparedness, detection and response.

I think it is important though, not to limit the description of AMR as only a health security issue when it is also a sustainability issue, an equity issue and a development issue. It is essentially a threat not only to the Agenda 2030 third goal of health and wellbeing but concerns the achievement and should be mainstreamed into the work towards several of the sustainable development goals.

AMR Control: What do you think are the greatest barriers to overcoming AMR?

Malin Grape: AMR is a kind of tragedy of scale. If it is only prioritized and counteracted by a few, then the curve is unlikely to turn. Right now, we need more countries and stakeholders to give AMR higher priority. And to ensure that the response is fully capitalized on, much more effective coordination and stronger governance is needed. Another lesson learnt from the pandemic is the matter of visibility. When numbers are reported daily, and everybody acknowledges the threat, powerful action is easily generated. But AMR concerns so many different diseases of varying seriousness and has so many faces that the same response will not be achieved straightforwardly. The general awareness that AMR concerns all of us must therefore be increased. The measures to prevent and tackle AMR need to be integrated into health and many other policy areas rather than managed within a silo as a separate, isolated problem.

Like climate change, AMR is not something threatening us in a gloomy future, but a problem here and now. Already, the 1.27 million deaths in 2019 resulting from bacterial infections resistant to antibiotics is greater than those caused by AIDS and malaria annually.

AMR Control: How do you see the role of NGO, academia and industry partnerships in addressing AMR?

Malin Grape: All sectors of society need to contribute from their own angle and ensure that we collaborate towards common goals. Partnerships are important and should be carefully managed to achieve their full potential and avoid becoming skewed towards a certain interest. In the best of worlds, they would also be placed in the context of an overarching coordination effort, assuring connections and synergies with other initiatives. One step towards this is hopefully the forthcoming establishment of the Multi-Stakeholder Partnership Platform on AMR, which is one of the key governance mechanisms recommended by the IACG on AMR to the UN Secretary General in 2019. Another is the One Health Global Leaders Group on AMR, which is up and running with our Swedish Minister of Health and Social Affairs, Lena Hallengren, as vice chair; a third essential pillar in this construction, the Independent Panel of Evidence for Action on AMR, is still worryingly pending.

AMR Control: How do you see AMR developing in 10 years' time?

Malin Grape: I have to be an optimist and expect that the world's response will be much stronger than it is now. However, it is not a threat that is easily overcome, but rather something we must learn to live with while preventing and counteracting its consequences as effectively as possible. It is most likely that resistance levels will not be lower in 10 years' time than our current levels. We should keep in mind that resistance to antimicrobial substances existed long before humans started to use and misuse them, and AMR will never completely disappear. Having said that, I do hope that we can find a much more sustainable way of co-existing with microorganisms – resistant or not – and ensure that finite resources such as antimicrobials are used in a much more responsible way. This is a lot to wish for in 10 years' time, but if this awareness of antimicrobials as global goods worthy of protection is at least significantly increased over the next decade, then I do have confidence in a future of life-saving prevention and treatment of common and serious infections. ■

Malin Grape holds an MSc in Pharmacy and her background is in research. Her doctoral thesis focused on antibiotic resistance. She has worked on antimicrobial resistance both nationally and internationally.

Yehoda Martei, Assistant Professor of Medicine and the Vice Chief of Diversity, Inclusion and Health Equity in the Division of Hematology-Oncology, University of Pennsylvania, USA

"The adverse effects of antimicrobial resistance (AMR) are already manifesting themselves in cancer care delivery in a big way. As a medical oncologist who primarily manages cancer patients admitted to the hospital, I commonly admit patients with complex infectious complications due to their underlying cancer or sequelae of immunosuppression from cancer-directed therapy. AMR may result in the undertreating of patients who are started on empirical antibiotics but later found to have culture growth with resistant organisms, e.g., extended-spectrum β-lactamases-producing *Enterobacteriaceae*, requiring more broad-spectrum antibiotics. This was the case in a young patient with colon cancer who had to spend more than a month in the hospital due to multiple complications from a drug-resistant infection. In addition, he could not start cancer-directed therapy due to infectious complications requiring surgical procedures, a prolonged antibiotics course and recovery. As a multidisciplinary care team, we were acutely aware of his rapidly advancing tumour on serial abdominal scan images, but were held hostage by his equally aggressive infectious complications from drug-resistant organisms. These patients are undoubtedly medically complex, often cared for by multiple specialty teams with ongoing reassessments of risks versus benefits of delaying cancer-directed therapy while treating ongoing infections. Fortunately, when practising in the United States, I have access to institutional resources and colleagues that promote antimicrobial stewardship. Additionally, antimicrobial diagnostics are ubiquitously available with fast turnarounds to inform clinical decisions, and patients receive excellent education and guidance on antimicrobial usage and adherence. Furthermore, cancer patients with resistant organisms and rare organisms are always co-managed with specific oncology infectious disease teams.

I also have the privilege of working in resource-constrained settings, where providers deliver the best care for cancer patients with infectious complications with much fewer resources. The burden of AMR is grossly underappreciated due to a lack of diagnostics, broad-spectrum antimicrobials and personnel resources. Therefore, AMR may be one of the biggest threats to cancer care delivery in these settings, which may further widen the already existing survival disparity in cancer outcomes. There is an urgent need to focus on capturing AMR data and expanding diagnostics and access to antimicrobials in these settings."

Dr Yehoda Martei is a medical oncologist, an Assistant Professor of Medicine, and the Vice Chief of Diversity, Inclusion and Health Equity in the Division of Hematology-Oncology at the University of Pennsylvania (Penn). She is also a global health scholar at the Center for Global Health and a Senior Fellow at the Leonard Davis Institute of Health Economics at Penn. She is an Adjunct Lecturer at the University of Botswana, where she conducts most of her research work related to access to essential medicines for cancer treatment. Her research is also focused on implementation strategies for eliminating global disparities in breast cancer and HIV outcomes by optimizing high- quality breast cancer therapy delivery in low-resource settings.

She has previously served as a Steering Committee member for the selection of the World Health Organization's List of Essential Cancer Medicines and currently serves on the Scientific Advisory Panel for the Medicine Patent Pool, the Access to Oncology Medicines Coalition, and the Medical Advisory Board of the Max Foundation. Dr Martei obtained her undergraduate and medical degrees at Harvard and Yale, respectively. She completed her internal medicine training at the University of California, San Francisco, before moving to Penn where she completed her Hematology-Oncology fellowship and Master of Science in Clinical Epidemiology.

Five barriers to addressing antimicrobial resistance

Rohan Kocharekar,
Research Fellow, Chatham House, UK

Elizabeth Taylor was famously quoted as saying, "It is bad enough that people are dying of AIDS, but no one should die of ignorance." From HIV/AIDS to cancer, these words continue to ring true as they relate to combatting public "ignorance" and political apathy to burgeoning global health crises. Over the last couple of years, the ongoing COVID-19 pandemic has largely consumed the spotlight of global health policy discussions. While the pandemic rages on, the global policy response to other global health crises has largely been sidelined. One clear example of this can be seen in the sidelining of antimicrobial resistance as the next, looming global health crisis.

Antimicrobial resistance (AMR) occurs when disease-causing microbes evolve over time and become resistant to treatment and medicine *(1)*. As a result, antibiotics, antivirals and other antimicrobial medicines become ineffective at treating bacterial infections. The rise of AMR threatens the world's ability to treat common infections, viruses and other deadly diseases. It is estimated that more than 700,000 people die every year as a direct result of drug-resistant diseases, with more than 10 million deaths expected by 2050 *(2)*. Global policy inaction on the prevention and treatment of drug-resistant infections will lead to riskier medical procedures and even higher death rates *(3)*.

New antibiotics and drug treatments will not solve this health crisis alone, nor will the mere call for increased investments remedy the issue (although, new investments in monitoring and surveillance systems will be vital). AMR interventions must be tackled systemically. This systemic approach calls for new conservation strategies for appropriate use of antimicrobials, better regulation on antimicrobial use, reduced usage of antimicrobials in agriculture, increased global awareness of the issue, improved sanitation practices and better incentives for pharmaceutical companies to develop new antibiotics *(4)*. Overuse of antimicrobials in medical and agricultural practices, coupled with the lack of access to antibiotics in most low- and middle-income countries (LMICs), have created a fractured, global health environment with diverging policy priorities.

AMR has often been cited by health experts and activists as the "silent pandemic," due to the pandemic-like nature of the crisis and the relative silence on the issue by national health policy leaders. There are serious policy challenges that remain in addressing this multifaceted issue. Outlined below are five major challenges for future global political and funding action towards addressing AMR.

First, there is the most basic issue of **raising global public awareness on AMR**. Ask the everyday citizen to define what AMR is, and they may respond quizzically to the question. Public knowledge of AMR is crucial to addressing the crisis, as overuse and misuse of antibiotics remain two of the most significant drivers in the development of drug-resistant pathogens *(5)*. Overprescribing antibiotics by medical professionals and over-the-counter drug purchases by individuals (mainly from high-income countries, but also in LMICs) have contributed to its misuse. Humans feed antibiotics to animals that end-up in our food supply chains. Humans are the ones who pollute that the environment through antibiotic manufacturing and byproducts that appear in water supply systems. It is, therefore, incumbent upon us to address these detrimental health and environmental effects through public awareness campaigns. Greater public awareness is essential in limiting overuse and misuse of certain drugs in order to slow the development of AMR.

Second, the **"ask" for AMR may be too much** for certain countries and policy leaders. Not only is it difficult to succinctly define the root causes of AMR, it is also difficult to succinctly define a clear policy solution on how to address it. Unlike other deadly viruses and diseases, which require funding and research to provide a potential cure, AMR requires a systemic change to a country's entire health-care system. The eradication of smallpox, for example, was attributed to the discovery of a single vaccine. By contrast, there is no single solution to "eradicate" AMR. It is a multisectoral health issue, involving various systemic interventions pertaining to economic incentives, sociological changes and new medical discoveries. The myriad policy interventions that are required to accurately address AMR make it difficult for policy leaders to properly comprehend the health and economic risks associated with the health crises. National policy leaders may view AMR

as a remote threat, similar in nature to a pandemic. National leaders may, therefore, view AMR as a secondary priority to other, more immediate health concerns they may perceive as more pressing such as health spending and development strategies.

Third, **AMR is hard to visualize.** Unlike with other global epidemics and deadly diseases, such as HIV, AMR is mostly an invisible crisis. If an individual does not make it to the operating table because of antibiotic resistance, it is difficult for the AMR cause to generate the kind of coordinated action that has been mobilized by individuals living with or experiencing the causes of other viruses and diseases. There is, therefore, a challenge in illustrating the real toll of AMR. For AMR infections, there are multiple species of drug-resistant bacteria that may cause the hundreds of thousands of deaths per year. The way those deaths may arise can similarly be expressed through multiple ways (i.e., through bone or blood-stream infections). While individuals may be recorded as dying from other causes, the resistance from certain drugs may be the underlying cause of death. The way that death is presented to human emotions has an immense effect on global health spending and national health strategies. Without a visual storyline that expresses the deadly impact of AMR, it will be difficult to mobilize the coordinated policy and funding commitments that will be needed to tackle the crisis.

Fourth, there is both a **lack of access to antimicrobials (especially in emerging economies) and poor surveillance mechanisms on AMR policy interventions.** Over the last several years, millions of dollars have been spent in raising awareness of the crisis and developing new financial incentives for antimicrobial research. It is difficult, however, to measure the effectiveness of these investments and the links between health programmes and improvements in antimicrobial use. While National AMR Action Plans (NAPs) have been critical to facilitating improvements in antimicrobial use, there are serious information and surveillance gaps that hinder effective policy responses to AMR. Current surveillance activities have not provided additional clarity on what interventions would be best suited to achieve various AMR policy goals at the national level *(6)*. Evidence-based policy interventions, informed by cultural and health system-specific contexts, will be needed to address these information gaps.

Fifth, a **lack of economic incentives exists for pharmaceutical companies to develop new antibiotics.** As noted recently by the World Health Organization (WHO), the clinical pipeline for new antimicrobials is "dry" *(7)*. Since 2019, WHO has identified 32 antibiotics within the clinical development pipeline. Of those 32, only six have been classified as "innovative". There is a clear market failure for discoveries of new antibiotics and treatments for drug-resistant infections. Several global funding initiatives have been set up to address this challenge. These include the AMR Multi-partner Trust Fund (AMR MPTF), the Global Antibiotic Research and Development Partnership (GARDP) and the AMR Action Fund. These global funding initiatives, however, do not completely address the financial incentives and other research needs to spur further innovation on new antimicrobial medicines, vaccines and diagnostic tools. More funding initiatives and reimbursement models for pharmaceutical companies will eventually be needed to find long-term solutions to the crisis.

Identifying these barriers to addressing AMR will be critical to preventing millions of future deaths. The issue of AMR is complex, requiring multisectoral and country-specific responses. It is a looming global health crisis that must be addressed through a systemic approach. Better global planning and funding coordination can help resolve existing information gaps and financing shortages. Ignorance on the issue, however, can no longer be an excuse for inaction. ■

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References

1. Cullen A (2022), "Antimicrobial resistance: A silent pandemic," Imperial College London, https://www.imperial.ac.uk/stories/antimicrobial-resistance/.
2. Dodson, K (2021), "Antimicrobial Resistance is the Silent Pandemic We Can No Longer Neglect," United Nations Foundation, 22 November 2021, https://unfoundation.org/blog/post/antimicrobial-resistance-is-the-silent-pandemic-we-can-no-longer-neglect/.
3. World Health Organization (2020), "Antimicrobial Resistance," WHO, https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance.
4. Sirec, T & Benedyk T (2017), "One Health: 10 ways to tackle antimicrobial resistance, 19 September 2017, https://fems-microbiology.org/one-health-10-ways-to-tackle-antibiotic-resistance/.
5. WHO (2020), "Antimicrobial resistance".
6. Rogers Van Katwyk S, et al (2020), ' Strengthening the science of addressing antimicrobial resistance: a framework for planning, conducting and disseminating antimicrobial resistance intervention research" *Health Re. Policy Syst.*, Volume 18(60), 8 June 2020, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7278195/.
7. Ibid.

NORWEGIAN CANCER SOCIETY

INTERNATIONAL CAMPAIGN FOR AN ANTIBIOTIC TREATY

We need a global, legally binding antibiotic treaty – now!

To save millions of lives we must change the way we use antibiotics globally. No one country can do the job alone. Support the international campaign for an antibiotic treaty!

There is a strong case for a new treaty on antimicrobial resistance (AMR). Ongoing international efforts are insufficient to effectively address the transboundary, cross-sectoral, and collective action required to address the challenges of AMR. In the light of mounting evidence of the harm caused by drug-resistant infections, the process of creating an AMR treaty must be framed as a strategic aim in a mission-oriented project to prevent and address the dramatic, global repercussions of AMR. Past treaty-making efforts offer valuable insights into how a diplomatic campaign for a new treaty can lead to a global transformation in how antimicrobials are used, developed and distributed.

The international campaign for an antibiotic treaty works to ensure that all national governments, international organizations and industry:

- Recognize that AMR is a threat to global public health;
- Recognize that a new international legal framework is needed to strengthen AMR control and ensure equitable access for everyone across the globe;
- Implement measures to support negotiations on a new international agreement to secure antibiotics for all.

Achieving these goals requires bold global advocacy and communication initiatives to mobilize and coordinate action towards a clear goal across borders and sectors. *The International Campaign for an Antibiotic Treaty is a cross-sectoral civil society initiative established by several Norwegian NGOs from the health, environment, international development, and food and agriculture sectors.* We call on the cancer community and other civil society groups to join the campaign to advance the political process towards an effective policy tool for controlling AMR.

The solution: A new antibiotic treaty

As a cross-sectoral problem, it is clear that the solution to the AMR health crisis requires global mechanisms that effectively encourage nations to act according to long-term global interests.

Existing political and legal frameworks have so far not been enough to solve the problems of misuse and overuse of antibiotics globally. A new and legally binding antibiotic treaty can provide a solution.

The Norwegian Cancer Society's work with AMR

In June 2017, a global campaign, *The Biggest Threat to Cancer Patients*, was launched with then Minister of Health, Bent Høie, to raise awareness of AMR and to mobilize support for government-driven initiatives to slow its development. This global campaign was the first of its kind under the auspices of a patient organization. On World Cancer Day in 2018, the Norwegian Cancer Society opened its exhibition Hanging by a thread, which was later shown at WHO Europe's HQ in Copenhagen and also in Stockholm and Brussels.

The Norwegian Cancer Society has engaged with AMR because one in five cancer patients will need antibiotics in their treatment. Resistant bacteria are a major threat to cancer treatment and will set back decades of progress. Patients receiving cancer immunotherapy will be at risk of dying from uncomplicated bacterial infections.

In most things we do, it is the user and patient point of view we take to give the "case a face" – regardless of diagnosis. This is our strength and why we are constantly asked to participate in councils and committees. ■

Guiding elements of an antibiotic treaty

Access: Provisions to ensure equitable global distribution and needs-based access to antimicrobals and preventive measures

Regulations: Regulation of the production, marketing, sale and use of antimicrobals across sectors.

Prohibitions: Prohibitions of practices that are especially harmful, such as prophylactic and growth-enhancing use of antimicrobals

Innovation: Finance mechanisms for research, developments of antimicrobals and preventive measures

Implementation: Provisions to reward countries that implement control measures (and penalize countries that decides not to join the treaty)

The impact of AMR on cancer care – reinvigorating the R&D pipeline

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Antibiotics are a crucial part of modern medicine, but resistance is growing and the development pipeline is waning. Innovation in this sector is required to deliver a steady and sustainable supply of new and novel antibiotics (as well as other antibacterials). Here we outline how antibiotic resistance is impacting cancer care and why a coordinated approach is required to create an innovative ecosystem for research and development and a sustainable market for antibacterials addressing the most critical public health needs.

Global patient needs versus diminishing returns – the pipeline paradox

Antimicrobial resistance (AMR) continues to represent an urgent global health challenge, with growing medical, social and economic impacts *(1–3)*. In 2019, 1.27 million people died as a direct result of antibiotic-resistant bacterial infections *(3)*, more than malaria or HIV, with death rates highest in sub-Saharan Africa and Asia *(3)*. At the current rate of emergence and spread, AMR is expected to lead to 10 million deaths annually by 2050, with associated economic costs of up to US$ 100 trillion *(2)*.

The increasingly rapid emergence and spread of resistance to antibiotics – accelerated in part due to over- and misuse across all One Health sectors (human, animal, environment and plant) – threatens to erode the transformative health and economic benefits of drugs that have become one of the most widely used classes of medication worldwide. Resistance to antibiotics threatens the success of modern health care, with devastating consequences for vulnerable patient populations, such as the close to 10 million people each year – and rising – who receive chemotherapy for cancer as a first-line treatment *(4)*.

Over the last five years, 12 new antibiotics have been approved by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA). However, the majority of these agents (10 out of 12) belong to existing antibiotic classes for which resistance mechanisms are already established, providing limited clinical benefit over already existing treatments. The most recent evaluation of antibacterials in clinical and preclinical development by the World Health Organization (WHO) *(5)* again highlights that innovation must be accelerated to combat AMR and address public health needs.

Despite the growing societal impacts of AMR, the antibacterial development pipeline remains insufficient. This is due to a variety of scientific, regulatory and commercial challenges along the pathway from research and development (R&D) to successful and sustainable market entry of antibiotics. It is scientifically challenging to discover new antibiotics for priority resistant bacteria, the time and financial costs of clearing regulatory hurdles are substantial and the commercial outlook is bleak for new products due to a combination of low prices and lack of return on investment due to restrictions on use, limiting volumes sold *(6,7)* – the pipeline paradox. Given these hurdles, many large pharmaceutical companies as well as small and medium enterprises (SMEs) have exited the field to focus on more lucrative sectors, such as oncology.

As resistance grows and the replenishment pipeline wanes, it is imperative that we stimulate innovation in this sector and ensure a steady and sustainable supply of new and novel antibiotics (as well as other antibacterials), especially for vulnerable patient groups such as cancer patients. Here we summarize how the insufficient antibiotic pipeline and the growing emergence and spread of resistance to antibiotics is impacting the care of cancer patients globally and outline how a coordinated approach is required to create an innovative ecosystem for R&D and a sustainable market for antibiotics addressing critical public health needs.

The impact of antibiotic resistance on cancer care

Although modern cancer care has resulted in increased survivorship globally, cancer continues to be a leading cause

of death worldwide, responsible for almost 10 million deaths in 2020 *(8)*, with a continuously growing burden, including within low- and middle-income countries (LMICs) *(9)*. By 2030, almost three-quarters of cancer deaths are forecast to be in LMICs *(10,11)*.

Antibiotics continue to be a crucial part of the supportive care of cancer patients, especially for those receiving immunosuppressing chemotherapy, hematopoietic stem cell transplantation (HSCT) or novel immunomodulatory therapies. There is growing evidence that antibacterial prophylaxis increases the frequency of blood-stream infections caused by resistant Gram-negative bacteria in HSCT patients *(12)*. Thus, infections caused by resistant bacteria are of major concern; they could increase the likelihood of infections or prolong hospitalization *(13)* and, in severe cases, result in death. Cancer patients are three times more likely to die of infections than non-cancer patients *(14)*. Over one-third (36%) of cancer patients will require surgery, often multiple times, with approximately 5% of these patients developing drug-resistant infections *(15)*. Following chemotherapy, it is estimated that over one-quarter (26·8%) of pathogens causing infections are resistant to standard prophylactic antibiotics *(16)*. A recent study pointed out that 95% of oncologists in the United Kingdom are concerned about the rise of drug-resistant bacteria *(15)*. In addition, the rapid advances of modern therapies directed against autoimmune and malignant diseases, and their widespread use, further increase the number of patients at risk. This has been recognized and acknowledged by infectious disease experts from the scientific community *(17)*.

Studies quantifying the economic impact of AMR on cancer care are scarce, but due to both increasing treatment costs and length of hospitalization, associated costs are expected to rise. For example, hospital stays are prolonged by a factor of three in head and neck cancer patients infected with methicillin-resistant *Staphylococcus aureus* (MRSA) *(18)*.

Without viable antibiotics to prevent and treat infections, key advances made in the care and treatment of cancer patients will be limited due to the risks of severe infections.

The financial landscape for developing antibiotics

The development pathway for antibiotics is extremely challenging. It is a time-consuming and expensive process, comprising up to 15 years, US$ 1–2 billion and high attrition rates – on average, only one in 15 (existing antibiotic classes) and 30 (new classes of antibiotics) preclinical candidates will reach patients *(19)*.

Although not an unfamiliar story when it comes to developing medicines – 90% of all clinical drug development fails *(20)* – the fact that the use of new and novel antibiotics is restricted to patients with resistant infections means that there is limited potential for developers to recoup their costs. The market for these so-called "Reserve" *(21)* antibiotics is challenging, with the return on investment failing to cover the costs companies incur along the pathway from R&D, regulatory clearance, commercialization and distribution. This has led to an unstable supply chain for existing antibiotics and a lack of novel and innovative antibacterial drugs entering the market *(5,7)*. The dire commercial outlook has resulted in many larger pharmaceutical companies exiting the field, leaving the academic spin-outs and SMEs – major innovators in the antibacterial sector accounting for 81% of all antibacterial programmes in the preclinical stages *(22)* and 75% of all late stages of development *(23)* – struggling to sustain their operations.

Based on data from the Global AMR R&D Hub's Dynamic Dashboard *(24)*, funding for R&D of therapeutics tackling human infections totalling ~US$ 2.6 billon (as at August 2022) has been invested by public and philanthropic sources since 2017. In comparison, this funding volume is >3x greater than for R&D of AMR diagnostics or vaccines (Figure 1). A significant fraction of this total investment – US$ 1.54 billion – is for the development of therapeutics targeting priority pathogens *(25,26)*, including the ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter spp.*), many of which are known as resistant pathogens in cancer patients *(15)*. Globally, public and philanthropic funders, including the National Institutes of Health

Figure 1: Global AMR R&D Hub – Dynamic Dashboard for AMR R&D funding. The Dynamic Dashboard provides collated information on public and philanthropic funding globally for AMR R&D since 2017. From over 12,700 projects in the Dynamic Dashboard totalling US$ >10 billion, ~22% target the development of human therapeutics, >3x more than investment in human AMR Diagnostics (Dx) or Vaccines (Vx). US$ = United States Dollar

Public/Philanthropic AMR R&D funding since 2017 – August 2022
dashboard.globalamrhub.org

Box 1: **Push and pull incentives**

Push incentives

Push Incentives are government or regulatory interventions which support R&D by directly lowering the costs of development.

These tools are input-based.

Examples include research funding grants, contracts, public and private partnerships and tax incentives.

Push mechanisms target current work and reduce a developer's cost and risk of researching and developing new products either by lowering the costs, decreasing the barriers to participation or by sharing the costs/risks across multiple parties.

Pull incentives

Pull incentives are policy tools to reward the successful development of a product by increasing or ensuring future revenue. Can be achieved through market-making (financial) tools or market-shaping (lego-regulatory policies) rewards.

These tools are output-based.

Examples include subscription models, which de-link revenues from volumes sold, higher reimbursement, market entry rewards, transferrable exclusivity extensions and accelerated approvals.

Each incentive – alone or in combination – has varying impacts on innovation, sustainability, stewardship and access.

See refs *7*, *30*, *31* for information on pull incentives and their different features.

(NIH), the Biomedical Advanced Research Development Authority (BARDA) and the Bill & Melinda Gates Foundation, are continuing to invest in and support the R&D of new therapeutics, including new and novel antibiotics *(26)*, across the spectrum from basic research to clinical trials. In tandem, public-private partnerships such as the Innovative Medicines Initiative (IMI), Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) and the Global Antibiotic Research and Development Partnership (GARDP) are further boosting the field by funding and supporting product development and clinical trials. There has also been renewed commitment to stimulate antibiotic development in the form of the AMR Action Fund – a US$ 1 billion initiative, primarily financed by the private sector, that is committed to the development of 2–4 antibiotics by 2030, focused on helping candidates through the later clinical phases of development. However, on their own these so-called "push incentives" (see Box 1) are still not enough to mitigate the multiple challenges associated with the development and post-market entry of antibiotics.

Studies commissioned and conducted by the Global AMR R&D Hub *(27,28)*, evaluating and quantifying the scale of the challenge facing new health technologies – including priority antibiotics – under current market conditions, highlighted the limited ability of market tools such as pricing, volume and patents to improve revenues and attract investors and developers back to the field, and that market interventions which de-link revenues from volumes sold are required. These studies, and others (e.g., 29), also recommend that the societal value of antibiotics – being at the core of well-functioning health systems – should be integrated into value assessments by governments (e.g., via Health Technology Assessments). Notably, the Global AMR R&D Hub's studies also raise the issue of access, in which effective antibiotics are not available at scale in the parts of the world where the need is most dominant and growing most rapidly – predominantly in LMICs *(27)*.

Recognizing that push incentives on their own are not sufficient to drive the development of new antibacterials beyond the R&D phase, the Global AMR R&D Hub and World Health Organization (WHO) jointly called on the Group of Seven (G7) countries for concerted and ambitious actions for the development and implementation of "pull incentives", policy tools that reward the successful development of antimicrobials by increasing or guaranteeing future revenues (see Info Box and refs *7*, *30*, *31*).

Some progress is being made in this direction (see Table 1 in ref. *7*), with the United Kingdom implementing, and the United States proposing, innovative delinked economic models for antibiotics. The United Kingdom is the first country in the world to pay drug companies (Pfizer, USA; Shionogi, Japan) a fixed fee (£10 million per year) for supplying antibiotics, and there is growing bipartisan support for The Pioneering Antimicrobial Subscriptions To End Upsurging Resistance Act of 2021 (PASTEUR Act) in the USA – a bill authorizing

the Department of Health and Human Services to enter into subscription contracts for critical-need antimicrobial drugs.

A sustainable R&D ecosystem for AMR?

The ongoing commitment to supporting a sustainable and buoyant innovation ecosystem for cancer innovation from both the public and private sector has resulted in prevention programmes, diagnostics and treatment advances that are saving the lives of millions of cancer patients globally *(32,33)*. In 2020, there were over 1,300 cancer medicines in development and more than 1,200 clinical trials initiated *(33)*. In comparison, the most recent analyses from WHO *(5)*, integrated within the Global AMR R&D Hub's Dynamic Dashboard, shows that there are currently only 27 new antibiotics in clinical development against WHO priority pathogens, with the majority of these in the early phases of clinical development (i.e., Phase I or II). Without an effective pipeline of new antibiotics – and antibacterials in general – outcomes for cancer patients are set to be negatively impacted and the recent gains in cancer outcomes endangered. The projected growth of cancer in LMICs *(10,11)* and the worsening gap in terms of access to antibiotics *(27)*, further intensifies the critical and global nature of this health challenge.

The scale and severity of the growing and urgent threat of AMR highlights the need for immediate, concerted and coordinated action across the push and pull continuum to redefine the pathway from R&D of antibacterials to innovative products, their sustainable commercialization and subsequent equitable access and prudent use. Incentivizing the development of new antibacterial treatments addressing public health needs requires renewed leadership and agenda-setting, further support and replenishment of push funding for AMR R&D, increased and coordinated pull incentives and advancement of equity and access through AMR development cooperation *(7)*.

Antibiotics are a central component of cancer care and an R&D ecosystem that encourages innovation and rewards success is crucial for a sustainable pipeline of new and novel drugs. Their development and use, however, needs to be placed in the framework of the full AMR toolkit, which also includes diagnostics and vaccines *(2)*. Effective diagnostics that can rapidly and accurately identify bacterial infections are key to reducing inappropriate use of these life-saving drugs. In tandem, vaccines are crucial tools for potentially preventing and curbing the spread of infection, thus reducing the dependency on antibiotics and helping to mitigate the risks posed by the current insufficient antibacterial pipeline. Renewed efforts in supporting R&D of effective, affordable and rapid diagnostics, alongside the development of vaccines against the most critical pathogens *(34,35)*, as well as incentives to ensure their uptake *(27)*, are key tools in our global response to combatting the threat of AMR and protecting vulnerable patient populations.

About the Global AMR R&D Hub

The Global Antimicrobial Resistance (AMR) Research and Development (R&D) Hub is a global knowledge centre for AMR R&D, fostering evidence-based decision-making and enhancing collaboration and coordination across the One Health continuum. The global partnership, launched in May 2018 following a call from G20 leaders, currently consists of 17 countries, the European Commission, the Wellcome Trust and the Bill & Melinda Gates Foundation, as well as Observers from the World Health Organization (WHO), Organization for Economic Co-operation and Development (OECD), World Organization for Animal Health (WOAH) and the Food and Agricultural Organisation (FAO).

The Global AMR R&D Hub's Strategic Pillars are to:

- Guide and support evidence-based decision-making;
- Enhance collaboration and coordination;
- Promote awareness, knowledge and visibility.

For more information, visit www.globalamrhub.org ■

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References

1. O'Neill J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. *Review on Antimicrobial Resistance 2014.* https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf [Accessed 25 July, 2022]
2. O'Neill, J. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. *The Review On Antimicrobial Resistance 2016.* https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf [Accessed July 25, 2022]
3. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet.* 2022 Feb 12;399(10325):629-655. doi: 10.1016/S0140-6736(21)02724-0.
4. Wilson BE, Jacob S, Yap ML, Ferlay J, Bray F, Barton MB. Estimates of global chemotherapy demands and corresponding physician workforce requirements for 2018 and 2040: a population-based study. *Lancet Oncol.* 2019 Jun;20(6):769-780. doi: 10.1016/S1470-2045(19)30163-9. Erratum in: Lancet Oncol. 2019 Jul;20(7):e346.
5. 2021 Antibacterial agents in clinical and preclinical development: an overview and analysis. Geneva: World Health Organization; 2022. Accessed 20 July, 2022 https://www.who.int/publications/i/item/9789240047655
6. Harbarth S, Theuretzbacher U, Hackett J; DRIVE-AB consortium. Antibiotic research and development: business as usual? *J Antimicrob Chemother.* 2015;70(6):1604-7. doi: 10.1093/jac/dkv020.
7. Global AMR R&D Hub, World Health Organization 2022. Incentivising the development of antibacterials: Progress report by the global AMR R&D Hub and WHO. Available here: https://globalamrhub.org/wp-content/uploads/2022/05/G7_ProgressReport_FINAL_16.05.2022.pdf
8. WHO Cancer Factsheet 2022. Available at: https://www.who.int/news-room/fact-sheets/detail/cancer
9. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin.* 2021 May;71(3):209-249. doi: 10.3322/caac.21660.
10. Soerjomataram I, Bray F. Planning for tomorrow: global cancer incidence and the role of prevention 2020-2070. *Nat Rev Clin Oncol.* 2021 Oct;18(10):663-672. doi: 10.1038/s41571-021-00514-z.
11. International Agency for Research on Cancer, WHO. Cancer Tomorrow. Global Cancer Observatory https://gco.iarc.fr/tomorrow/en (2021). [Accessed 25 July 2022]
12. Kern WV, Weber S, Dettenkofer M, Kaier K, Bertz H, Behnke M, Weisser M, Götting T, Widmer AF, Theilacker C; Hospital Infection Surveillance System for Patients with Haematologic/Oncologic Malignancies Study Group (ONKO-KISS). Impact of fluoroquinolone prophylaxis during neutropenia on bloodstream infection: Data from a surveillance program in 8755 patients receiving high-dose chemotherapy for haematologic malignancies between 2009 and 2014. *J Infect.* 2018 Jul;77(1):68-74. doi: 10.1016/j.jinf.2018.05.004
13. Bos MM, Verburg IW, Dumaij I, Stouthard J, Nortier JW, Richel D, van der Zwan EP, de Keizer NF, de Jonge E. Intensive care admission of cancer patients: a comparative analysis. *Cancer Med.* 2015 Jul;4(7):966-76. doi: 10.1002/cam4.430.
14. Nanayakkara AK, Boucher HW, Fowler VG Jr, Jezek A, Outterson K, Greenberg DE. Antibiotic resistance in the patient with cancer: Escalating challenges and paths forward. *CA Cancer J Clin.* 2021 Nov;71(6):488-504. doi: 10.3322/caac.21697.
15. The Longitude Prize. Effectiveness of Cancer Treatments Threatened by Rising Antibiotic Resistance. longitudeprize.org/resources/effectiveness-cancer-treatments-threatened-rising-antibiotic-resistance [Accessed 25 July 2022]
16. Teillant A, Gandra S, Barter D, Morgan DJ, Laxminarayan R. Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study. *Lancet Infect Dis.* 2015 Dec;15(12):1429-37. doi: 10.1016/S1473-3099(15)00270-4.
17. Reinwald M, Silva JT, Mueller NJ, Fortún J, Garzoni C, de Fijter JW, Fernández-Ruiz M, Grossi P, Aguado JM. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Intracellular signaling pathways: tyrosine kinase and mTOR inhibitors). *Clin Microbiol Infect.* 2018 Jun;24 Suppl 2:S53-S70. doi: 10.1016/j.cmi.2018.02.009.
18. Watters K, O'Dwyer TP, Rowley H. Cost and morbidity of MRSA in head and neck cancer patients: what are the consequences? *J Laryngol Otol.* 2004 Sep;118(9):694-9. doi: 10.1258/0022215042244732.
19. Wellcome (2020). Why is it so hard to develop new antibiotics https://wellcome.org/news/why-is-it-so-hard-develop-new-antibiotics [Accessed 25 July 2022]
20. Sun D, Gao W, Hu H, Zhou S. Why 90% of clinical drug development fails and how to improve it? *Acta Pharm Sin B.* 2022 Jul;12(7):3049-3062. doi: 10.1016/j.apsb.2022.02.002.
21. 2021 WHO AWARE Classification. https://www.who.int/publications/i/item/2021-aware-classification [Accessed 25 July 2022]
22. Theuretzbacher U, Outterson K, Engel A, Karlén A. The global preclinical antibacterial pipeline. *Nat Rev Microbiol.* 2020 May;18(5):275-285. doi: 10.1038/s41579-019-0288-0.
23. Access to Medicine Foundation 2021. Biotechs are saving the world from superbugs. Can they also save themselves? https://accesstomedicinefoundation.org/publications/biotechs-are-saving-the-world-from-superbugs-can-they-also-save-themselves [Accessed 25 July 2022]
24. The Global AMR R&D Hub's Dynamic Dashboard provides data on investments in AMR R&D from public and philanthropic sources globally. https://dashboard.globalamrhub.org [Accessed 25 July 2022]
25. The Global AMR R&D Hub's Dynamic Dashboard includes the priority pathogen lists from the World Health Organization, Centre for Disease Control and European Centre for Disease Prevention and Control. https://globalamrhub.org/dynamic-dashboard/library/infectious-agent-in-scope/ [Accessed 25 July 2022]
26. Global AMR R&D Hub (2021) Annual Report 2021: The Global AMR R&D Funding Landscape. https//globalamrhub.org/annual-report-2021-the-global-amr-rd-funding-landscape/ [Accessed 25 July 2022]
27. Global AMR R&D Hub (2021). Estimating Global Patient Needs and Market Potential for Priority Health Technologies Addressing Antimicrobial Resistance. https://globalamrhub.org/our-work/studies/market-potential-and-priority-patient-needs/ [Accessed 25 July 2022]
28. Gesündheit Österreich (2021). Novel policy options for reimbursement, pricing and procurement of AMR health technologies. Study commissioned by the Global AMR R&D Hub. https://globalamrhub.org/our-work/studies/studies-gesundheit-osterreich-forschungs-und-planungs-gmbh/ [Accessed 25 July 2022]
29. Drive AB (2018). Revitalizing the antibiotic pipeline. Stimulating innovation while driving sustainable use and global access. drive-ab.eu/wp-content/uploads/2018/01/CHHJ5467-Drive-AB-Main-Report-180319-WEB.pdf [Accessed 25 July 2022]
30. Årdal C, Røttingen JA, Opalska A, Van Hengel AJ, Larsen J. Pull Incentives for Antibacterial Drug Development: An Analysis by the Transatlantic Task Force on Antimicrobial Resistance. *Clin Infect Dis.* 2017 Oct 15;65(8):1378-1382. doi: 10.1093/cid/cix526.
31. Boluarte T, Schulze U (2022). The Case for a Subscription Model to Tackle Antimicrobial Resistance. https://www.bcg.com/publications/2022/model-for-tackling-antimicrobial-resistance [Accessed 25 July 2022]
32. Max Roser and Hannah Ritchie (2015), Cancer. Published online at OurWorldInData.org. https://ourworldindata.org/cancer [Accessed 25 July 2022]
33. https://efpia.eu/media/636663/building-a-european-ecosystem-to-beat-cancer.pdf [Accessed July 25, 2022]
34. WHO (2022). Bacterial vaccines in preclinical and clinical development 2021. https://www.who.int/publications/i/item/9789240052451 [Accessed 25 July 2022]
35. Boston Consulting Group (2021). Vaccines to tackle drug resistant infections An evaluation of R&D opportunities. https://vaccinesforamr.org/wp-content/uploads/2018/09/Vaccines_for_AMR.pdf [Accessed 25 July 2022]

Antimicrobial resistance: Our future depends on what we do today

BD is leveraging its extensive global capabilities to meaningfully engage around five key strategies to reduce the burden of drug-resistant infections.

Our global public health efforts seek to expand access and drive capacity-building through partnerships with leading organizations and governments. We engage in advocacy with governments, funders and health agencies to advance innovations to address the world's leading public health needs, including drug-resistant infections.

We possess important capabilities that are instrumental in containing antimicrobial resistance (AMR). We offer a wide range of medical products, platforms and offerings that can be used to prevent the spread of infection in health-care facilities, such as diagnostic systems to screen, test and diagnose infection, including drug-resistant strains, as well as state-of-the-art surveillance and reporting capabilities to monitor, track and predict AMR outbreaks.

Enabled by our innovative programmes and technologies, BD country teams across the globe are directly engaging with AMR leaders in government, academia, and professional societies to strengthen AMR awareness, health systems capacities and infection prevention and diagnostic practices.

Halting and reversing this massive challenge will require the combined resources and efforts of both public and private sectors. AMR has no single solution, and the challenges cannot be solved without multiple players working collectively on a common AMR agenda. BD will continue to collaborate with global leaders around the world to address this urgent global health concern.

AMR is a global problem, right here, right now, and threatens every person on Earth.

But, together, we *can* make an impact, now, today.

Learn more at https://amr.bd.com/ or scan the QR code:

BD
Advancing the world of health™

We need a "moonshot project" to control antimicrobial resistance

Magnus Løvold, Co-founder, Norwegian Academy of International Law, Oslo, Norway; **Sigrid Bratlie,** Strategic Advisor, The Norwegian Cancer Society, Norway; **Kjølv Egeland,** Post-Doctoral Fellow, Centre for International Studies, Sciences Po, Paris, France and **Torbjørn Graff Hugo,** Co-founder, Norwegian Academy of International Law, Oslo, Norway


MAGNUS LØVOLD


SIGRID BRATLIE


KJØLV EGELAND


TORBJØRN GRAFF HUGO

The threat of antimicrobial resistance (AMR) requires urgent political action. Ongoing international efforts are likely to be insufficient to address the transboundary, cross-sectoral, collective action problem of AMR. A process towards a new antimicrobial treaty may be framed as a strategic "node" in a mission-oriented project to prevent the dramatic, global repercussions of AMR. Past treaty-making efforts offer valuable insights into how a diplomatic campaign for a new treaty may lead to a global transformation in how antimicrobials are used, developed and distributed. A bold civil society advocacy initiative capable of mobilizing and monitoring political support for an AMR treaty across sectors and borders will be the key to success.

The problem of antimicrobial resistance

Antimicrobial resistance (AMR) is an increasingly urgent threat to people, societies and the global economy. In January 2021, a major study published in *The Lancet* suggested that drug-resistant bacterial infections kill an estimated 1.27 million people globally each year *(1)*. If no action is taken, the number of annual fatalities could increase tenfold, to as many as 10 million by 2050 *(2)*. In this scenario, cancer care will be set back by decades *(3)*. One in five cancer patients need antibiotics during their cancer treatment to stave off life-threatening infections. Thus, without effective antibiotics most cancer treatments will be extremely risky to perform. Cancers that affect the immune system, such as leukaemia and lymphoma, cannot be treated without antibiotics. In addition to the lives lost, AMR is expected to create global social and economic problems of dramatic proportions as it impacts on labour supply (human health) and livestock production (animal health). In a business-as-usual scenario, AMR may result in a more than US$ 3.4 trillion decline in the world's annual gross domestic product (GDP) over 10 years and force an estimated 24 million people into extreme poverty *(4)*.

From the perspective of international governance, AMR appears as a transboundary, collective action problem *(5)*. Drug-resistant microbes, like other microbes, spread across national borders. Individually, a country may be tempted to disregard AMR, hoping that other countries will shoulder the burden of tackling the problem. But if most, or all, countries act as if the problem does not exist, all countries will end up as long-term losers. AMR is also a cross-sectoral problem. While the most conspicuous repercussions of AMR may be described in terms of global health, AMR will likely also have serious adverse social, economic and development consequences. Moreover, important drivers of AMR are found in agriculture and other non-health sectors *(6)*. In particular, antibiotics are used as prophylactic treatments and growth promotors in livestock production *(7)*. Tackling AMR therefore requires a One Health approach *(8)*.

Over the years, many policy initiatives have been developed to address AMR. In 2015, the World Health Assembly (WHA) adopted a global action plan that commits all countries to reduce the incidence of infection and optimize the use of antimicrobial medicines *(9)*. In 2016, the United Nations General Assembly (UNGA) adopted a political declaration on AMR, in which UN member states committed to developing national action plans and taking steps to develop or strengthen effective surveillance, monitoring and regulatory frameworks on the preservation, use and sale of antimicrobial medicines *(10)*.

So far, however, there is little evidence to suggest that these efforts have even begun to stem the global tide of drug-resistant bacterial infections *(11)*. A recent review of the WHA global action plan revealed serious deficiencies, including the lack of a shared understanding amongst governments of the potential outcomes of implementation efforts, inadequate monitoring of implementation, insufficient prioritization of control measures, and weak resource mobilization *(12)*. John Hopkins Bloomberg School of Public Health and ReAct (an independent network

dedicated to the problem of AMR) highlighted further concerns about the lack of accountability in the implementation of the commitments, limited cross-sectoral engagement and involvement of civil society, insufficient focus on the lack of access to effective antimicrobials in developing countries, and undue industry influence in AMR governance *(13)*.

These deficiencies prompt the question of whether existing international tools are fit for purpose? Neither the global action plan nor the political declaration are legally binding documents; they rely on voluntary contributions and the efforts of national governments. Moreover, while the World Health Organization (WHO) has attempted to involve other UN agencies in implementation efforts *(14)*, discussions about AMR have largely been confined to WHO's sphere of activities. Although initiatives have been made to push the issue higher up on the agenda of national governments *(15)*, this does not appear to have led to a broader public discussion about the important consequences of AMR and the need for urgent action.

A "moonshot project" to solve AMR

Preventing the global repercussions of drug-resistant infections requires a mission-oriented "moonshot" project; that is, the mobilization of a wide range of actors across sectors around "a clear, ambitious and urgent goal with a deadline" *(16)*. A new treaty on AMR may be a strategic node in such a project. History suggests that when treaties are well crafted, they can be effective tools for solving transboundary, cross-sectoral, collective action problems *(17)*. A prominent example is the Montreal Protocol, which has prevented hundreds of millions of cancer cases and largely healed the stratospheric ozone layer. Similarly, the Mine Ban Treaty and the Convention on Cluster Munition have, through a remarkable process of global normative entrepreneurship, protected countless civilians from the indiscriminate effects of these weapons *(18)*.

Through focused processes of negotiation and implementation, the treaties mobilized a wide range of actors across sectors, countries, and institutional boundaries around clear, ambitious and urgent goals *(19)*. The processes required purpose-driven leadership, significant risk-taking and experimentation in how the required societal, environmental and technological change might be achieved, as well as organizational agility and flexibility, notably within and across the government agencies, international organizations and nongovernmental organizations NGOs involved in the process. By drawing on the lessons learned from successful treaty-making efforts, a process towards a new treaty on AMR could generate what ongoing efforts have so far failed to achieve: across-sectoral, high-level, purpose-driven political project to urgently control AMR in a manner that benefits current and future generations.

Getting it right: Achieving an AMR treaty

Given how states have opted to address transboundary, cross-sectoral collective action problems in the past, there is a strong case for an AMR treaty that binds states to a set of rules and standards based on a common understanding of the issue and a clear goal. Several experts and organizations have already called for an AMR treaty and have even proposed rules and provisions for such a treaty *(20)*. These calls have intensified because of the process to develop a WHO treaty on pandemic preparedness and response *(21)*.

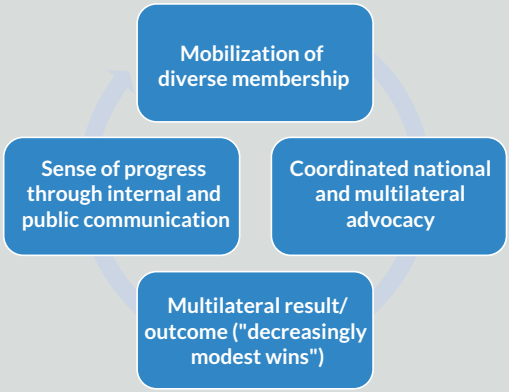
Detailing the form or legal content of a new treaty prematurely may inadvertently hamper efforts to build political momentum *(22)*. However, a new treaty should, at a minimum, include provisions to ensure needs-based global distribution of antimicrobials and preventive measures. It should strengthen the regulation of the production, marketing, sale and use of antimicrobials across sectors. Practices that are especially harmful, such as prophylactic and growth-enhancing use of antimicrobials, should be prohibited outright. A new treaty should also set up new finance mechanisms for research and development (R&D) of antimicrobials and infection prevention measures, and include provisions to reward countries that implement AMR control measures and penalize countries that decide to not join the treaty *(23)*.

Currently, however, the key question is not primarily what a new treaty should contain, but rather how a diplomatic process towards a new treaty could be initiated. Past treaty-making efforts offer valuable insights into how a civil society-led diplomatic campaign for a new AMR treaty may be designed *(24)*. Three lessons are particularly relevant:

Firstly, a process towards a new AMR treaty needs to be centred around a shared understanding of the nature and urgency of the problem. Marshalling evidence demonstrating the inadequacy of existing policies and practices is a first, essential, step. Available evidence suggests that AMR will lead to a social and economic upset. Yet, this evidence appears not to have challenged the prevailing, vertically-focused view of AMR as a global health issue or injected an appropriate level of urgency into policy discussions. In past processes, NGOs,

Figure 1: A productive feedback loop

Figure 2: **The cycle of mobilizing support**

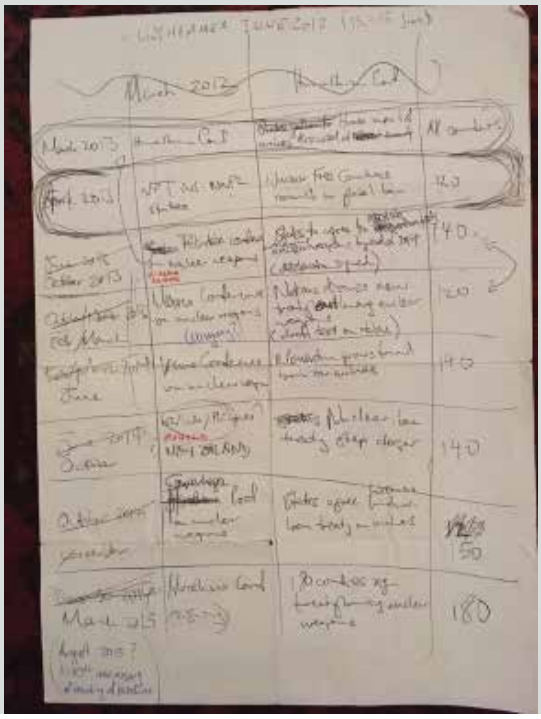


researchers and other dedicated individuals have played an important role in advancing and reframing international health policy. In some cases, these reframing activities have created productive "feedback loops" between evidence and policy (Figure 1) *(25)*. Such "feedback loops" can help expand governments' political scope of action by reframing the debate from a focus on what is politically feasible towards a focus on what imperatively must be done to prevent and address an unacceptable situation for humanity.

Secondly, a process towards a new AMR treaty needs a plan Illustration 1: Often, building new solutions requires critical engagement with existing processes. Challenging lowest-common-denominator approaches centred on achieving full consensus among states has often been a key aspect in the planning of successful diplomatic processes. Largely free from traditional institutional or bureaucratic constraints, NGOs play an important role in exploring and putting forward ambitious proposals. They cannot, however, pursue these solutions alone. Successful advocacy initiatives have therefore established flexible networks and partnerships of trust with diplomats, representatives of international organizations and other stakeholders to develop and build support for a proposed plan of action *(26)*. Often, these partnerships have led to the creation of a "core group"; that is, a group of champion states working in close coordination with civil society and other actors towards a new treaty.

Thirdly, debates will not change, and proposals will not succeed, without a group of individuals with the capacity, ability and willingness to organize a sustained advocacy initiative around the goal of a new treaty. Often, convincing decision-makers of the feasibility of a desired goal is more challenging than stipulating the details of the goal itself. Past efforts have overcome this challenge by identifying and pursuing a series of "modest wins", such as a statement in support of a specific proposal. The sense that "something big is happening" may mobilize further support, which in turn

Illustration 1: **The plan, drafted in Vienna in 2012, for a diplomatic process to ban nuclear weapons. It outlines an ambitious timeline of key developments, a series of conferences outside established arenas and the expected number of states in support of the proposed ban treaty. Five years after this plan was drafted, the 2017 Treaty on the Prohibition of Nuclear Weapons was adopted by 122 states at the United Nations in New York**



may help produce successively more ambitious advocacy wins (Figure 2).

The Antibiotic Campaign

For the cancer community, tackling AMR is of paramount importance. Failing to prevent the worst-case scenario will undermine decades of progress in cancer treatment and dramatically decrease cancer survival rates. An antimicrobial treaty may be necessary to prevent and address the dramatic, global repercussions of AMR. This requires a bold global advocacy and communication initiative to mobilize and coordinate actions towards a clear goal across borders and sectors. The Antibiotic Campaign, a cross-sectoral, civil society campaign coalition established in 2021 *(27)*, aims to do just that. The Norwegian Cancer Society and its campaign partners therefore call on the cancer community to join this campaign effort. ■

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References

1. Christopher JL Murray et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis, *The Lancet* 2022; 399: 629-655.
2. The Review on Antimicrobial Resistance, Tackling Drug-Resistant Infections Globally: Final Report and Recommendations, 2016.
3. See page 46.
4. See https://www.fao.org/antimicrobial-resistance/background/what-is-it/en/.
5. A transboundary, collective action problem is a situation i n which all or many countries would be better off cooperating but fail to do so because of conflicting interests between countries that discourage joint action.
6. WHO, Fact Sheet: *Antimicrobial Resistance*, 2021.
7. Thi Thu Hao Van et al. Antibiotic use in food animals worldwide, with a focus on Africa: Pluses and minuses; *Journal of Global Antimicrobial Resistance* 2020; 20: 170-177.
8. According to the One Health High-Level Expert Panel, an advisory panel to the One Health Quadripartite made up of FAO, WHO, OIE and UNEP, defines "One Health" as "an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals and ecosystems. It recognizes the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are closely linked and inter-dependent. The approach mobilizes multiple sectors, disciplines and communities at varying levels of society to work together to foster well-being and tackle threats to health and ecosystems, while addressing the collective need for clean water, energy and air, safe and nutritious food, taking action on climate changes and contributing to sustainable development".
9. WHO, Global Action Plan on Antimicrobial Resistance, 2015.
10. UN General Assembly, Political Declaration of the High-Level Meeting of the General Assembly on Antimicrobial Resistance: draft resolution/submitted by the President of the General Assembly, 71st session: 2016-2017.
11. Christopher JL Murray et al. 2022.
12. WHO, Comprehensive Review of the WHO Global Action Plan on Antimicrobial Resistance - Volume 1: Report, 2021.
13. Johns Hopkins Bloomberg School of Public Health and ReAct, The Global Action Plan on Antimicrobial Resistance at a Crossroads: Insights from the WHO's comprehensive review, 2022.
14. Notably the FAO, the World Organization for Animal Health (OIE) and, to a lesser extent, the UN Environment Programme (UNEP).
15. Notably through the establishment of a Global Leaders Group on Antimicrobial Resistance.
16. In *Mission Economy*, the Italian economist Mariana Mazzucato describes how a "mission-oriented" approach to public policy-making may help solve "wicked" global problems. Based on an analysis of the Apollo programme, which succeeded, in a mere eight years, in landing the first humans on the moon, Mazzucato outlines a theory of how the social, environmental, and economic challenges of the UN's Agenda 2030 for Sustainable Development could be overcome. The concept of "mission" stands at the crux of the theory, which may be understood as the mobilization of a wide range of actors across sectors around "a clear, ambitious and urgent goal with a deadline". Through a prime focus on outcomes rather than costs, public policy-making should, according to Mazzucato, motivate various sectors "to truly collaborate on investing in solutions, having a long-run view, and governing the process to make sure it is done in the public interest". Mariana Mazzucato, *Mission Economy: A Moonshot Guide to Changing Capitalism*, London: Penguin Random House UK, 2021
17. There are several reasons why legally binding intergovernmental agreements are better suited to solve transboundary, cross-sectoral collective action problems than more informal agreements, such as non-binding global action plans and political declarations. First, unless otherwise specified, treaties permanently bind states, and not merely the governments that happen to be in power when an agreement is concluded. This expands the time horizon for policy-making, which is a *sine qua non* for solving "wicked" global problems like AMR. Second, treaties are outcomes of formal intergovernmental negotiations, which deepen governments' accountability to, and ownership of, the commitments undertaken. The fact that treaties are subject to signature by heads of government or foreign ministers and, in most cases, ratification by national parliaments, encourages sustained high-level engagement, citizen involvement, and cross-sectoral collaboration within countries. Third, treaties, in contrast to informal agreements, allow for the adoption of "harder" implementation measures such as export restrictions or other penalizing measures on states not party or not compliant. Such measures are likely necessary to overcome the challenges of implementing the WHA's global action plan on AMR.
18. John Borrie, Unacceptable Harm: A History of How the Treaty to Ban Cluster Munitions Was Won, Geneva: United Nations Institute of Disarmament Research, 2009
19. Richard Elliot Benedick, *Ozone Diplomacy: New Directions in Safeguarding the Planet.* Cambridge: Harvard University Press, 1998; Scott Barrett, *Environment & Statecraft.* Oxford: Oxford University Press, 2003; and John Borrie 2009.
20. Already in 2010, Jonathan Anomaly argued that AMR "generate[s] a global collective action problem that only a well-designed international treaty can overcome". In a series of articles in 2015 and 2016, Steven J. Hoffman, Jon Arne Røttingen et al. argued forcefully that "an international legal framework" was needed to address the triple challenge of achieving antimicrobial access, conservation and innovation. Some have looked to other successful multilateral instruments for guidance on what to do about AMR. In 2017, Charles Kenny et al. made the case for a global AMR treaty modelled on the 1987 Montreal Protocol. In 2018, Ponnu Padiyara of Yale School of Public Health and Hajime Inoue and Marc Sprenger argued that "legally binding governance mechanisms on AMR would be one of the most effective ways to maintain [antimicrobial effectiveness] and manage antimicrobials as a common good". More recently, in 2019, David Heymann and Emma Ross of Chatham House's global health programme made the case for a "legally binding global treaty to curb the misuse and overuse of antibiotics". A "legally binding convention or treaty such as the WHO Framework Convention on Tobacco Control (FCTC) or the FAO Treaty on Plant Genetic Resources for Food and Agriculture" has also been identified as an option for the Tripartite Global Development and Stewardship Framework (GDSF) on AMR. In its 2019 report to the UN Secretary-General, the Interagency Coordination Group on Antimicrobial Resistance (IACG) recommended that states "consider the need for new international instruments".
21. Lindsay A. Wilson et al. A Global Pandemic Treaty Must Address Antimicrobial Resistance. *Journal of Law, Medicine & Ethics* 2021; 49(4): 688-691.
22. For a discussion of how a new AMR treaty may draw inspiration from other treaties, see, for example, Susan Rogers Van Katwyk et al. Exploring models for an international legal agreement on the global antimicrobial commons: lessons from climate agreements. *Health Care Analysis* 2020; 1-22
23. For a discussion of the content and structure of an AMR treaty, see e.g., S. Hoffman and A. Behdinan. Towards an international treaty on antimicrobial resistance. *Ottawa Law Review* 2016, 47(2).
24. Examples include the processes led by the International Campaign to Ban Landmines (ICBL), the Coalition for the International Criminal Court (ICC), Child Soldiers International (CSI), the Framework Convention Alliance (FCA), the International Campaign to Abolish Nuclear Weapons (ICAN), the International Campaign Against Enforced Disappearances (ICAEID), Control Arms, the Campaign to Stop Killer Robots, the Global Coalition to Protect Education from Attack (GCPEA), and the International Network on Explosive Weapons (INEW).
25. John Borrie and Tim Caughley (eds), Viewing nuclear weapons through a humanitarian lens. Geneva: UNIDIR, 2013.
26. Richard Moyes and Thomas Nash, Global Coalitions: An introduction to working in international civil society partnerships. London: Globalcoalitions.org, 2011.
27. The Norwegian Cancer Society is in the process of launching an international advocacy campaign for an antibiotics treaty, in collaboration with Bellona, Médecins Sans Frontières Norway, the Norwegian Academy of International Law and Rethink Food. For more information, see https://antibiotikakampanjen.no/english/.

David E Greenberg, Professor of Infectious Diseases and Microbiology, University of Texas Southwestern Medical Center, USA

"Sometimes we forget that the transformative gains that have been made in the care of the cancer patient would not have been possible without an armamentarium of effective antibiotics. Given the crisis of antibiotic resistance, one must consider a sombre question: how can treatment of the cancer patient continue if these life-saving therapies are no longer available? When I am in the hospital, I am asked on a weekly basis to help our oncology colleagues in treating a patient with a multidrug-resistant bacterial infection. If we are to continue our great strides in cancer care, this vulnerable patient population will depend upon a robust supply of active antibiotics to carry them through the successful treatment of their malignancy."

David Greenberg, MD is Professor of Infectious Diseases and Microbiology at UT Southwestern Medical Center, USA. He is also a Distinguished Teaching Professor and a past recipient of the Regents' Outstanding Teaching Award for the UT System. After graduating from Johns Hopkins University, he attended Baylor College of Medicine, USA, where he completed medical school, an internal medicine residency and served as a Chief Resident. Dr Greenberg then received his infectious diseases training at the National Institutes of Health. Dr Greenberg's research interests revolve around the increasing crisis of antibiotic resistance. He is actively involved in developing innovative strategies to develop new therapeutics to combat drug-resistant bacteria.

Superbugs and You: Russell McGowan tells his story

Superbugs and You is a podcast series that tells true stories from scientists and patients around the world. The podcast series focuses on exploring the threat of antimicrobial resistance, which occurs when bacteria, viruses, fungi and parasites change over time and no longer respond to antibiotics and other medicines. In other words, they become superbugs. In the podcast, we have discussions with patients, physicians and scientists to find out what's causing antimicrobial resistance, how it affects the lives of ordinary people, and, most importantly, what can we do to stop it? The series is co-created by the Center for Infectious Disease Research and Policy at the University of Minnesota and the Antimicrobial Resistance Fighter Coalition. In Season 2, we had an episode on "Silent superheroes – antibiotics in the fight against cancer". We highlight excerpts from the episode below.

Excerpts from the podcast:

My name is Russell McGowan, and I live in Canberra, Australia. I'm a longstanding bone marrow cancer survivor. My story is one of a medical miracle combined with bouts of iatrogenesis, so harm that's occurred to me as a result of my treatment. But I've learned some lessons from this, and that's what I want to pass on.

I was a healthy male in my early 40s when I was diagnosed with my myelofibrosis, a bone marrow cancer. I was married and the father of three young daughters at the time, and I had unexplained anemia that was affecting my ability to run. So I got checked out and after 6 to 12 months, I got a diagnosis of the myelofibrosis. The proposed solution was a bone marrow transplant, which was fairly heavy duty stuff for somebody who hadn't interacted with the health system particularly up until that time. I had to move out of my state for my bone marrow transplant, so it was quite a complex and delayed procedure and during the delay they decided to take my spleen out.

I had drugs such as cyclosporin which suppressed the immune system for some time. I had intravenous infraglobulin which boosted my immune system, and antibiotics, initially Bactrim, but I had sensitivity to that and had to revert to the components of that antibiotic, which was Dapsone and trimethoprim.

I was doing pretty well and gradually came off those medications only to be hit suddenly with a fulminant sepsis episode out of nowhere. I was taken by ambulance to our local emergency department, where I went into a coma. During that time, I was treated with various frontline intravenous antibiotics but they were unsuccessful. After I had been in the coma for three days, they managed to get a culture of the causitive agent which was *Streptococcus pneumonia*. This was surprising because they assumed that my vaccination against pneumococcus before my transplant would have stood me in good stead against that particular bacteria. I had the pneumococcal vaccination after my splenectomy, but unfortunately I didn't have it again after the bone marrow transplant. It was a relatively common bacteria, which they hadn't expected, and had not responded to the initial antibiotics. Once penicillin was started, I eventually came out of the coma, left the intensive care unit after 10 days, and recovered over a couple of months in the hospital.

Concluding remarks from interview:

This is an example of why it's so important to preserve the efficacy of the antibiotics we do have, because they were critical to Russell's recovery. Russell has continued his commitment to improved patient care by becoming a consumer advocate for health care. Health literacy is critical and he shares both his experiences and learnings with others.

Antibiotics played a key part in Russell's recovery. It wasn't "all plain sailing", but from Russell's perspective, he learned that even with the best of intentions, practitioners in the health-care system do not always get it right. Therefore, health literacy by people receiving treatment can help guard against adverse events. This is a perspective he wanted to bring into this discussion of superbugs and antimicrobial resistance – the importance of using antibiotics correctly and deploying stewardship programmes to maintain the effectiveness of antibiotics. ■

To hear Russell's full story and hear from front-line clinicians and researchers driving policy at a national level, visit https://antimicrobialresistancefighters.org/podcasts?season=12781.

Kevin Outterson, Professor of Law, Boston University and Executive Director, CARB-X

"Cancer and chemotherapy treatments can suppress the immune system and can expose patients to health care-associated sources of infection. Because of this, cancer patients may be more susceptible to getting infections, which is their second leading cause of death. Bacteria and fungi develop resistance to the drugs we use to control them, eventually rendering antibiotics and antifungals powerless to stop infections. Investing in new treatments for infections is critical to make chemotherapy and surgery safer, and increase the rates at which cancer patients survive.

Innovation is robust for cancer, with thousands of products in development. But for bacterial and fungal infections, the pipeline is remarkably thin. Due to microbial evolution, every successful antibiotic and antifungal needs to be replaced in future generations. The unique aspects of this process of resistance has led to calls to revolutionize how we pay for antibiotics, de-linking reimbursement from volume and paying instead based on social value. These concepts have been put into place now in the United Kingdom, and have been endorsed by the G7 Health Ministers in 2022. The time to act is now, if we want to survive both cancer and infections."

Professor Outterson teaches health-care law at Boston University, where he co-directs the Health Law Programme. He serves as the founding Executive Director and Principal Investigator for CARB-X, a >US$ 800 million international public-private partnership to accelerate global antibacterial innovation. Key partners of CARB-X include the US Government – Biomedical Advanced Research and Development Authority (BARDA) and the US National Institute of Allergy and Infectious Diseases (NIAID) – Wellcome in the United Kingdom and the German government – the Global AMR Innovation Fund and the Federal Ministry of Education and Research – and the Bill & Melinda Gates Foundation.

Professor Outterson's research focuses on the law and economics of AMR, particularly push and pull incentives for antimicrobials. He has served as a senior author on many key research reports on antibiotic innovation, including Chatham House, ERG , DRIVE-AB, and the Lancet Commission. Professor Outterson received the 2015 Leadership Award from the Alliance for the Prudent Use of Antibiotics for his research and advocacy work. He has testified before the US Congress, Parliamentary working groups in the United Kingdom, the World Health Organization (WHO), and state legislatures. Since August 2016, he has led CARB-X, the world's most innovative antibiotic accelerator.

AMR and cancer treatment

Antibiotic resistance in the patient with cancer: Escalating challenges and paths forward

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Infection is the second leading cause of death in patients with cancer. Loss of efficacy in antibiotics due to antibiotic resistance in bacteria is an urgent threat against the continuing success of cancer therapy. In this review, the authors focus on recent updates on the impact of antibiotic resistance in the cancer setting, particularly on the ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter spp.*). This review highlights the health and financial impact of antibiotic resistance in patients with cancer. Furthermore, the authors recommend measures to control the emergence of antibiotic resistance, highlighting the risk factors associated with cancer care. A lack of data in the etiology of infections, specifically in oncology patients in United States, is identified as a concern, and the authors advocate for a centralized and specialized surveillance system for patients with cancer to predict and prevent the emergence of antibiotic resistance. Finding better ways to predict, prevent, and treat antibiotic-resistant infections will have a major positive impact on the care of those with cancer.

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Bacterial resistance to penicillin was encountered in patients *(1)* within 2 years after mass production of the antibiotic began in 1945 *(2,3)*. Since then, the emergence of antibiotic resistance has been reported against virtually all antibiotics developed to date *(4)*. Organizations such as the World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC) have recognized antimicrobial resistance (AMR) as a global threat *(5,6)*. The misuse and overuse of antibiotics is a significant driver for increasing antibiotic resistance *(4,7)*. If the scientific community fails to manage and replenish our antibiotic supply, nearly 10 million extra deaths are predicted by 2050 due to drug-resistant infections *(8-10)*.

In a postantibiotic era, many interventions that we currently take for granted will be threatened. These include medical advances that have occurred in general surgery *(11)*, treatment of immunocompromised patients *(12)*, organ transplant recipients *(13)*, and patients with prosthetic implants *(14)*. Importantly, increasing levels of antibiotic resistance are already having a profound impact on the care of patients with cancer *(15)*. *End cancer as we know* it is a major priority of the Biden Administration *(16)* as well as medical societies *(17)*, but achieving that goal will also require action against drug-resistant microbes.

Infections are common in patients with cancer, and they depend upon effective antibiotics to both prevent and treat bacterial infections. Antibiotic failure in patients with cancer increases the frequency of sepsis, sepsis-related mortality, and sepsis-associated costs of care *(18-23)*. Thus it is not surprising that oncologists have been among the first to point out the clinical impact of increasing antibacterial resistance. For example, a recent study in the United Kingdom reported that 46% of the oncologists in the United Kingdom are worried that chemotherapy as a treatment for cancer will be difficult as a result of drug-resistant infections *(24)*. Optimizing the use of current antibiotics and discovery of novel antibiotics

Table 1: **Antibiotic-resistance mechanisms in ESKAPE bacteria**[a]

Resistance t ype (Blair 2015[28])	Examples of molecular mechanisms (Bax & Griffin 2012[29])	Effected antibiotics classes (Kapoor 2017[30])	Examples of antibiotic-resistant isolates from patients with cancer (Reference)
Antibiotic inactivation	β-Lactamases	Penicillins	**ESBL-producing** *K. pneumoniae* (Zhang 2016[31])[b]
	Aminoglycoside-modifying enzymes	Aminoglycosides	**ESBL-producing** *E. coli* (Cornejo-Juarez 2015[32]) **CRE** *K. pneumoniae* (Satlin 2027[33])c **Carbapenem-resistant** *A. baumannii* (Bodro 2014[34]) **Methicillin-resistant** *S. aureus (MRSA)* (Bodro 201434) **Metallo β-lactamase–producing** *P. aeruginosa* (Toleman 2004[35])
Antibiotic target modification et al. 2017[65])	Alteration of the peptidogly can synthesis pathway	Glycopeptides	**Vancomycin-resistant** *E. faecium* (Alatorre-Fernandez et al. 2017[65])
	Mutations in DNA gyrase	Fluoroquinolones	**Fluoroquinolone-resistant clinical isolates of** *E. coli* (Conrad 1996[37])
	Ribosomal mutations	Tetracyclines	
Antibiotic efflux	Overexpression of multidrug-resistant	Tetracyclines and Fluoroquinolones	**Efflux pump-overexpressing** *K. pneumoniae* and *E. coli* (Hamed 2018[38])
Reduced permeability of antibiotic	Downregulation or mutations in porin proteins	Penicillins	*K. pneumoniae* with porin deletions (Satlin 2013[39])
		Cephalosporins	

Abbreviations: CRE, carbapenem-resistant Enterobacterales-like; ESBL, extended-spectrum β-lactamase.
[a]ESKAPE indicates Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp.
[b]ESBLs break down and destroy some commonly used antibiotics, including penicillins and cephalosporins (Centers for Disease Control and Prevention 2019[40]).
[c]CRE-like E. coli and K. pneumoniae develop resistance to the group of antibiotics called carbapenems (Centers for Disease Control and Prevention 2019[41]).

are critically important to protect patients with cancer from antibiotic-resistant infections in the future because antibiotic resistance threatens to undo much of the hard-won progress against cancer *(25)*.

Antibiotic resistance is defined as the ability of microorganisms to survive when exposed to antibiotics that usually would kill them or prevent their growth *(26)*. Some of the key factors contributing to antibiotic resistance are misuse of antibiotics in humans and animals, use of antibiotics in animal and food industries, lack of rapid diagnosis procedures, and the presence of antibiotics in the environment *(27)*. Antibiotic resistance can be intrinsic or acquired due to various genetic mechanisms. We have highlighted the major mechanisms of antibiotic resistance in Table 1 *(28-41)*. Some mechanisms can lead to antibiotic resistance in 1 or 2 classes of antibiotics, whereas others result in multidrug-resistant (MDR) isolates, which are characterized by exhibiting resistance to ≥3 different classes of antibiotics *(42,43)*. In 2008, Rice et al designated 6 groups of bacteria (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *A. baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter spp.*) that were commonly associated with antibiotic resistance in the hospital environment and referred to them as ESKAPE pathogens *(44)*. In this review, we focus on recent updates regarding antibiotic-resistant ESKAPE infections, including risk factors, antibiotic use, management, and prevention of antibiotic resistance in patients with cancer.

The use of antibiotics and the burden of antibiotic resistance in patients with cancer

Infections are one of the most frequent complications seen in patients with cancer *(45)*, and a patient with cancer has a 3 times greater risk of dying from a fatal infection than a patient without cancer *(46)*. Infections are thought to play a primary or associated role in the cause of death in approximately 50% of patients with hematological malignancies or solid tumours *(47)*, even if drug-resistant infections are rarely recorded as the official cause of death on death certificates *(48)*. Bacteria are the most common cause of infections in patients with cancer*(47, 49)*. Risks of developing an infection include disruption of anatomic barriers *(50)*, surgery, *(51)* chemotherapy-related and radiation-related neutropenia *(52)*, and stem cell transplantation *(53)*. More recently, an increased risk of infection is reportedly caused by toxicity mitigation strategies using newer immunotherapies against cancer *(54-56)*. Under neutropenic conditions, patients with cancer are subjected to prolonged treatment of antibiotics prophylactically and empirically *(57,58)*. However, widespread and prolonged use of broad-spectrum antibiotics to reduce mortality and morbidity from infections in patients with cancer are likely contributors to the emergence of resistance *(59-61)*. In addition, patients with cancer are vulnerable to health care-acquired infections as a major source of antibiotic-resistant organisms *(32,62,63)*.We have summarized several

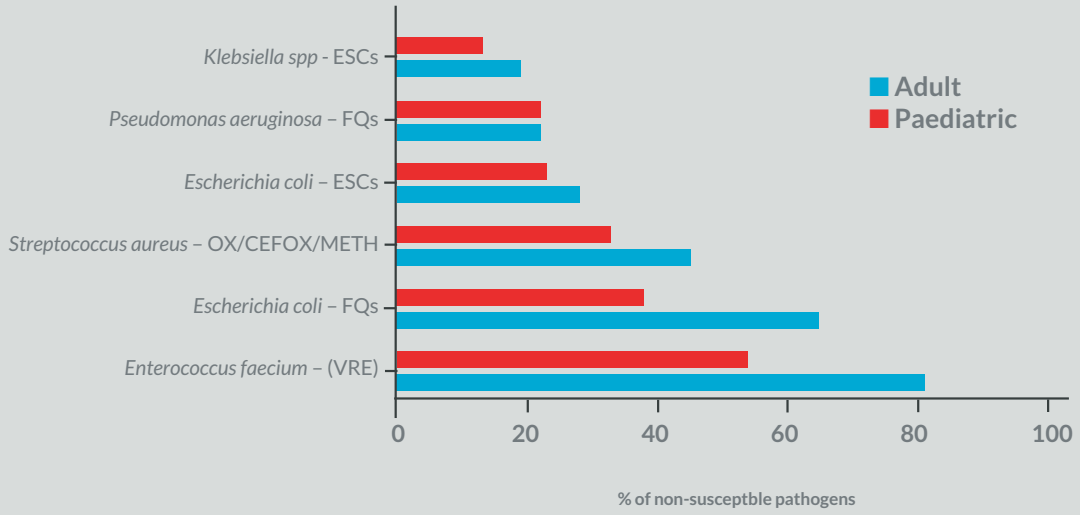
Table 2: Antibiotic resistance in patients with cancer: highlights from the last 5 years

POPULATION STUDIED	RESISTANT MICROORGANISMS	RISK FACTORS FOR DEVELOPMENT OF ANTIBIOTIC RESISTANCE	INTERPRETATIONS	REFERENCE
BSI episodes in patients with cancer (January 1995 to May 2015)	*Enterococcus faecium* (EF)	• Prolonged antibiotic exposure	• 403 Episodes of EF BSIs from 21,695 positive blood cultures • Increase in BSIs due to EF infections observed from 2005 to 2015	Tedim 2017 [60]
Hematologic neutropenic patients (July 2009 to July 2012)	*Enterococcus faecium*	• Previous hospitalization • Levofloxacin extended prophylaxis	• Ampicillin-resistant EF (AREfm) colonization was detected in 32 of 52 patients (61.4%) • Multidrug-resistant (MDR) clones of AREfm in intestine of patients with cancer increase the development of bacteremia	Sanchez-Diaz 2016 [64]
BSIs in patients with hematologic malignancies (January 2008 to December 2012)	*Enterococcus faecium*	• Prophylactic antibiotics • Vancomycin therapy during the previous 3 mo	• 58 Episodes of EF BSI episodes from a total of 15,095 blood cultures • Higher mortality was associated with vancomycin-resistant isolates	Alatorre-Fernandez 2017 [65]
BSIs in malignant hematology and oncology patients (2008-2014)	*Enterococcus faecium*	• Prior antibiotic exposure	• 96 Patients with EF BSIs were included in the study • Higher 30-d mortality was associated with vancomycin-resistant isolates	Xie 2020 [59]
BSIs in patients with hematologic malignancies (January 2012 to December 2014)	*Pseudomonas* aeruginosa (PA)	• Previous hospitalization • Prior use of fluoroquinolones	• 64 Patients with PA BSIs were studied • 37.5% Isolates were MDR • PA is an important pathogen in patients who have hematologic malignancies associated with high mortality	Tofas 2020 [61]
BSIs in patients with hematologic malignancies and hematopoietic cell transplant recipients (January 2012 to March 2018)	*Pseudomonas aeruginosa*	• Fluoroquinolone prophylaxis	• 55 Episodes of PA bacteremia among 51 patients • Fluoroquinolone prophylaxis was associated with nonsusceptibility to meropenem, but not to anti-pseudomonal β–lactams or aminoglycosides	Hakki 2019 [66]
BSIs in neutropenic patients with cancer (January 2006 to May 2018)	*Pseudomonas aeruginosa*	• Prior therapy with piperacillin-tazobactam • Prior anti-pseudomonal carbapenem use • Fluoroquinolone prophylaxis	• 1217 Episodes of BSI due to PA across 34 centers in 12 countries • The rate of MDR increased significantly over the study period	Gudiol 2020 [67]
Respiratory infections in patients with lung cancer (September 2017 to October 2018)	*Klebsiella pneumoniae* (KP)	• HAIs	• KP was identified in 27 of 47 patients who had lung cancer with respiratory infection • 51.4% KP isolates were MDR and the dominant strain causing lung infection in patients with lung cancer in the study	Ding 2020 [68]
Patients who had cancer with BSIs, HAIs, and intra-abdominal infections (February to July 2013)	*Klebsiella pneumoniae*	• History of systemic steroid • Combination antimicrobial therapy	• In total, 230 consecutive cases of KP infection were studied • 12.6% of hypervirulent KP isolates produced extended-spectrum β–lactamase	Zhang 2016 [31]
BSIs in malignant hematology and oncology patients (January 2014 to September 2018)	*Klebsiella pneumoniae*	• Carbapenem exposure within 30 d before the onset of BSIs	• 89 patients with KP bacteremia were included in the study • Carbapenem-resistant KP caused more mortality than carbapenem-susceptible KP (55.0% vs 15.9%; *P*=.001)	Liu 2019 [69]
Patients with cancer (2006 to March 2015)	*Methicillin-resistant Staphylococcus aureus (MRSA)*	• HAIs	• 21.1% of MRSA was documented from 450 patients reported with *S. aureus* infection • Protective factors for mortality included catheter removal and initiation of adequate treatment for *S. aureus* <48 h after positive blood cultures	Bello-Chavolla 2018 [70]
Patients with erythrodermic cutaneous T-cell lymphoma (CTCL) (2012-2016)	*Staphylococcus aureus*		• Of 50 events, 17 (34%) were due to MRSA • The MRSA prevalence was high in patients with erythrodermic CTC	Emge 2020 [71]
Patients with cancer (June 2014 to March 2016)	Methicillin-resistant *Staphylococcus aureus*		• 120 Isolates (40 community-acquired and 80 hospital-acquired MRSA) were included in the study • Patients with community-acquired MRSA showed remarkable ability to acquire MDR after irradiation	Shehata 2019 [72]
Patients with cancer (July 2017 to January 2018)	*cinetobacter baumanni (AB)i*		• 48 AB isolates were recovered from 520 blood samples • Carbapenemases were identified as the main mechanism of carbapenem resistance in AB	Wasfi 2020 [73]
Patients with cancer—outbreak initiated from a single patient (March 2011)	*Acinetobacter baumannii*	• HAIs	• 66 AB strains (62.3%) were considered infection, and 40 (37.7%) were considered colonization • Highlighted the threat that represents the transfer of colo nized patients with MDR strains between institutions	Cornejo-Juarez 2020 [62]
Patients with malignant hematology (January 2014 to June 2015)	*Acinetobacter baumannii*	• Previous carbapenem exposure • Previous hospitalization	• 40 Patients with AB bacteremia were identified, accounting for 2.9% (40 of 1358) of bacteremia cases • Patients who had carbapenem-resistant AB infections had significantly longer hospital stays	Wang 2017 [74]

Abbreviations: BLIs, bloodstream infections; HAIs, hospital-acquired infections.

studies in which ESKAPE pathogens were isolated from patients with cancer since 2015 in Table 2 *(31,59-62,64-74)*. These illustrate the prevalence of MDR in different ESKAPE pathogens and highlight that prior antibiotic exposure and hospital-acquired infections are the major risk factors for developing antibiotic resistance in patients with cancer. For Figure 1, we derived data from the National Healthcare Safety Network (NHSN) 2015 to 2017 adult and pediatric antibiotic resistance reports *(75,76)*. to illustrate differences between the percentage of central line-associated bloodstream

Figure 1: Antibiotic resistance is common in patients with cancer. This bar graph displays the percentage of pathogens reported from adult and paediatric central line- associated bloodstream infections (CLABSIs) that tested nonsusceptible (NS) to selected antimicrobial agents in hospital oncology units in the United States from 2015 to 2017



*Data for the graph were obtained from the National Healthcare Safety Network 2015 to 2017 adult and pediatric antibiotic resistance reports. *Klebsiella spp. include K. oxytoca and K. pneumoniae. ESCs indicates extended- spectrum cephalosporins (cefepime, cefotaxime, ceftazidime, or ceftriaxone); FQs, fluoroquinolones (ciprofloxacin or levofloxacin); OX/CEFOX/METH, oxacillin, cefoxitin, or methicillin; VRE, vancomycin- resistant Enterococcus.*

infections by ESKAPE pathogens that tested nonsusceptible to selected antimicrobial agents. Vancomycin resistance in *E. faecium* and fluoroquinolone nonsusceptibility in *Escherichia coli* appear to be significantly higher in adult oncology patients compared with pediatric patients.

Antibiotic resistance is related to unfavourable outcomes in patients with cancer

Antibiotic resistance leads to detrimental effects in patients with cancer, who rely on antibiotics to prevent and treat infections *(77-79)*. A meta-analysis by Teillant et al found that, in postchemotherapy infections, 26.8% of pathogens were identified as resistant to the standard prophylactic antibiotics that had been prescribed. That study forecasted that a reduction in antibiotic efficacy of 30% to 70% would result in nearly 4,000 to 10,000 additional infections and 500 to 1,000 additional deaths per year in the United States among patients who go through chemotherapy for hematological malignancies *(15)*.

Multiple studies demonstrate the impact of increasing resistance on outcomes in this vulnerable population *(80-82)*. Bodro et al reported increased persistence of bacteremia (25% vs 9.7%), metastatic infection (8% vs 4%), and early case-fatality rates (23% vs 11%) among patients with cancer who had infections caused by antibiotic-resistant ESKAPE pathogens compared with other bacterial pathogens. Risk factors that were associated with having an antibiotic-resistant infection included comorbidities, prior antibiotic therapy, having a urinary catheter, and a urinary tract source of infection. Those authors identified a wide variety of pathogens, including: methicillin-resistant *S. aureus* (MRSA), extended-spectrum β-lactamase (ESBL)–producing *K. pneumoniae*, carbapenem-resistant *A. baumannii*, carbapenem-resistant and quinolone-resistant *P. aeruginosa*, and de-repression of chromosomal β-lactamase and ESBL-producing *Enterobacter* species *(34)*.

A study in 2015 found that 58 of 282 deaths (23%) among patients with cancer who required intensive care were caused by hospital-acquired infections. In 51 of those 58 cases (88%), an MDR pathogen was identified. The overall prevalence of MDR pathogens was nearly 40% in microorganisms collected from patients who were admitted to the intensive care unit. Of the identified MDR pathogens, 20% were caused by *E. coli* (94.4% of these were ESBL producers), 12% were caused by *S. aureus* (90.6% of these were MRSA), 12% were caused by *E. faecium* (18.7% were vancomycin resistant), and 6% were caused by *A. baumannii* (all were MDR) *(32)*.

In 109 patients with hematological diseases who were undergoing chemotherapy, overall survival at 30 days was analyzed in those who had Gram-negative bloodstream infections (BSIs). In patients who had infections caused by MDR bacteria, survival was significantly lower compared with the survival of those who had infections caused by non-MDR isolates (85.6% vs 55.9%; P <.001) *(83)*. In addition,

numerous recent studies support the association of antibiotic resistance with unfavourable outcomes in patients with both hematological malignancies and solid tumours *(84-88)*. The impact of resistance is not limited to the adult population. In a tertiary children's hospital from 2010 to 2014, carbapenem-resistant versus carbapenem-susceptible BSI was associated with a longer duration of bacteremia (mean, 3.8 vs 1.7 days), a higher risk for intensive care unit hospitalization (44.4% vs 10.1%), and a higher mortality rate (33% vs 5.8%) in patients with hematological malignancies and after hematopoietic stem cell transplantation *(89)*.

Infections with antibiotic-resistant bacteria have been studied less in patients with solid tumours than in those with hematological malignancies *(90)*. This could be because of a lower incidence of BSIs reported in solid tumours compared with hematological malignancies in neutropenic patients with cancer *(91)*. One main difference in infections between solid and hematological malignancies is the source of infection: pneumonia and urinary tract infections were frequent among patients with solid tumours, whereas endogenous sources and catheter-related BSIs were frequent in patients with hematological malignancies *(91)*. The risk of infection in patients with solid tumours can be increased by factors such as chemotherapy-related or radiation therapy-related neutropenia, disruption of anatomic barriers from medical devices and surgical or diagnostic procedures, and obstruction due to primary or metastatic tumours, resulting in postobstructive pneumonia, lung abscess, or urinary tract infections. Common sites of infection in patients with solid tumours include BSIs related to neutropenia and postsurgical site infections in breast, bone, central nervous system, and skin *(45)*. Recent epidemiologic data highlight the high prevalence of MDR pathogens in these patients *(92-94)*. One study reported that patients older than 70 years with solid tumours had more frequent infections because of MDR organisms compared with patients younger than 70 years *(87)*. Another study demonstrated that patients with solid tumours were more susceptible to bacteremic cholangitis caused by *Enterobacteriaceae* and *E. faecium*, highlighting the emergence of MDR as a special concern, especially in patients who have a second episode of bacteremia *(95)*. AMR can become important even during the diagnostic evaluation of solid tumours. For example, recent literature has demonstrated complications such as increased hospitalization and death due to antibiotic-resistant infections after prostate biopsies *(96,97)*. Extensive use of fluoroquinolone prophylaxis may be associated with an increase in resistant *E. coli* strains, which can result in infections after prostate biopsies *(98)*; as a result, broad-spectrum and longer duration of prophylaxis is recommended *(96,99)*. Importantly, targeted antibiotic prophylaxis with prebiopsy screening has reduced the number of infections after the biopsy *(100,101)*.

Cancer and antibiotic resistance also converge to worsen health disparities. Certain communities of colour in the United States, including African American, Latinx, and indigenous communities, experience higher cancer incidence and lower survival rates for many types of cancers. Many complex factors drive these disparities *(102)*. Similarly, experts have identified many reasons to suspect a disparate impact of AMR, including differences regarding the use of prescribed and nonprescribed antibiotics, barriers to medical care, higher rates of foreign travel to regions with high AMR burden, and more likely employment in food animal production *(103)*. Taken together, the joint epidemics of cancer and AMR can contribute significantly to persistent health inequities.

AMR and the cost of treating cancer

The decline of antibiotic effectiveness due to AMR has imposed a massive burden on health-care costs, with an increase in hospital admissions *(104)*. Antibiotic resistance is estimated to cost nearly US$ 20 billion in health care and US$ 35 billion a year in lost productivity in the US economy *(4,105)*. The cost of treating infections in patients with cancer adds a significant amount to the overall cost of cancer treatment. For example, of all-cause health-care costs during first-line chemotherapy, neutropenia-related costs accounted for 32.2% in patients with non-small lung cancer who were diagnosed with febrile neutropenia *(106)*. On the basis of a study published with 91,560 and 16,859 cancer-related neutropenia hospitalizations among adults and children, respectively, the cost of cancer-related neutropenia hospitalization was US$ 24,770 per stay for adults and US$ 26,000 per stay for children in the United States *(107)*. Tori et al reported that the cost of treatment for an episode of febrile neutropenia after chemotherapy, on average, was from US$ 50,000 to US$ 60,000 in 2020 *(108)*.

Although studies have estimated the increased cost of health care caused by AMR, the direct costs of AMR related to cancer therapy have rarely been studied. In 2004, Watters et al reported the cost associated with the treatment of patients with head and neck cancer who become colonized or infected with MRSA after major surgical procedures. Patients who were colonized or infected with MRSA had up to a 3 times more prolonged hospital stay compared with those who were not positive for MRSA. Furthermore, the authors reported that the cost of antibiotics increased by US$ 2,470 per patient because of MRSA *(109)*.

Strategies for preventing antibiotic resistance in patients with cancer

Prevention of infection—minimizing antibiotic usage

Antibiotic prophylaxis is a common practice for preventing

infections and infection-related complications under neutropenic conditions in patients who have cancer *(110,111)*.

With neutropenic conditions, patients are prone to develop fever (febrile neutropenia), indicating possible infection. The mortality rate can go up to 11% in patients who have cancer with febrile neutropenia *(112,113)* and can be as high as 50% during severe sepsis conditions *(114)*. According to some studies, prophylactic use of quinolones reduces the incidence of fever, probable infections, hospitalizations, *(115,116)* and the overall mortality rate *(110,117)*. These gains must be balanced with observations that patients with cancer who receive prolonged antibiotic prophylaxis are at risk for developing breakthrough antibiotic-resistant infections *(67,118-120)*.

Previous antibiotic exposure has been recognized as one of the main risk factors for AMR development in some patients with cancer *(59-61,67)*. In fact, there remains ongoing debate in clinical oncology settings about the overall use or duration of quinolone prophylaxis in some patients with cancer because the procedure failed to reduce overall mortality and increased the emergence of resistant strains in some studies *(121-124)*.

Minimizing infections provides an opportunity to reduce the use of antibiotics in patients with cancer who have neutropenia or those undergoing surgeries and other invasive procedures. The CDC, the American Cancer Society, and the National Comprehensive Cancer Network provide guidance to patients with cancer, caregivers, and their health-care teams to prevent infections in patients who have cancer. These include educating patients and caregivers about day-to-day good practices to prevent infections or to detect infections early *(125-127)*.

Antibiotic or chemotherapy administration can result in gut microbiota dysbiosis, altering the diversity of bacteria *(128-130)*. Dysbiosis in the gut microbiota can increase the risk for resistance bacteria in the microbiota *(131)*, invasive infections, *(50)* post-transplant complications (such as graft-versus-host disease in those who undergo hematopoietic stem cell transplantation) *(132)*, and reduced efficacy in patients who have cancer treated with immunotherapy *(133)*. Monitoring gut microbiota for its composition, administering protective commensal bacteria to reduce antibiotic-resistant infections, and promoting a healthy microbiome could be promising approaches for preventing antibiotic resistance, minimizing antibiotic use, and leading to positive outcomes in these patients *(134-136)*.

Another area of concern for patients with cancer is the recognition that there is geographical variability in antibiotic resistance. Resistance to antibiotics frequently originates in one locality,only to spread to others. For example,vancomycin-resistant *Enterococci* was identified in 1987 in Europe and, within 10 years, it represented >25% of *Enterococci* associated with BSIs in hospitalized patients in the United States *(137)*. A study by Arcilla et al in 2017 found that 34.3% of 1,847 travelers who were ESBL-negative before traveling from the Netherlands had acquired ESBL *Enterobacterales* during their international travel, with examples of transmission within households *(138)*. Furthermore, medical tourists travel between health facilities in locations with different rates of antibiotic resistance, potentially disseminating resistant pathogens *(139)*. With international travel poised to rebound after COVID-19, vulnerable groups such as patients with cancer should remain aware of infectious risks, including information on the prevalence of drug-resistant pathogens that might be present in the locations to which they travel.

Promoting the appropriate use of antibiotics among health-care practitioners and patients will prevent the misuse and overuse of antibiotics as well as decreasing costs *(140-142)*. Most importantly, this will allow for continued use of the existing antibiotic armamentarium *(143-145)*. The required duration of antibiotic therapy is inexact and has been disputed in oncology settings, leading to unnecessarily extended courses of antibiotics and heterogeneity of use between practice sites *(146-148)*. Well defined guidelines are required after comprehensive studies to establish the optimal duration of antibiotic administration to reduce antibiotic overuse in oncology settings *(149)*. For example, vancomycin has been shown to be inappropriately prescribed as empirical treatment resulting in vancomycin resistance *(150)*. Fever and neutropenia guidelines published by the Infectious Diseases Society of America indicate that vancomycin is not recommended as a standard part of the initial antibiotic regimen for fever and neutropenia and should be considered for specific clinical indications. Furthermore, these guidelines emphasize the importance of discontinuing vancomycin in the absence of Gram-positive organisms *(151)*. Antibiotic de-escalation and discontinuation should be considered when the patient is stabilized or the causative agent is determined to reduce overuse *(152)*. Early discontinuation of empirical antibacterial therapy in patients with fever of unknown origin has been demonstrated to be safe, *(153,154)* and emerging data indicate that continuation of empirical antibiotics until absolute neutrophil count recovery could be unnecessary *(155,156)*. De-escalating and discontinuation strategies have been successfully demonstrated in high-risk neutropenic patients who have cancer, with a significant reduction in antibiotic use *(157-159)*.

Antibiotic stewardship to optimize antibiotic use

Antimicrobial stewardship has been defined as selection of the best antimicrobial treatment at the optimal dose and duration, resulting in the best clinical outcome for treating and

preventing infection with minimal toxicity and a minimal effect on subsequent resistance *(160,161)*.

In health-care settings, antimicrobial stewardship teams, ideally led by infectious diseases physicians in partnership with infectious diseases pharmacists, clinical microbiologists, and infection preventionists, are charged with this important initiative. Antimicrobial stewardship is especially important for patients with cancer and/or those undergoing hematopoietic stem cell transplantation, who are prone to serious infections and receive multiple courses of antimicrobial therapy during the treatment process *(162)*. These patients may have the most potential to benefit from antibiotic stewardship because past antibiotic exposure is a critical risk factor for developing an antibiotic-resistant infection. As discussed above, patients who have cancer with antibiotic-resistant infections have worse outcomes than those who have antibiotic-susceptible infections *(163)*. Rosa et al evaluated patient outcomes related to antibiotic stewardship in patients with febrile neutropenia, specifically, mortality in those with hematological malignancies and solid tumours. Their study indicated that adherence to antibiotic stewardship was independently associated with lower mortality *(164)*. However, according to a review published by Pillinger et al in 2020, these patient populations are frequently excluded from studies of antibiotic stewardship, and more efforts are needed to determine the broader impact of different stewardship strategies in this vulnerable patient population *(165)*. Nevertheless, several other studies in hospital-wide intervention programmes have demonstrated the impact of antibiotic stewardship on decreasing antibiotic resistance system wide and reducing antimicrobial expenditures *(166-170)*. Although more data in this patient population are needed, it is reasonable to conclude that decreases in infections caused by antibiotic-resistant pathogens in a health-care system would translate to improved outcomes across a diverse range of patient populations. The Centers for Medicare and Medicaid Services require acute care hospitals and long-term care facilities to have antibiotic stewardship programmes in place, but their impact is uneven because many hospitals lack sufficient resources to fully implement stewardship protocols *(171)*. Only recently has stewardship become a focus in outpatient settings, where high levels of inappropriate antibiotic prescriptions persist. Recently implemented Core Elements of Outpatient Antibiotic Stewardship by the CDC focus on a framework for antibiotic stewardship for outpatient clinicians and facilities that routinely provide antibiotic treatment *(173)*. Increased resources will be critical to the universal adoption of stewardship, and patients at greatest risk for increased morbidity and mortality because of antibiotic-resistant infections – such as those with cancer – have the most to gain *(173)*.

Other than health-care settings, it is important to focus on more general areas that contribute to the occurrence of antibiotic-resistant bacteria. Agriculture, such as the livestock and poultry industries *(174)*, is one important area of concern. These industries consume large quantities of antibiotics to protect animals from infection and also to promote growth *(175,176)*. According to the *2019 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals* by the US Food and Drug Administration, 54% of nearly 11 metric tons of antibiotics used in animal agriculture are medically important, such as tetracyclines and penicillins *(174)*. Antibiotic-resistant bacteria occurring in these settings can be transmitted to humans *(177-179)*. Although no studies have been performed to correlate antibiotic resistance in farm animals and patients with cancer, it is likely that such patients could face complications because of colonization of antibiotic-resistant species in their intestines. Tackling antibiotic resistance will require a sustained, multi-faceted approach in numerous segments of society.

Antibiotic-resistance surveillance systems for patients with cancer: Prediction and prevention of outbreaks

The CDC has defined surveillance as systematic, ongoing collection, analysis, and interpretation of health data essential for planning, implementing, and evaluating public health practice integrated closely with timely dissemination to those who need the data *(180)*. Various countries have developed their own guidelines for the surveillance of antibiotic-resistant bacteria *(181-183)*. Surveillance of AMR involves the tracking and analysis of antibiotic-susceptibility test results in bacteria isolated from clinical samples. These results, combined with clinical and demographic data obtained from patients, enable clinicians to provide meaningful interventions to reduce the burden of antibiotic resistance *(184)*. Surveillance data can be used for predictions. The data from surveillance, merged with other risk factors, can be used to develop prediction models for antibiotic-resistance development in clinically relevant bacterial pathogens. In 2020, Gudiol et al developed a clinical prediction model available online that could identify neutropenic patients with cancer who are at high risk of bloodstream infections because of MDR *P. aeruginosa*, centered on parameters such as patient age and prior antibiotic use. Although the study has not been replicated yet by other groups, the investigators reported good prediction results in patients with cancer from across 34 centres in 12 countries, indicating that the model may benefit these patients by improving the administration of specific empirical antibiotic

treatment and that it may also help optimize the effective- ness of antibiotic stewardship programmes *(67)*. A comprehensive and predictive model of ESKAPE pathogens theoretically could be a useful tool for predicting the emergence of antibiotic resistance in oncology settings and driving the efficient utilization of antibiotics. The CDC has increased antibiotic-resistance surveillance in accordance with the first National *Action Plan for Combating Antibiotic Resistant Bacteria*, but significant gaps in our knowledge remain *(185)*. For example, adult and pediatric antibiotic-resistance reports issued from 2015 to 2017 by the NHSN highlighted health care- associated infections from 17 adult and 8 pediatric oncology facilities only. The number of oncology facilities that reported data was relatively low compared with the total number of healthcare facilities that reported data in the NHSN (5,626 adult centers and 2,545 paediatric centres) *(75,76)*. Furthermore, the report separately revealed the percentage of antibiotic non-susceptible pathogens recorded from oncology units, as summarized in Figure 1. A comparison of the percentage of non-susceptible pathogens between adult and pediatric oncology units reveals higher levels of vancomycin-resistant *E. faecium* and fluoroquinolone-resistant *E. coli*. However, similar data were not found for oncology facilities from previous reports by the NHSN, so comparisons from previous years could not be made *(186-189)*. Having chronological surveillance data on antibiotic resistance in oncology settings will be critical for tracking trends and linking rates of resistance to interventions made in these patients. Ongoing and future efforts by the CDC will help in this regard.

Future innovations in antibiotics and their impact on resistance

Although several international and governmental organizations have helped fund new efforts, such as CARB-X (Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator), to spur the development of innovative antibiotics, *(190)* several expert reports have warned that antibiotic business models are uniquely broken and require significant reform to bring innovative new antibacterials to patients *(191-195)*. Because physicians frequently reserve new antibiotics as a last resort treatment for infections, this results in a low volume of sales *(4)*. An analysis by Towse et al in 2017 estimated that the cost of developing an antibiotic is approximately US$ 1,581 million, whereas the average annual revenue from an antibiotic's sales is roughly US$46 million *(196)*. This results in significant obstacles for the pharmaceutical industry to developing new antibiotics *(4)*. A predictable return on investment for antibiotic development will likely require the support of the federal government enacting policies that could help prevent the collapse of the antibiotic pipeline. Financial incentives for antibiotic innovation should target drugs that will provide the most clinical benefit for patients with the most significant unmet medical needs *(197)*.

The vast majority of antibiotics used clinically are broad-spectrum. Broad-spectrum antibiotics are usually active against multiple bacterial species, not just the specific pathogen that might be targeted in a particular patient scenario *(198)*.

One major drawback of broad-spectrum antibiotics is the development of AMR not only in pathogenic bacteria but also in the non-pathogenic commensal bacteria that comprise the normal microbiome *(199)*. The development of narrow-spectrum antibiotics is considered an attractive approach to overcoming antibiotic-resistant bacterial infections because more specific antibiotics can reduce the selection pressure in non-targeted pathogens *(200,201)*. Examples of experimental narrow-spectrum antibiotics for ESKAPE pathogens include bacteriophages, *(202,203)* monoclonal antibodies *(204)*, bacteriocins *(205,206)*, and antisense molecules, such as peptide-conjugated phosphorodiamidate morpholino oligomers *(207-209)*. Bacteriophages are bacterial viruses that infect bacterial cells, which can cause the bacterium to lyse *(210)*. Bacteriophages are specific for bacteria and selectively attach to specific receptors on the surface of the host cell *(211)*. Similar to phages, human monoclonal antibodies also can be developed for specific bacteria and can be targeted by the immune system *(212,213)*. Bacteriocins are peptides of different sizes produced by various bacteria that exhibit bactericidal activity against other bacteria *(205,214)*. Bacteriocins bind various receptors on the surface of the target bacteria to trigger bactericidal effects *(215)*. Phosphorodiamidate morpholino oligomers are designed to target mRNA and block translation of the gene of interest *(207)*. Continuing advances in the rapid identification of pathogens will enable the opportunity of using narrow-spectrum antibiotics. Recent developments in diagnostic tests, such as next-generation sequencing, *(36,216-218)* matrix-assisted laser desorption ionization–time-of-flight mass spectrometry *(219)*, and rapid antigen testing, *(220)* have made the prospect of pathogen-specific therapy a viable strategy. Additional policies are needed to strengthen diagnostic innovation and clinical integration of diagnostics, including better outcomes studies to inform clinical use and justify appropriate reimbursement *(221)*. Recently, the Infectious Diseases Society of America issued new guidelines to treat antimicrobial-resistant, Gram-negative infections focusing on the efficiency of different antibiotics according to the etiology of the infection. These guidelines provide preferred or alternative antibiotic treatment options with dosages for ESBL-producing *Enterobacterales*, carbapenem-

resistant *Enterobacterales*, and difficult-to-treat *P. aeruginosa* according to the source of infection *(222)*.

Conclusion

Drug-resistant infections are growing in number and cost and significantly threaten our ability to care for patients with cancer. The cancer community – patients, loved ones, clinicians, and scientists – have successfully advocated for significant investments in research and public health strategies to prevent cancer and increase therapeutic options, with the goal of saving and extending lives *(223)*. Because antibiotic resistance threatens to undo much of this hard-won progress, cancer advocates should consider focusing their considerable political power on this public health crisis. Cancer and infectious diseases experts must unite to drive the federal policy changes necessary to prevent, diagnose, and treat drug-resistant infections and to protect the gains that have been made against cancer over the past few decades. ■

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References

1. Spink WW, Ferris V. Penicillin- resistant staphylococci: mechanisms involved in the development of resistance. *J Clin Invest*. 1947;26:379-393 . doi:10.1172/ JCI10 1820
2. Aminov RI. A brief history of the antibiotic era: lessons learned and challenges for the future. *Front Microbiol*. 2010;1:134. doi:10.3389/fmicb.2010.00134
3. Hamilton KW. Miracle Cure: The Creation of Antibiotics and the Birth of Modern Medicine. *Emerging Infect Dis.* 2019;25:196. doi:10.3201/eid25 01.181184
4. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. P T. 2015;40:277-283.
5. Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2019 (2019 AR Threats Report). Accessed February 25, 2021. cdc.gov/drugresistance/biggest-threats.html.
6. World Health Organization. Global action plan on antimicrobial resistance. 2021. Accessed February 25, 2021. who.int/publications/i/item/97892 41509763
7. Goossens H, Ferech M, Vander Stichele R, Elseviers M, ESAC Project Group. Outpatient antibiotic use in Europe and association with resistance: a cross- national database study. *Lancet*. 2005;365:579- 587. doi:10.1016/S0140- 6736(05)17907 - 0
8. O'Neill J. Review on Antimicrobial Resistance. Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations. *Review on Antimicrobial Resistance; 2014*. Accessed February 25. 2021. amr-review.org/sites /default/files/AMR%20Rev iew%20Paper%20-%20Tackling %20a%20crisis%20for%20the%20health%20and%20wealth%20of%20 nations_1.pdf
9. de Kraker ME, Stewardson AJ, Harbarth S. Will 10 million people die a year due to antimicrobial resistance by 2050? *PLoS Med*. 2016;13:e1002184. doi:10.1371/ journ al.pmed.1002184
10. Hollis A, Ahmed Z. Preserving antibiotics, rationally. *N Engl J Med*. 2013;369:2474-2476. doi:10.1056/NEJMp 1311479
11. Cohen ME, Salmasian H, Li J, et al. Surgical antibiotic prophylaxis and risk for postoperative antibiotic-resistant in- fections. *J Am Coll Surg*. 2017;225:631- 638.e3. doi:10.1016/j.jamco llsurg.2017. 08.010
12. DeNegre AA, Ndeffo Mbah ML, Myers K, Fefferman NH. Emergence of antibiotic resistance in immunocompromised host populations: a case study of emerging antibiotic resistant tuberculosis in AIDS patients. *PLoS One*. 2019;14:e0212969. doi:10.1371/ journal.pone.0212969
13. Bartoletti M, Giannella M, Tedeschi S, Viale P. Multidrug- resistant bacterial infections in solid organ transplant candidates and recipients. *Infect Dis Clin North Am*. 2018;32:551-580 . doi:10.1016/j.idc. 2018.04.004
14. Ravi S, Zhu M, Luey C, Young SW. Antibiotic resistance in early periprosthetic joint infection. *ANZ J Surg*. 2016;86:1014- 1018. doi:10.1111/ans.13720
15. Teillant A, Gandra S, Barter D, Morgan DJ, Laxminarayan R. Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study. *Lancet Infect Dis*. 2015;15:1429- 1437. doi:10.1016/S1473 - 3099(15)00270 - 4
16. Gourd E. Biden determined to "end cancer as we know it." *Lancet Oncol*. 2021;22:759. doi:10.1016/S1470 - 2045(21)00282 - 5
17. Ma J, Jemal A, Fedewa SA, et al. The American Cancer Society 2035 challenge goal on cancer mortality reduction. *CA Cancer J Clin*. 2019;69:351- 362. doi:10.3322/caac.21564
18. Vazquez- Lopez R, Rivero Rojas O, Ibarra Moreno A, et al. Antibiotic- resistant septicemia in pediatric oncology patients associated with post-therapeutic neutropenic fever. *Antibiotics* (Basel). 2019;8:106. doi:10.3390/antib iotic s8030106
19. Williams MD, Braun LA, Cooper LM, et al. Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. *Crit Care*. 2004;8:R291- R298. doi:10.1186/ cc2893
20. Montassier E, Batard E, Gastinne T, Potel G, de La Cochetiere MF. Recent changes in bacteremia in patients with cancer: a systematic review of epidemiology and antibiotic resistance. *Eur J Clin Microbiol Infect Dis*. 2013;32:841-850 . doi:10.1007/ s1009 6- 013-1819- 7
21. Moghnieh R, Estaitieh N, Mugharbil A, et al. Third generation cephalosporin resistant Enterobacteriaceae and multidrug resistant Gram-negative bacteria causing bacteremia in febrile neutropenia adult cancer patients in Lebanon, broad spectrum antibiotics use as a major risk factor, and correlation with poor prognosis. *Front Cell Infect Microbiol*. 2015;5:11. doi:10.3389/fcimb.2015.00011
22. Trecarichi EM, Tumbarello M. Antimicrobial- resistant Gram- negative bacteria in febrile neutropenic patients with cancer: current epidemiology and clinical impact. *Curr Opin Infect Dis*. 2014;27:200-210 . doi:10.1097/QCO.00000 00000 000038
23. Thorpe KE, Joski P, Johnston KJ. Antibiotic- resistant infection treatment costs have doubled since 2002, now exceeding $2 billion annually. *Health Aff* (Millwood). 2018;37:662- 669. doi:10.1377/hltha ff.2017.1153
24. The Longitude Prize. Effectiveness of Cancer Treatments Threatened by Rising Antibiotic Resistance. Accessed November 24, 2020. longitude prize.org/resources/effectiveness-cancer-treatments-threatened-rising-antibiotic-resistance
25. Lee CR, Cho IH, Jeong BC, Lee SH. Strategies to minimize antibiotic resistance. *Int J Environ Res Public Health*. 2013;10:4274- 4305. doi:10.3390/ijerp h1009 4274
26. Li B, Webster TJ. Bacteria antibiotic resistance: new challenges and opportunities for implant- associated orthopedic infections. *J Orthop Res*. 2018;36:22-32. doi:10.1002/ jor.23656
27. Giacomini E, Perrone V, Alessandrini D, Paoli D, Nappi C, Degli Esposti L. Evidence of antibiotic resistance from population- based studies: a narrative review. *Infect Drug Resist*. 2021;14:849- 858. doi:10.2147/IDR.S289741
28. Blair JM, Webber MA, Baylay AJ, Ogbolu DO, Piddock LJ. Molecular mechanisms of antibiotic resistance. *Nat Rev Microbiol*. 2015;13:42-51. doi:10.1038/ nrmic ro3380
29. Bax R, Griffin D. Introduction to antibiotic resistance. Handb Exp Pharmacol. 2012;211:1- 12. doi:10.1007/978- 3- 642- 28951 - 4_1
30. Kapoor G, Saigal S, Elongavan A. Action and resistance mechanisms of antibiotics: a guide for clinicians. *J Anaesthesiol Clin Pharmacol*. 2017;33:300-305. doi:10.4103/joacp.JOACP_349_15
31. Zhang Y, Zhao C, Wang Q, et al. High prevalence of hypervirulent Klebsiella pneumoniae infection in China: geographic distribution, clinical characteristics, and antimicrobial resistance. *Antimicrob Agents Chemother*. 2016;60:6115-6120. doi:10.1128/AAC.01127- 1 6
32. Cornejo- Juarez P, Vilar-Compte D, Perez- Jimenez C, Namendys-Silva SA, Sandoval-Hernandez S, Volkow- Fernandez P. The impact of hospital- acquired infections with multidrug-resistant bacteria in an oncology intensive care unit. *Int J Infect Dis*. 2015;31:31-34. doi:10.1016/j. ijid.2014.12.022
33. Satlin MJ, Chen L, Patel G, et al. Multicenter clinical and molecular epidemiological analysis of bacteremia due to carbapenem-resistant Enterobacteriaceae (CRE) in the CRE epicenter of the United States. *Antimicrob Agents Chemother*. 2017;61:e02349- 16. doi:10.1128/AAC.02349 - 16
34. Bodro M, Gudiol C, Garcia-Vidal C, et al. Epidemiology, antibiotic therapy and outcomes of bacteremia caused by drug- resistant ESKAPE pathogens in cancer patients. *Support Care Cancer*. 2014;22:603- 610. doi:10.1007/s0052 0-013- 2012- 3
35. Toleman MA, Rolston K, Jones RN, Walsh TR. blaVIM- 7, an evolutionarily distinct metallo-beta- lactamase gene in a Pseudomonas aeruginosa isolate from the United States. *Antimicrob Agents Chemother*. 2004;48:329- 332. doi:10.1128/AAC.48.1.329-332.2004
36. Kim J, Greenberg DE, Pifer R, et al. VAMPr: VAriant Mapping and Prediction of antibiotic resistance via explainable features and machine learning. *PLoS Comput Biol*. 2020;16:e1007511. doi:10.1371/journal.pcbi.1007511
37. Conrad S, Oethinger M, Kaifel K, Klotz G, Marre R, Kern WV. gyrA mutations in high- level fluoroquinolone- resistant clinical isolates of Escherichia coli. *J Antimicrob Chemother*. 1996;38:443- 455. doi:10.1093/jac/38.3.443
38. Hamed SM, Elkhatib WF, El- Mahallawy HA, Helmy MM, Ashour MS, Aboshanab KMA. Multiple mechanisms contributing to ciprofloxacin resistance among Gram negative bacteria causing infections to cancer patients. *Sci Rep*. 2018;8:12268. doi:10.1038/s4159 8- 018- 30756 - 4
39. Satlin MJ, Calfee DP, Chen L, et al. Emergence of carbapenem- resistant Enterobacteriaceae as causes of bloodstream infections in patients with hematologic malignancies. *Leuk Lymphoma*. 2013;54:799- 806. doi:10.3109/10428 194. 2012.723210
40. Centers for Disease Control and Prevention (CDC). ESBL- Producing Enterobacterales in Healthcare Settings. CDC; 2019. Accessed July 19, 2021. cdc.gov/hai/ organ isms/ESBL.html
41. Centers for Disease Control and Prevention (CDC). Carbapenem-Resistant Enterobacterales (CRE). CDC; 2019. Accessed July 19, 2021. cdc.gov/hai/organisms/cre/index.html
42. Centers for Disease Control and Prevention. Antibiotic Resistance & Patient Safety Portal. Accessed May 28, 2021. arpsp.cdc.gov/profile/antibiotic-resis tance ?tab=antibiotic -resistance
43. Centers for Disease Control and Prevention. Glossary of Terms Related to Antibiotic Resistance. Accessed May 28, 2021. cdc.gov/narms/resources/glossary.html
44. Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. *J Infect Dis*. 2008;197:1079- 1081. doi:10.1086/533452
45. Rolston KV. Infections in cancer patients with solid tumors: a review. *Infect Dis Ther*. 2017;6:69- 83. doi:10.1007/s4012 1- 017- 0146- 1
46. Zheng Y, Chen Y, Yu K, et al. Fatal infections among cancer patients: a population- based study in the United States. *Infect Dis Ther*. 2021;10:871- 895. doi:10.1007/s4012 1- 021-00433 - 7
47. Zembower TR. Epidemiology of infections in cancer patients. *Cancer Treat Res*. 2014;161:43- 89. doi:10.1007/978- 3- 319- 04220 - 6_2
48. O'Dowd A. Death certificates should record antimicrobial resistance as cause of deaths, says CMO. BMJ. 2018;362:k3832. doi:10.1136/k3832
49. O'Connor D, Bate J, Wade R, et al. Infection- related mortality in children with acute lymphoblastic leukemia: an analysis of infectious deaths on UKALL2003. *Blood*. 2014;124:1056- 1061. doi:10.1182/blood - 2014- 03- 560847
50. Taur Y, Pamer EG. Microbiome mediation of infections in the cancer setting. *Genome Med*. 2016;8:40. doi:10.1186/s1307 3- 016- 0306- z
51. Park SY, Kim MS, Eom JS, Lee JS, Rho YS. Risk factors and etiology of surgical site infection after radical neck dissection in patients with head and neck cancer. *Korean J Intern Med*. 2016;31:162- 169. doi:10.3904/kjim.2016.31.1.162
52. Rapoport BL. Management of the cancer patient with infection and neutropenia. *Semin Oncol*. 2011;38:424- 430. doi:10.1053/j.semin oncol.2011.03.013
53. Alonso CD, Marr KA. Clostridium difficile infection among hematopoietic stem

References continued

cell transplant recipients: beyond colitis. *Curr Opin Infect Dis*. 2013;26:326- 331. doi:10.1097/QCO.0b013 e3283 630c4c

54. Kyi C, Hellmann MD, Wolchok JD, Chapman PB, Postow MA. Opportunistic infections in patients treated with immunotherapy for cancer. *J Immunother Cancer*. 2014;2:19. doi:10.1186/2051- 1426- 2- 19
55. Hotchkiss RS, Monneret G, Payen D. Sepsis- induced immunosuppression: from cellular dysfunctions to immunotherapy. *Nat Rev Immunol*. 2013;13:862- 874. doi:10.1038/nri3552
56. Del Castillo M, Romero FA, Arguello E, Kyi C, Postow MA, Redelman-Sidi G. The spectrum of serious infections among patients receiving immune checkpoint blockade for the treatment of melanoma. *Clin Infect Dis*. 2016;63:1490- 1493. doi:10.1093/cid/ciw539
57. Lustberg MB. Management of neutropenia in cancer patients. *Clin Adv Hematol Oncol*. 2012;10:825- 826.
58. Scheler M, Lehrnbecher T, Groll AH, et al. Management of children with fever and neutropenia: results of a survey in 51 pediatric cancer centers in Germany, Austria, and Switzerland. *Infection*. 2020;48:607- 618. doi:10.1007/s1501 0- 020- 01462 - z
59. Xie O, Slavin MA, Teh BW, Bajel A, Douglas AP, Worth LJ. Epidemiology, treatment and outcomes of bloodstream infection due to vancomycin-resistant enterococci in cancer patients in a vanB endemic setting. *BMC Infect Dis*. 2020;20:228. doi:10.1186/s1287 9- 020- 04952 - 5
60. Tedim AP, Ruiz-Garbajosa P, Rodriguez MC, et al. Long-term clonal dynamics of Enterococcus faecium strains causing bloodstream infections (1995- 2015) in Spain. *J Antimicrob Chemother*. 2017;72:48- 55. doi:10.1093/jac/dkw366
61. Tofas P, Samarkos M, Piperaki ET, et al. Pseudomonas aeruginosa bacteraemia in patients with hematologic malignancies: risk factors, treatment and outcome. *Diagn Microbiol Infect Dis*. 2017;88:335-341 . doi:10.1016/j.diagm icrobio.2017.05.00 3
62. Cornejo- Juarez P, Cevallos MA, Castro- Jaimes S, et al. High mortality in an outbreak of multidrug resistant Acinetobacter baumannii infection introduced to an oncological hospital by a patient transferred from a general hospital. *PLoS One*. 2020;15:e0234684. doi:10.1371/journ al.pone.0234684
63. Cornejo-Juarez P, Vilar- Compte D, Garcia-Horton A, Lopez- Velazquez M, Namendys-Silva S, Volkow- Fernandez P. Hospital-acquired infections at an oncolog- ical intensive care cancer unit: differences between solid and hematological cancer patients. *BMC Infect Dis*. 2016;16:274. doi:10.1186/s1287 9-016 - 1592-1
64. Sanchez-Diaz AM, Cuartero C, Rodriguez JD, et al. The rise of ampicillin-resistant Enterococcus faecium high-risk clones as a frequent intestinal colonizer in oncohaematological neutropenic patients on levofloxacin prophylaxis: a risk for bacteraemia? *Clin Microbiol Infect*. 2016;22:59.e1-59.e8 . doi:10.1016/j.cmi. 2015.08.008
65. Alatorre- Fernandez P, Mayoral-Teran C, Velazquez- Acosta C, et al. A polyclonal outbreak of bloodstream infections by Enterococcus faecium in patients with hematologic malignancies. *Am J Infect Control*. 2017;45:260-266 . doi:10.1016/j.ajic.2016.10.002
66. Hakki M, Humphries RM, Hemarajata P, et al. Fluoroquinolone prophylaxis selects for meropenem-nonsusceptible Pseudomonas aeruginosa in patients with hematologic malignancies and hematopoietic cell transplant recipients. *Clin Infect Dis*. 2019;68:2045-2052. doi:10.1093/cid/ciy825
67. Gudiol C, Albasanz- Puig A, Laporte- Amargos J, et al. Clinical predictive model of multidrug resistance in neutropenic cancer patients with bloodstream infection due to Pseudomonas aeruginosa. *Antimicrob Agents Chemother*. 2020;64:e02494- 19. doi:10.1128/AAC.02494- 1 9
68. Ding L, Yang Z, Lu J, et al. Characterization of phenotypic and genotypic traits of Klebsiella pneumoniae from lung cancer patients with respiratory infection. *Infect Drug Resist*. 2020;13:237- 245. doi:10.2147/IDR.S229085
69. Liu J, Wang H, Huang Z, et al. Risk factors and outcomes for carbapenem- resistant Klebsiella pneumoniae bacteremia in onco- hematological patients. *J Infect Dev Ctries*. 2019;13:357- 364. doi:10.3855/jidc.11189
70. Bello- Chavolla OY, Bahena-Lopez JP, Garciadiego- Fosass P, et al. Bloodstream infection caused by S. aureus in patients with cancer: a 10- year longitudinal single-center study. *Support Care Cancer*. 2018;26:4057- 4065. doi:10.1007/s0052 0- 018- 4275- 1
71. Emge DA, Bassett RL, Duvic M, Huen AO. Methicillin- resistant Staphylococcus aureus (MRSA) is an important pathogen in erythrodermic cutaneous T- cell lymphoma (CTCL) patients. *Arch Dermatol Res*. 2020;312:283-288 . doi:10.1007/s0040 3- 019- 02015 - 7
72. Shehata MMK, Radwan SM, Ali SAM. Effects of gamma-irradiation on anti- biotic resistance and diagnostic molecular markers of methicillin-resistant Staphylococcus aureus in Egyptian cancer patients. *Int J Radiat Biol*. 2019;95:1728- 1743. doi:10.1080/09553 002.2019.1664785
73. Wasfi R, Rasslan F, Hassan SS, Ashour HM, Abd El- Rahman OA. Co- existence of carbapenemase- encoding genes in Acinetobacter baumannii from cancer patients. *Infect Dis Ther*. 2021;10:291- 305. doi:10.1007/s4012 1- 020- 00369 - 4
74. Wang X, Zhang L, Sun A, et al. Acinetobacter baumannii bacteraemia in patients with haematological malignancy: a multicentre retrospective study from the Infection Working Party of Jiangsu Society of Hematology. *Eur J Clin Microbiol Infect Dis*. 2017;36:1073- 1081. doi:10.1007/s1009 6- 016- 2895- 2
75. Weiner- Lastinger LM, Abner S, Benin AL, et al. Antimicrobial-resistant pathogens associated with pediatric healthcare-associated infections: sum- mary of data reported to the National Healthcare Safety Network, 2015- 2017. *Infect Control Hosp Epidemiol*. 2020;41:19- 30. doi:10.1017/ice.2019.297
76. Weiner- Lastinger LM, Abner S, Edwards JR, et al. Antimicrobial-resistant patho- gens associated with adult healthcare- associated infections: summary of data reported to the National Healthcare Safety Network, 2015- 2017. *Infect Control Hosp Epidemiol*. 2020;41:1- 18. doi:10.1017/ice.2019.296
77. Allam O, Park KE, Chandler L, et al. The impact of radiation on lymphedema: a review of the literature. *Gland Surg*. 2020;9:596-602. doi:10.21037/ gs.2020.03.20
78. Paskett ED, Stark N. Lymphedema: knowledge, treatment, and impact among breast cancer survivors. *Breast J*. 2000;6:373- 378. doi:10.1046/j.1524- 4741.2000.99072.x
79. Moore JX, Akinyemiju T, Bartolucci A, Wang HE, Waterbor J, Griffin R. A prospective study of cancer survivors and risk of sepsis within the REGARDS cohort. *Cancer Epidemiol*. 2018;55:30- 38. doi:10.1016/j.canep.2018.05.001
80. Johnson K, Boucher HW. Editorial commentary: imminent challenges: carbapenem-resistant Enterobacteriaceae in transplant recipients and patients with hematologic malignancy. *Clin Infect Dis*. 2014;58:1284- 1286. doi:10.1093/cid/ ciu056
81. Zhao Y, Lin Q, Liu L, et al. Risk factors and outcomes of antibiotic-resistant Pseudomonas aeruginosa bloodstream infection in adult patients with acute leukemia. *Clin Infect Dis*. 2020;71(suppl 4):S386- S393. doi:10.1093/cid/ciaa1522
82. Pouch SM, Satlin MJ. Carbapenem- resistant Enterobacteriaceae in special populations: solid organ transplant recipients, stem cell transplant recipients, and patients with hematologic malignancies. *Virulence*. 2017;8:391- 402. doi:10.1080/21505594.2016.1213472
83. Scheich S, Weber S, Reinheimer C, et al. Bloodstream infections with gram- negative organisms and the impact of multidrug resistance in patients with hematological malignancies. *Ann Hematol*. 2018;97:2225- 2234. doi:10.1007/s0027 7- 018- 3423- 5
84. Cattaneo C, Di Blasi R, Skert C, et al. Bloodstream infections in haematological cancer patients colonized by multidrug- resistant bacteria. *Ann Hematol*. 2018;97:1717-1726 . doi:10.1007/s0027 7- 018- 3341- 6
85. Levene I, Castagnola E, Haeusler GM. Antibiotic- resistant Gram- negative blood stream infections in children with cancer: a review of epidemiology, risk factors, and outcome. *Pediatr Infect Dis J*. 2018;37:495- 498. doi:10.1097/INF.00000 00000 001938
86. Marin M, Gudiol C, Garcia- Vidal C, Ardanuy C, Carratala J. Bloodstream infections in patients with solid tumors: epidemiology, antibiotic therapy, and outcomes in 528 episodes in a single cancer center. *Medicine* (Baltimore). 2014;93:143- 149. doi:10.1097/MD.00000 00000 000026
87. Antonio M, Gudiol C, Royo-Cebrecos C, Grillo S, Ardanuy C, Carratala J. Current etiology, clinical features and outcomes of bacteremia in older patients with solid tumors. *J Geriatr Oncol*. 2019;10:246- 251. doi:10.1016/j.jgo.2018.06.011
88. Zhang Y, Zheng Y, Dong F, et al. Epidemiology of febrile neutropenia episodes with Gram- negative bacteria infection in patients who have undergone chemotherapy for hematologic malignancies: a retrospective study of 10 years' data from a single center. *Infect Drug Resist*. 2020;13:903- 910. doi:10.2147/IDR.S241263
89. Vinker- Shuster M, Stepensky P, Temper V, Shayovitz V, Masarwa R, Averbuch D. Gram-negative bacteremia in chil- dren with hematologic malignancies and following hematopoietic stem cell transplantation: epidemiology, resistance, and outcome. *J Pediatr Hematol Oncol*. 2019;41:e493- e498. doi:10.1097/ MPH.00000 00000 001556
90. Gudiol C, Aguado JM, Carratala J. Bloodstream infections in patients with solid tumors. *Virulence*. 2016;7:298- 308. doi:10.1080/21505 594.2016.1141161
91. Marin M, Gudiol C, Ardanuy C, et al. Bloodstream infections in neutropenic patients with cancer: differences between patients with haematological malignancies and solid tumours. *J Infect*. 2014;69:417- 423. doi:10.1016/j.jinf.2014.05.018
92. Shrestha G, Wei X, Hann K, et al. Bacterial profile and antibiotic resistance among cancer patients with urinary tract infection in a national tertiary cancer hospital of Nepal. *Trop Med Infect Dis*. 2021;6:49. doi:10.3390/tropi calme d6020049
93. Fentie A, Wondimeneh Y, Balcha A, Amsalu A, Adankie BT. Bacterial profile, antibiotic resistance pattern and associated factors among cancer patients at University of Gondar Hospital, Northwest Ethiopia. *Infect Drug Resist*. 2018;11:2169- 2178. doi:10.2147/IDR.S183283
94. Islas- Munoz B, Volkow- Fernandez P, Ibanes- Gutierrez C, Villamar- Ramirez A, Vilar-Compte D, Cornejo- Juarez P. Bloodstream infections in cancer patients. Risk factors associated with mortality. *Int J Infect Dis*. 2018;71:59- 64. doi:10.1016/j.ijid.2018.03.022
95. Royo- Cebrecos C, Gudiol C, Garcia J, et al. Characteristics, aetiology, antimicrobial resistance and outcomes of bacteraemic cholangitis in patients with solid tumours: a prospective cohort study. *J Infect*. 2017;74:172- 178. doi:10.1016/j. jinf.2016.10.008
96. Boehm K, Siegel FP, Schneidewind L, et al. Antibiotic prophylaxis in prostate biopsies: contemporary practice patterns in Germany. *Front Surg*. 2018;5:2. doi:10.3389/fsurg.2018.00002

References continued

97. Johansen TEB, Zahl PH, Baco E, et al. Antibiotic resistance, hospitalizations, and mortality related to prostate biopsy: first report from the Norwegian Patient Registry. *World J Urol*. 2020;38:17- 26. doi:10.1007/s0034 5- 019- 02837 - 0
98. Derin O, Fonseca L, Sanchez- Salas R, Roberts MJ. Infectious complications of prostate biopsy: winning battles but not war. World J Urol. 2020;38:2743- 2753. doi:10.1007/ s0034 5- 020- 03112 - 3 99. Sieczkowski M, Gibas A, Wasik A, et al. Drug- eluting biopsy needle as a novel strategy for antimicrobial prophylaxis in transrectal prostate biopsy. *Technol Cancer Res Treat*. 2017;16:1038- 1043. doi:10.1177/15330 34617 722080
100. Ryu JW, Jung SI, Ahn JH, et al. Povidone- iodine rectal cleansing and targeted antimicrobial prophylaxis using rectal swab cultures in men undergoing transrectal ultrasound- guided prostate biopsy are associated with reduced incidence of postoperative infectious complications. *Int Urol Nephrol*. 2016;48:1763- 1770. doi:10.1007/s1125 5- 016- 1394- 9
101. Cussans A, Somani BK, Basarab A, Dudderidge TJ. The role of targeted prophylactic antimicrobial therapy before transrectal ultrasonography-guided prostate biopsy in reducing infection rates: a systematic review. *BJU Int*. 2016;117:725- 731. doi:10.1111/ bju.13402
102. Zavala VA, Bracci PM, Carethers JM, et al. Cancer health disparities in racial/ ethnic minorities in the United States. *Br J Cancer*. 2021;124:315-332 . doi:10.1038/ s4141 6- 020- 01038 - 6
103. Nadimpalli ML, Chan CW, Doron S. Antibiotic resistance: a call to action to prevent the next epidemic of inequality. *Nat Med*. 2021;27:187-188 . doi:10.1038/ s4159 1- 020- 01201 - 9
104. Dadgostar P. Antimicrobial resistance: implications and costs. *Infect Drug Resist*. 2019;12:3903- 3910. doi:10.2147/ IDR.S234610
105. Nelson RE, Hatfield KM, Wolford H, et al. National estimates of healthcare costs associated with multidrug-resistant bacterial infections among hospitalized patients in the United States. *Clin Infect Dis*. 2021;72(suppl 1):S17- S26. doi:10.1093/cid/ciaa1581
106. Stokes ME, Muehlenbein CE, Marciniak MD, et al. Neutropenia- related costs in patients treated with first- line chemotherapy for advanced non- small cell lung cancer. *J Manag Care Pharm*. 2009;15:669- 682. doi:10.18553/ jmcp. 2009.15.8.669
107. Tai E, Guy GP, Dunbar A, Richardson LC. Cost of cancer- related neutropenia or fever hospitalizations, United States, 2012. J Oncol Pract. 2017;13:e552- e561. doi:10.1200/ JOP.2016.019588
108. Tori K, Tansarli GS, Parente DM, Kalligeros M, Ziakas PD, Mylonakis E. The cost-effectiveness of empirical antibiotic treatments for high- risk febrile neutropenic patients: a decision analytic model. *Medicine* (Baltimore). 2020;99:e20022. doi:10.1097/ MD.00000 00000 020022
109. Watters K, O'Dwyer TP, Rowley H. Cost and morbidity of MRSA in head and neck cancer patients: what are the consequences? *J Laryngol Otol*. 2004;118:694- 699. doi:10.1258/00222 15042 244732
110. Gafter- Gvili A, Fraser A, Paul M, et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. *Cochrane Database Syst Rev*. 2012;1:CD004386. doi:10.1002/14651 858.CD004 386.pub3
111. Ziegler M, Landsburg D, Pegues D, et al. Fluoroquinolone prophylaxis is highly effective for the prevention of central line- associated bloodstream infections in autologous stem cell transplant patients. *Biol Blood Marrow Transplant*. 2019;25:1004-1010. doi:10.1016/j.bbmt. 2018.11.023
112. Carmona- Bayonas A, Jimenez- Fonseca P, Virizuela Echaburu J, et al. Prediction of serious complications in patients with seemingly stable febrile neutropenia: validation of the Clinical Index of Stable Febrile Neutropenia in a prospective cohort of patients from the FINITE study. *J Clin Oncol*. 2015;33:465- 471. doi:10.1200/JCO.2014.57.2347
113. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. *Cancer*. 2006;106:2258- 2266. doi:10.1002/ cncr.21847
114. Legrand M, Max A, Peigne V, et al. Survival in neutropenic patients with severe sepsis or septic shock. *Crit Care Med*. 2012;40:43- 49. doi:10.1097/CCM. 0b013 e3182 2b50c2
115. Bucaneve G, Micozzi A, Menichetti F, et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. *N Engl J Med*. 2005;353:977- 987. doi:10.1056/ NEJMo a044097
116. Cullen M, Steven N, Billingham L, et al. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. *N Engl J Med*. 2005;353:988- 998. doi:10.1056/NEJMo a050078
117. Gafter- Gvili A, Fraser A, Paul M, Leibovici L. Meta- analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. Ann Intern Med. 2005;142 (12 pt 1):979-995 . doi:10.7326/0003- 4819- 142- 12_part_1- 20050 6210- 00008
118. Razonable RR, Litzow MR, Khaliq Y, Piper KE, Rouse MS, Patel R. Bacteremia due to viridans group Streptococci with diminished susceptibility to levofloxacin among neutropenic patients receiving levofloxacin prophylaxis. *Clin Infect Dis*. 2002;34:1469-1474. doi:10.1086/340352
119. Zervos MJ, Hershberger E, Nicolau DP, et al. Relationship between fluoroquinolone use and changes in susceptibility to fluoroquinolones of selected pathogens in 10 United States teaching hospitals, 1991-2000 . *Clin Infect Dis*. 2003;37:1643- 1648. doi:10.1086/379709
120. Kern WV, Steib-Bauert M, de With K, et al. Fluoroquinolone consumption and resistance in haematology-oncology pa- tients: ecological analysis in two university hospitals 1999- 2002. *J Antimicrob Chemother*. 2005;55:57- 60. doi:10.1093/ jac/dkh510
121. Mikulska M, Averbuch D, Tissot F, et al. Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines. *J Infect*. 2018;76: 20- 37. doi:10.1016/j.jinf.2017.10.009
122. Ramasamy K. Reducing infection-related morbidity and mortality in patients with myeloma. *Lancet Oncol*. 2019;20:1633- 1635. doi:10.1016/S1470- 2045(19)3064 9- 7
123. Slavin MA, Worth LJ, Seymour JF, Thursky KA. Better sepsis management rather than fluoroquinolone prophylaxis for patients with cancer-related immuno- suppression. *J Clin Oncol*. 2019;37:1139- 1140. doi:10.1200/JCO.18.01474
124. Verlinden A, Schroyens WA, Gadisseur AP. Clinical and microbiological impact of long-term discontinuation of fluoroquinolone prophylaxis in haematological patients with prolonged profound neutropenia. *Eur J Haematol*. 2021;107:377- 379. doi:10.1111/ ejh.13670
125. Centers for Disease Control and Prevention. Preventing Infections in Cancer Patients. Accessed November 11, 2020. cdc.gov/cance r/preve ntinf ectio ns/ index.htm
126. American Cancer Society. Infections in People With Cancer. Accessed November 11, 2020. cancer.org/treatment/treatments -and -side-effects/physical-side-effects/low-blood - count s/infec tions. html
127. National Comprehensive Cancer Network. Prevention and Treatment of Cancer-Related Infections. Accessed February 26, 2021, nccn.org/professionals/physician_gls/ default.aspx
128. Montassier E, Gastinne T, Vangay P, et al. Chemotherapy- driven dysbiosis in the intestinal microbiome. *Aliment Pharmacol Ther*. 2015;42:515- 528. doi:10.1111/ apt.13302
129. Dethlefsen L, Huse S, Sogin ML, Relman DA. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. *PLoS Biol*. 2008;6:e280. doi:10.1371/ journal.pbio.0060280
130. Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proc Natl Acad Sci USA*. 2011;108(suppl 1):4554- 4561. doi:10.1073/pnas.10000 87107
131. Pilmis B, Le Monnier A, Zahar JR. Gut microbiota, antibiotic therapy and antimicrobial resistance: a narrative review. *Microorganisms*. 2020;8:269. doi:10.3390/microorgan isms8 020269
132. Holler E, Butzhammer P, Schmid K, et al. Metagenomic analysis of the stool microbiome in patients receiving allogeneic stem cell transplantation: loss of diversity is associated with use of systemic antibiotics and more pronounced in gastrointestinal graft- versus- host disease. *Biol Blood Marrow Transplant*. 2014;20:640- 645. doi:10.1016/j.bbmt.2014.01.030
133. Petrelli F, Iaculli A, Signorelli D, et al. Survival of patients treated with antibiotics and immunotherapy for cancer: a systematic review and meta- analysis. *J Clin Med*. 2020;9:1458. doi:10.3390/ jcm90 51458
134. Kim SG, Becattini S, Moody TU, et al. Microbiota- derived lantibiotic restores resistance against vancomycin-resistant Enterococcus. *Nature*. 2019;572:665-669. doi:10.1038/s4158 6- 019- 1501- z
135. Koh AY. Potential for monitoring gut microbiota for diagnosing infections and graft- versus- host disease in cancer and stem cell transplant patients. *Clin Chem*. 2017;63:1685- 1694. doi:10.1373/clinc hem.2016.259499
136. Salgia NJ, Bergerot PG, Maia MC, et al. Stool microbiome profiling of patients with metastatic renal cell carcinoma receiving anti- PD-1 immune checkpoint inhibitors. *Eur Urol*. 2020;78:498- 502. doi:10.1016/j.eururo.2020.07.011
137. Willems RJ, Top J, van Santen M, et al. Global spread of vancomycin- resistant Enterococcus faecium from distinct nosocomial genetic complex. *Emerg Infect Dis*. 2005;11:821- 828. doi:10.3201/1106.041204
138. Arcilla MS, van Hattem JM, Haverkate MR, et al. Import and spread of extended-spectrum beta- lactamase- producing Enterobacteriaceae by international travellers (COMBAT study): a prospective, multicentre cohort study. *Lancet Infect Dis*. 2017;17:78-85. doi:10.1016/S1473 - 3099(16)30319 - X
139. Frost I, Van Boeckel TP, Pires J, Craig J, Laxminarayan R. Global geographic trends in antimicrobial resistance: the role of international travel. *J Travel Med*. 2019;26;taz036. doi:10.1093/jtm/taz036
140. Carling P, Fung T, Killion A, Terrin N, Barza M. Favorable impact of a multidisciplinary antibiotic management program conducted during 7 years. *Infect Control Hosp Epidemiol*. 2003;24:699- 706. doi:10.1086/502278
141. Schentag JJ, Ballow CH, Fritz AL, et al. Changes in antimicrobial agent usage resulting from interactions among clinical pharmacy, the infectious disease division, and the microbiology laboratory. *Diagn Microbiol Infect Dis*. 1993;16:255- 264. doi:10.1016/0732-8893(93)90119 - r
142. Ansari F, Gray K, Nathwani D, et al. Outcomes of an intervention to improve hospital antibiotic prescribing: interrupted time series with segmented regression analysis. *J Antimicrob Chemother*. 2003;52:842- 848. doi:10.1093/jac/dkg459
143. Cole KA, Rivard KR, Dumkow LE. Antimicrobial stewardship interventions to combat antibiotic resistance: an update on targeted strategies. *Curr Infect Dis Rep*. 2019;21:33.

References continued

doi:10.1007/s1190 8- 019- 0689- 2

144. Klepser ME, Adams AJ, Klepser DG. Antimicrobial stewardship in outpatient settings: leveraging innovative physician- pharmacist collaborations to reduce antibiotic resistance. *Health Secur.* 2015;13:166- 173. doi:10.1089/ hs.2014.0083

145. Zhang ZG, Chen F, Ou Y. Impact of an antimicrobial stewardship programme on antibiotic usage and resistance in a tertiary hospital in China. *J Clin Pharm Ther.* 2017;42:579-584 . doi:10.1111/ jcpt.12544

146. Petrelli F, Ghidini M, Ghidini A, et al. Use of antibiotics and risk of cancer: a systematic review and meta- analysis of observational studies. *Cancers* (Basel). 2019;11:1174. doi:10.3390/cance rs110 81174

147. Peyrony O, Gerlier C, Barla I, et al. Antibiotic prescribing and outcomes in cancer patients with febrile neutropenia in the emergency department. *PLoS One.* 2020;15:e0229828. doi:10.1371/journal.pone.0229828

148. Spellberg B. The new antibiotic mantra— "shorter is better." *JAMA Intern Med.* 2016;176:1254- 1255. doi:10.1001/jamai ntern med.2016.3646

149. Koenig C, Schneider C, Morgan JE, Ammann RA, Sung L, Phillips B. Association of time to antibiotics and clinical outcomes in patients with fever and neutropenia during chemotherapy for cancer: a systematic review. *Support Care Cancer*. 2020;28:1369-1383. doi:10.1007/ s0052 0- 019- 04961 - 4

150. Kim NH, Koo HL, Choe PG, et al. Inappropriate continued empirical vancomycin use in a hospital with a high prevalence of methicillin- resistant Staphylococcus aureus. *Antimicrob Agents Chemother.* 2015;59:811-817 . doi:10.1128/ AAC.04523 - 14

151. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2011;52:e56- 93. doi:10.1093/cid/cir073

152. Schmidt- Hieber M, Teschner D, Maschmeyer G, Schalk E. Management of febrile neutropenia in the perspective of antimicrobial de- escalation and discontinuation. *Expert Rev Anti Infect Ther.* 2019;17:983- 995. doi:10.1080/14787 210.2019.1573670

153. Le Clech L, Talarmin JP, Couturier MA, et al. Early discontinuation of empirical antibacterial therapy in febrile neutropenia: the ANTIBIOSTOP study. *Infect Dis* (Lond). 2018;50:539- 549. doi:10.1080/23744 235.2018.1438649

154. Heinz WJ, Buchheidt D, Christopeit M, et al. Diagnosis and empirical treatment of fever of unknown origin (FUO) in adult neutropenic patients: guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). *Ann Hematol*. 2017;96:1775- 1792. doi:10.1007/s0027 7- 017-3098- 3

155. Rearigh L, Stohs E, Freifeld A, Zimmer A. De- escalation of empiric broad spectrum antibiotics in hematopoietic stem cell transplant recipients with febrile neutropenia. *Ann Hematol.* 2020;99:1917- 1924. doi:10.1007/s0027 7- 020- 04132 - 0

156. Aguilar- Guisado M, Espigado I, Martin- Pena A, et al. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long Study): an open-label, randomised, con- trolled phase 4 trial. *Lancet Haematol.* 2017;4:e573- e583. doi:10.1016/S2352 - 3026(17)30211 - 9

157. la Martire G, Robin C, Oubaya N, et al. De- escalation and discontinuation strategies in high- risk neutropenic patients: an interrupted time series analyses of antimicrobial consumption and impact on outcome. *Eur J Clin Microbiol Infect Dis.* 2018;37:1931- 1940. doi:10.1007/ s1009 6- 018- 3328- 1

158. Puerta- Alcalde P, Cardozo C, Suarez- Lledo M, et al. Current time- to- positivity of blood cultures in febrile neutropenia: a tool to be used in stewardship de- escalation strategies. *Clin Microbiol Infect.* 2019;25:447- 453. doi:10.1016/ j.cmi.2018.07.026

159. Byun JM, Jeong DH. Antibiotic prophylaxis for gynecologic cancer surgery. *Taiwan J Obstet Gynecol.* 2020;59:514- 519. doi:10.1016/j.tjog.2020.05.008

160. Gerding DN. The search for good antimicrobial stewardship. *Jt Comm J Qual Improv.* 2001;27:403- 404. doi:10.1016/ s1070 - 3241(01)27034 -5

161. Doron S, Davidson LE. Antimicrobial stewardship. *Mayo Clin Proc.* 2011;86:1113-1123. doi:10.4065/mcp.2011.0358

162. Gudiol C, Carratala J. Antibiotic resistance in cancer patients. *Expert Rev Anti Infect Ther.* 2014;12:1003- 1016. doi:10.1586/14787 210.2014.920253

163. Wolf J, Margolis E. Effect of antimicrobial stewardship on outcomes in patients with cancer or undergoing hematopoietic stem cell transplantation. *Clin Infect Dis.* 2020;71:968- 970. doi:10.1093/cid/ ciz903

164. Rosa RG, Goldani LZ, dos Santos RP. Association between adherence to an antimicrobial stewardship program and mortality among hospitalised cancer patients with febrile neutropaenia: a prospective cohort study. *BMC Infect Dis.* 2014;14:286. doi:10.1186/1471- 2334- 14- 286

165. Pillinger KE, Bouchard J, Withers ST, et al. Inpatient antibiotic stewardship interventions in the adult oncology and hematopoietic stem cell transplant population: a review of the literature. *Ann Pharmacother.* 2020;54:594- 610. doi:10.1177/10600 28019 890886

166. Bantar C, Sartori B, Vesco E, et al. A hospitalwide intervention program to optimize the quality of antibiotic use: impact on prescribing practice, antibiotic consumption, cost savings, and bacterial resistance. *Clin Infect Dis.* 2003;37:180- 186. doi:10.1086/375818

167. Rahal JJ, Urban C, Horn D, et al. Class restriction of cephalosporin use to control total cephalosporin resistance in nosocomial Klebsiella. *JAMA.* 1998;280:1233- 1237. doi:10.1001/ jama.280.14.1233

168. Cook PP, Catrou P, Gooch M, Holbert D. Effect of reduction in ciprofloxacin use on prevalence of meticillin-resistant Staphylococcus aureus rates within individual units of a tertiary care hospital. *J Hosp Infect.* 2006;64:348- 351.
doi:10.1016/j.jhin.2006.06.033

169. Raymond DP, Pelletier SJ, Crabtree TD, et al. Impact of a rotating empiric antibiotic schedule on infectious mortality in an intensive care unit. *Crit Care Med.* 2001;29:1101-1108. doi:10.1097/00003 246- 20010 6000- 00001

170. Timbrook TT, Hurst JM, Bosso JA. Impact of an antimicrobial stewardship program on antimicrobial utilization, bacterial susceptibilities, and financial expenditures at an academic medical center. *Hosp Pharm.* 2016;51:703- 711.
doi:10.1310/hpj51 09- 703

171. Doernberg SB, Abbo LM, Burdette SD, et al. Essential resources and strategies for antibiotic stewardship programs in the acute care setting. *Clin Infect Dis.* 2018;67:1168-1174. doi:10.1093/cid/ciy255

172. Centers for Disease Control and Prevention. Core Elements of Outpatient Antibiotic Stewardship. Accessed May 24, 2020. cdc.gov/antibiotic use/core- elements/outpatient.html

173. Marcelin JR, Chung P, Van Schooneveld TC. Antimicrobial stewardship in the outpatient setting: a review and proposed framework. *Infect Control Hosp Epidemiol.* 2020;41:833- 840. doi:10.1017/ice.2020.94

174. US Food and Drug Administration. 2019 Summary Report on Antimicrobials Sold or Distributed for Use in Food- Producing Animals. Accessed May 24, 2021. fda. gov/animal- veterinary/ cvm- updates/ fda- releases-annual- summary-report- antimicrobials- sold-or- distributed- 2019- use- food- producing

175. Martin MJ, Thottathil SE, Newman TB. Antibiotics overuse in animal agriculture: a call to action for health care providers. *Am J Public Health*. 2015;105:2409- 2410. doi:10.2105/AJPH.2015.302870

176. Landers TF, Cohen B, Wittum TE, Larson EL. A review of antibiotic use in food animals: perspective, policy, and potential. *Public Health Rep.* 2012;127:4- 22.
doi:10.1177/00333 54912 12700103

177. Angulo FJ, Nargund VN, Chiller TC. Evidence of an association between use of anti-microbial agents in food animals and anti- microbial resistance among bacteria isolated from humans and the human health consequences of such resistance. *J Vet Med B Infect Dis Vet Public Health.* 2004;51:374- 379. doi:10.1111/j.1439- 0450.2004.00789.x

178. Centers for Disease Control and Prevention. Food and Food Animals. Accessed May 24, 2021. cdc.gov/drugr esist ance/food.html

179. Chen Y, Hammer EE, Richards VP. Phylogenetic signature of lateral exchange of genes for antibiotic production and resistance among bacteria highlights a pattern of global transmission of pathogens between humans and livestock. *Mol Phylogenet Evol.* 2018;125:255- 264. doi:10.1016/j.ympev.2018.03.034

180. Thacker SB, Berkelman RL. Public health surveillance in the United States. *Epidemiol Rev.* 1988;10:164- 190. doi:10.1093/oxfor djour nals.epirev.a036021

181. Simonsen GS. Antimicrobial resistance surveillance in Europe and beyond. *Euro Surveill.* 2018;23:1800560. doi:10.2807/1560- 7917.ES.2018.23.42. 1800560

182. Perez F, Villegas MV. The role of surveillance systems in confronting the global crisis of antibiotic-resistant bacteria. *Curr Opin Infect Dis.* 2015;28:375- 383. doi:10.1097/QCO.00000 00000 000182

183. Tsutsui A, Suzuki S. Japan Nosocomial Infections Surveillance (JANIS): a model of sustainable national antimicrobial resistance surveillance based on hospital diagnostic microbiology laboratories. *BMC Health Serv Res.* 2018;18:799. doi:10.1186/s1291 3-018- 3604- x

184. Johnson AP. Surveillance of antibiotic resistance. *Philos Trans R Soc Lond B Biol Sci.* 2015;370:20140080. doi:10.1098/ rstb.2014.0080

185. Kadri SS, Boucher HW. U.S. Efforts to curb antibiotic resistance— are we saving lives? N Engl J Med. 2020;383:806- 808. doi:10.1056/NEJMp 2004743

186. Hidron AI, Edwards JR, Patel J, et al. NHSN annual update: antimicrobial- resistant pathogens associated with healthcare- associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006- 2007. *Infect Control Hosp Epidemiol.* 2008;29:996- 1011. doi:10.1086/591861

187. Lake JG, Weiner LM, Milstone AM, Saiman L, Magill SS, See I. Pathogen distribution and antimicrobial resistance among pediatric healthcare- associated infections reported to the National Healthcare Safety Network, 2011-2014 . *Infect Control Hosp Epidemiol.* 2018;39:1- 11. doi:10.1017/ice.2017.236

188. Sievert DM, Ricks P, Edwards JR, et al. Antimicrobial- resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009-2010. *Infect Control Hosp Epidemiol.* 2013;34:1- 14. doi:10.1086/668770

189. Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. *Infect Control Hosp Epidemiol.* 2016;37:1288- 1301. doi:10.1017/ice.2016.174

190. Alm RA, Gallant K. Innovation in antimicrobial resistance: the CARB- X perspective. *ACS Infect Dis.* 2020;6:1317- 1322. doi:10.1021/acsin fecdis.0c00026

191. Rex JH, Fernandez Lynch H, Cohen IG, Darrow JJ, Outterson K. Designing

References continued

development programs for non- traditional antibacterial agents. *Nat Commun.* 2019;10:3416. doi:10.1038/s4146 7- 019-11303 - 9
192. Rex JH, Outterson K. Antibiotic reimbursement in a model delinked from sales: a benchmark- based worldwide approach. *Lancet Infect Dis.* 2016;16:500- 505. doi:10.1016/S1473 - 3099(15)00500 - 9
193. Ardal Cm Findlay D, Savic M, et al. Revitalizing the Antibiotic Pipeline: Stimulating Innovation While Driving Sustainable Use and Global Access. Final Report. DRIVE-AB; 2018. Accessed February 21, 2021. drive - ab.eu/wp- conte nt/uploads/2018/01/DRIVE - AB- Final - Repor t- Jan20 18.pdf
194. Presidential Advisory Council on Combating Antibiotic- Resistant Bacteria (PACCARB). Recommendations for Incentivizing the Development of Vaccines, Diagnostics, and Therapeutics to Combat Antibiotic-Resistance. PACCARB; 2017. Accessed February 21, 2021. hhs.gov/ web/508/sites/ defau lt/files/ pacca rb- final - incen tives - repor t- sept- 2017.pdf
195. O'Neill J. Review on Antimicrobial Resistance. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. *Review on Antimicrobial Resistance*; 2016. Accessed February 21, 2021. amr-amr - review.org/ sites/ defau lt/files/ 160518_Final %20pap er_with%20cov er.pdf
196. Towse A, Hoyle CK, Goodall J, Hirsch M, Mestre- Ferrandiz J, Rex JH. Time for a change in how new antibiotics are reimbursed: development of an insurance framework for funding new antibiotics based on a policy of risk mitigation. *Health Policy.* 2017;121:1025- 1030. doi:10.1016/j.healt hpol.2017.07.011
197. Dutescu IA, Hillier SA. Encouraging the development of new antibiotics: are financial incentives the right way forward? A systematic review and case study. *Infect Drug Resist.* 2021;14:415- 434. doi:10.2147/IDR.S287792
198. Spaulding CN, Klein RD, Schreiber HLT, Janetka JW, Hultgren SJ. Precision antimicrobial therapeutics: the path of least resistance? *NPJ Biofilms Microbiomes.* 2018;4:4. doi:10.1038/ s41522-018-0048-3
199. Karam G, Chastre J, Wilcox MH, Vincent JL. Antibiotic strategies in the era of multidrug resistance. *Crit Care.* 2016;20:136. doi:10.1186/s1305 4- 016- 1320- 7
200. Boucher HW, Ambrose PG, Chambers HF, et al. White paper: developing antimicrobial drugs for resistant pathogens, narrow- spectrum indications, and unmet needs. *J Infect Dis.* 2017;216:228- 236. doi:10.1093/infdi s/jix211
201. Melander RJ, Zurawski DV, Melander C. Narrow- spectrum antibacterial agents. *Medchemcomm.* 2018;9:12- 21. doi:10.1039/C7MD0 0528H
202. Schooley RT, Biswas B, Gill JJ, et al. Development and use of personalized bacteriophage- based therapeutic cocktails to treat a patient with a disseminated resistant Acinetobacter baumannii infection. *Antimicrob Agents Chemother.* 2017;61:e00954- 17. doi:10.1128/AAC.00954 -1 7
203. Regeimbal JM, Jacobs AC, Corey BW, et al. Personalized therapeutic cocktail of wild environmental phages rescues mice from Acinetobacter baumannii wound infections. *Antimicrob Agents Chemother.* 2016;60:5806- 5816. doi:10.1128/AAC.02877 - 15
204. Nielsen TB, Pantapalangkoor P, Luna BM, et al. Monoclonal antibody protects against Acinetobacter baumannii infection by enhancing bacterial clearance and evading sepsis. *J Infect Dis.* 2017;216:489- 501. doi:10.1093/infdi s/jix315
205. Cotter PD, Ross RP, Hill C. Bacteriocins—a viable alternative to antibiotics? *Nat Rev Microbiol.* 2013;11:95- 105. doi:10.1038/ nrmic ro2937
206. Ghequire MG, Dingemans J, Pirnay JP, De Vos D, Cornelis P, De Mot R. O serotype-independent susceptibility of Pseudomonas aeruginosa to lectin- like pyocins. *Microbiologyopen.* 2014;3:875- 884. doi:10.1002/mbo3.210
207. Howard JJ, Sturge CR, Moustafa DA, et al. Inhibition of Pseudomonas aeruginosa by peptide-conjugated phosphorodiami- date morpholino oligomers. *Antimicrob Agents Chemother.* 2017;61:e01938- 16. doi:10.1128/AAC.01938 - 16
208. Moustafa DA, Wu AW, Zamora D, et al. Peptide-conjugated phosphorodi-amidate morpholino oligomers retain activity against multidrug-resistant Pseudomonas aeruginosa in vitro and in vivo. mBio. 2021;12:e02411- 20. doi:10.1128/mBio.02411 - 20
209. Geller BL, Li L, Martinez F, et al. Morpholino oligomers tested in vitro, in biofilm and in vivo against multidrug- resistant Klebsiella pneumoniae. *J Antimicrob Chemother.* 2018;73:1611- 1619. doi:10.1093/jac/dky058
210. Sulakvelidze A, Alavidze Z, Morris JG Jr. Bacteriophage therapy. *Antimicrob Agents Chemother.* 2001;45:649- 659. doi:10.1128/AAC.45.3.649- 659.2001
211. Drulis- Kawa Z, Majkowska-Skrobek G, Maciejewska B, Delattre AS, Lavigne R. Learning from bacteriophages— advantages and limitations of phage and phage- encoded protein applications. *Curr Protein Pept Sci.* 2012;13:699- 722. doi:10.2174/13892 03128 04871193
212. Zurawski DV, McLendon MK. Monoclonal antibodies as an antibacterial approach against bacterial pathogens. *Antibiotics* (Basel). 2020;9:155. doi:10.3390/antib iotic s9040155
213. Motley MP, Banerjee K, Fries BC. Monoclonal antibody- based therapies for bacterial infections. *Curr Opin Infect Dis.* 2019;32:210- 216. doi:10.1097/ QCO.00000 00000 000539
214. Joerger RD. Alternatives to antibiotics: bacteriocins, antimicrobial peptides and bacteriophages. *Poult Sci.* 2003;82:640- 647. doi:10.1093/ps/82.4.640
215. Yang SC, Lin CH, Sung CT, Fang JY. Antibacterial activities of bacteriocins: application in foods and pharmaceuticals. *Front Microbiol.* 2014;5:241. doi:10.3389/ fmicb.2014.00241
216. Shelburne SA, Kim J, Munita JM, et al. Whole- genome sequencing accurately identifies resistance to extended- spectrum beta- lactams for major Gram- negative bacterial pathogens. *Clin Infect Dis.* 2017;65:738- 745. doi:10.1093/ cid/cix417
217. Li X, Lin J, Hu Y, Zhou J. PARMAP: a pan- genome- based computational framework for predicting antimicrobial resistance. *Front Microbiol.* 2020;11:578795. doi:10.3389/ fmicb.2020.578795
218. Hubbard ATM, Mason J, Roberts P, et al. Piperacillin/tazobactam resistance in a clinical isolate of Escherichia coli due to IS26- mediated amplification of blaTEM- 1B. *Nat Commun.* 2020;11:4915. doi:10.1038/s4146 7- 020- 18668 - 2
219. Maurer FP, Christner M, Hentschke M, Rohde H. Advances in rapid identification and susceptibility testing of bacteria in the clinical microbiology laboratory: implications for patient care and antimicrobial stewardship programs. *Infect Dis Rep.* 2017;9:6839. doi:10.4081/idr.2017.6839
220. Maxson T, Mitchell DA. Targeted treatment for bacterial infections: prospects for pathogen-specific antibiotics coupled with rapid diagnostics. *Tetrahedron.* 2016;72:3609- 3624. doi:10.1016/j.tet.2015. 09.069
221. Trevas D, Caliendo AM, Hanson K, Levy J, Ginocchio CC. Diagnostic tests can stem the threat of antimicrobial resistance: infectious disease professionals can help. *Clin Infect Dis.* 2021;72:e893- e900. doi:10.1093/cid/ ciaa1527
222. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Guidance on the treatment of extended- spectrum beta- lactamase producing Enterobacterales (ESBL- E), carbapenem-resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with difficult- to- treat resistance (DTR- P. aeruginosa). *Clin Infect Dis.* 2021;72:e169- e183. doi:10.1093/cid/ciaa1478
223. Baselga J, Bhardwaj N, Cantley LC, et al. AACR Cancer Progress Report 2015. *Clin Cancer Res.* 2015;21(19 suppl):S1-S128. doi:10.1158/1078-0432 .CCR- 15-184 6

The impact of antibiotic resistance on cancer treatment, especially in low- and middle-income countries, and the way forward

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The growing antibiotic resistance (ABR) burden is a global public health issue that needs to be addressed urgently, particularly in low- and middle-income countries (LMICs) where health infrastructure is lacking or under-resourced and cancer treatment is already difficult to access, expensive, and requires high out-of-pocket expenditure. This article considers the challenges faced by the cancer community, how antibiotics are used in cancer treatments and the impact of ABR on LMICs, and offers four key areas that need to be addressed by the cancer community in order to make progress against the threat of ABR.

Cancer is the second leading cause of death worldwide, accounting for 10 million deaths in 2020, of which 70% occurred in low- and middle-income countries (LMICs) *(1)*. Compared to the general population of patients, cancer patients are more prone to develop serious infections due both to the illness itself and the cancer treatment they receive *(2)*. Despite efforts to prevent infections, they still remain the second leading cause of death in patients with cancer *(3)*. Neutropenia (i.e., an abnormally low concentration of white blood cells) due to treatment with cytotoxic drugs, altered gut flora, skin disruption, and epithelial surface damage are some of the causes that increase cancer patients' susceptibility to infections *(4)*. Pneumonia and sepsis (a bacterial infection of the blood) are two of the most common reasons for cancer patients to be admitted to intensive care units. In fact, it is estimated that severe sepsis accounts for 8.5% of cancer deaths *(5)*. Bloodstream infections have been the leading complications in cancer patients, making it necessary to use antibiotics routinely in the treatment of these patients. It is evident that the significant burden of infections in cancer patients makes antibiotics indispensable for cancer treatment, both for prevention and treatment of bacterial infections. More specifically, it is estimated that one in every five cancer patients requires antibiotics during their cancer treatment *(6)*. Today, we have a worldwide problem with increasing antibiotic resistance (ABR), where bacteria overcome the action of antibiotics, making them ineffective. This has a devastating impact on cancer treatment, jeopardizing key advances in cancer care and cancer patients' survival. The growing ABR burden is a global public health issue that needs to be addressed urgently *(7)*, particularly in LMICs where health infrastructure is lacking or under-resourced, and cancer treatment is already difficult to access, expensive and requires high out-of-pocket expenditure, thus the costs associated with treating resistant infections would make it altogether inaccessible *(8)*. In most LMICs, the diagnosis of cancer is almost a death sentence due to the lack of access to anticancer drugs and higher costs of treatment alluded to above.

Challenges of cancer care in LMICs

Lung cancer is the leading cause of cancer death worldwide and is the most serious burden in LMICs *(9)*. The reasons for the unacceptably high cancer mortality rates in LMICs are multifactorial, including late-stage diagnosis and treatment, lack of health infrastructure including cancer screening facilities, scarcity of trained cancer care professionals and a higher burden of ABR *(10)*. In fact, more than 90% of high-

income countries (HICs) reported comprehensive cancer treatment services in the public health system, compared to less than 15% of low-income countries in 2019 *(11)*. Other factors critically increasing LMICs cancer-related mortality are a result of rising rates of obesity an increasingly sedentary lifestyle; dietary factors; excessive use of tobacco and alcohol; and persistent infections such as *Helicobacter pylori*, hepatitis B virus and human papillomavirus *(12,13)*. In contrast to HICs, where infection-related cancer mortality is rare, LMICs bear a disproportionate burden of infection-related cancer mortality, including gastric cancer, hepatocellular carcinoma and cervical cancer *(14)*. Disparities in the allocation of resources, established infrastructure, organization and access to medical care will almost certainly result in higher cancer fatality rates in LMICs, where the population is extremely vulnerable, diagnoses are made at later stages of the disease and access to care remains a significant challenge *(15)*. The lack of awareness in the lay and medical communities, delay in seeking medical advice, late-stage presentation, insufficient manpower, and training deficits and poverty are well documented among the challenges of treating cancer in LMICs *(16)*.

Cancer treatment is costly and the high price of cancer medicines has a significant impact on access in LMICs. For example, a standard course of treatment (doxorubicin, docetaxel, cyclophosphamide and trastuzumab) for early-stage human epidermal growth factor receptor 2 positive (HER2+) breast cancer would cost approximately 10 years' average annual wages in India and South Africa.

Large portions of the population in LMICs have limited access to medicines, either due to a lack of availability or because patients must bear the cost of treatment (out-of-pocket) in the absence of government reimbursements, insurance or exclusive access schemes. As a result, they are forced into poverty, or early death *(17)*. The World Health Organization (WHO) identifies four key components of cancer control which include:

- prevention;
- early detection and diagnosis;
- treatment;
- palliative and survivorship care.

Inadequacies in these areas in LMICs impairs the efficacy and sustainability of cancer control programmes in already resource-constrained settings *(18)*. Data from LMICs on the current state of cancer care and infrastructure are limited. Furthermore, the majority of LMICs lack adequate cancer registries, impeding the evolution of an adequate oncology infrastructure *(19)*. The challenges connected with access to cancer care, especially in LMICs, are further exacerbated by the development and spreading of ABR, which decreases (and/or neutralizes) the effectiveness of antibiotics, threatening the survival of people living with cancer.

Use of antibiotics in patients with cancer

Cancer patients are often prescribed with prolonged and varied courses of antibiotic agents either to prevent or treat infection during their treatment. This is because during radiotherapy and cancer chemotherapy, cells that are part of the defence mechanism against infections are adversely affected. These treatments are used to kill harmful cancer cells, but they end up harming other cells that are required for defence against bacterial infections. This means that cancer patients' immune systems are weakened, leaving them prone to infections, including infections caused by resistant pathogens. This is particularly crucial in patients with blood cancer and severe neutropenia *(20)*. For example, patients undergoing haematopoietic stem cell transplantation (HSCT) or induction chemotherapy for acute leukemia are prescribed with antimicrobial prophylaxis, including prophylaxis for invasive fungal infections. These patients suffer from prolonged periods of neutropenia as a side effect of treatment *(21)*. The prolonged use of antibiotics on cancer patients can also lead to lethal bloodstream infections (BSI). *Staphylococcus aureus*, a common Gram-positive bacterium causing bloodstream infections in human beings, is often methicillin-resitant (MRSA). Nonetheless, MRSA is not covered by the recommended initial antibiotic therapy for cancer patients with BSI *(22)*, hence increasing patients' exposure to MRSA infections, and so the associated mortality and economic burden worldwide *(23)*. Similarly, high mortality rates are associated with the Gram-negative carbapenem-resistant *Klebsiella pneumoniae* (CRKP), accounting for about 60% mortality in neutropenic haematological patients *(24)*.

Antibiotics are crucial for patients undergoing chemotherapy, surgery and radiation therapy due to their anti-proliferative, pro-apoptotic and anti-epithelial-mesenchymal-transition (EMT) capabilities (or ability to stop cancerous cells) *(25)*. Antibiotics, such as ciprofloxacin, salinomycin, doxorubicin and mitomycin, are effective against multiple solid cancers *(25,26)*. They are used to treat secondary infections that may be caused by tissue damage, ulcers and compromised wound healing, which allow disease-causing bacteria to infect patients *(27)*.

Impact of ABR on cancer care in LMICs

Cancer patients are at a threefold greater risk of dying from a fatal infection than those who do not have cancer *(28)*. Patients with cancer are treated prophylactically and empirically with antibiotics under neutropenic conditions *(29)*. The widespread and prolonged use of antibiotics to reduce mortality and

morbidity from infections in patients with cancer is likely to contribute to the emergence of antibiotic resistance *(30–32)*. In addition, patients with cancer are vulnerable to health-care-acquired infections as a major source of antibiotic-resistant organisms *(33,34)*. Although comparable data are lacking on a global scale, several hospital microbial surveillance studies in LMICs have shown an increase in antibiotic-resistant microorganisms in cancer patients. In India, for example, about 73% of patients with blood cancers harboured carbapenem-resistant bacteria in their gut *(35)*. In Ethiopia, a study found that bacterial infections in cancer patients accounted for 19.4% of all cases, and multidrug resistance was common *(36)*. Another study in Uganda, where 85% of a certain class of bacteria (Enterobacteriaceae) that cause bloodstream infections in cancer patients were multidrug resistant *(37)*. These findings suggest that key advances in medicines, including newer immunotherapies for cancer patients, may be at risk because of the increasing threat of antibiotic resistance globally. Cases of carbapenem-resistant *Klebsiella pneumoniae* infection following a stem cell transplant were reported in 53.4% of 52 Italian centres in a retrospective study. Even the diagnosis of cancer poses a risk to patients due to resistant pathogens. For example, taking a biopsy to diagnose prostate cancer can be life-threatening because 10% of patients will develop a severe infection. Without effective preventive antibiotic treatment, the risk of infection following a prostatic biopsy is approximately 50% *(38)*.

Infections caused by antibiotic-resistant pathogens, such as vancomycin-resistant *Enterococcus*, FQ-resistant streptococci, and multidrug-resistant Gram-negative bacteria (including extended-spectrum beta-lactamase–producing and carbapenem-resistant (CR) strains) are becoming more common in cancer patients. This is crucial for cancer patients, where delays in proper treatment are associated with significantly increased mortality *(39)*. The problem of antimicrobial overuse extends beyond antibiotic resistance and includes fungal and viral resistance as well as *Clostridium difficile* infections *(40)*. In LMICs, although diagnostic capacity for HIV, TB and malaria has been integrated into the respective control programmes for these disease groups, anecdotal evidence suggests that diagnostic microbiology is not consistently available in the management of cancer patients to either identify sources of infection or the infecting microbes *(41)*. Similarly, cancer medicines and second-line antibiotics used to treat resistant pathogens are very costly and frequently not available in LMICs. There is a lack of knowledge and awareness about the impact of ABR on cancer patient outcomes within the cancer community. Moreover, the World Health Organization recently stated that the threat of ABR is booming at an alarming rate. The joint epidemics of cancer and ABR can contribute significantly to the impact on persistent health inequities in LMICs.

Addressing ABR for better cancer care in LMICs

Although data are still scarce, it is evident that ABR poses an increasing challenge to cancer treatment. This information is critical for quantifying ABR's contribution to preventable deaths among cancer patients, as well as raising awareness, supporting advocacy and guiding policy actions to combat ABR on a national scale.

- **Implement an (inter)national surveillance system:** Cancer organizations and infectious disease societies can work together with national cancer registries to guide data collection on variables relevant to antibiotic resistance and work with health-care professionals and hospitals to develop rigorous policies and data collection mechanisms for antibiotic surveillance and stewardship *(42)*. Accurate reporting of deaths by ABR in cancer patients will allow for: 1) a better overview of the ABR magnitude; 2) implement timely interventions; and 3) restrict the spread of resistant infections to other cancer patients.
- **Ensure access to effective medical countermeasures:** The availability, affordability and sustained access to quality-assured medicines and microbial diagnostics is another important area of focus in LMICs for combatting ABR in patients with cancer *(43)*. To provide successful cancer treatment, people living with cancer need effective antibiotics. Hence, it is important to focus on research and development for discovering and introducing new medicines and diagnostics, as few new classes of antibiotics have been discovered since the 1980s.

  Patients have shared experiences of feeling they had received a death sentence when they received a cancer diagnosis, as they realized they could not afford the costly treatments. Most could not pay the high cost of diagnostics and treatments, and stockouts often disrupted their treatment regimens and schedules.
- **Strengthen infection, prevention and control (IPC):** Robust clinical guidelines, patient advice, sustainable water, sanitation and hygiene (WASH) infrastructure and improved IPC measures are also required for better management of ABR in cancer patients. Similarly, courses and training for health practitioners will be a big step towards containing the development and spread of ABR.
- **Raise awareness and seek joint action:** At present, there is a lack of knowledge and awareness in the cancer community about the link between ABR and cancer, and the impact of ABR on cancer care outcomes. It is crucial to highlight the need to raise awareness about the relationship between these two global health threats

among the oncology health workforce, programme managers, patient groups, cancer advocates and other stakeholders working in the field of cancer. To overcome the challenge that ABR poses to cancer patients and caregivers worldwide, the cancer community and relevant stakeholders must join forces with other global health actors, including stakeholders in communicable diseases, to bring together best practices and resources. ■

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References

1. Girmenia C, Rossolini GM, Piciocchi A, et al. Infections by carbapenem-resistant Klebsiella pneumoniae in SCT recipients: a nationwide retrospective survey from Italy. *Bone Marrow Transplant.* 2015;50(2):282-288. doi:10.1038/bmt.2014.231
2. Epidemiology of Infections in Cancer Patients | SpringerLink. Accessed 16 June 2022. https://link.springer.com/chapter/10.1007/978-3-319-04220-6_2
3. Antibiotic resistance in the patient with cancer: Escalating challenges and paths forward - Nanayakkara - 2021 - *CA: A Cancer Journal for Clinicians* - Wiley Online Library. Accessed June 16, 2022. https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21697
4. Singh R, Jain S, Chabbra R, Naithani R, Upadhyay A, Walia M. Characterization and anti-microbial susceptibility of bacterial isolates: Experience from a tertiary care cancer center in Delhi. *Indian J Cancer.* 2014;51(4):477. doi:10.4103/0019-509X.175305
5. Cherif DH. Successful cancer treatment relies on effective antibiotics. :11.
6. What are the consequences of antibiotic resistance for cancer patients? Norwegian Cancer Society. Accessed 2 May 2022. https://kreftforeningen.no/en/antimicrobial-resistance-amr/what-are-the-consequences-of-antibiotic-resistance-for-cancer-patients/
7. Cars O, Chandy SJ, Mpundu M, Peralta AQ, Zorzet A, So AD. Resetting the agenda for antibiotic resistance through a health systems perspective. *Lancet Glob Health.* 2021;9(7):e1022-e1027. doi:10.1016/S2214-109X(21)00163-7
8. Iragorri N, de Oliveira C, Fitzgerald N, Essue B. The Out-of-Pocket Cost Burden of Cancer Care—A Systematic Literature Review. *Curr Oncol.* 2021;28(2):1216-1248. doi:10.3390/curroncol28020117
9. Lung cancer is more deadly in poorer nations. This is how to level the burden of this disease. World Economic Forum. Accessed 3 May 2022. https://www.weforum.org/agenda/2021/11/lung-cancer-poorer-nations/
10. Brand NR, Qu LG, Chao A, Ilbawi AM. Delays and Barriers to Cancer Care in Low- and Middle-Income Countries: A Systematic Review. *The Oncologist.* 2019;24(12):e1371-e1380. doi:10.1634/theoncologist.2019-0057
11. Mitchell C, https://www.facebook.com/pahowho. PAHO/WHO | WHO outlines steps to save 7 million lives from cancer. Pan American Health Organization / World Health Organization. Published 4 February 2020. Accessed 3 May 2022. https://www3.paho.org/hq/index.php?option=com_content&view=article&id=15708:who-outlines-steps-to-save-7-million-lives-from-cancer&Itemid=1926&lang=en
12. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. *Lancet Glob Health.* 2016;4(9):e609-616. doi:10.1016/S2214-109X(16)30143-7
13. de Martel C, Ferlay J, Franceschi S, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncol.* 2012;13(6):607-615. doi:10.1016/S1470-2045(12)70137-7
14. Danaei G, Vander Hoorn S, Lopez AD, Murray CJL, Ezzati M, Comparative Risk Assessment collaborating group (Cancers). Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. *Lancet Lond Engl.* 2005;366(9499):1784-1793. doi:10.1016/S0140-6736(05)67725-2
15. Barrios CH. Global challenges in breast cancer detection and treatment. *The Breast.* 2022;62:S3-S6. doi:10.1016/j.breast.2022.02.003
16. Non-communicable diseases in the developing world - Cancer Control. Published May 16, 2014. Accessed May 3, 2022. http://www.cancercontrol.info/cc2014/jenkin/
17. Availability, Affordability, Access, and Pricing of Anti-cancer Medicines in Low- and Middle-Income Countries: A Systematic Review of Literature - PMC. Accessed May 3, 2022. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8120029/#B2
18. Shah SC, Kayamba V, Peek RM, Heimburger D. Cancer Control in Low- and Middle-Income Countries: Is It Time to Consider Screening? *J Glob Oncol.* 2019;5:JGO.18.00200. doi:10.1200/JGO.18.00200
19. Hanna TP, Kangolle AC. Cancer control in developing countries: using health data and health services research to measure and improve access, quality and efficiency. *BMC Int Health Hum Rights.* 2010;10:24. doi:10.1186/1472-698X-10-24
20. World Cancer Day: Cancer patients rely on effective antibiotics – 2020. ReAct. Accessed 3 May 2022. https://www.reactgroup.org/news-and-views/news-and-opinions/year-2020/world-cancer-day-cancer-patients-rely-on-effective-antibiotics/
21. Flowers Randy AT Erin B Kennedy, Eric J Bow, Jennie Crews, Charise Gleason, Douglas K Hawley, Amelia A Langston, Loretta J Nastoupil, Michelle Rajotte, Kenneth V Rolston, Lynne Strasfeld, and Christopher R. Antimicrobial Prophylaxis for Adult Patients with Cancer-related Immunosuppression. Accessed 3 May 2022. https://www.idsociety.org/practice-guideline/antimicrobial-prophylaxis-for-adult-patients-with-cancer-related-immunosuppression/
22. Baden LR, Swaminathan S, Angarone M, et al. Prevention and Treatment of Cancer-Related Infections, Version 2.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Cancer Netw JNCCN.* 2016;14(7):882-913. doi:10.6004/jnccn.2016.0093
23. Otto M. MRSA virulence and spread. *Cell Microbiol.* 2012;14(10):1513-1521. doi:10.1111/j.1462-5822.2012.01832.x
24. Girmenia C, Rossolini GM, Piciocchi A, et al. Infections by carbapenem-resistant Klebsiella pneumoniae in SCT recipients: a nationwide retrospective survey from Italy. *Bone Marrow Transplant.* 2015;50(2):282-288. doi:10.1038/bmt.2014.231
25. Gao Y, Shang Q, Li W, et al. Antibiotics for cancer treatment: A double-edged sword. *J Cancer.* 2020;11(17):5135-5149. doi:10.7150/jca.47470
26. Cytotoxic Antibiotics. Information about Cytotoxic Antibiotics. Accessed June 16, 2022. https://patient.info/doctor/cytotoxic-antibiotics
27. Cherif DH. Successful cancer treatment relies on effective antibiotics.
28. Zheng Y, Chen Y, Yu K, et al. Fatal Infections Among Cancer Patients: A Population-Based Study in the United States. *Infect Dis Ther.* 2021;10(2):871-895. doi:10.1007/

References continued

s40121-021-00433-7

29. Lustberg MB. Management of Neutropenia in Cancer Patients. *Clin Adv Hematol Oncol HO*. 2012;10(12):825-826.
30. Xie O, Slavin MA, Teh BW, Bajel A, Douglas AP, Worth LJ. Epidemiology, treatment and outcomes of bloodstream infection due to vancomycin-resistant enterococci in cancer patients in a vanB endemic setting. *BMC Infect Dis.* 2020;20(1):228. doi:10.1186/s12879-020-04952-5
31. Tedim AP, Ruíz-Garbajosa P, Rodríguez MC, et al. Long-term clonal dynamics of Enterococcus faecium strains causing bloodstream infections (1995–2015) in Spain. *J Antimicrob Chemother.* 2017;72(1):48-55. doi:10.1093/jac/dkw366
32. Tofas P, Samarkos M, Piperaki ET, et al. Pseudomonas aeruginosa bacteraemia in patients with hematologic malignancies: risk factors, treatment and outcome. *Diagn Microbiol Infect Dis.* 2017;88(4):335-341. doi:10.1016/j.diagmicrobio.2017.05.003
33. Cornejo-Juárez P, Cevallos MA, Castro-Jaimes S, et al. High mortality in an outbreak of multidrug resistant Acinetobacter baumannii infection introduced to an oncological hospital by a patient transferred from a general hospital. *PLOS ONE.* 2020;15(7):e0234684. doi:10.1371/journal.pone.0234684
34. Hospital-acquired infections at an oncological intensive care cancer unit: differences between solid and hematological cancer patients | *BMC Infectious Diseases* | Full Text. Accessed 3 May 2022. https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-016-1592-1
35. Kumar A, Mohapatra S, Bakhshi S, et al. Rectal Carriage of Carbapenem-Resistant Enterobacteriaceae: A Menace to Highly Vulnerable Patients. *J Glob Infect Dis.* 2018;10(4):218-221. doi:10.4103/jgid.jgid_101_17
36. Fentie A, Wondimeneh Y, Balcha A, Amsalu A, Adankie BT. Bacterial profile, antibiotic resistance pattern and associated factors among cancer patients at University of Gondar Hospital, Northwest Ethiopia. *Infect Drug Resist.* 2018;11:2169-2178. doi:10.2147/IDR.S183283
37. Lubwama M, Phipps W, Najjuka CF, et al. Bacteremia in febrile cancer patients in Uganda. *BMC Res Notes.* 2019;12(1):464. doi:10.1186/s13104-019-4520-9
38. WHO-EURO-2020-1628-41379-56382-eng.pdf. Accessed 4 May 2022. https://apps.who.int/iris/bitstream/handle/10665/337511/WHO-EURO-2020-1628-41379-56382-eng.pdf
39. Baker TM, Satlin MJ. The growing threat of multidrug-resistant Gram-negative infections in patients with hematologic malignancies. *Leuk Lymphoma.* 2016;57(10):2245-2258. doi:10.1080/10428194.2016.1193859
40. Aitken SL, Nagel JL, Abbo L, et al. Antimicrobial Stewardship in Cancer Patients: The Time is Now. *J Natl Compr Canc Netw.* 2019;17(7):772-775. doi:10.6004/jnccn.2019.7318
41. Kouassi V. Addressing antimicrobial resistance for better care in cancer patients - by Yehoda M. Martei and Shalini J. Zürn. REVIVE. Accessed 3 May 2022. https://revive.gardp.org/addressing-antimicrobial-resistance-for-better-care-in-cancer-patients/
42. How drug-resistant infections are undermining modern medicine | Reports. Wellcome. Accessed May 4, 2022. https://wellcome.org/reports/how-drug-resistant-infections-are-undermining-modern-medicine-and-why-more-research-needed
43. 5 questions to… Cary Adams, CEO of the Union for International Cancer Control (UICC). IFPMA. Accessed 4 May 2022. https://www.ifpma.org/global-health-matters/5-questions-to-cary-adams-ceo-of-the-union-for-international-cancer-control-uicc/

Antimicrobial Resistance Fighter Coalition

The Antimicrobial Resistance Fighter Coalition is a bold collective of like-minded organizations, leaders, and individuals united in their commitment to address the threat and burden of antimicrobial resistance.

To change behaviours and practices around antibiotic utilization, the risk of drug-resistant infections needs to better understood by organizations and individuals. Antimicrobial resistance (AMR) is a complex problem that involves human health, animal management and enviromental practices.

The Antimicrobial Resistance Fighter Coalition is a coalition of individuals and organizations committed to improved awareness and action against drug-resistant infections.

Learn more about AMR by listening to *Superbugs and You: True Stories from Scientists and Patients around the World* with you on a walk or run. On this podcast, you will hear from patients, clinicians, and researchers from around the world on the work that they are leading to combat AMR.

- How do drug-resistant infections affect patients and their families?
- How are front-line clinicians managing these challenges?
- How are leaders driving policy and innovation?

Are you ready to take action against drug-resistant infections?

Download Activation Kits from the Anticrobial Resistant Fighter Coaltion's website. Each kit includes an introduction and overview on how the specific audience can use the kit, talking points and messaging, materials to use in digital and news media, specific action items you can take to combat AMR, and resources to use within your community to reach decision-makers.

Share your story and become an Antimicrobial Resistance Fighter

ANTIMICROBIAL RESISTANCE FIGHTER COALITION

Leveraging information systems that integrate cancer registries with microbiology databases to improve clinical care and address antimicrobial resistance in oncology

Scott C Howard, Professor, University of Tennessee Health Science Center, Memphis, USA; **Miguela A Caniza,** Professor, St Jude Children's Research Hospital, Memphis, USA and Co-Chair, Global Health Network Supportive Care Working Group, International Society of Pediatric Oncology, Meierskappel, Switzerland; **Ryan Combs,** Vice President of Analytics, Resonance, Memphis, USA; **Aman Patel,** Chief Technology Officer, Resonance, Memphis, USA; **Ligia Fu,** Chief, Pediatric Oncology Ward, Hospital Escuela Tegucigalpa, Honduras; **Jennifer A Lowe,** Vice President of Clinical Trials, Resonance, Memphis, USA and **Catherine G Lam,** Director, Health Systems Unit, Global Pediatric Medicine Department and Co-Director, World Health Organization Collaborating Centre for Childhood Cancer, St Jude Children's Research Hospital, Memphis, USA


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Antimicrobial resistance (AMR) increases toxic death in people receiving cytotoxic chemotherapy. When infection occurs during periods of neutropenia, immediate treatment with empiric and effective antibiotics should be initiated within one hour of fever onset. Selection of antibiotic therapy can be tailored once the infecting organism is identified, and its antibiotic sensitivities determined. Resistant organisms are common, and patterns of resistance change over time, so an integrated information system is needed to generate real-time, patient-specific antibiograms and convert them to actionable guidance for a clinician. Such integration is now feasible thanks to free and open-source software like Resonance Patient Center and the AMR (R) package.

Background

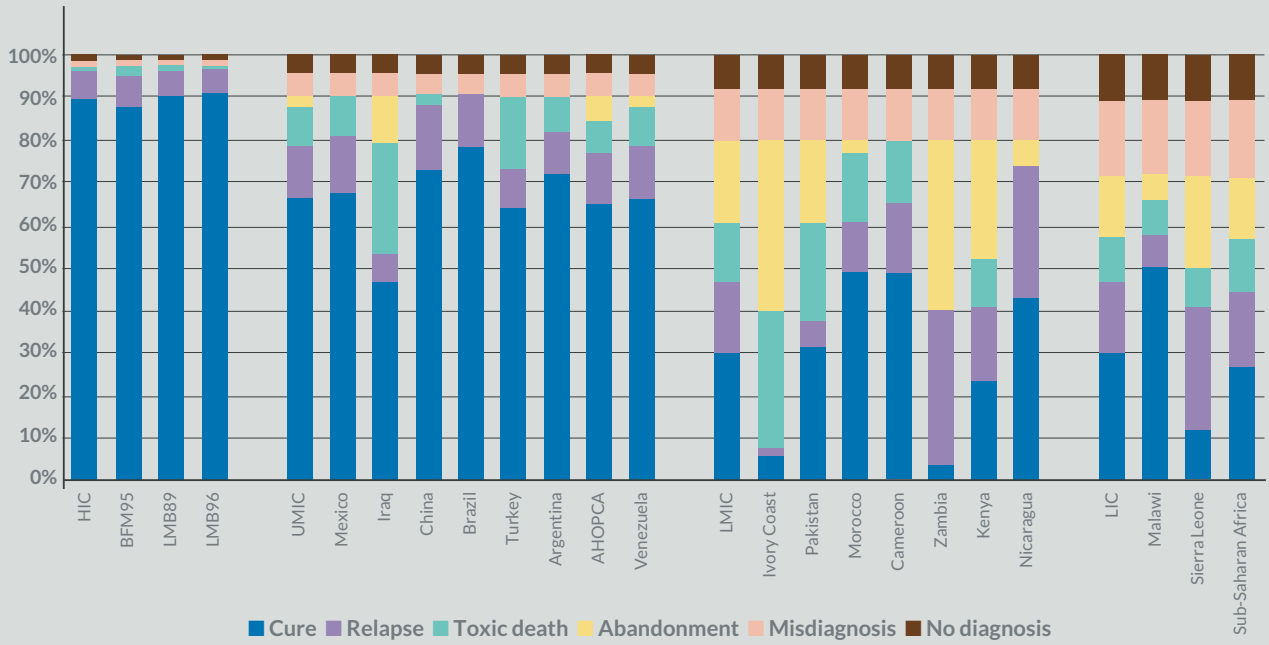
Antimicrobial resistance in people with cancer increases toxic death and relapse

Antimicrobial resistance (AMR) occurs more frequently in people receiving anticancer therapies and impacts outcomes in all countries by increasing rates of treatment-related mortality and interfering with anticancer therapy delivery and reducing disease control *(1-12)*. Toxic death during cancer therapy is comprised of disease-related toxic death and treatment-related mortality. Disease-related toxic death refers to complications of the cancer itself, which occur at the time of diagnosis when the tumour burden is high and cancer masses may impinge on critical organs or cause metabolic complications from tumour lysis syndrome. Note that disease-related toxic death differs from death from progressive cancer, which remains the most common cause of treatment failure. Once oncologic emergencies have been addressed and anticancer treatment has been initiated, disease-related death rates are negligible in the absence of relapsed or progressive cancer. By contrast, treatment-related mortality (TRM), which refers to death due to toxicities of anticancer therapy, can affect patients at any time during their therapy *(13)*.

Bacterial infections are the most common cause of treatment-related mortality

The most common cause of TRM is infection, which is associated with the depth and duration of neutropenia caused by cytotoxic chemotherapy agents or other myelosuppressive treatments. Of all resistant infectious agents, most worrisome are resistant bacteria, which contribute the most to morbidity and mortality from infection by causing sepsis and septic shock *(1-4)*. In low- and middle-income countries (LMICs), rates of death from sepsis are much higher than those in high-income countries (HICs); thus, AMR takes a greater toll on patients in LMICs *(5,6,10,14)*. The growing global challenge of AMR

Figure 1: Causes of treatment failure for children with non-Hodgkin lymphoma in high-income, middle-income and low-income countries



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was highlighted in 2015 in the World Health Organization's Global Action Plan *(15)*. Despite global stakeholder support, much remains to be done, and a key gap includes the lack of information systems *(15-17)*.

Treatment-related mortality from infection disproportionately affects people in low- and middle-income countries

In addition to treatment failure from lack of diagnosis, misdiagnosis, abandonment of treatment, and relapse, people with cancer in LMICs also experience a greater risk of toxic death, mostly due to TRM (Figure 1) *(18,19)*. Indeed, children with non-Hodgkin lymphoma have a 1% toxic death rate in HICs, which is higher than 20% in some LMICs (Figure 1) *(20)*. Common risk factors for TRM in LMICs include low socioeconomic status, reduced access to prompt supportive care due to long travel times to reach the hospital, personnel shortages that delay care, overworked health-care providers, shortages of microbiology equipment and supplies, hospital infrastructure gaps, and other reasons *(21)*. In one study in El Salvador, 12% of children with acute lymphoblastic leukaemia died of infections within two months of starting treatment *(14,22)*. A major cause was severe delay in administration of the first dose of antibiotic when an immunosuppressed patient developed fever. The gold standard for cancer patients with fever and neutropenia is to administer the first dose of antibiotic within one hour of the onset of fever, the so-called "golden hour." In El Salvador, before a series of interventions was undertaken, the median time to the first dose was 16 hours, much too late to save the life of children with sepsis or septic shock *(21)*.

Lack of information impedes progress to better prevent and manage AMR in people with cancer

Information systems typically require computer hardware, costly software licensing contracts, trained personnel with expertise in information technology (IT), data management staff, and time and effort from health-care providers to manage information and apply it to clinical care. In HICs, most cancer centres maintain an electronic medical record (EMR), cancer registry, research databases, and administrative databases. Each of these is supported by a team of informaticists and integration or data transfers among systems can be developed and maintained with support from data scientists and statisticians. Unfortunately, non-integrated systems are costly due to individual software licences and hardware requirements, the need for multiple teams of IT professionals, integrations and data transfer pipelines that are costly to develop and maintain, and a strong data science programme to support analysis. Such programmes are difficult to fund and maintain in HICs, and nearly impossible in LMICs. Inexpensive or free integrated solutions are needed to effectively address the pressing challenge of AMR in cancer patients *(23-25)*.

Integrated information systems facilitate analysis and quality improvement

Cancer registries are common, even in LMICs, but they provide

little clinical information and never include microbiology data elements, so cannot be used to study AMR and assess the effectiveness of interventions to address it. Microbiology and infectious disease databases provide the necessary granular information to assess gaps in infection control and detect the development of AMR, but lack details about the patient's cancer and its outcome. An integrated solution is needed to leverage the strengths of both types of database and facilitate analysis without the need for duplicate data entry and two teams of IT and data management staff. Regular analysis of outcomes before and after each intervention lays the foundation for continuous quality improvement.

Resonance Patient Center and integrated information systems

Resonance Patient Center (RPC) is a web-based application provided at no cost to users by Resonance (ResonanceHealth.org), an organization dedicated to amplifying health through research, education and technology. Resonance Patient Center serves as an electronic health-care data storage and retrieval system featuring fit-for-purpose registries (e.g., cancer registries), integration with the R statistical package, customization by diverse users, and decision support tools to improve patient care in real time. It is used to collect data at the facility level, but such data can be rolled up into national databases to support national and international AMR-reduction programmes, such as the Global Antimicrobial Resistance and Use Surveillance System (GLASS) of the World Health Organization (WHO), which was launched in 2015 to strengthen the AMR evidence base by harmonized global reporting of official national AMR and antimicrobial consumption data (https://www.who.int/publications/ i/item/9789240027336) (*26*). Development, dissemination, and sustained operation of RPC and similar integrated information systems are needed to track AMR and measure the effectiveness of AMR reduction strategies, as highlighted by the WHO in its report "Monitoring and evaluation of the global action plan on antimicrobial resistance: framework and recommended indicators." (https://apps.who.int/iris/bitstream/handle/10665/325006/9789241515665-eng.pdf?ua=1).

Methods

The Union for International Cancer Control (UICC) developed the AMR Task Force, which included diverse stakeholders and experts in oncology, infectious diseases, programme development, and research. UICC colleagues convened a series

Figure 2: **Meeting of the UICC Antimicrobial Resistance Task Force, 31 May 2022**

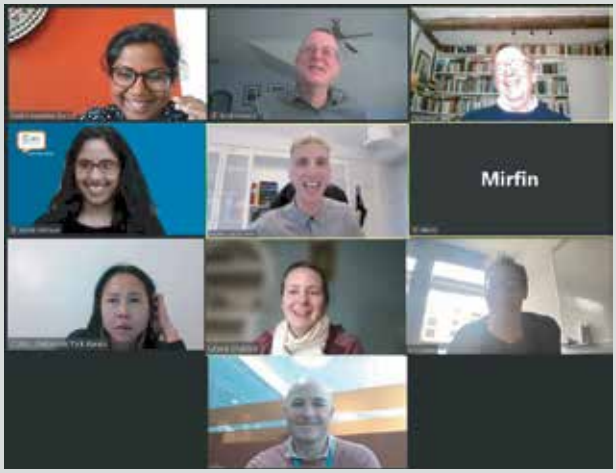


Figure 3: **Antimicrobial susceptibilities to commonly prescribed antibiotics from a bloodstream infection of a child with cancer**

Micro Reports | **Susceptibilities** | Specimen | Action List

	A	B	C	D	E
1	Klebsiella pneumoniae				
2		MIC (Rapid)	Interpretation (Rapid)	MIC (Dilution)	Interpretation (Dilution)
3	Amikacin	<=4	S	<=2	S
4	Aztreonam	>=32	R		
5	Cefepime	>=32	R	2	R
6	Ceftazidime	>=32	R	8	R
7	Ceftriaxone	>=8	R	>=64	R
8	Ciprofloxacin	>=8	R	>=4	R
9	Ertapenem	0.25	S	<=0.5	S
10	Gentamicin	16	R	>=16	R
11	Meropenem	<=0.25	S	<=0.25	S
12	Tobramycin	8	I	8	I
13	Amoxicillin/Clavulanic Acid			16	I
14	Ampicillin			>=32	R
15	Cefuroxime			>=64	R
16	Levofloxacin			>=8	R
17	Piperacillin/Tazobactam			16	S
18	Trimeth/Sulfa			>=320	R
19	ESBL			Pos	Pos

Antimicrobial resistance testing confirms that the patient's bloodstream infection was caused by a highly resistant bacteria expressing extended-spectrum beta-lactamase that confers resistance to cefepime, the drug typically used for empiric therapy.

MIC, minimum inhibitory concentration; ESBL, extended spectrum beta-lactamase (a bacterial enzyme that confers resistance to a wide range of beta-lactam antibiotics); S, sensitive; I, intermediate sensitivity; R, resistant.

of meetings during which key themes were developed, including the need for integrated information systems (Figure 2).

In this article, we discuss features of information systems with the potential to integrate hospital-based cancer registry functions and data with clinical and microbiologic data to facilitate analysis of the impact of infection and AMR on oncology outcomes. Free and open-source software is preferred, since it is equally available to people in LMICs and HICs, and international user groups can support each other by enhancing features and sharing best practices for data collection and analysis *(23-26)*.

Results and discussion

Initial management of a cancer patient with suspected bacterial infection

When a patient presents with febrile neutropenia, the first step is to obtain cultures from the blood and other potential sites of infection, followed immediately by administration of empiric antibiotics. Empiric antibiotics are chosen based on the clinical presentation to cover the most common bacterial infections in patients managed at the treating centre using an antibiogram. Once a positive blood culture has allowed identification of the bacteria, the preliminary laboratory result is used to choose an antibiotic predicted to be effective based on the specific bacterial species. When sensitivity testing is complete, the overall AMR profile of the identified microorganism is used to select the best antibiotic or combination of antibiotics (Figures 3 and 4). Additional benefits of accurate microbiological diagnosis include improved outbreak management and enhanced environmental controls to reduce exposure of other people to resistant organisms.

Automated generation of a patient-specific antibiogram

The Clinical and Laboratory Standards Institute (CLSI) provides guidelines to create a hospital-based antibiogram, which is based on aggregate data showing the percentages of organisms tested that are susceptible to a particular antibiotic (Figure 5). CLSI recommends annual updates to the antibiogram including only the first isolate per patient and only organisms for which ≥30 isolates are tested during the period analyzed. Antibiograms are compiled by microbiologists in collaboration with clinicians, infection preventionists and pharmacists. Because the process is time-consuming and requires extraction, synthesis and analysis of large quantities of data, some hospitals do not update the antibiogram annually or do not adhere to other CLSI guidelines *(27)*. In an informal survey of colleagues in LMICs, the time elapsed since the last update ranged from two to eight years. A manually produced, frequently out of date, antibiogram has several disadvantages: 1) antibiotic resistance patterns can change quickly, leading to patient harm while awaiting the new antibiogram; 2) the time-consuming process pulls busy clinicians and laboratory personnel away from their daily patient care duties; and 3) individual patients may have acquired their infection in different environments, which may have different sensitivity patterns.

For example, patients who develop a pseudomonas infection after spending two months in the intensive care unit on a ventilator are much more likely to have contracted a resistant strain than a person who acquired their infection outside the hospital. An intensive care unit-specific antibiogram would provide better guidance since it would use only the most relevant information for the specific patient. Similarly, a patient who has received outpatient therapy in the oncology ward and infusion centre may have different exposures than a premature baby in the neonatal unit. A unit-specific antibiogram would be more relevant for these situations than a general one. Automated generation of specific antibiograms using the combined tools available in the free Resonance Patient

Figure 4: Antibiotic sensitivity testing identified resistant *Acinetobacter baumannii*

Información de identificación	**Tiempo de análisis:** 5,80 horas	**Estado:** Final	
Organismo seleccionado	99% Probabilidad	**Acinetobacter baumannii**	
	Bionúmero:	0041010300500210	
Mensajes de análisis de ID			

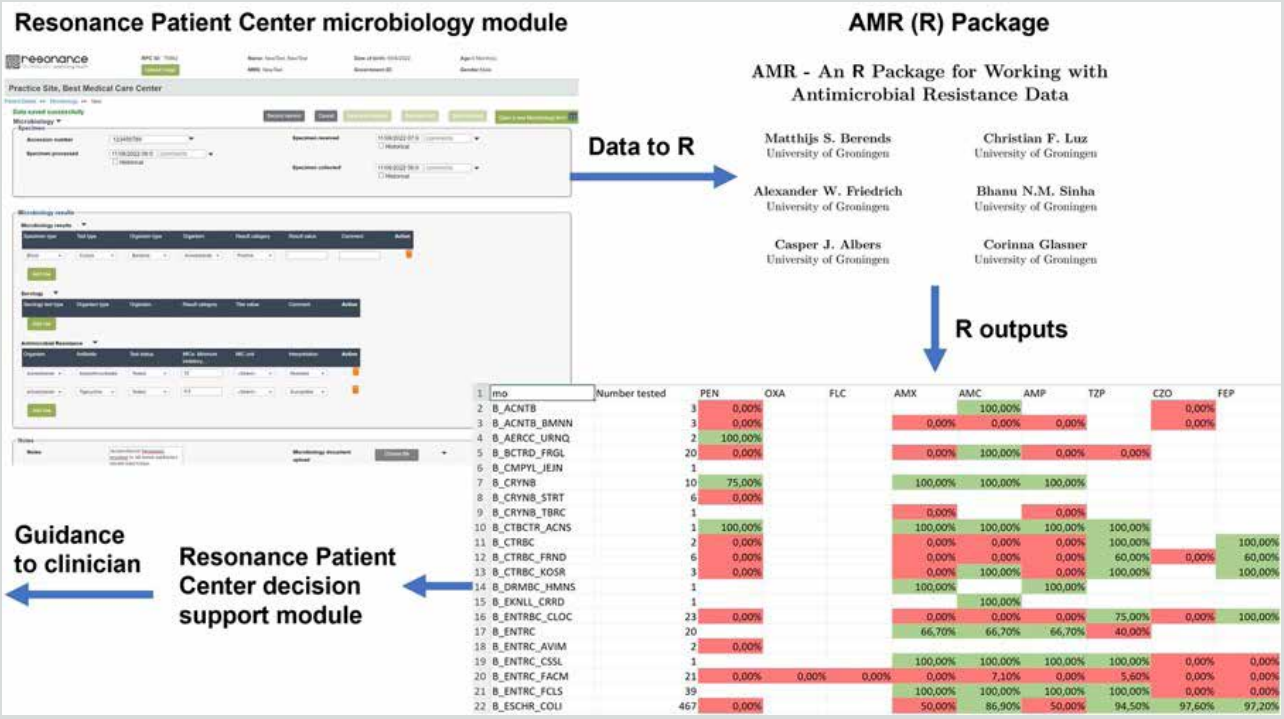
Información de sensibilidad	**Tiempo de análisis:** 16,07 horas	**Estado:** Final

Antibiótico	CMI	Interpretación	Antibiótico	CMI	Interpretación
Ampicilina/Sulbactam	>= 32	R	Meropenem	>= 16	R
Piperacilina/Tazobactam	>= 128	R	Amicacina	>= 64	R
Ceftazidima	>= 64	R	Tigeciclina	<= 0,5	S
Imipenem	>= 16	R			

The photograph shows a 19-year-old who presented with premature labour at the time of leukemia diagnosis and bloodstream infection with a resistant strain of Acinetobacter baumannii that was sensitive only to tigecycline (tigeciclina). With rapid testing for resistance, the appropriate antibiotic was administered and mother and baby are healthy. Photograph used with written permission.

CMI, minimum inhibitory concentration; S, sensitive; I, intermediate sensitivity; R, resistant.

Figure 5: An automatically generated patient-centred antimicrobiogram can leverage data from the Resonance Patient Center or other information systems to produce customized antimicrobiograms based on specific criteria relevant for care of each patient



mo	Number tested	PEN	OXA	FLC	AMX	AMC	AMP	TZP	CZO	FEP
B_ACNTB	3	0,00%				100,00%			0,00%	
B_ACNTB_BMNN	3	0,00%			0,00%	0,00%	0,00%		0,00%	
B_AERCC_URNQ	2	100,00%								
B_BCTRD_FRGL	20	0,00%			0,00%	100,00%	0,00%	0,00%		
B_CMPYL_JEJN	1									
B_CRYNB	10	75,00%			100,00%	100,00%	100,00%			
B_CRYNB_STRT	6	0,00%								
B_CRYNB_TBRC	1				0,00%		0,00%			
B_CTBCTR_ACNS	1	100,00%			100,00%	100,00%	100,00%	100,00%		
B_CTRBC	2	0,00%			0,00%	0,00%	0,00%	100,00%		100,00%
B_CTRBC_FRND	6	0,00%			0,00%	0,00%	0,00%	60,00%	0,00%	60,00%
B_CTRBC_KOSR	3	0,00%			0,00%	100,00%	0,00%	100,00%		100,00%
B_DRMBC_HMNS	1				100,00%		100,00%			
B_EKNLL_CRRD	1					100,00%				
B_ENTRBC_CLOC	23	0,00%			0,00%	0,00%	0,00%	75,00%	0,00%	100,00%
B_ENTRC	20				66,70%	66,70%	66,70%	40,00%		
B_ENTRC_AVIM	2	0,00%								
B_ENTRC_CSSL	1				100,00%	100,00%	100,00%	100,00%	0,00%	0,00%
B_ENTRC_FACM	21	0,00%	0,00%	0,00%	0,00%	7,10%	0,00%	5,60%	0,00%	0,00%
B_ENTRC_FCLS	39				100,00%	100,00%	100,00%	100,00%	0,00%	0,00%
B_ESCHR_COLI	467	0,00%			50,00%	86,90%	50,00%	94,50%	97,60%	97,20%

RPC, Resonance Patient Center (ResonanceHealth.org); R statistical package (www.R-project.org).

Center with the integrated AMR package in the statistical programming language "R" overcomes all three disadvantages of a general antibiogram and saves time (Figure 5). In future work, the integrated decision support will consider any past infections that have been documented and prior antimicrobial therapy received by the patient that could predispose them to infection by a resistant organism *(23-26)*.

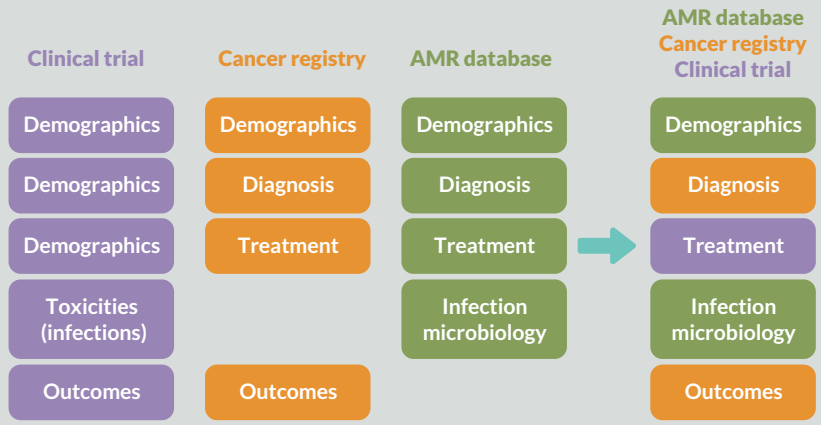
Integrated software available at no cost to manage cancer, microbiology, infectious disease and outcome data

To overcome the difficulties and costs highlighted in the introduction, Resonance Patient Center includes R integration so that it can take advantage of R packages and other open-source tools to support clinical care and hospital operations. Data entered into Resonance Patient Center can be automatically transferred to the R statistical system to run any number of open-source packages with distinct functionality. In the case of AMR (R), the R package processes microbiology data and automatically produces the antibiogram. It is an example of a multi-use information system that can serve as a cancer registry, clinical trials management

Figure 6: An automatically generated patient-centred antibiogram leverages data from Resonance Patient Center or other information systems to produce customized antibiograms based on relevant patient-specific criteria

RPC, Resonance Patient Center (ResonanceHealth.org).

Figure 7: Multi-use integrated information systems improve efficiency and data quality



Integrated information systems facilitate the use of research data to support clinical care and clinical data to inform research. Used with permission of Scott C Howard

system, microbiology system and antibiogram generator, thanks to native functionality plus integration of key open-source packages (Figure 6). The R project for statistical computing and free software downloads can be found at https://www.r-project.org or by using the version integrated into Resonance Patient Center at ResonanceHealth.org. These integrations allow for a multi-use integrated system that improves efficiency, avoids the need for duplicate data entry and decreases the probability of data errors (Figure 7).

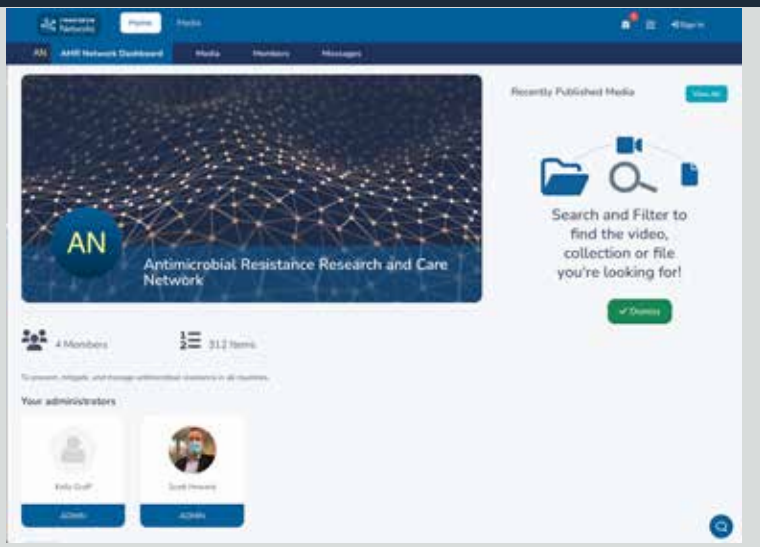
Education, training, and networking facilitate research and quality improvement

The International Society for Pediatric Oncology (SIOP) Global Health Network (GHN) convenes health-care professionals and researchers to improve outcomes for children with cancer in all countries. Because of the critical role infection control plays in children with cancer, the SIOP GHN Supportive Care Working Group (https://siop-online.org/supportive-care-working-group/) is co-chaired by Miguela Caniza, an infectious diseases expert focusing on children with cancer. The recently-established Antimicrobial Resistance Research and Care Network (https://networks.resonancehealth.org/networks/amr-network, Figure 8) was modeled after the Global Neuroblastoma Network (https://networks.resonancehealth.org/networks/gnn), which brings together health-care professionals and researchers from LMICs and HICs to discuss difficult-to-manage patients, quality improvement opportunities, best practices, supportive care and protocol development *(28)*. The goal is to provide a forum for both research and care that combines the strengths and experience of health-care professionals, researchers, government, non-profit organizations and members of civil society.

Integration with the health system and future directions

We have described an integrated information system to facilitate real-time detection of AMR and production a patient-specific antimicrobiogram to guide individual therapy. This effort not only improves care at the individual and facility level, but creates data assets that can be rolled up to the national and international level, as in the case of WHO GLASS, and combined with other data assets, such as those of hospital-based and national cancer registries. Several free software systems are available to support cancer registration. The addition of micriobiological data to all cancer registry software platforms and training of data entry personnel to manage patient-level micriobiological information could support real-time analysis of resistance patterns. The addition of the open-source R package to produce antibiograms based on the data opens the door to real-time production of patient-specific antibiograms that can deliver decision support to users of the system that allows them to select the most appropriate antibiotic for each patient based on their cancer type and recent clinical history *(23-26)*. The Resonance Patient Center already includes this integration, but ongoing development is focused on improvements to the user interface and adaptation

Figure 8: Antimicrobial Resistance Research and Care Network



Available at https://networks.resonancehealth.org/networks/amr-network

to mobile devices for point-of-care use. Country- and site-specific lists of available antibiotics will also be needed to avoid recommending antibiotics that are not accessible.

Conclusions

Information systems that integrate data from oncology registries and clinical microbiology facilitate prevention and management of AMR in immunosuppressed and myelosuppressed patients receiving anticancer therapy. Applying such integrated information to daily clinical care can reduce toxic death from infection and potentially reduce relapse caused by interruptions in anticancer therapy during treatment of infections. ■

Professor Scott C Howard is a paediatric oncologist, epidemiologist, and information scientist who specializes in oncology supportive care and programme development in low- and middle-income countries. His research uses integrated information systems and networks of experts to streamline health care and research. He founded Resonance (ResonanceHealth.org) to amplify health everywhere through research, education, and technology, and established the Global Neuroblastoma Network and Acute Leukemia Research and Care Network, where AMR is frequently discussed.

Dr Miguela A Caniza is a paediatrician and infectious disease specialist with two decades of experience improving the standards for prevention and care of infections in immunocompromised children at St. Jude Children's Research Hospital, where she directs the Global Infectious Diseases Programme to improve the standards of prevention and care of infections in children worldwide. She completed her paediatric residency in New York; and Paediatric Infectious Diseases fellowship at Duke University Medical Center.

Ryan Combs is the Vice President of Analytics at Resonance, where he develops and deploys the Resonance Patient Center analytics platform to support analytics and data management for research studies and patient care. He works with the research, education, and technology teams at Resonance to create integrated solutions for clinicians and other stakeholders involved in research and patient care.

Aman Patel serves as Chief Technology Officer for Resonance, where he leads teams that develop software for clinical research, quality improvement, medical records, learning information management, and networking. He has extensive experience architecting and developing web applications and systems, including the St. Jude PeCan Pediatric Cancer data portal with decision support and clinical tools to visualize genomic data sets. He has a Master of Computer Science from the University of Memphis.

Dr Ligia Fu completed medical and paediatric haematology training at the Universidad Nacional Autónoma de Honduras and Instituto Nacional de Pediatría in Mexico City. She has 22 years of experience caring for children with cancer in Honduras and directs the Leukaemia Programme and Retinoblastoma Programme. Ligia is an active member of AHOPCA, MISPHO, SLAOP and SIOP and Chief of the Paediatric Oncology Ward in Hospital Escuela, Tegucigalpa, Honduras.

Jennifer A Lowe is the Vice President of Clinical Research at Resonance, where she develops and executes global clinical research and health impact research efforts. She has extensive experience in paediatric oncology and capacity building in low- and middle-income countries, and a keen interest in access to care research. She completed her Fulbright Research Fellowship and MSc Public Health for Development thesis on access to care for paediatric oncology patients in India.

Catherine G Lam is a paediatric haematologist/oncologist dedicated to applying health systems science and policy research to improve outcomes for children with cancer and catastrophic diseases globally. Dr Lam directs the Health Systems Unit and Asia Pacific Regional Programme at St Jude Children's Research Hospital, as well as the WHO Collaborating Centre for Childhood Cancer established at St Jude in 2018. She is a Commissioner in the Lancet Commission on Cancer and Health Systems.

References

1. Gudiol C, Albasanz-Puig A, Cuervo G, Carratala J. Understanding and Managing Sepsis in Patients With Cancer in the Era of Antimicrobial Resistance. *Front Med (Lausanne)* 2021;8:636547.
2. Armitage R, Nellums LB. Cancer treatment, infection and antimicrobial resistance. *Public Health* 2021;190:e16-e7.
3. Jung SM, Kim YJ, Ryoo SM, et al. Cancer patients with neutropenic septic shock: etiology and antimicrobial resistance. *Korean J Intern Med* 2020;35:979-87.
4. Vahedian-Ardakani HA, Moghimi M, Shayestehpour M, Doosti M, Amid N. Bacterial Spectrum and Antimicrobial Resistance Pattern in Cancer Patients with Febrile Neutropenia. *Asian Pac J Cancer Prev* 2019;20:1471-4.
5. Fazeli H, Moghim S, Zare D. Antimicrobial Resistance Pattern and Spectrum of Multiple-drug-resistant Enterobacteriaceae in Iranian Hospitalized Patients with Cancer. *Adv Biomed Res* 2018;7:69.
6. Cardoso NT, Santos BA, Barbosa AV, Superti SV, Teixeira LM, Neves FP. Serotypes, antimicrobial resistance and genotypes of Streptococcus pneumoniae associated with infections in cancer patients in Brazil. *Diagn Microbiol Infect Dis* 2017;87:281-5.
7. See I, Freifeld AG, Magill SS. Causative Organisms and Associated Antimicrobial Resistance in Healthcare-Associated, Central Line-Associated Bloodstream Infections From Oncology Settings, 2009-2012. *Clin Infect Dis* 2016;62:1203-9.
8. Murata S, Mushino T, Hosoi H, et al. Real-time monitoring of antimicrobial use density to reduce antimicrobial resistance through the promotion of antimicrobial heterogeneity in a haematology/oncology unit. *J Antimicrob Chemother* 2015;70:2661-4.
9. El-Mahallawy HA, Hassan SS, El-Wakil M, Moneer MM, Shalaby L. Increasing Antimicrobial Resistance Monitored in Surveillance Analysis of Blood Stream Infections in Febrile Neutropenic Pediatric Oncology Patients. *Asian Pac J Cancer Prev* 2015;16:5691-5.
10. Bhattacharya S, Goel G, Mukherjee S, Bhaumik J, Chandy M. Epidemiology of antimicrobial resistance in an oncology center in eastern India. *Infect Control Hosp Epidemiol* 2015;36:864-6.
11. Gudiol C, Bodro M, Simonetti A, et al. Changing aetiology, clinical features, antimicrobial resistance, and outcomes of bloodstream infection in neutropenic cancer patients. *Clin Microbiol Infect* 2013;19:474-9.
12. Bow EJ. Fluoroquinolones, antimicrobial resistance and neutropenic cancer patients. *Curr Opin Infect Dis* 2011;24:545-53.
13. Alexander S, Pole JD, Gibson P, et al. Classification of treatment-related mortality in children with cancer: a systematic assessment. *Lancet Oncol* 2015;16:e604-10.
14. Caniza MA, Odio C, Mukkada S, et al. Infectious complications in children with acute lymphoblastic leukemia treated in low-middle-income countries. *Expert Rev Hematol* 2015;8:627-45.
15. WHO. Global action plan on antimicrobial resistance. 2015.
16. WHO. Monitoring and evaluation of the global action plan on antimicrobial resistance: framework and recommended indicators. 2019.
17. WHO. Comprehensive Review of the WHO Global Action Plan on Antimicrobial Resistance - Volume 1 Report. 2021.
18. Lam CG, Howard SC, Bouffet E, Pritchard-Jones K. Science and health for all children with cancer. *Science* 2019;363:1182-6.
19. Howard SC, Zaidi A, Cao X, et al. The My Child Matters programme: effect of public-private partnerships on paediatric cancer care in low-income and middle-income countries. *Lancet Oncol* 2018;19:e252-e66.
20. Chantada G, Lam CG, Howard SC. Optimizing outcomes for children with non-Hodgkin lymphoma in low- and middle-income countries by early correct diagnosis, reducing toxic death and preventing abandonment. *Br J Haematol* 2019;185:1125-35.
21. Gavidia R, Fuentes SL, Vasquez R, et al. Low socioeconomic status is associated with prolonged times to assessment and treatment, sepsis and infectious death in pediatric fever in El Salvador. *PLoS One* 2012;7:e43639.
22. Gupta S, Bonilla M, Gamero M, Fuentes SL, Caniza M, Sung L. Microbiology and mortality of pediatric febrile neutropenia in El Salvador. *J Pediatr Hematol Oncol* 2011;33:276-80.
23. Luz C. Data Science for Infection Management and Antimicrobial Stewardship. PhD thesis, University of Groningen 2021.
24. C BMLCFASBACG. AMR - An R Package for Working with Antimicrobial Resistance Data. Journal of Statistical Software. *J Statistical Software* 2021.
25. Berends M. A New Instrument for Microbial Epidemiology: Empowering Antimicrobial Resistance Data Analysis. PhD thesis, University of Groningen 2021.
26. Team RC. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2022.
27. Xu R, Polk RE, Stencel L, et al. Antibiogram compliance in University HealthSystem Consortium participating hospitals with Clinical and Laboratory Standards Institute guidelines. *Am J Health Syst Pharm* 2012;69:598-606.
28. Matthay KK, Hylton J, Penumarthy N, et al. Global Neuroblastoma Network: An international multidisciplinary neuroblastoma tumor board for resource-limited countries. *Pediatr Blood Cancer* 2022;69:e29568.

Dr Zipporah Ali, Palliative Care Physician and Public Health Specialist

"The effectiveness of antimicrobials is decreasing due to the rapid rise of drug-resistant pathogens. Antimicrobial resistance (AMR) or drug resistance is a global public health issue that must be addressed urgently. The toll this silent pandemic is taking on cancer patients cannot be overlooked. Antimicrobial medicines are crucial in the treatment of cancer. However, the rise in drug-resistant infections is causing treatment delays, extended stays in hospitals and unnecessary deaths due to infection. This must stop!

The rise in AMR is due to several factors, including excessive use and misuse of antimicrobials. One factor is the sale of antimicrobials over the counter (OTC). This is an issue in many countries, where a sale without a prescription, although not legal, happens very often.

Increasing awareness and educating the public on this issue is a vital step. Along with this, addressing the issue of clinicians who tend to overprescribe is also important. We need stronger regulatory mechanisms to address OTC sales of antimicrobials (including antibiotics), and to share best practices and encourage training among the health-care community to ensure appropriate and prudent use of these medicines."

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Conserving antibiotics

Antimicrobial stewardship and optimizing antimicrobial use in the cancer community

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DEBORAH TONG


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Infections are common in people with cancer. Broad-spectrum antimicrobial use predisposes cancer patients to unintended negative consequences such as drug-resistant infections. Antimicrobial stewardship programmes promote the responsible use of antimicrobials to help improve patient outcomes and mitigate antimicrobial resistance. Tools are available to support the implementation of integrated antimicrobial stewardship activities at national and health-care facility levels. Select antimicrobial stewardship interventions are supported by evidence for safety and efficacy in cancer patients and could be prioritized.

Effective antimicrobials play a crucial role in preventing and treating infections in people with cancer. Treatment-related agranulocytosis and stem cell transplantation increase the risk, frequency and severity of infection, especially in those with haematologic malignancies and neutropenia *(1)*. Repeated and prolonged contact with health-care settings, breaches in anatomical barriers and surgery also increase the risk of infection in cancer patients. A person with cancer is three times more likely to die from a fatal infection than a person without cancer *(2)*, with approximately half of all deaths in patients with underlying haematological malignancies or solid organ tumours estimated to be infection-related *(3)*.

Broad-spectrum antimicrobials are often prescribed for both prophylaxis and empirical therapy in cancer patients. While this has been shown to reduce morbidity and mortality in patients with chemoradiation-induced neutropenia *(4)*, alterations to the microbiome related to broad-spectrum antimicrobial use is associated with adverse drug reactions, colonization and infection with multidrug-resistant (MDR) organisms and reduced clinical response to some cancer treatment options *(5)*. Antimicrobial therapy prescribed in haematology and oncology patients is not always considered appropriate and concordant with guidelines *(6)*, thereby exposing this vulnerable population to unnecessary unintended negative consequences of antimicrobial use.

In particular, the emergence and increase in drug-resistant infections, largely driven by antimicrobial misuse and overuse, threatens the ability to treat cancer safely and effectively. It is estimated that 27% of pathogens causing post-chemotherapy infections are resistant to standard prophylactic antibiotics in the United States (7). Infections caused by drug-resistant *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa* and *Enterobacter spp.* (ESKAPE), were associated with increased persistence of bacteraemia, metastatic infection and early case-fatality rate in cancer patients *(8)*. Thirty-day survival was significantly lower in patients with haematological diseases undergoing chemotherapy who had MDR Gram-negative bloodstream infections than those who had infections caused by non-MDR organisms *(9)*. The detrimental effects of drug-resistant infections in people with cancer, together with the anticipated rise in both the prevalence and impact of cancer and antimicrobial resistance (AMR), and their interaction, warrants antimicrobial stewardship (AMS) interventions as a critical part of care for people with cancer.

The World Health Organization (WHO) defines AMS as a coherent set of integrated actions which promote the responsible and appropriate use of antimicrobials to help improve patient outcomes across the continuum of care *(10)*. AMS, including the integrated approach to strengthening governance, improving access to and regulation of antimicrobials, raising awareness about AMR, strengthening infection prevention measures and surveillance of AMR and antimicrobial use, is a key strategy to prevent the emergence and spread of AMR *(10)*.

WHO guidance is available to assist in the implementation of

integrated AMS programmes at the national *(10)* and health-care facility levels *(11)*, which can be used by programme managers and policy-makers dealing with cancer as well as oncologists providing clinical care. Assessment tools evaluate AMS preparedness based on essential national and health-care facility core elements and assist in the development of stepwise implementation and monitoring plans *(10)*. The governance and accountability of AMS programmes should be clearly defined and agreed upon, including identification of leadership commitment and oversight, as well as designation of an AMS committee, including with representation from haematology/oncology *(11)*. Due consideration and planning should be given for the human, financial and information technology resources required for AMS activities for cancer patients. Resources could also be leveraged through effectively engaging with relevant stakeholders and partners at all levels.

Tailored local AMS interventions are central to improving antimicrobial prescribing and use and clinical outcomes among cancer patients. Special attention should be given to overprescribing of broad-spectrum antimicrobials, the use of unnecessary combination therapy and inappropriate antimicrobial regimens, particularly antimicrobial treatment with the wrong choice, dose, route or duration *(11)*. There should be a clear linkage of AMS with early diagnosis of infectious diseases by improving microbiology laboratory services. Similarly, infection prevention and control services tailored for cancer patients in health-care facilities and in their communities are crucial. Including cancer patients in the surveillance of health-care-associated infections and AMR is an important step towards mitigating the impact of drug-resistant infections among cancer patients.

The WHO AWaRe classification of antibiotics is a tool designed to support AMS efforts *(12)*. Antibiotics are classified into three groups, Access, Watch and Reserve, based on the impact of different antibiotic agents and classes on AMR and the importance of their appropriate use. At the health-care facility level, the AWaRe classification could be used as a basis for formulary restrictions, to prioritize antibiotics for audit and feedback and for setting targets for antibiotic consumption. The AWaRe classification does not group other antimicrobials, such as antifungals and antivirals, which are often used for prophylaxis and treatment in cancer care regimens, and these should be incorporated into AMS programmes wherever possible.

Barriers exist in implementing AMS interventions in people with cancer because of the high risk of infection and subsequent mortality rates. People with cancer are also often excluded from studies evaluating AMS interventions. Treatment guidelines help prescribers select initial therapy and lead to improved, standardized care for common infectious diseases and form the cornerstone of AMS programmes *(11)*. Guidelines and clinical pathways for empirical treatment of febrile neutropenia and management of sepsis have been shown to improve outcomes, including antimicrobial use *(13,14)* and mortality (*14,15)*. These should be based on national antimicrobial guidelines and informed by local epidemiology of bloodstream and other infections, with regular audit and feedback to ensure compliance.

Prospective audit and feedback, the real-time assessment of antibiotic prescriptions for choice, dose, dosing interval, route and duration, with feedback on ways in which one or more of these areas can be improved, is key to advancing AMS interventions for cancer patients *(11)*. Such interventions could include ceasing glycopeptides in patients with febrile neutropenia who do not have evidence of Gram-positive infection or recommending antimicrobials based on previous colonization with MDR organisms *(16)*. Prospective audit and feedback reduce targeted antimicrobial use in the haematology/oncology setting *(17)*, but more studies are required to determine the impact of this intervention type on patient outcomes.

International guidelines have varying recommendations for de-escalation, the change from an antimicrobial to a narrower-spectrum antimicrobial, and duration of empirical therapy for febrile neutropenia. Early de-escalation or discontinuation of antimicrobials prior to neutrophil recovery in adults with cancer decreases the use of broad-spectrum antibiotics without having adverse clinical impacts *(18)*. Similarly, de-escalation of empirical antibiotic therapy for sepsis in oncology patients did not result in adverse clinical events *(19,20)*, although further studies are needed to determine the safety of doing so in haematology patients.

Antibiotic allergy assessments, which include evaluation of allergy history, graded challenges and de-labelling as appropriate, assist in maximizing the number of antimicrobial agents, including narrower-spectrum agents and those with less propensity for resistance, available for prevention and treatment of infections. In people with cancer, penicillin skin tests and oral drug provocation have been shown to be safe and lead to greater use of penicillin-based antibiotics *(21,22)*.

The safety and efficacy of other AMS interventions require further research in people with cancer. Similarly, much of the existing evidence for the safety and efficacy of antimicrobial stewardship interventions in people with cancer are focused on improving the prescribing and use of antibiotics, and further studies are required to evaluate antifungal and antiviral stewardship activities in this population. Various process and outcome measures can be used to evaluate the impact of AMS activities on antibiotic prescribing and use, as well as clinical and patient outcomes *(11)*, with the need especially urgent

in people with cancer in order to demonstrate the safety and effectiveness of interventions.

The cancer community is a key stakeholder and plays a central role in tackling AMR at all levels. Institutions and health-care professionals providing cancer care, as well as people with cancer and their caregivers, should champion and contribute to the planning, implementation and monitoring of integrated AMS activities. These efforts will optimize the use of antimicrobials and help strengthen the evidence base in the haematology/oncology setting, improve patient outcomes, mitigate AMR and preserve the effectiveness of antimicrobials. ■

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References

1. Nanayakkara AK, Boucher HW, Fowler Jr VG, et al. Antibiotic resistance in the patient with cancer: escalating challenges and paths forward. *CA Cancer J Clin.* 2021;71:488-504.
2. Zheng Y, Chen Y, Yu K, et al. Fatal infections among cancer patients: a population-based study in the United States. *Infect Dis Ther.* 2021;10(2):871-95.
3. Zembower TR. Epidemiology of infections in cancer patients. *Cancer Treat Res.* 2014;161:43-89.
4. Viscoli C, on behalf of the EORTC International Antimicrobial Therapy Group. Management of infection in cancer patients: studies of the EORTC International Antimicrobial Therapy Group (IATG). *Eur J Cancer.* 2002;38(Suppl. 4):82-7.
5. Ghanem S, Kim CJ, Dutta D, et al. Antimicrobial therapy during cancer treatment: Beyond antibacterial effects. *J Intern Med.* 2021;290:40-56.
6. Douglas AP, Hall L, James RS, et al. Quality of inpatient antimicrobial use in hematology and oncology patients. *Infect Control Hosp Epidemiol.* 2021;42(10):1235-44.
7. Teillant A, Gandra S, Barter D, et al. Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study. *Lancet Infect Dis.* 2015;15:1429-1437.
8. Bodro M, Gudiol C, Garcia-Vidal C, et al. Epidemiology, antibiotic therapy and outcomes of bacteremia caused by drug-resistant ESKAPE pathogens in cancer patients. *Support Care Cancer.* 2014;22:603-610.
9. Scheich S, Weber S, Reinheimer C, et al. Bloodstream infections with gram-negative organisms and the impact of multidrug resistance in patients with hematological malignancies. Ann Hematol. 2018;97:2225-2234.
10. World Health Organization (WHO). WHO policy guidance on integrated antimicrobial stewardship activities. Geneva: WHO, 2021.
11. World Health Organization (WHO). Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries. A practical toolkit. Geneva: WHO, 2019.
12. World Health Organization (WHO). 2021 AWaRe classification. 2021 (https://www.who.int/publications/i/item/2021-aware-classification, accessed July 2022).
13. Madran B, Keske Ş, Tokça G, et al. Implementation of an antimicrobial stewardship program for patients with febrile neutropenia. *Am J Infect Control.* 2018;46(4):420-4.
14. Thursky K, Lingaratnam S, Jayarajan J, et al. Implementation of a whole of hospital sepsis clinical pathway in a cancer hospital: impact on sepsis management, outcomes and costs. *BMJ Open Qual.* 2018;7:e000355.
15. Rosa RG, Goldani LZ, dos Santos RP. Association between adherence to an antimicrobial stewardship program and mortality among hospitalised cancer patients with febrile neutropaenia: a prospective cohort study. *BMC Infect Dis.* 2014;14:286.
16. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* 52(4);e56-93.
17. So M, Mamdani MM, Morris AM, et al. Effect of an antimicrobial stewardship programme on antimicrobial utilisation and costs in patients with leukaemia: a retrospective controlled study. *Clin Microbiol Infect.* 2018;24(8):882-8.
18. Pillinger KE, Bouchard J, Withers ST, et al. Inpatient antibiotic stewardship interventions in the adult oncology and hematopoietic stem cell transplant population: a review of the literature. *Ann Pharmacother.* 2020;54(6):594-610.
19. Mokart D, Slehofer G, Lambert J, et al. De-escalation of antimicrobial treatment in neutropenic patients with severe sepsis: results from an observational study. *Intensive Care Med.* 2014;40(1):41-9.
20. Paskovaty A, Pastores SM, Gedrimaite Z, et al. Antimicrobial de-escalation in septic cancer patients: is it safe to back down? *Intensive Care Med.* 2015;41:2022-3.
21. Trubiano JA, Grayson ML, Phillips EJ, et al. Antibiotic allergy testing improves antibiotic appropriateness in patients with cancer. *J Antimicrob Chemother.* 2018;73:3209-11.
22. Trubiano JA, Smibert O, Douglas A, et al. The safety and efficacy of an oral penicillin challenge program in cancer patients: a multicenter pilot study. *Open Forum Infect Dis.* 2018;5:ofy306.

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

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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. ■

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References

1. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet.* 2022;399(10325):629-55.
2. Scheich S, Weber S, Reinheimer C, Wichelhaus TA, Hogardt M, Kempf VAJ, et al. Bloodstream infections with gram-negative organisms and the impact of multidrug resistance in patients with hematological malignancies. *Ann Hematol.* 2018;97(11):2225-34.
3. Cattaneo C, Di Blasi R, Skert C, Candoni A, Martino B, Di Renzo N, et al. Bloodstream infections in haematological cancer patients colonized by multidrug-resistant bacteria. *Ann Hematol.* 2018;97(9):1717-26.
4. Sulis G, Sayood S, Katukoori S, Bollam N, George I, Yaeger LH, et al. Exposure to World Health Organization's AWaRe antibiotics and isolation of multidrug resistant bacteria: a systematic review and meta-analysis. *Clin Microbiol Infect.* 2022.
5. Almagor J, Temkin E, Benenson I, Fallach N, Carmeli Y, consortium D-A. The impact of antibiotic use on transmission of resistant bacteria in hospitals: Insights from an agent-based model. *PLoS One.* 2018;13(5):e0197111.
6. Ulrich N, Vonberg RP, Gastmeier P. Outbreaks caused by vancomycin-resistant Enterococcus faecium in hematology and oncology departments: A systematic review. *Heliyon.* 2017;3(12):e00473.
7. Delgado A, Reveles IA, Cabello FT, Reveles KR. Poorer outcomes among cancer patients diagnosed with Clostridium difficile infections in United States community hospitals. *BMC Infect Dis.* 2017;17(1):448.
8. Pillinger KE, Bouchard J, Withers ST, Mediwala K, McGee EU, Gibson GM, et al. Inpatient Antibiotic Stewardship Interventions in the Adult Oncology and Hematopoietic Stem Cell Transplant Population: A Review of the Literature. *Ann Pharmacother.* 2020;54(6):594-610.
9. Wilson BE, Routy B, Nagrial A, Chin VT. The effect of antibiotics on clinical outcomes in immune-checkpoint blockade: a systematic review and meta-analysis of observational studies. *Cancer Immunol Immunother.* 2020;69(3):343-54.
10. Yu Y, Zheng P, Gao L, Li H, Tao P, Wang D, et al. Effects of Antibiotic Use on Outcomes in Cancer Patients Treated Using Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis. *J Immunother.* 2021;44(2):76-85.
11. Chambers LM, Kuznicki M, Yao M, Chichura A, Gruner M, Reizes O, et al. Impact of antibiotic treatment during platinum chemotherapy on survival and recurrence in women with advanced epithelial ovarian cancer. *Gynecol Oncol.* 2020;159(3):699-705.
12. World Health Organization. Global Action Plan on Antimicrobial Resistance 2015.
13. Sharland M, Gandra S, Huttner B, Moja L, Pulcini C, Zeng M, et al. Encouraging AWaReness and discouraging inappropriate antibiotic use-the new 2019 Essential Medicines List becomes a global antibiotic stewardship tool. *Lancet Infect Dis.* 2019;19(12):1278-80.
14. Klein EY, Milkowska-Shibata M, Tseng KK, Sharland M, Gandra S, Pulcini C, et al. Assessment of WHO antibiotic consumption and access targets in 76 countries, 2000-15: an analysis of pharmaceutical sales data. *Lancet Infect Dis.* 2021;21(1):107-15.
15. Bagger K, Nielsen AB, Siersma V, Bjerrum L. Inappropriate antibiotic prescribing and demand for antibiotics in patients with upper respiratory tract infections is hardly different in female versus male patients as seen in primary care. *Eur J Gen Pract.* 2015;21(2):118-23.
16. World Health Organization Model List of Essential Medicines - 22nd List, 2021. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/345533, accessed 5 July 2022).
17. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis.* 2018;18(3):318-27.
18. Tawfick MM, Alshareef WA, Bendary HA, Elmahalawy H, Abdulall AK. The emergence of carbapenemase blaNDM genotype among carbapenem-resistant Enterobacteriaceae isolates from Egyptian cancer patients. *Eur J Clin Microbiol Infect Dis.* 2020;39(7):1251-9.
19. Perez F, Adachi J, Bonomo RA. Antibiotic-resistant gram-negative bacterial infections in patients with cancer. *Clin Infect Dis.* 2014;59 Suppl 5:S335-9.
20. World Health Organization. Implementation manual to prevent and control the spread of carbapenem-resistant organisms at the national and health care facility level. 2019.
21. Yahav D, Tau N, Shepshelovich D. Assessment of Data Supporting the Efficacy of New Antibiotics for Treating Infections Caused by Multidrug-resistant Bacteria. *Clin Infect Dis.* 2021;72(11):1968-74.
22. World Health Organization. Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries. *A practical toolkit.* 2019.

Sonali Johnson, Head of Knowledge, Advocacy and Policy, Union for International Cancer Control

"Antimicrobial resistance (AMR) is a huge threat to cancer care. In order to improve cancer care outcomes, appropriate and timely treatment for infections is crucial. The causes of AMR most often discussed are overuse and the irrational use of medicines due to bad prescribing practices, and lack of diagnostics. These are very important aspects of addressing AMR. However, the issue of substandard or falsified medicines is sometimes overlooked and needs the same attention. Substandard, falsified and poor-quality medicines are also an important driver of AMR. According to the World Health Organization, antimalarials and antibiotics are amongst the most commonly reported substandard and falsified medical products and an estimated 1 in 10 medical products in low- and middle-income countries are substandard or falsified. This is an unacceptable situation with dangerous consequences for the medical community and for people living with cancer, and needs to be addressed through actions such as strengthening regulatory systems, improving access to quality-assured medicines, improving supply chain barriers and improving awareness of the scale of the problem in governments and with patient education."

Sonali Johnson is Head of Knowledge, Advocacy and Policy at the Union for International Cancer Control (UICC). Her main area of work is to ensure that cancer prevention, treatment, and care is positioned within the global health and development agenda, including plans for Universal Health Coverage. During her professional career, Sonali has worked on a range of public health issues including cancer control, gender and HIV/AIDS, reproductive and sexual health, gender-based violence, knowledge translation, research ethics and health and human rights.

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mHealth and a blended learning approach to antimicrobial stewardship in Abia State: A case study

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The inappropriate use of antibiotics both in health facilities and in the community contributes to the rising prevalence of antimicrobial resistance (AMR) globally *(1)*. AMR often affects cancer patients more because of their compromised immunity. Infections with drug-resistant organisms are known to be associated with poor clinical and economic outcomes in drug therapy *(2,3)*. Up to 22% of Nigerian health-care providers misuse antibiotics in the treatment of malaria, while 46% of parents wrongly use antibiotics for upper respiratory tract infections *(3)*. The use of mobile applications for health (mHealth) as part of antimicrobial stewardship programmes (ASP) to support antibiotics decisions by clinicians is beneficial, but this practice is not common in Nigeria *(4)*. This case study describes the innovative use of mHealth, blended for a multidisciplinary ASP initiative in Nigeria.

The Abia Cancer Control Group (ACCG), a consortium of clinicians, hospitals, academics and non-governmental organizations, has been leading efforts to improve outcomes for cancer patients locally. Using their successful model of an online cancer reporting system, ACCG collaborated with Canadian Firstline to deploy the Abia Antibiotic Guidelines. This provided point-of-care information on antibiotic choices to clinicians. The guidelines were developed by a multidisciplinary team including physicians, pharmacists, nurses and laboratory scientists. Also, the group developed the android-based *Bugs n Drugs* mobile application to report antimicrobial susceptibility testing (AST) from local laboratories and to document antibiotic prescriptions from clinicians.

Bugs n Drugs was developed following extensive testing by local clinical and laboratory experts. Data from the app were designed to be used in creating a local antibiogram that would inform the antimicrobial recommendations provided through Firstline. Before the development of B*ugs n Drugs*, the only publicly available software to document AST was the WHO Windows-based WHONET software. The use of WHONET was limited in Nigeria as it was desktop-based and required a stable power supply to operate sustainably, as compared to the smartphone-based *Bugs n Drugs*.

Following the deployment of Firstline and Bugs n Drugs, ACCG organized a multidisciplinary, asynchronous, blended learning course to train clinicians on antimicrobial stewardship and how to use the apps. The online component was delivered through Google Classroom while in-person workshops were organized to practise clinical skills relevant to ASP. Standardized patients were used during the workshops to simulate different clinical conditions, such as upper respiratory tract infections during cancer treatment. This approach helped providers to improve their competence and confidence in making antibiotic-related decisions, as well as master the use of both applications. Course participants self-registered from across Nigeria.

Outcome

Data from 160 patients, with an average age of 34.82 (±15.45) years and mostly from the outpatient setting (85%, 136/160), were used in the pilot project. Organisms with high susceptibility (i.e. ≥50%) were *N. gonorrhoea* (Cephalexin = 100%), *E. coli* (Ampicillin-cloxacillin = 50%) and *S. aureus* (Erythromycin = 50%). Figure 1 shows the pattern of resistance.

Antibiotics with the widest spectrum of cumulative sensitivity were Amoxicillin-Clavulanate (i.e. Augmentin, six out of eight organisms) and Levofloxacin (five out of eight organisms). With the support of Firstline, the proportion of participants who chose to prescribe antibiotics for upper respiratory tract infections or malaria decreased by 22% and 18%, respectively, as shown by the trendline in Figure 2.

Discussion

This project sought to empower participants with knowledge and tools that will improve ASP in Abia State. The results showed that the mHealth approach involving Firstline and *Bugs*

Figure 1: Trends in resistance by drug classification in Abia State

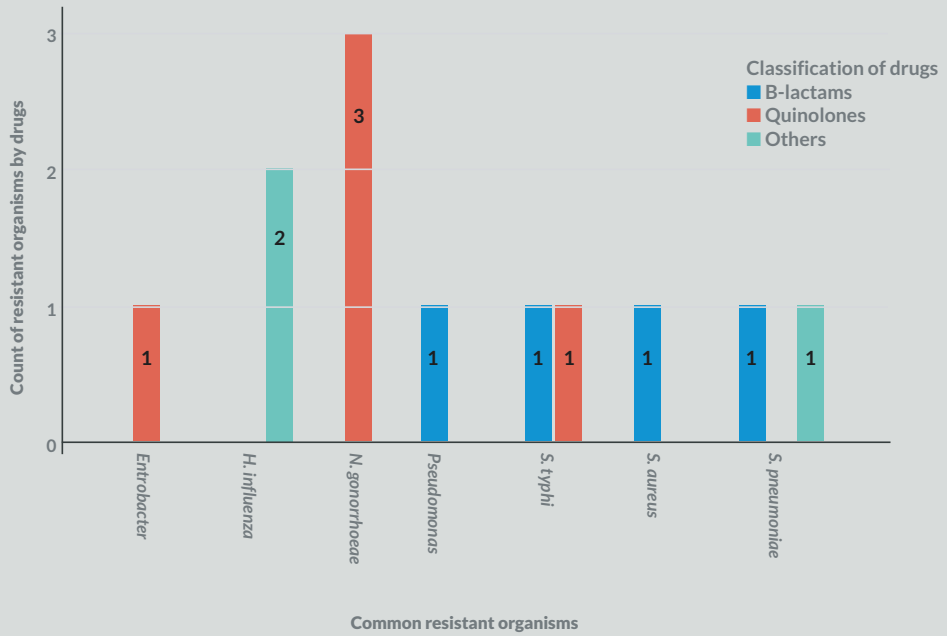
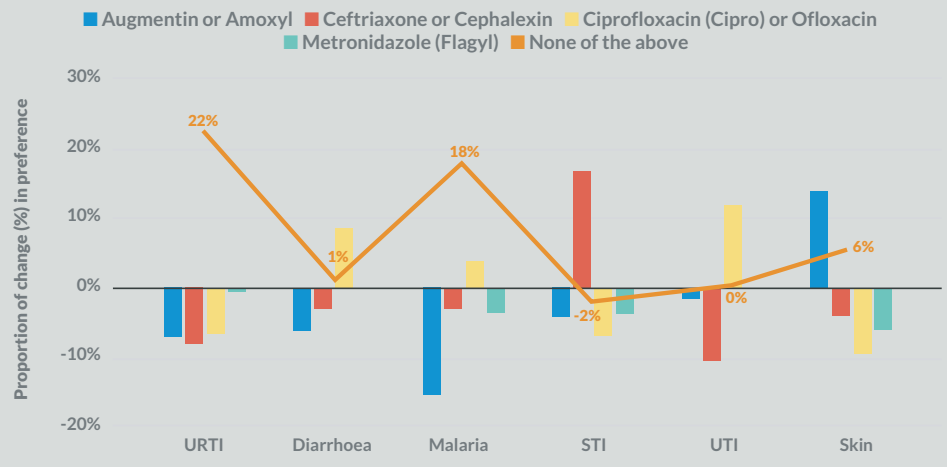


Figure 2: Change in antibiotics preference for common conditions, Abia 2020



STI, sexually transmitted infection; URTI, upper respiratory tract infection; UTI, urinary tract infection.

n Drugs helped to improve the pattern of appropriate antibiotic use by health-care providers. Collaborative community engagement is being used to expand the use of *Bugs n Drugs* and Abia antibiotic guidelines through Firstline. Funding is required to sustain this innovative project. ■

References

1. Yevutsey S, Buabeng K, Aikins M, et al. Situational analysis of antibiotic use and resistance in Ghana: policy and regulation. *BMC Public Health*. 2017;17(1):1-7.
2. Fadare J, Ogunleye O, Iliyasu G, et al. Status of antimicrobial stewardship programmes in Nigerian tertiary healthcare facilities: Findings and implications. *Journal of Global Antimicrobial Resistance*. 2019;17:132-136.
3. Nnah K, Eguzo K, Akpanudo U, et al. Using Blended-Learning Approach to Improve Education on Antimicrobial Stewardship for Healthcare Providers in Abia State (Nigeria): Study Protocol. *The Nigerian Journal of Pharmacy*. 2021;55(2):7-14.
4. Helou R, Foudraine D, Catho G, Peyravi LA, Verkaik N, Verbon A. Use of stewardship smartphone applications by physicians and prescribing of antimicrobials in hospitals: A systematic review. *PLoS One*. 2020;15(9): e0239751

Useful links

- Abia Antimicrobial Guidline on Firstline: https://app.firstline.org/en/clients/297-nigerian-christian-hospital or https://bit.ly/3zHM7hZ
- Abia Antimicrobia Guideline download link: https://drive.google.com/file/d/12ysV1k7ePSyD-p9HOJre6QQZMOfRvXkt/view?usp=sharing
- *Bugs n Drugs* App: https://play.google.com/store/apps/details?id=com.majoriebash.bugsndrugs or https://bit.ly/3biSFub

Dr Zisis Kozlakidis, Head of Laboratory Services and Biobanking, International Agency for Research on Cancer, World Health Organization (IARC/WHO)

"Without a shift in our policies, current estimates anticipate a major increase in cancer mortality globally, and particularly in resource-restricted settings. Effective cancer control must include raising awareness of the causes of cancer, effective prevention strategies for those identified causes, as well as early detection, coupled with access to effective treatments and palliative care.

Ensuring access to timely and appropriate cancer treatment includes access to antimicrobials to address infections. Especially as cancer patients are at a higher risk of infections due to the lowering of immune responses; for example, due to certain blood cancers and/or resulting from their treatment, such as chemotherapy. Thus, infections in cancer patients are a common occurrence, often resulting in multiple treatments with antibiotics, often also to the development of antimicrobial resistance (AMR).

When looking at resource-restricted settings, it becomes clear that in such contexts, cancer patients are suffering from a double bottleneck in terms of timely diagnoses, both for the cancer types as well as for microbial pathogens. Unfortunately, there is a great paucity of data, as clinical microbiology laboratories might exist in isolated pockets of excellence or be altogether absent – and at different localities to cancer centres. Therefore, while there is a wide consensus, as led by the UICC and the Wellcome Trust, that increasing AMR poses a threat to the improvement of cancer patient outcomes, the evidence tends to be weak. IARC, through the BCNet (https://bcnet.iarc.fr/), is promoting the education and standardization of laboratory and biobanking practices in resource-restricted settings, skills that are directly relevant to clinical laboratory activities of any scale, such as distal clinical microbiology units enabled via the Minilab (https://fondation.msf.fr/en/projects/mini-lab), or through greater collaborations of existing vertical surveillance structures."

Dr Zisis Kozlakidis is the Head of Laboratory Services and Biobanking at the International Agency for Research on Cancer, World Health Organization (IARC/WHO). He is responsible for one of the largest and most varied international collections of clinical samples in the world, focusing on gene–environment interactions and disease-based collections. This WHO infrastructure supports multinational efforts in making treatments possible and delivering these to resource-restricted settings. Dr Kozlakidis has significant expertise in the field of biobanking and has served as President of ISBER, and as board member.

Countering the AMR challenge

Diagnostics: An essential tool to combat the ongoing pandemic of antimicrobial resistance

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CECILIA FERREYRA


BIRGITTA GLEESON


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Diagnostics can play a key role in ensuring that existing and future antimicrobials are used rationally and appropriately to prevent the development and spread of antimicrobial resistance (AMR). This can only be achieved through the development and use of affordable diagnostics, especially for low- and middle-income countries. This article looks at the role of diagnostics in preventing AMR, the priorities for developing new diagnostic tools for rational antimicrobial use and for surveillance, and how this impacts on cancer treatment.

The World Health Organization (WHO) has declared antimicrobial resistance (AMR) to be one of the top 10 global health threats facing humanity *(1)*. By any rational scale, we are in the midst of an AMR pandemic; according to recent estimates, 4.95 million deaths were associated with bacterial AMR globally in 2019, 1.27 million of which were directly attributable to resistance *(2)*. The incidence of AMR is projected to increase over time, with annual cases of multidrug-resistant (MDR) bloodstream infections and pneumonia predicted to rise from 5.4 million in 2020 to 8.3 million by 2040 *(3)*. There is an urgent need to ensure that existing and future antimicrobials are used rationally and appropriately to prevent the further development and spread of AMR *(4)*. This can only be achieved through the development and use of affordable diagnostics.

In addition to guiding treatment decisions, diagnostics are also central to AMR surveillance. Accurate tracking of the spread of AMR locally and nationally is important to guide decision-making at every level of a health system from primary care management to national public health measures.

However, the availability of diagnostic tests needed for antimicrobial stewardship (AMS) and AMR surveillance is limited *(5)*. This is especially true for tests suitable for use in low- and middle-income countries (LMICs), where the burden of AMR is highest *(2)*. With drug-resistant infections on the rise, and the list of available treatments decreasing, there is an urgent need for investment in diagnostics to prevent the further development of AMR and to protect new antimicrobials in development. Gaps and priorities for AMR diagnostic development are summarized below and in Figure 1.

Role of diagnostics in preventing AMR

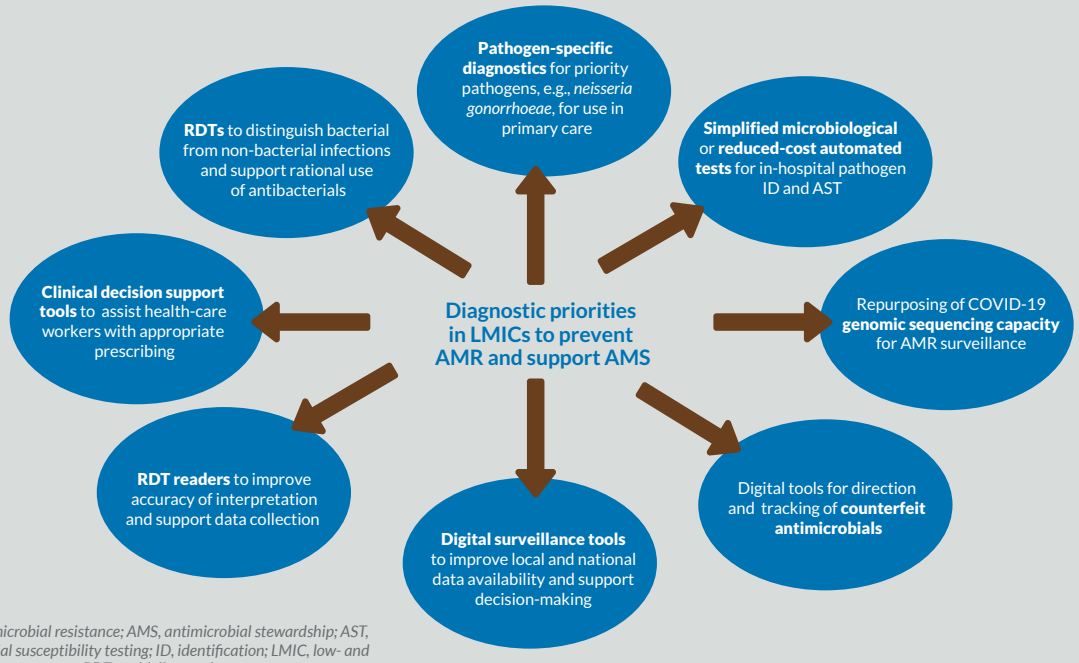
Empiric prescription frequently leads to misuse or overuse of antibiotics, which drives AMR development. Appropriate use of antibiotics requires an evidence-based approach based on the causative pathogen. Diagnostic tools that can determine the nature of the infection, for example, whether it is bacterial or viral, or identify the specific pathogen, are essential to reducing misuse and decreasing the overall demand for antimicrobials. Furthermore, in patients with antimicrobial-resistant infections, determining the resistance profile of a pathogen is key to selecting the most appropriate antibiotic, optimizing patient outcomes, and preventing the further development and spread of resistance. Diagnostics that can determine the susceptibility of an infection-causing pathogen to different antimicrobial agents form the core of this approach.

Gaps and priorities for AMR diagnostic development

Diagnostics to ensure rational use of antibiotics

Acute febrile illnesses (AFI), particularly in young children, represent a major global disease burden *(6)*. Determining the cause of the illness is often challenging, as signs and symptoms tend to be highly non-specific, with considerable overlap between bacterial and non-bacterial causes *(7)*. The emergence of SARS-CoV-2 has also confounded differential diagnoses. In many LMICs, diagnosis is further complicated by the presence of endemic malaria and dengue fever as possible causative agents *(7,8)*. Furthermore, diagnosis of AFI in LMICs often takes place at the community level, where health-care workers may have limited access to diagnostic tools, as well as training and experience. As such, misuse and overuse of antimicrobials in patients with AFI is common *(9)*.

Figure 1: Gaps and priorities for AMR diagnostic development



AMR, antimicrobial resistance; AMS, antimicrobial stewardship; AST, antimicrobial susceptibility testing; ID, identification; LMIC, low- and middle-income country; RDT, rapid diagnostic test

Rapid diagnostic tests (RDTs) are easy-to-use diagnostics that are affordable, have short turnaround times, and can be used at the point of care (POC). RDTs can play a key role in evidence-based prescribing at the community level. The widespread implementation of malaria RDTs, for example, has substantially reduced the consumption of antimalarial drugs *(10)*. A rapid POC diagnostic that can differentiate bacterial from non-bacterial infections would enable health-care workers to move beyond empirical treatment of AFI *(6,11)*. To date, however, development of such a test has proven challenging. Although tests that measure host biomarkers, such as C-reactive protein and procalcitonin, are often used in clinical practice to indicate a bacterial infection, studies suggest that these biomarkers perform poorly in LMICs, since they may also be elevated in common non-bacterial diseases, including malaria, severe dengue fever and COVID-19 *(6,12–15)*.

Support for health-care workers in diagnosing, treating and managing AFI and other infections is provided through guidelines such as the Integrated Management of Childhood Illness (IMCI), a tool developed by WHO and UNICEF that consists of numerous clinical algorithms and training materials for the diagnosis and management of illness in children under five years of age. Digitized versions of such tools, known as electronic clinical decision-support algorithms (eCDA), can combine an individual's health information with the health-care worker's knowledge and clinical protocols to assist with treatment decisions *(16)*, and have been shown to increase adherence to clinical guidelines *(17)*. When POC diagnostic tests are included in the algorithms, eCDA can lead to reduced over-prescription of antibiotics *(18)*. Approaches comprising validated, evidence-based eCDAs combined with POC diagnostics would provide a powerful tool to prevent AMR.

Another disease area in which enhanced diagnostics are urgently needed to support AMS is sexually transmitted infections (STIs) *(19)*. Gonorrhoea, caused by the bacterium *Neisseria gonorrhoeae*, is the second most common bacterial STI, with an estimated annual global burden of 87 million cases *(20)*. The bacterium has progressively developed resistance to the majority of available antibiotics, with failures to last-line treatment reported in several countries *(21)*. Currently, a syndromic approach to the diagnosis of STIs has been used, especially in LMICs, to decide the treatment course *(22)*. However, with increasing rates of AMR, there is a need to move away from the currently used syndromic approach to the use of specific diagnostics to ensure targeted antibiotic treatment. Although molecular tests for *N. gonorrhoeae* are available, they require significant infrastructure, resources and equipment, and are not suitable for use in LMICs *(19)*. Diagnostic tests for *N. gonorrhoeae* that can be used at the primary care level in LMICs are urgently needed *(19,22)*.

Treatment of MDR infections requires identification of the causative pathogen and determination of its antimicrobial susceptibility or resistance profile. In high-income settings, this can be achieved with nucleic acid-based molecular testing such as polymerase chain reaction (PCR) tests. However, in low-

income settings, cost and resource constraints limit the use of such tests.

Severely ill, hospitalized patients with MDR bloodstream infections or pneumonia, including adults and neonates, harbour a large proportion of the burden of MDR *(3)*, and the bacteria responsible for the majority of these infections are classed as "critical" or "high" in the WHO priority pathogen list for the development of new antibiotics *(23)*. Many patients acquire these infections whilst hospitalized *(24)*. There is a need for simplified microbiological diagnostic technologies, such as blood culture systems, or price reductions for existing automated systems, to support rational use of antibiotics in people with MDR infections in LMICs. A single test that can quickly detect these critical pathogens and perform antibiotic susceptibility testing at the hospital level in LMICs could significantly improve outcomes for hospitalized patients and reduce the spread of MDR organisms.

AMR surveillance and data collection

The WHO Global AMR and Use Surveillance System (GLASS) fosters global surveillance of AMR and antimicrobial consumption to inform AMR containment strategies *(25)*. A key component of GLASS is surveillance at the national level. However, AMR data from LMICs are limited, in part because databases are fragmented across different health-care centres such as hospitals, universities and the private sector, and across veterinary and agricultural sources *(26,27)*. Digital platforms that can aggregate AMR data from these numerous sources could help to build capacity for surveillance at all levels. In particular, robust local surveillance would enable better use of actionable data at the hospital level, allowing early detection and response to outbreaks of health-care-associated MDR infections, and can be used to inform local empiric treatment guidelines. Notably, capacity for genomic sequencing in many LMICs has been substantially increased in response to the COVID-19 pandemic, as it is required to track the emergence of new SARS-CoV-2 variants. This capacity has enormous potential to be repurposed for the surveillance of drug-resistant pathogens. Before sequencing can be routinely implemented, a large body of work remains to fully elucidate and characterize the phenotypic and genotypic AMR profiles of infection-causing bacteria.

In the meantime, low-cost tests such as RDTs also have the potential to reduce antimicrobial consumption, however, they present challenges for data collection. Results from RDTs, if collected at all, are commonly filed on paper, from which collation and interpretation may be more challenging, leading to a high risk of error and loss of data *(28)*. This can be prevented through the use of digital readers, which can enhance the accuracy of the interpretation of the RDT results, as well as transmitting the results to local and national databases. Cost and technological requirements often prohibit their use in LMICs, but devices with limited hardware requirements, for example, smartphone apps that utilize the camera for photographic analysis, are under development and could represent a giant leap in data management *(28)*.

AMR diagnostics and cancer

Empiric antibiotics are frequently prescribed to patients with cancer, especially those undergoing immunosuppressive chemotherapies, since any delay in treatment can lead to poor outcomes *(30)*. Because time is of the essence, and the differential diagnosis of possible infecting pathogens is often wide, broad-spectrum antibiotics are frequently given. While logical, this approach may foster AMR, which is of consequence both to the individual under treatment, who often undergoes multiple rounds of chemotherapy and antimicrobial treatment for infectious complications, and the community at large. In the absence of AMR surveillance data in LMICs, empiric treatment guidelines may not be adequate enough to successfully treat the infection. Diagnostics for AMR may be of particular value in this population to ensure appropriate treatment and prevent further development of resistance. In LMICs, where the burden of AMR is already high, the incidence of cancer is rising *(31)*. AMR diagnostics appropriate for use in LMICs will therefore become increasingly important for cancer management.

Conclusions

Diagnostics are an essential component of AMS programmes, yet numerous gaps in the availability of AMR diagnostics exist. Investment in development of diagnostics must be urgently accelerated to prevent further development of AMR and to protect the efficacy of existing and future antimicrobials. ■

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Birgitta Gleeson is a scientist working with the Antimicrobial Resistance (AMR) Team at FIND since 2021. The focus of her work is in preventing AMR by developing and improving diagnostic systems in low- and middle-income countries. Prior to joining FIND, Birgitta spent a number of years working with Médecins Sans Frontières implementing health system strengthening projects in Afghanistan, Uzbekistan. Birgitta holds a PhD in Medicine from University College Cork, Ireland and MSc in Immunology and Global Health.

Dr Daniel Bausch, MD, MPH&TM, FASTMH is the Senior Director of Emerging Threats and Global Health Security at FIND. He leads FIND`s efforts on pandemic preparedness and response. He is trained in internal medicine, infectious diseases, tropical medicine, and public health. Dr Bausch specializes in the research and control of emerging tropical. Previously, he served as Director of the United Kingdom's Public Health Rapid Support team (2017–21), to respond and conduct research to prevent and control outbreaks of dangerous infectious diseases around the world. He has also held posts at WHO in Geneva, Switzerland; US Naval Medical Research Unit No. 6 in Lima, Peru; Tulane School of Public Health and Tropical Medicine in New Orleans, USA; and the US Centers for Disease Control and Prevention in Atlanta, USA. In addition to his role at FIND, Dr Bausch is a Professor of Tropical Medicine at the London School of Hygiene and Tropical Medicine and is the current President of the American Society of Tropical Medicine and Hygiene.

References

1. World Health Organization (WHO). Antimicrobial resistance 2021 [Available from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance accessed 19 May 2022.
2. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 2022 doi: 10.1016/S0140-6736(21)02724-0 [published Online First: 2022/01/24]
3. Global AMR R&D Hub. Estimating Global Patient Needs and Market Potential for Priority Health Technologies Addressing Antimicrobial Resistance. 2021. https://globalamrhub.org/our-work/studies/market-potential-and-priority-patient-needs/ (accessed 03 February 2022)
4. Laxminarayan R. The overlooked pandemic of antimicrobial resistance. *Lancet* 2022 doi: 10.1016/S0140-6736(22)00087-3 [published Online First: 2022/01/24]
5. World Health Organization (WHO). Landscape of diagnostics against antibacterial resistance, gaps and priorities. 2019. https://apps.who.int/iris/handle/10665/326480 (accessed 23 May 2022)
6. Leticia Fernandez-Carballo B, Escadafal C, MacLean E, et al. Distinguishing bacterial versus non-bacterial causes of febrile illness - A systematic review of host biomarkers. *The Journal of infection* 2021;82(4):1-10. doi: 10.1016/j.jinf.2021.01.028 [published Online First: 2021/02/22]
7. Crump JA, Morrissey AB, Nicholson WL, et al. Etiology of severe non-malaria febrile illness in Northern Tanzania: a prospective cohort study. *PLoS Negl Trop Dis 2013*;7(7):e2324. doi: 10.1371/journal.pntd.0002324 [published Online First: 2013/07/23]
8. Nkenfou CN, Fainguem N, Dongmo-Nguefack F, et al. Enhanced passive surveillance dengue infection among febrile children: Prevalence, co-infections and associated factors in Cameroon. *PLoS Negl Trop Dis 2021*;15(4):e0009316. doi: 10.1371/journal.pntd.0009316 [published Online First: 2021/04/17]
9. Fink G, D'Acremont V, Leslie HH, et al. Antibiotic exposure among children younger than 5 years in low-income and middle-income countries: a cross-sectional study of nationally representative facility-based and household-based surveys. *The Lancet Infectious Diseases 2020*;20(2):179-87. doi: 10.1016/S1473-3099(19)30572-9 [published Online First: 2019/12/18]
10. D'Acremont V, Kahama-Maro J, Swai N, et al. Reduction of anti-malarial consumption after rapid diagnostic tests implementation in Dar es Salaam: a before-after and cluster randomized controlled study. *Malar J 2011*;10:107. doi: 10.1186/1475-2875-10-107 [published Online First: 2011/05/03]
11. Dittrich S, Tadesse BT, Moussy F, et al. Target Product Profile for a Diagnostic Assay to Differentiate between Bacterial and Non-Bacterial Infections and Reduce Antimicrobial Overuse in Resource-Limited Settings: An Expert Consensus. *PloS one 2016*;11(8):e0161721. doi: 10.1371/journal.pone.0161721 [published Online First: 2016/08/26]
12. Wilairatana P, Mahannop P, Tussato T, et al. C-reactive protein as an early biomarker for malaria infection and monitoring of malaria severity: a meta-analysis. *Sci Rep 2021*;11(1):22033. doi: 10.1038/s41598-021-01556-0 [published Online First: 2021/11/13]
13. Khetpal A, Godil A, Alam MT, et al. Role of C- reactive proteins and liver function tests in assessing the severity of dengue fever. J Pak Med Assoc 2021;71(3):810-15. doi: 10.47391/JPMA.170 [published Online First: 2021/06/01]
14. Yitbarek GY, Walle Ayehu G, Asnakew S, et al. The role of C-reactive protein in predicting the severity of COVID-19 disease: A systematic review. *SAGE Open Med 2021*;9:20503121211050755. doi: 10.1177/20503121211050755 [published Online First: 2021/10/19]
15. Hu R, Han C, Pei S, et al. Procalcitonin levels in COVID-19 patients. *Int J Antimicrob Agents 2020*;56(2):106051. doi: 10.1016/j.ijantimicag.2020.106051 [published Online First: 2020/06/14]
16. Pelle KG, Rambaud-Althaus C, D'Acremont V, et al. Electronic clinical decision support algorithms incorporating point-of-care diagnostic tests in low-resource settings: a target product profile. *BMJ Global Health 2020*;5(2):e002067. doi: 10.1136/bmjgh-2019-002067 [published Online First: 2020/03/18]
17. Sarrassat S, Lewis JJ, Some AS, et al. An Integrated eDiagnosis Approach (IeDA) versus standard IMCI for assessing and managing childhood illness in Burkina Faso: a stepped-wedge cluster randomised trial. *BMC Health Serv Res 2021*;21(1):354. doi: 10.1186/s12913-021-06317-3 [published Online First: 2021/04/18]
18. Keitel K, Kagoro F, Samaka J, et al. A novel electronic algorithm using host biomarker point-of-care tests for the management of febrile illnesses in Tanzanian children (e-POCT): A randomized, controlled non-inferiority trial. *PLoS Med 2017*;14(10):e1002411. doi: 10.1371/journal.pmed.1002411 [published Online First: 2017/10/24]
19. Ferreyra C, Osborn J, Moussy F, et al. Developing target product profiles for Neisseria gonorrhoeae diagnostics in the context of antimicrobial resistance: An expert consensus. *PloS one 2020*;15(9):e0237424. doi: 10.1371/journal.pone.0237424 [published Online First: 2020/09/02]
20. Rowley J, Vander Hoorn S, Korenromp E, et al. Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. *Bull World Health Organ* 2019;97(8):548-62P. doi: 10.2471/BLT.18.228486 [published Online First: 2019/08/07]
21. Wi T, Lahra MM, Ndowa F, et al. Antimicrobial resistance in Neisseria gonorrhoeae: Global surveillance and a call for international collaborative action. *PLoS Med* 2017;14(7):e1002344. doi: 10.1371/journal.pmed.1002344 [published Online First: 2017/07/08]
22. Wi TE, Ndowa FJ, Ferreyra C, et al. Diagnosing sexually transmitted infections in resource-constrained settings: challenges and ways forward. *J Int AIDS Soc 2019*;22 Suppl 6:e25343. doi: 10.1002/jia2.25343 [published Online First: 2019/08/31]
23. World Health Organization (WHO). WHO publishes list of bacteria for which new antibiotics are urgently needed 2017 [Available from: https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed accessed 19 May 2022]
24. Maki G, Zervos M. Health Care-Acquired Infections in Low- and Middle-Income Countries and the Role of Infection Prevention and Control. *Infect Dis Clin North Am 2021*;35(3):827-39. doi: 10.1016/j.idc.2021.04.014 [published Online First: 2021/08/08]
25. World Health Organization (WHO). Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report 2021 [Available from: https://www.who.int/publications/i/item/9789240027336 accessed 14 June 2021]
26. Iskandar K, Molinier L, Hallit S, et al. Surveillance of antimicrobial resistance in low- and middle-income countries: a scattered picture. *Antimicrob Resist Infect Control 2021*;10(1):63. doi: 10.1186/s13756-021-00931-w [published Online First: 2021/04/02]
27. Gandra S, Alvarez-Uria G, Turner P, et al. Antimicrobial Resistance Surveillance in Low- and Middle-Income Countries: Progress and Challenges in Eight South Asian and Southeast Asian Countries. *Clin Microbiol Rev 2020*;33(3) doi: 10.1128/CMR.00048-19 [published Online First: 2020/06/12]
28. Kadam R, White W, Banks N, et al. Target Product Profile for a mobile app to read rapid diagnostic tests to strengthen infectious disease surveillance. P*loS one 2020*;15(1):e0228311. doi: 10.1371/journal.pone.0228311 [published Online First: 2020/01/30]
29. Kelesidis T, Falagas ME. Substandard/counterfeit antimicrobial drugs. *Clin Microbiol Rev 2015*;28(2):443-64. doi: 10.1128/CMR.00072-14 [published Online First: 2015/03/20]
30. Gudiol C, Albasanz-Puig A, Cuervo G, et al. Understanding and Managing Sepsis in Patients With Cancer in the Era of Antimicrobial Resistance. *Front Med (Lausanne)* 2021;8:636547. doi: 10.3389/fmed.2021.636547 [published Online First: 2021/04/20]
31. Torre LA, Siegel RL, Ward EM, et al. Global Cancer Incidence and Mortality Rates and Trends-An Update. *Cancer Epidemiol Biomarkers Prev 2016*;25(1):16-27. doi: 10.1158/1055-9965.EPI-15-0578 [published Online First: 2015/12/17]

The AMR challenge – Perspectives from the life science industry

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Without action, we risk losing effective antibiotics which could undo decades of medical progress, including in cancer treatment and care, with significant potential impact on cancer patients. Industry leaders, through the AMR Industry Alliance, are actively contributing solutions to ensure antibiotics continue to be a powerful tool in our medical arsenal. This includes investing in research and development for AMR-relevant products, supporting access and stewardship efforts, and addressing the environmental risks from antibiotic manufacturing. No single actor can tackle this challenge on their own. A long-term, sustainable effort is needed from governments and other stakeholders to succeed. Advocacy and support from relevant communities, such as in cancer care, is essential to stimulate and maintain action by governments.

Antimicrobial resistance (AMR) is one of the leading, most pervasive health threats globally. At the end of 2020, the World Health Organization (WHO) designated it as one of 10 global health issues to track *(1)*, right as the deadliest pandemic of our lifetime was unfolding. This year, we were confronted with a reality check. New data revealed AMR to have been directly responsible in 2019 for 1.3 million deaths globally, with close to 5 million deaths associated with AMR *(2)*, much greater than was previously thought. This suggests the burden was previously grossly underestimated, or AMR has spread at a worrying pace in the last five years – or both. If no action is taken, the death toll could rise to 10 million annually by 2050, and result in a US$ 100 trillion global GDP loss *(3)*.

Antibiotics have been a staple in care ever since Alexander Fleming discovered penicillin in 1928. This was a watershed moment for modern medicine. In the decades that followed, we have seen significant innovation and new classes of antibiotics being developed. Further, diagnostic testing has evolved to help optimize the use of antibiotics by identifying the pathogen causing infection and providing susceptibility testing to ensure the right antibiotic is given at the right time.

However, the rules of evolution apply to every living organism on the planet, and bacteria have learned to adapt to our tools. Whenever an antibiotic is used, appropriately or not, resistance can develop. Today, multi-resistant infections pose an increased risk, where, in some cases, no appropriate treatment is available. Industry has been taking a leading role in contributing solutions to slow down the pace of resistance – for example, the use of diagnostics that rapidly identify a pathogen and determine suitable treatment options has helped minimize inappropriate use. Diagnostic tools also support the measurement of drug resistance in health care, providing a warning signal to epidemiologists of impending risks. That is how we have come to know the six leading pathogens responsible for deaths associated with resistance *(2)*.

Additionally, increasing the uptake of existing AMR-relevant vaccines and enabling the development of new ones is a crucial complementary effort in managing the spread of AMR and infectious disease more generally *(4)*. Preventing bacterial infections reduces the opportunities for AMR to develop and reduces antibiotic use, and vaccines against some viral diseases like influenza can also help reduce antibiotic use by reducing opportunities for inappropriate antibiotic prescriptions, as well as preventing potential secondary bacterial infections which would require antibiotic treatment. Collectively, these approaches form critical aspects of antimicrobial stewardship to ensure the antibiotics we have, and those industry is developing, remain viable tools for years to come.

We have come to rely on effective antibiotics being available, and often take them for granted. While the primary role of antibiotics is to treat individual bacterial infections, this is far from their only purpose. Antibiotics are the great enablers of modern medicine. Anything from the simplest procedures, like a tooth extraction, to more complex ones like hip replacement or cancer surgery, rely on antibiotics to prevent infections. This also applies to cancer care – as many as one in five cancer patients will be hospitalized due to an infection at some point during their treatment. However, a recent UK survey of 100 oncologists shows that 95% of them are concerned about the threat of resistant bacteria and the implications on cancer care *(5)*.

Figure 1: Global deaths (counts) attributable to and associated with bacterial resistance by pathogens, 2019

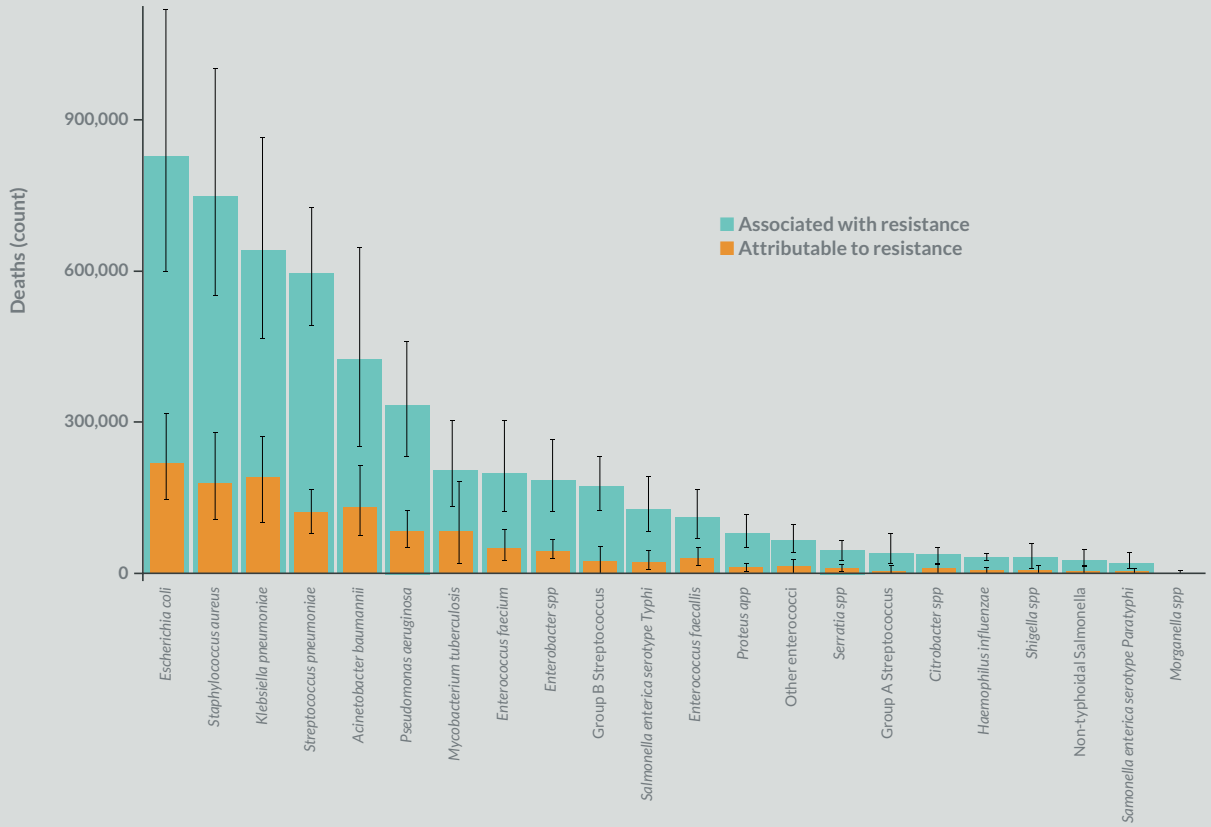

Figure taken from Murray, C., Ikuta, K., Sharara, F., Swetschinski, L., Robles Aguilar, G., & Gray, A. et al. (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet, 399(10325), 629-655. doi: 10.1016/s0140-6736(21)02724-0. Used under CC BY 4.0 license.

Key challenges for developing new antibiotics

Unfortunately, this broad value of antibiotics is generally poorly recognized by health systems. Coupled with a challenging environment and long timelines for research and development (R&D), and prospects of successful innovation not being appropriately recognized, development of new antibiotics has slowed. New antibiotics need to be used extremely sparsely in order to preserve their effectiveness – the more they are used, the more bacteria can develop resistance. But just having them available gives us confidence we will be able to treat patients when necessary – in a way, they are like a fire extinguisher of modern medicine *(6)*. As a result, given the need for good stewardship, the total US sales of the 17 antibiotics approved by the US Food and Drug Administration (FDA) since 2010 was only US$ 714 million, with a median of ~US$ 16 million *(7)*. Even companies that successfully developed an antibiotic in the last few years have had their viability put to question *(8)*, which risks leaving a gap in terms of expertise, skills, and support to patients. Consequently, the pipeline is fragile and widely considered to be insufficient relative to the challenge *(9)*.

Despite these challenges, industry continues to invest in AMR-relevant R&D and has taken a leading role in proposing solutions that would allow a reinvigoration of the pipeline. Members of the AMR Industry Alliance collectively invested US$ 1.8–1.9 billion annually in 2019 and 2020, including in diagnostics *(10)*. Further stepping up to the challenge, in 2020 the biopharmaceutical industry led the establishment of a US$ 1 billion AMR Action Fund, with the aim to bring to market two to four new antibiotics by 2030 *(11)*. In April this year, the Fund announced its first two investments, with plans to commit over US$ 100 million in 2022 alone *(12)*. While the Fund can buy time by bridging the clinical funding gap, it will not solve the fundamental market challenges of antibiotic development. For that, sustainable market-based incentives are needed.

Similarly, the Alliance reported that industry investment levels are threatened if market conditions do not improve. On the other hand, Alliance companies reported plans to increase investment levels in AMR R&D if market conditions improved through the introduction of new policy reforms. In this respect, the most impactful solution would be so-called "pull incentives" *(10)* which reward successful antibiotic development beyond sales volumes. Pull incentives can take on several forms – some of the most commonly discussed ones include lump-sum market entry rewards, subscription-style rewards paid over a period of time, and transferable exclusivity extensions. A recent best estimate has put the globally required reward

at US$ 4.2 billion per antibiotic *(13)* on average, with the aim of providing the developer with an appropriate return on investment that could support further sustained investment into antimicrobial R&D.

Opportunities for new incentives

Pull incentives for antibiotics have been part of the global discussion for many years and have featured in virtually all G7 and G20 communiqués of the last several years, perhaps most notably under G7 UK in 2021 *(14)*. While no effective pull incentive has yet been implemented, some countries are leading the charge. One such intervention, the draft PASTEUR Act in the United States, which proposes a US$ 750 million to US$ 3 billion reward per antibiotic through a subscription model *(15)*, could move the needle significantly if implemented in its current form. The model is sometimes referred to as the "Netflix model", where subscribers pay a fixed annual sum and can watch content regardless of hours. In the case of PASTEUR, such a model would pay out a fixed annual fee over a certain period of years for all the government-procured antibiotics regardless of the volume (i.e. according to need), and based on additional determinants of a given antibiotic's value such as novelty, improving clinical outcomes, targeting priority pathogens, and others. The model is also able to support appropriate stewardship.

In the United Kingdom, a subscription model is already being piloted for two antibiotic products. The pilot is being implemented in England through National Health Service England and is capped at £10 million per product per year. The signing of contracts was announced in June, 2020 *(16)*. Although the pilot was capped, in April 2022, UK National Institute for Health and Care Excellence (NICE) published draft guidance for the two products, which specifically captured the additional societal value of these products, exceeding the initial cap *(17)*. This was achieved by recognizing the additional quality-adjusted life years (QALYs) for the products' incremental net health benefit, accounting for additional value which is captured as STEDI in the United Kingdom *(18)*. Although more work is needed to properly quantify and take into account the broader benefits antibiotics deliver beyond treating individual infections, this is an important first step. While these are positive developments, other countries need to follow suit if we are to be successful. Importantly, we need all of the G7 and the European Union to implement solutions of their own in the next few years. Given the potential impact on cancer care, we welcome a call from the cancer community for the implementation of sustainable solutions to revitalize the ecosystem and ensure that new antibiotics are available in the future. Further, there is a need for increased education and awareness among all key groups impacted.

Broad industry action and way forward

New antibiotics will always be needed and, collectively, we need to do more to ensure that they are developed. The industry is also cognizant that reinvigorating the antibiotic pipeline is not the only AMR-related challenge we face today, despite its utmost importance. Through the AMR Industry Alliance, the life sciences industry works to actively contribute to tackling the challenges of access, improving stewardship globally, and advancing manufacturing practices with respect to the environment, and has been reporting on industry progress since 2018.

To support global access, the Alliance is developing a framework for scaling access to antibiotics and diagnostics in low- and middle-income country (LMIC) hospital settings and developing a sustainability framework for off-patent antibiotics. By developing a set of best practices and clear implementation roadmaps, the Alliance, representing more than 100 biotech, large R&D pharmaceutical, generics, and diagnostics companies, can achieve significant impact.

To ensure that antibiotics are used appropriately, the Alliance has encouraged innovation in stewardship through the 2021 Stewardship Prize, which was again announced for 2022. This programme rewards stewardship programmes in LMICs that have demonstrated their ability to improve the appropriate use of antibiotics, and which can be adopted and scaled up elsewhere to further support stewardship principles. The Alliance is also supporting efforts to understand the barriers to diagnostic use in stewardship programmes in high-resource settings to encourage policy, payment, and product innovations in support of antimicrobial stewardship.

Another area of significant engagement of industry has been to encourage the responsible manufacturing of antimicrobials. Manufacturing is just one of many potential sources of antimicrobials in the environment (alongside normal human and agricultural use). In the production of these medicines, emissions in manufacturing waste streams can increase the selection pressure on bacteria in the environment to develop resistance to the antimicrobials they encounter. Since 2018, in the absence of international standards, the Alliance has been providing clear guidance to manufacturers in the global antibiotic supply chain to ensure that their antibiotics are made responsibly, helping to minimize the risk of the environmental dimension of antimicrobial resistance. In June 2022, the Alliance launched its Antibiotic Manufacturing Standard, which aims to formalize its work to date. An associated certification scheme in partnership with the British Standards Institute is set to follow in 2023 *(19)*.

Industry has an important role to play as a partner and solutions provider in the global fight against AMR. Working together to invest in R&D that meets the global health

needs with new innovative diagnostics and treatments, improving access to high-quality antibiotics and ensuring that new ones are available to all, and working to reduce the development of AMR through improved stewardship are the key commitments of the Alliance members. But, to truly solve the challenge, all stakeholders need to work jointly. While we have seen progress, it has so far been uneven both in terms of geography and policy areas, as shown by the 2021 AMR Preparedness Index *(20)*. Given the impact of AMR on all facets of health care, it is crucial that patients, including those suffering from cancer, health-care professionals and other affected communities have their voices heard. Only then can the full extent of the AMR challenge be properly understood, and action prioritized. ■

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References

1. 10 global health issues to track in 2021. WHO (2020). Accessed 25 July 2022, from https://www.who.int/news-room/spotlight/10-global-health-issues-to-track-in-2021
2. Murray C, Ikuta K, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet*. 2021; 399(10325), 629-655. doi: 10.1016/s0140-6736(21)02724-0
3. O'Neill J. Tackling Drug-Resistant Infections Globally: Final Report and recommendations. *Review on Antimicrobial Resistance* (2016). London: HM Government. doi: 10.1016/j.jpha.2015.11.005 Accessed from: https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf
4. Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance: An Action Framework. WHO (2020). Accessed from: https://cdn.who.int/media/docs/default-source/immunization/product-and-delivery-research/action-framework-final.pdf
5. Effectiveness of Cancer Treatments Threatened by Rising Antibiotic Resistance. Longitude Prize. (2020). Accessed 25 July 2022, from https://longitudeprize.org/resources/effectiveness-of-cancer-treatments-threatened-by-rising-antibiotic-resistance/
6. Rex J. Fire Extinguishers of Medicine. AMR.Solutions. Accessed 25 July 2022, from https://amr.solutions/fire-extinguishers-of-medicine/
7. Outterson K, Orubu E, Rex J, Ardal C, Zaman M. Patient Access in 14 High-Income Countries to New Antibacterials Approved by the US Food and Drug Administration, European Medicines Agency, Japanese Pharmaceuticals and Medical Devices Agency, or Health Canada, 2010-2020 (2021). *Clinical Infectious Diseases* (2022), 74(7), 1183-1190. doi: https://doi.org/10.1093/cid/ciab612.
8. McKenna M. The antibiotic paradox: why companies can't afford to create life-saving drugs. *Nature* 2020. Accessed 26 July 2022, from https://www.nature.com/articles/d41586-020-02418-x
9. 2020 antibacterial agents in clinical and preclinical development: an overview and analysis. WHO (2021). Accessed from https://apps.who.int/iris/bitstream/handle/10665/340694/9789240021303-eng.pdf?sequence=1&isAllowed=y
10. Progress Report. AMR Industry Alliance (2022). Accessed 25 July 2022, from https://www.amrindustryalliance.org/progress-report/
11. Antimicrobial Resistance Research & Development. AMR Action Fund. Accessed 25 July 2022, from https://www.amractionfund.com/
12. AMR Action Fund Announces First Investments in Adaptive Phage Therapeutics and Venatorx Pharmaceuticals (2022). Accessed 25 July 2022, from https://www.prnewswire.com/news-releases/amr-action-fund-announces-first-investments-in-adaptive-phage-therapeutics-and-venatorx-pharmaceuticals-301514936.html
13. Outterson K. Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines. *Health Affairs* (2021), 40(11), 1758-1765. doi: 10.1377/hlthaff.2021.00688
14. G7 Finance Ministers' Statement on Actions to Support Antibiotic Development. Gov. UK (2021). Accessed 25 July 2022, from https://www.gov.uk/government/publications/g7-finance-ministers-statement-on-actions-to-support-antibiotic-development
15. 117th Congress 1st Session-PASTEUR Act. Accessed from BON21821 (senate.gov)
16. NHS lands breakthrough in global battle against superbugs. NHS England (2022). Accessed 25 July 2022, from https://www.england.nhs.uk/2022/06/nhs-lands-breakthrough-in-global-battle-against-superbugs/
17. Models for the evaluation and purchase of antimicrobials. National Institute for Health and Care Excellence. Accessed 25 July 2022, from https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials
18. Outterson K, Rex J. Evaluating for-profit public benefit corporations as an additional structure for antibiotic development and commercialization. *Translational Research* (2020), 220, 182-190. doi: 10.1016/j.trsl.2020.02.006
19. Responsible Manufacturing. AMR Industry Alliance (2022). Accessed 25 July 2022, from https://www.amrindustryalliance.org/shared-goals/common-antibiotic-manufacturing-framework/
20. 2021 AMR Preparedness Index. Global Coalition on Aging (2021). Accessed 25 July 2022, from https://globalcoalitiononaging.com/wp-content/uploads/2021/06/GCOA-AMR-Preparedness-Index_FINAL.pdf

The world needs more antimicrobial innovation to avert a future catastrophe

In 2019, AMR was directly responsible for **1.3 million deaths globally**. Each year, the threat is becoming **more difficult to manage** and the AMR community is aligned – **the current antibiotic pipeline is insufficient relative to the challenge.** Unique dynamics of the antibiotics market now call for unique measures to address them.

The biopharmaceutical industry is playing its part, including by having created the USD 1 billion **AMR Action Fund** to bridge the clinical funding gap and bring to market 2-4 new antibiotics by 2030.

However, without new market incentives to support sustained R&D investment to keep pace with growing resistance, the world risks losing effective antibiotics. This could undo decades of medical progress.

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Improving the lives of cancer patients is inextricably linked to tackling drug resistance

Jennifer Cohn, Rohit Malpani and **Michelle Childs,**
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Bacterial infections are among the leading causes of morbidity and mortality for individuals with cancer. Many infections are resistant to multiple lines of antibiotic treatments. Unfortunately, even as the risks for antimicrobials grow, the current biomedical research and development (R&D) system does not provide sufficient incentives for developing new antibiotics, resulting in a weak pipeline for increasingly resistant bacteria. This article will discuss the barriers that contribute to the lack of antibiotic R&D and access, explore ways to overcome these barriers and describe how the cancer care community can help to contain the rising threat of antimicrobial resistance.

Antimicrobial resistance (AMR) has been called the "silent pandemic," yet to the growing number of those impacted by AMR and its effects it is too evident. This is especially true for those living with conditions, such as cancer, that may put them at higher risk for bacterial infections, particularly those that are resistant to multiple treatments. Infections have a number of serious impacts on individuals and health systems. Bacterial infections are among the leading causes of morbidity and mortality for individuals with cancer *(1)*. Infections may also limit or delay the use of effective drugs that cause immunosuppression, thus increasing the risk of cancer progression or therapy failure. Infections also extend hospital stays – increasing costs for health systems and patients.

If the cancer care community is to succeed in improving outcomes, it must simultaneously address AMR by reducing the risk of acquiring resistant infections and increasing access to safe and effective treatments.

The growing burden of AMR

The burden of AMR is greater than we previously thought. The recent Global Research on AntiMicrobial resistance (GRAM) study revealed that AMR directly caused 1.27 million deaths and was associated with 4.95 million deaths in 2019 *(2)*. This is higher than the number of deaths from HIV/AIDS or malaria worldwide in 2019. The report showed that 70% of deaths that resulted from AMR were caused by resistance to antibiotics, often considered the first line of defence against severe infections. Critically, the GRAM study also found that most of the deaths were caused by six bacterial pathogens and that low- and middle-income countries (LMICs) were hardest hit by AMR, although there is rising resistance across the world.

While various organisms – bacteria, fungi, viruses – can infect those with cancer, bacterial infections are the most common across cancer types *(3,4)*. A variety of factors increase not only the risk of bacterial infections, but of AMR in individuals with cancer. These risks include hospital and health-care exposure, procedures and devices (including long-term intravenous catheters), surgery, immunosuppressive medications, immunosuppression from the cancer itself, particularly in haematologic malignancies, and increased exposure to antibiotics used as treatment or prophylaxis.

Because of the nature of the disease and treatments, those with haematologic malignancies, such as leukaemia and lymphoma, are at particularly high risk for serious bacterial infections. Epidemiologic studies over the last decade performed in the United States and Europe have shown that rates of serious bacterial infections for individuals with haematologic malignancies can be around 80% *(5)*. People with haematologic malignancies, particularly those who need stem cell transplants or whose treatments or disease cause extended periods of neutropenia (when a certain type of white blood cell level is low and thus the individual has a weakened immune system) may also receive antibiotics as prophylaxis. Individuals with solid tumours, such as those with breast, prostate or colon cancer, are also at risk. In one US study of over 37,000 operations, serious post-operative infection for solid tumours occurred in nearly 1

in 10 operations and increased in-hospital deaths 12-fold *(6)*. Many of these infections are resistant to antibiotics *(7)*.

Lack of innovation and lack of access to existing and new antibiotics

As the risks for AMR grow, a range of scientific challenges, as well as the structure of the R&D system that is employed to develop antibiotics, hinders our collective ability to develop innovative antibiotics, resulting in a weak pipeline for increasingly resistant bacteria. This article focuses on how and why the current biomedical R&D system does not provide sufficient incentives for developing new antibiotics, as well as the lack of access to existing and new antibiotics that are brought to market.

There are several reasons that the existing biomedical R&D system is poorly suited to address a pervasive problem such as AMR. First, many of the new antibiotics that are required to target unmet needs have a small target market, and therefore are commercially unattractive. This is because newer antibiotics are often developed to target multidrug-resistant pathogens for which there are few or no effective alternatives, and thus such treatments are used in limited situations to preserve their long-term use and viability.

Second, incentives to pay for R&D, whether through so-called push funding or through pull incentives, may be inadequate to sustain private R&D, which is the prevailing biomedical model to address AMR. Third, even where funding or incentives have been introduced, they may not target the most critical needs, or may not be well designed to overcome the so-called "valley of death" that often delays the development and commercialization of new treatments.

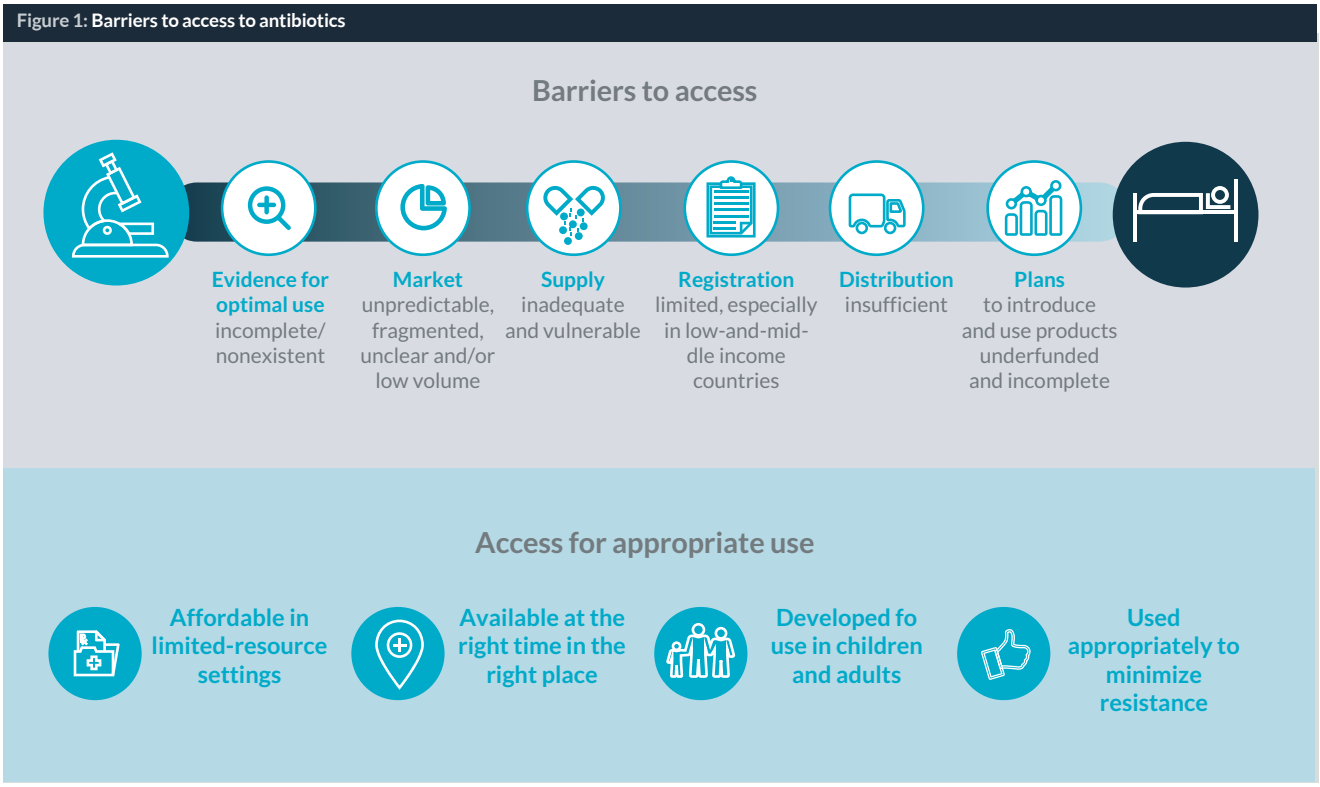
However, even once antibiotics are successfully developed, access is far from a given (Figure 1). A recent study found that the majority of the 18 new antibacterials approved and launched between 2010 and 2020 were accessible in only 3 out of 14 high-income countries (United States, United Kingdom, and Sweden) *(8)*. In LMICs, the problem is even worse. Only 10 of the 25 new antibiotics that entered the market between 1999 and 2014 were registered in more than 10 countries *(9)*. Age, in addition to geography, may create a barrier to access. Paediatric development of novel antibiotics is regularly delayed, which limits treatment options for newborns and children.

Access is not only a challenge for novel antibiotics, but also for older antibiotics that should be readily available for use in all health systems. Presently, there are shortages of older off-patent antibiotics, which due to generic competition may be at prices that are too low to sustain commercial interest. As generic manufacturers diversify their portfolios, the low margins of older antibiotics, especially injectable antibiotics, may result in these manufacturers de-prioritizing or divesting from antibiotic manufacture.

What can be done to improve access?

First, there is a need for a substantial increase in both funding and financing of AMR R&D and access. sThis must be done through both push and pull funding that could help fill empty R&D pipelines and support access to existing and

Figure 1: **Barriers to access to antibiotics**



new treatments. Push mechanisms include grants that can pay for one or all stages of R&D, hybrid investments that combine funding from several sources, including the private sector, or tax incentives that defray costs or "crowd-in" private investment.

While all of these funding channels can accelerate development, funding should be prioritized to address unmet needs and the largest drivers of morbidity and mortality. Such R&D funding must also ensure that it addresses challenges related to access that otherwise emerge when the product is first commercialized. To do so, funders can introduce conditions on such R&D funding that enables access. This can include requirements to license a compound for additional development, manufacture and commercialization by other private, public or not-for-profit entities. It can include requirements for a recipient to assure wide registration in high-burden countries, or to work through mechanisms that facilitate registration, such as those hosted by the World Health Organization (WHO). It can also require transparency, both of data generated through clinical trials and post-marketing surveillance and the prices that may be charged in different countries. More broadly, push funding can help contribute to a wider policy objective, validated by Heads of State through the UN High-Level Declaration on AMR, to separate or fully de-link R&D costs from product prices and high-volume sales. This can accomplish several objectives at once – it can assure access and affordability. It can also avoid or prevent inappropriate use since de-linkage reduces the incentive to increase payment through increasing volumes of sales, which will therefore reduce or eliminate one of the rationales for overuse driven by marketing.

Additionally, pull incentives can complement push funding to ensure that there are means to assist developers, whether private or not-for-profit, to complete development and commercialization of a priority treatment. Several pull incentives that encourage private investment have been proposed, including both substantial prizes (i.e. market entry rewards) that are intended to provide a substantial reward to a developer that successfully registers a new antibiotic that addresses an unmet need. Other pull incentives could also be introduced, such as milestone prizes that can be provided to developers at various stages of clinical development and whose size depends on the stage at which such prizes are provided and what conditions or obligations may be attached to such prizes.

Each pull incentive can both generate opportunities to strengthen access but can also create new challenges. For example, public funding or support for market entry rewards may come with access conditions described above for push funding, and these requirements can ensure a new compound brought to market is available, affordable and used appropriately.

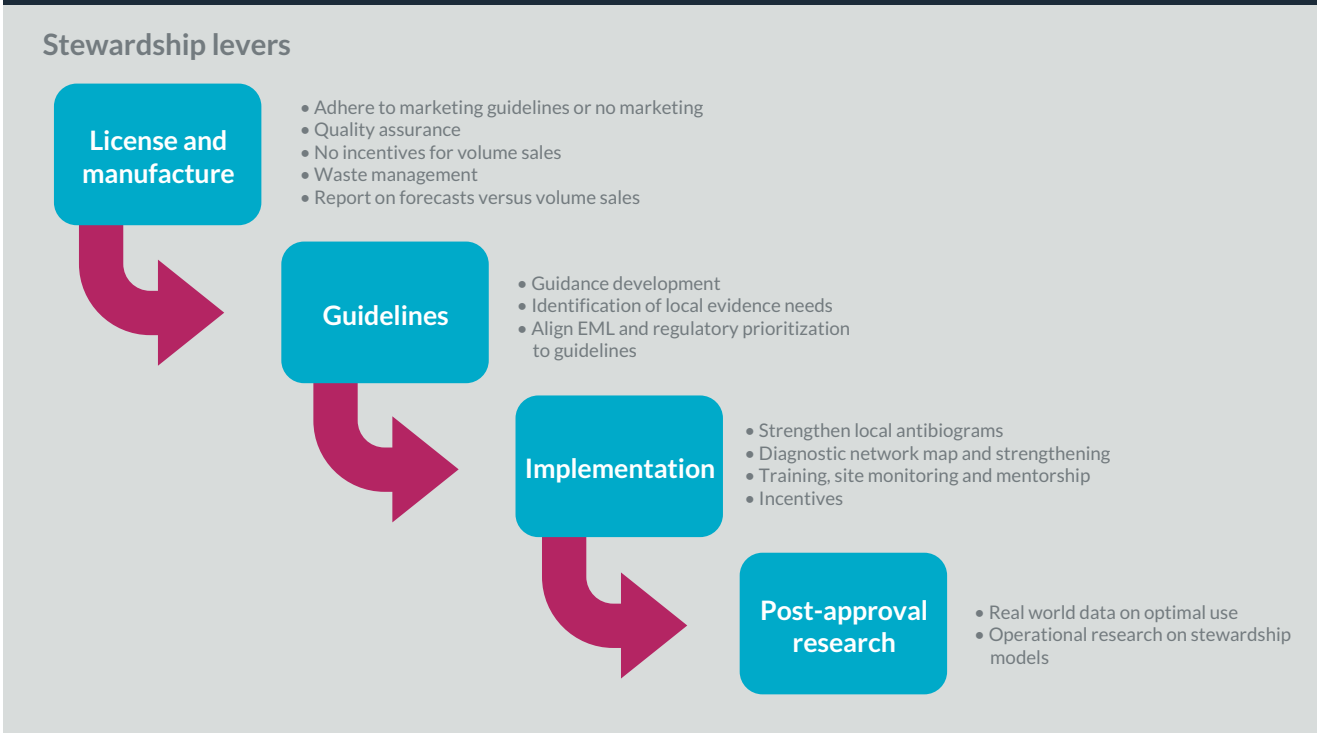
However, there are also access concerns. Various proposals seek to expand market exclusivities for new antibiotics as a means to generate an additional incentive for private companies to develop and introduce new treatments. These measures, such as patent term extensions or data exclusivity, lengthen the term of a monopoly, and therefore may delay the entry of low-cost generic manufacturers who can be better suited to ensure affordability and are often more willing and able to register treatments in LMICs.

A separate proposal currently under consideration, known as a transferable exclusivity voucher, seeks to pay for the development of one health product by providing a recipient with the right to extend the exclusivity on a different health product (or sell such "rights" to a third party). Since this would provide a recipient with additional monopoly rights for another product, it would give the holder the power to charge higher prices for best-selling medicines for a longer period of time. It is likely that such extensions would be applied to cancer medicines, which tend to be some of the most expensive, and best-selling medicines, in most countries with profitable pharmaceutical markets. This approach raises concerns that it could lead to significant costs that may be too high for both governments and householders alike.

According to one study, the cost of one new antibiotic to the European Union, under such a programme, would be US$ 3.2 billion *(10)*. A separate study, through a retrospective analysis of 10 antimicrobials that would have secured such an extension in the United States between 2007 and 2016, concludes that "while market exclusivity extensions are a politically appealing mechanism to encourage novel antibiotic development, this approach would cost public and private payers billions of dollars. Finally, exclusivity extensions do not incentivize improved stewardship of the antibiotic in question" *(11,12)*.

Finally, several countries, especially in Europe, and including the United Kingdom and Sweden, have introduced subscription-based reimbursement models to pay for antibiotics. A subscription-based reimbursement model involves one or more payments to a supplier in exchange for an appropriate supply of drugs to treat a defined population for a determined period. This model has also been called a "Netflix model" and differs from payment based on the volume of drugs sold. These subscriptions treat the provision of an antibiotic as a service and de-link the payment to manufacturers from the number of units sold. An annual fee structure can mean that use is not discouraged by high per unit prices and ensures that manufacturers are not incentivized to encourage greater volumes. The results of these pilots will help to inform future initiatives. Currently, the investment case to apply subscription models to LMICs has not yet been fully developed. Prior to adopting such models, it will be critical to propose models, investigate if these will be feasible in LMICs (and how and why they may differ from those models used in high-income countries) and test them for how they affect sustainable and appropriate access.

Figure 2: : Levers to improve antibiotic stewardship



However, ensuring equitable access across health systems cannot be addressed solely through appropriate push funding and pull incentive mechanisms. Pooled procurement or other types of cooperative purchasing hold promise to reduce buyer fragmentation, increase buying power and lower prices. Lower prices may be due to both increased negotiating power from buyers as well as reduced transactional costs.

Cooperative purchasing can take many forms and may be applied within a given country, region or globally. Access barriers may also be reduced by using regulatory pathways, such as the WHO prequalification collaborative procedure for accelerated registration, or regional regulatory harmonization schemes. Leveraging these regulatory efficiencies may reduce transactional costs, accelerate approval and extend approval to less attractive markets. Additionally, new mechanisms to support governments to forecast demand, register products, assure supply and improve access and appropriate use, are needed. GARDP, working with WHO and other health agencies, is piloting a new partnership, called SECURE, that seeks to support health systems, especially those in LMICs, to meet these needs *(13)*.

Stewardship – the appropriate use of antibiotics to delay or prevent the development of resistance – can be supported across access interventions (Figure 2). Stewardship levers are diverse, but can include tying push or pull incentives to ensuring appropriate manufacturing waste management or adhering to good marketing guidelines. Funding is needed from both public and private health systems to strengthen diagnostic systems and improve stewardship programmes, including human resources devoted to stewardship. Finally, national regulatory bodies can strengthen requirements for post-approval research to fill evidence gaps for optimal use.

Conclusion

The fight to improve the lives of those living with cancer and to improve access to antibiotics to contain AMR are intertwined. The two communities can work together to call on funders, policy-makers, researchers and industry to support robust R&D and appropriate access to new and existing antibiotics. The cancer community is in a powerful position to give a voice to the silent AMR pandemic and ensure that those living with cancer – and other populations – have access to effective antibiotics when they need them. ■

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References

1. Elhadi M, Khaled A & Msherghi A. Infectious diseases as a cause of death among cancer patients: a trend analysis and population-based study of outcome in the United States based on the Surveillance, Epidemiology, and End Results database. *Infect Agents Cancer.* 2021; 16(72). https://doi.org/10.1186/s13027-021-00413
2. The GRAM study (Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet.* 2022 Feb 12;399(10325):629-655. doi: 10.1016/S0140-6736(21)02724-0. Epub 2022 Jan 19. PMID: 35065702; PMCID: PMC8841637.
3. Cannas G, Pautas C, Raffoux E, et al. Infectious complications in adult acute myeloid leukemia: analysis of the Acute Leukemia French Association-9802 prospective multicenter clinical trial. *Leuk Lymphoma.* 2012;53(6):1068–76.
4. Rolston KV. Infections in Cancer Patients with Solid Tumors: A Review. *Infect Dis Ther.* 2017;6(1):69-83. doi: 10.1007/s40121-017-0146-1. Epub 2017 Feb 3. PMID: 28160269; PMCID: PMC5336421.
5. Nesher L, Rolston KV. The current spectrum of infection in cancer patients with chemotherapy related neutropenia. *Infection.* 2014 Feb;42(1):5-13. doi: 10.1007/s15010-013-0525-9. Epub 2013 Aug 23. PMID: 23975584.
6. Avritscher EB, Cooksley CD, Rolston KV, et al. Serious postoperative infections following resection of common solid tumors: outcomes, costs, and impact of hospital surgical volume. *Support Care Cancer.* 2014;22(2):527-35. doi: 10.1007/s00520-013-2006-1. Epub 2013 Oct 19. PMID: 24141699.
7. Nanayakkara AK, Boucher HW, Fowler VG Jr, et al. Antibiotic resistance in the patient with cancer: Escalating challenges and paths forward. *CA Cancer J Clin.* 2021 Nov;71(6):488-504. doi: 10.3322/caac.21697. Epub 2021 Sep 21. PMID: 34546590.
8. Outterson K, Orubu ESF, Rex J, et al. Patient Access in 14 High-Income Countries to New Antibacterials Approved by the US Food and Drug Administration, European Medicines Agency, Japanese Pharmaceuticals and Medical Devices Agency, or Health Canada, 2010-2020. *Clin Infect Dis.* 2022;74(7):1183-1190. doi: 10.1093/cid/ciab612. PMID: 34251436; PMCID: PMC8994582.
9. Kållberg C, Årdal C, Blix HS, et al. Introduction and geographic availability of new antibiotics approved between 1999 and 2014. PLOS ONE. 2018; 13 (10): e0205166 DOI: 10.1371/journal.pone.0205166
10. Årdal C, Lacotte Y, Ploy MC, on behalf of the European Union Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI), Financing Pull Mechanisms for Antibiotic-Related Innovation: Opportunities for Europe. *Clinical Infectious Diseases.* 2020;71(8):1994–1999, https://doi.org/10.1093/cid/ciaa153
11. Rome BN, Kesselheim AS. Transferrable Market Exclusivity Extensions to Promote Antibiotic Development: An Economic Analysis. *Clin Infect Dis.* 2020 Oct 23;71(7):1671-1675. doi: 10.1093/cid/ciz1039
12. Boston Consulting Group. The case for a subscription model to tackle antimicrobial resistance. Available at Incentivizing Innovation to Tackle Antimicrobial Resistance | BCG. Accessed on 17 July 2022.
13. Global Antibiotic Research and Development Partnership. SECURE. Available at SECURE: Expanding Sustainable Access to Antibiotics - GARDP. Accessed on 17 July 2022.

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"Every time an antibiotic is used inappropriately, the development of antimicrobial resistance (AMR) can accelerate. The misuse of antimicrobials is mainly a consequence of individual behaviours that originate from inadequate awareness and understanding of the severity of the consequences. If the use of antibiotics increases by one daily dose per 1,000 people, the prevalence of resistance increases by ~1.5% *(1)*. Currently, the main focus seems to be on research and development for new medicines and diagnostics, while the focus on activities to raise awareness and increase knowledge is sometimes overlooked. This is unfortunate, as raising awareness is key in the fight against AMR.

One of the most significant actions in tackling the AMR threat is raising the awareness and knowledge of people living with cancer about infection prevention and control (IPC), the need to address AMR, and improving their behaviour towards antimicrobial consumption. People living with cancer should be informed and involved in the decision-making process related to the treatment of infections. This way, their concerns on AMR and antibiotic misuse will be heard and duly addressed by their health-care professional.

Simultaneously, training on AMR for the health workforce needs to be strengthened and reinforced. This training needs to be provided not only at the primary health-care level but also at cancer care centres.

In the end, we should not forget about raising awareness of AMR among politicians, policy-makers, and hospital administrators as well. We must convey the message that not addressing AMR will have a substantial direct and indirect cost on our health and economy, and we must adopt evidence-based standards and guidelines on IPC and addressing AMR on a global level now."

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1. Davies D & Verde E. (2013). Antimicrobial Resistance: In Search of a Collaborative Solution - World Innovation Summit for Health. World Innovation Summit for Health. Retrieved 3 August 2022, from https://www.wish.org.qa/reports/antimicrobial-resistance-in-search-of-a-collaborative-solution/#:~:text=This%20report%20focuses%20on%20how,across%20species%20and%20national%20borders.

Resistance beyond antibiotics – antifungal resistance

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Fungal infections are important complications in adults and children receiving cancer treatments such as myelosuppressive chemotherapy. This article reviews the epidemiology of invasive fungal disease, the measurement of antifungal resistance and its epidemiology, and the impact of antifungal resistance on patients with cancer. It also offers recommendations on how to move forward to better understand and contain antifungal resistance.

Infections are important complications in adults and children receiving myelosuppressive chemotherapy, with the highest risk among those with profound and prolonged neutropenia *(1)*. The most important pathogens associated with morbidity and mortality during chemotherapy-induced myelosuppression are bacterial and fungal organisms. Clinical practice guidelines have been developed for this patient population, focusing on the prevention of infection *(2,3)*, and empiric management of fever *(4)*. Antimicrobial resistance (AMR) is an increasingly important issue, resulting in morbidity, mortality and increased health-care utilization. While growing attention has been focused on antibacterial resistance in patients with cancer, less attention has been focused on antifungal resistance, which can result in substantial morbidity and mortality *(5)*. Consequently, the objectives of this article are to review the epidemiology of invasive fungal disease (IFD), the measurement of antifungal resistance and the epidemiology and the impact of antifungal resistance among patients with cancer.

One of the major challenges in addressing antifungal resistance is the limited number of antifungal pharmacological agents available. Developing drug therapy for fungi is challenging, in part, because fungi are eukaryotes and, thus, are more similar to human cells than bacteria or viruses. Fungal cellular structure includes an outer cell wall and an inner plasma membrane. There are three general classes of pharmacological agents that can be used to treat IFD, namely polyenes, azoles and echinocandins:

- Polyenes include conventional and lipid formulations of amphotericin B and work by binding to ergosterol, which is located in the fungal cells' inner plasma membrane.
- Azoles include triazoles such as fluconazole, itraconazole, voriconazole, posaconazole and isavuconazole. Azoles inhibit lanosterol-14α-demethylase, thereby blocking ergosterol production. This enzyme is encoded by ERG11 in yeasts and CYP51 in moulds.
- Echinocandins include caspofungin, micafungin and anidulafungin. Their antifungal activity arises from preventing synthesis of *(1,3)* β-d-glucan, which is an important component of fungal cells' outer cell walls.

Epidemiology of invasive fungal disease

Fungi are an important cause of infection worldwide and affect more than 2 million people per year, with documented rates of IFD increasing over time *(6)*. Most patients with IFD are immunocompromised, such as patients with cancer or haematopoietic stem cell transplant (HSCT) recipients. Once infection occurs, outcomes are poor, with mortality rates often exceeding 50% *(7)*. IFD accounts for more than 1 million deaths per year. Moreover, IFD incidence and mortality are almost certainly underestimated because of diagnostic challenges and the limited availability of diagnostic tools, particularly in low- and middle-income countries.

Fungi can be broadly categorized as yeasts or moulds. The most common yeast causing IFD is invasive *Candida spp*., which is linked to mortality rates as high as 40% *(8)*. In high-income countries, invasive candidiasis is the most common IFD among hospitalized patients *(8)*. Infection with *Candida spp*. may cause fungemia and metastatic organ involvement of the kidney, liver, spleen and eye, for example.

Moulds are organisms frequently found in soil, water and vegetation. The most common mould to cause IFD is *Aspergillus* spp. Frequent sites of infection include the lungs, sinuses and skin. Angioinvasion is common in immunocompromised patients *(9)* and pulmonary invasive aspergillosis can result in life-threatening haemoptysis. In contrast to *Candida* infection, fungemia is uncommon with *Aspergillus* infection.

Measurement of antifungal resistance

The standard approach to assessing antibacterial resistance is to determine *in vitro* minimum inhibitory concentration (MIC) for various drug and organism combinations. However, the ability to determine MIC is not ubiquitous for fungal isolates.

There is far greater uncertainty in defining breakpoints for fungal isolates in comparison to bacterial isolates for several reasons *(10)*. Fungi grow at a much slower rate than bacteria, prolonging the timeframe needed to determine susceptibility. More importantly, many fungal isolates do not grow in culture. Instead, they are detected through histopathology or through use of biomarkers such as galactomannan or fungal polymerase chain reaction (PCR). This challenge impedes our understanding of the epidemiology of antifungal resistance. Even among fungal isolates that can be grown in culture, breakpoints do not exist for many drug and organism combinations. In addition, correlation with clinical outcomes is challenging because isolate sensitivity is only one of many factors that impact on infection control and survival. Other factors impacting these outcomes including resolution of neutropenia, extent of IFD and patient comorbidities. Finally, fungal infection often occurs within specific microenvironments such as lung cavities, and thus, *in vitro* conditions may be markedly different compared to clinical conditions.

Nonetheless, there are breakpoints that exist for some *Candida* and *Aspergillus* spp. Fungal breakpoints were first established for *Candida* spp. Breakpoints were later established for *Aspergillus* spp. by the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) *(11)*.

Antifungal resistance

Antifungal resistance is increasing over time and presents a major problem. Antifungal resistance may result in IFDs that cannot be treated with our current armamentarium of antifungal agents and may be associated with worse clinical outcomes. One study evaluated 67 episodes of candidemia in adult patients with acute leukemia *(12)*. Almost all (94%) were receiving antifungal prophylaxis at the time of candidemia. Non-susceptibility to caspofungin and multidrug resistance were both statistically significantly associated with an increase in 14-day all-cause mortality.

The two general types of antifungal resistance are intrinsic and acquired resistance *(13)*. Intrinsic resistance is inherent; it is genetically coded and, thus, is not dependent on environmental exposure to antifungal agents. An example is the resistance of *Aspergillus fumigatus* to fluconazole. In contrast, acquired resistance is developed as a consequence of exposure to antifungal agents.

There are several factors that have had an undesirable impact on rates of resistance over time and consequently have increased resistance to antifungal agents *(13)*. Exposure to antifungal agents is increasing as a result of both medical and agricultural use. Insufficient antifungal drug exposure may also increase antifungal resistance. This can result from inappropriate prescribing practices or the presence of biofilms, foreign bodies such as catheters and abscesses.

Two important examples of antifungal resistance include fluconazole-resistant *Candida* spp. and azole-resistant *Aspergillus* spp. *Candida* spp. is a common cause of infection in patients with cancer. Increasing prevalence of intrinsically resistant non-albicans spp. (such as *C. glabrata*, *C. parapsilosis* and *C. tropicalis*) and acquired fluconazole resistance are problematic *(14)*. Examples include infection with *C. krusei*, intrinsically resistant to fluconazole, and *C. glabrata*, with acquired resistance to fluconazole. The increase in non-albicans *Candida* infection has been associated with a decline in *C. albicans* infection.

Candida auris is a recently identified species that is often multidrug resistant and may be resistant to all classes of antifungal agents *(15)*. It was the first globally-emergent fungal pathogen with both multidrug resistance and the potential for nosocomial transmission. It emerged almost concurrently on four continents, suggesting that resistant *C. auris* arose from widespread exposure to antifungal agents rather than arising from a common source. It has been responsible for hospital outbreaks. The Centers for Disease Control and Prevention (CDC) issued an alert in June 2016 *(16)* requesting the reporting of identified cases to the local health units and to the CDC *(17)*.

Azole-resistant *Aspergillus* spp. is also an escalating problem, with an increase in pan-azole-resistant *Aspergillus fumigatus* *(18)*. A common mechanism of azole resistance in *Aspergillus* spp. is a mutation of the Cyp51A gene. This mutation alters the lanosterol 14-α-demethylase enzyme, which is targeted by azoles *(19)*. The mutation often confers cross-resistance to azoles in general. Azole-resistant *Aspergillus* may arise where there is high regional prevalence of resistance or in single cases of long-term exposure to azole therapy *(20)*. It has also been linked to agricultural azole utilization. The epidemiology of azole-resistant *Aspergillus* spp. has been evaluated by the Surveillance Collaboration on Aspergillus Resistance in Europe (SCARE) Network *(21)*. In one study, 22 centres from 19 countries participated from January 2009 to January 2011; each centre screened for azole resistance for 12 months. Among 3,788 *Aspergillus* isolates screened, *A. fumigatus* was identified in 77.6% of cases. Prevalence of azole resistance among patients with *A. fumigatus* was 3.2%. Among 195 cases with invasive aspergillosis, azole resistance was found in 10 (5.1%) cases.

Because of the importance of IFD and the consequence of increasing resistance to antifungal agents, it is important that antifungal resistance be more strongly emphasized in policy related to AMR. In the absence of such efforts, it is expected that resistance to antifungal agents will continue to rise and

result in greater morbidity and mortality among patients with cancer.

Future needs

With the increasing prevalence of both IFD and antifungal resistance, there are several areas that require attention in the near future. First, a basic understanding of the epidemiology of antifungal resistance is lacking. Without this knowledge, empiric and therapeutic antifungal strategies are challenging, and patients may receive initial antifungal therapy that is suboptimal. To address this problem, non-culture approaches to measuring antifungal resistance need to be developed and systematically implemented. As IFD is rare, well-designed, multicentre, observational studies describing the extent of antifungal resistance and factors associated with increased resistance are required. As there is geographical variation in IFD prevalence, international collaboration will be necessary to fully understand antifungal resistance epidemiology.

Secondly, new effective approaches to treat resistant fungi must be identified. This will require the development, evaluation and licensing of new antifungal agents. As the infection is rare, treatment trials will require a multicentre design. Examples of agents currently in clinical trials include ibrexafungerp, rezafungin and oteseconazole *(18)*.

Thirdly, strategies to reduce antifungal resistance are required, including the development of standards and clinical practice guidelines focused on antifungal use. There are a number of antifungal stewardship programmes that have been established and these will likely be important in limiting the spread of antifungal resistance *(22)*.

Conclusions

Antifungal resistance is a growing problem in patients with cancer. Increasing intrinsic and acquired resistance have been observed and the latter has been linked to rising exposure related to medical and agricultural use. Pan-resistant isolates such as *C. auris* have begun to emerge and are of major concern. Future efforts should focus on establishing multicentre collaborations, advancing non-culture approaches to detect antifungal resistance and establishing antifungal stewardship programmes. ■

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References

1. Lehrnbecher T, Sung L. Anti-infective prophylaxis in pediatric patients with acute myeloid leukemia. *Expert Rev Hematol.* 2014;7(6):819-30.
2. Lehrnbecher T, Fisher BT, Phillips B, et al. Guideline for Antibacterial Prophylaxis Administration in Pediatric Cancer and Hematopoietic Stem Cell Transplantation. *Clin Infect Dis.* 2020;71(1):226-36.
3. Lehrnbecher T, Fisher BT, Phillips B, et al. Clinical Practice Guideline for Systemic Antifungal Prophylaxis in Pediatric Patients With Cancer and Hematopoietic Stem-Cell Transplantation Recipients. *J Clin Oncol.* 2020;38(27):3205-16.
4. Lehrnbecher T, Robinson P, Fisher B, et al. Guideline for the Management of Fever and Neutropenia in Children With Cancer and Hematopoietic Stem-Cell Transplantation Recipients: 2017 Update. *J Clin Oncol.* 2017;35(18):2082-94.
5. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet.* 2022;399(10325):629-55.
6. Schmiedel Y, Zimmerli S. Common invasive fungal diseases: an overview of invasive candidiasis, aspergillosis, cryptococcosis, and Pneumocystis pneumonia. *Swiss Med Wkly.* 2016;146:w14281.
7. Brown GD, Denning DW, Gow NA, et al. Hidden killers: human fungal infections. *Sci Transl Med.* 2012;4(165):165rv13.
8. Kullberg BJ, Arendrup MC. Invasive Candidiasis. N Engl J Med. 2015;373(15):1445-56.
9. McCarthy M, Rosengart A, Schuetz AN, Kontoyiannis DP, Walsh TJ. Mold infections of the central nervous system. *N Engl J Med.* 2014;371(2):150-60.
10. Lamoth F, Lewis RE, Kontoyiannis DP. Role and Interpretation of Antifungal Susceptibility Testing for the Management of Invasive Fungal Infections. *J Fungi* (Basel). 2020;7(1).
11. Guinea J. Updated EUCAST Clinical Breakpoints against Aspergillus, Implications for the Clinical Microbiology Laboratory. *J Fungi* (Basel). 2020;6(4).
12. Wang E, Farmakiotis D, Yang D, et al. The ever-evolving landscape of candidaemia in patients with acute leukaemia: non-susceptibility to caspofungin and multidrug resistance are associated with increased mortality. *J Antimicrob Chemother.* 2015;70(8):2362-8.
13. Ben-Ami R, Kontoyiannis DP. Resistance to Antifungal Drugs. *Infect Dis Clin North Am.* 2021;35(2):279-311.
14. Seiler GT, Ostrosky-Zeichner L. Investigational Agents for the Treatment of Resistant Yeasts and Molds. *Curr Fungal Infect Rep.* 2021;15(3):104-15.
15. Lockhart SR, Etienne KA, Vallabhaneni S, et al. Simultaneous Emergence of Multidrug-Resistant Candida auris on 3 Continents Confirmed by Whole-Genome Sequencing and Epidemiological Analyses. *Clin Infect Dis.* 2017;64(2):134-40.
16. Vallabhaneni S, Kallen A, Tsay S, et al. Investigation of the First Seven Reported Cases of Candida auris, a Globally Emerging Invasive, Multidrug-Resistant Fungus - United States, May 2013-August 2016. *MMWR Morb Mortal Wkly Rep.* 2016;65(44):1234-7.
17. Farmakiotis D, Kontoyiannis DP. Epidemiology of antifungal resistance in human pathogenic yeasts: current viewpoint and practical recommendations for management. *Int J Antimicrob Agents.* 2017;50(3):318-24.
18. Walker TA, Lockhart SR, Beekmann SE, et al. Recognition of Azole-Resistant Aspergillosis by Physicians Specializing in Infectious Diseases, United States. *Emerg Infect Dis.* 2018;24(1).
19. Chen P, Liu J, Zeng M, Sang H. Exploring the molecular mechanism of azole resistance in Aspergillus fumigatus. *J Mycol Med.* 2020;30(1):100915.
20. Chowdhary A, Sharma C, Kathuria S, Hagen F, Meis JF. Prevalence and mechanism of triazole resistance in Aspergillus fumigatus in a referral chest hospital in Delhi, India and an update of the situation in Asia. *Front Microbiol.* 2015;6:428.
21. van der Linden JW, Arendrup MC, Warris A, et al. Prospective multicenter international surveillance of azole resistance in Aspergillus fumigatus. *Emerg Infect Dis.* 2015;21(6):1041-4.
22. Johnson MD, Lewis RE, Dodds Ashley ES, et al. Core Recommendations for Antifungal Stewardship: A Statement of the Mycoses Study Group Education and Research Consortium. *J Infect Dis.* 2020;222(Suppl 3):S175-S98.

AMR CONTROL SUPPLEMENT
THE CHALLENGE FOR THE CANCER COMMUNITY

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UNION FOR INTERNATIONAL CANCER CONTROL

THE CHALLENGE OF AMR • AMR AND CANCER TREATMENT
CONSERVING ANTIBIOTICS • COUNTERING THE AMR CHALLENGE • RESOURCES

PUBLISHED IN OFFICIAL ASSOCIATION WITH THE UNION FOR INTERNATIONAL CANCER CONTROL (UICC)

To access the electronic editions of this *AMR Control Supplement: The Challenge for the Cancer Community* please visit one of the following websites at:

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www.cancercontrol.info
www.globalhealthdynamics.co.uk
www.uicc.org

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global health dynamics

Resources

Leading the cancer community

The Union for International Cancer Control (UICC) has been a crucial voice for the global cancer community since 1933. We unite the people and organisations that make a difference in cancer control on the world stage.

In the last decade, we have reached millions of people with World Cancer Day, welcomed more than 15,000 delegates at our World Cancer Congresses, and launched five new organisations and initiatives: the International Cancer Control Partnership, the McCabe Centre for Law & Cancer, City Cancer Challenge Foundation, the NCD Alliance and the ATOM Coalition.

Our sustained advocacy efforts have led to several key milestones, including:

- United Nations NCD High-Level Meetings in 2011, 2014 and 2018
- World Health Assembly Palliative Care Resolution in 2014
- World Health Assembly Cancer Resolution in 2017
- WHO Strategy on the Elimination of Cervical Cancer in 2020

Science and evidence at our core

- **TNM Classification of Malignant Tumours,** the global standard for cancer staging; regularly reviewed and updated by the UICC TNM Project, alongside its companion publications, **TNM Supplement** and **TNM Atlas.**
- The **International Journal of Cancer,** UICC's official journal since 1966; a world-renowned, leading publication in experimental, clinical and epidemiological research.
- The **Manual of Clinical Oncology**, a concise reference covering state-of-the-art multidisciplinary clinical oncology.
- Partnership with the American Society of Clinical Oncology on the open-access, online-only **JCO Global Oncology publication.**

Our mission

UICC unites and supports the cancer community to reduce the global cancer burden, to promote greater equity, and to ensure that cancer control continues to be a priority in the world health and development agenda.

uicc
global cancer control

These three pillars form the foundation of what we do:

Convening

Connecting the minds and voices of the global cancer community

- Raising awareness and catalysing personal, collective and government action through World Cancer Day
- Uniting cancer professionals and policy-makers in premier events like the World Cancer Congress and World Cancer Leaders' Summit
- Supporting collaboration through our increasing network of members and partners

Capacity Building

Increasing the impact of the cancer community

- Accelerating learning through training, expert guidance and peer-to-peer connections
- Developing and empowering leaders to sustain and advance cancer control for the future
- Providing resources and investing to support national-level initiatives
- Building a powerful portfolio of offline and online resources to expand knowledge

Advocacy

Bringing cancer to the attention of global leaders

- Engaging United Nations agencies, UICC members, civil society and other stakeholders to achieve the implementation of global cancer and non-communicable disease (NCD) commitments
- Keeping our members' perspectives at the forefront of global health discussions, strategies and events
- Ensuring that all countries develop and implement a national cancer control plan and that national health investments in cancer control and other NCDs increase over time

The UICC-led Task Force on Antimicrobial Resistance and Cancer Care

In 2020, the Union for International Cancer Control (UICC) set up a task force of experts – from the infectious disease community and the cancer community. This UICC-led Task Force was established to guide UICC in highlighting current evidence on antimicrobial resistance (AMR), identify research gaps in knowledge of cancer and AMR, share best practices and engage the cancer community to collaborate and mobilize policy change, which includes addressing the threat of AMR for better cancer care outcomes.

Member of Taskforce	Organization
Cary Adams	Union for International Cancer Control
Sonali Johnson	Union for International Cancer Control
Shalini Jayasekar Zürn	Union for International Cancer Control
Manica Balasegaram	The Global Antibiotic Research and Development Partnership
Jon Kirknes	Norwegian Cancer Society
Ulrika Årehed Kågström	Union of International Cancer Control and Swedish Cancer Society
Danielle Rodin	Union of International Cancer Control and Princess Margaret Cancer Centre
Grace Dubois	The NCD Alliance
Zipporah Ali	Kenya Hospices and Palliative Care Association
Mirfin Mpundu	ReAct Africa
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André Ilbawi	World Health Organization
Benjamin Anderson	World Health Organization
Thomas Joseph	World Health Organization
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- The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)
- The Norwegian Cancer Society

Antimicrobial resistance (AMR) is a growing public health issue that needs urgent attention, especially within the cancer community. The significant and growing threat of AMR is undermining key advances being made in cancer care by adversely affecting cancer treatment outcomes and threatening the survival of people living with cancer. As many as one in five cancer patients undergoing treatment are hospitalized due to infection and antibiotics are the main line of defence. Action to address AMR for better cancer care outcomes is urgently needed.

To sustain focus on the issue and mobilize action on addressing AMR, a special supplement of *AMR Control* has been created with the Union for International Cancer Control to focus on the impact of AMR on cancer care outcomes and what can be done to counter this. Written by over 50 experts committed to researching the scale of AMR and to finding workable solutions, the supplement is an excellent reference for the cancer community as well as being a key resource for advocacy efforts.

"Infections are a leading cause of mortality and morbidity for cancer patients, and the marked increase of drug-resistant infections in cancer patients is alarming. Along with medicines for cancer, surgery, radiotherapy and palliative care, antibiotics are a vital part of cancer treatment and are used for the prevention and treatment of infections. Without access to appropriate antibiotics, patients undergoing cancer treatment will have to face delays in treatment, longer stays in hospital and death due to the infection. Many studies have demonstrated this impact of antimicrobial resistance (AMR) on cancer patients. The global threat of AMR is also a threat to positive cancer care outcomes and will undo all the progress made today in cancer care if we don't act now and address it.

We must encourage a multidisciplinary approach to include addressing AMR in cancer treatment, monitor the effect of AMR on treatment outcomes and ensure access to appropriate and timely treatments. I urge the oncology health workforce and cancer patient groups to come together and reach out to AMR advocates to ensure alignment and work together to ensure a better future for cancer care outcomes."

Professor Jeff Dunn, Chief of Mission and Head of Research at the Prostate Cancer Foundation of Australia and President-elect of the Union for International Cancer Control

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